IN THE MATTER OF:
THE PATENTS ACT 1970 (as amended in 2005),
THE PATENTS RULES 2005

IN THE MATTER of a representation
under Section 25(1) read with Rule 55

IN THE MATTER OF:
Indian Application No. 6087/DELNP/2005 dated 27.12.2005

Filed by GILEAD PHARMASSET LLC, USA;

..... APPLICANT

BDR Pharmaceuticals Ltd.

... OPPONENT

REPLY TO PRE-GRANT REPRESENTATION

Paper Book Of Reply to representation under section 25(1) On behalf of Applicant

Dated this August 07, 2015.

SANJEV K. TIWARI & AMRISH TIWARI
[K&S PARTNERS]
ATTORNEYS FOR THE APPLICANT

The Controller of Patents

IPO DELHI 07-08-2015 17:16
IN THE MATTER OF:

THE PATENTS ACT 1970 (as amended in 2005),
THE PATENTS RULES 2005

IN THE MATTER of a representation
under Section 25(1) read with Rule 55

IN THE MATTER OF:

Indian Application No. 6087/DELNP/2005 dated 27.12.2005
Filed by GILEAD PHARMASSET LLC, USA;
...... APPLICANT

BDR Pharmaceuticals International Pvt. Ltd.
... OPPONENT

REPLY TO PRE-GRANT REPRESENTATION

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Exhibit J  Appleby et al., Structural Basis for RNA Replication by the Hepatitis C Virus Polymerase, Science 2015 347:771-775  408 – 412

Dated this August 07, 2015.

SANJEEV K. TIWARI & AMRISH TIWARI
[K&S PARTNERS]
ATTORNEY FOR THE APPLICANT

The Controller of Patents
BEFORE THE CONTROLLER OF THE PATENTS
PATENT OFFICE, DELHI

IN THE MATTER OF THE PATENTS (AMENDMENT) ACT, 2005

AND

IN THE MATTER OF
an application for the grant of a patent
of 27.12.2005 filed in the name of
GILEAD PHARMASSET LLC
having a principal place of business at
Gilead Sciences, Inc., 333 Lakeside Drive,
Foster City, California 94404,
USA

... Applicant

AND

IN THE MATTER OF pre-grant representation filed
to the grant of patent on subject application
under Section 25(1) of said Act by
BDR Pharmaceuticals International Pvt. Ltd.
Sharda Chambers, Vitthaladas Thackersey Marg,
New Marine Lines, Marine Lines,
Mumbai, Maharashtra-400 002
INDIA

... Opponent

REPLY STATEMENT ON BEHALF OF THE APPLICANT

We, Gilead Pharmasset LLC, (hereinafter referred to as “Applicant”), submit our
reply to the pre-grant representation as under.

At the outset, we submit that the opposition of BDR Pharmaceuticals International
Pvt. Ltd. (“Opponent”) is baseless, misconceived and frivolous, and should be
dismissed *in limine*. All the allegations and averments made in the opposition petition under reply are denied unless specifically admitted herein.

The Applicant's response and submissions, in detail, are herein under:

1. That the averments at paragraph 1 are denied for want of knowledge. It is denied that the Opponent has any *locus standi* or interest in opposing the patent application in question or that the Opponent would be prejudiced if the patent application is allowed. Further, the averments at paragraph 1 are facts on record. The contents of this paragraph relating to Application Number, Title, Indian Filing Date, PCT Publication Number, PCT Filing Date, and Priority etc. are matter of record and need no specific reply. As such the Applicant has no comments as they are mere narration of matters on record.

2. In paragraph 2, the Opponent purports to recite the claims of the present patent application. The Opponent's recitation is denied and disputed as the same is inaccurate. The present applicant's claims have been amended, as illustrated in Exhibit A submitted herewith.

3. In reply to Grounds I-V of the opposition petition, it is submitted that none of cited grounds applies in the present case. The present application discloses and claims an invention pertaining to New Chemical Entities (NCEs). The disclosed and claimed compounds are novel, inventive and patentable within the meaning of Patents Act, 1970. Accordingly, Grounds I-V should be rejected and the application granted.

The present application is directed to (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides and their corresponding monophosphate, diphosphate, and triphosphate forms. In particular, the present application claims a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside of the following formula:
wherein

R¹ and R⁷ are independently H, a monophosphate, a diphosphate, or a triphosphate; and

R³ is H and R⁴ is NH₂ or OH.

The Applicant has demonstrated that compounds of this formula have high levels of activity against hepatitis C virus ("HCV"),¹ low toxicities and other favorable characteristics.

Without prejudice to the above and solely to expedite the grant, the Applicant presently amends the claims. A copy of marked-up claims along with its clean copy is enclosed herewith as Exhibit A. The averments made elsewhere in the present reply may be read as part reply to the present paragraph.

4. As explained in more detail below, Opponent's opposition is completely baseless and frivolous and without any merit and ought to be dismissed in limine.

¹ HCV is a member of the Flaviviridae virus family.
REPLY ON MERITS

In view of the above, all the averments made in the pre-grant opposition are false and hereby denied. No averment may be deemed to be admitted for want of traverse. For purposes of brevity the Applicant herein addresses the main issues in the opposition without going into specific denials. However, it is clarified that none of the averments made in the opposition are admitted. We now proceed to analyze and reply to the pre-grant opposition:

5. The Present Invention:

The present invention is directed towards compounds useful for the treatment of HCV infection. HCV infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, and ultimately death in a substantial number of infected individuals, estimated to be about 170 million worldwide and about 18 million in India.

As of the present application’s effective filing date, interferons (IFNs) had been commercially available for the treatment of chronic HCV infection for approximately a decade. Unfortunately, the effect of IFNs is temporary, and a sustained virologic response (a cure of HCV) occurs in only 8% - 9% of patients chronically infected with HCV (Gary L. Davis. Gastroenterology 18: S104-S114, 2000). Further, most patients have difficulty tolerating IFN treatment, which causes severe flu-like symptoms, weight loss, and lack of energy and stamina. Another drug, ribavirin (1-(3-D-ribofuranosyl)-1-1, 2, 4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name Virazole (The Merck Index, 11th edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, p. 304, 1989). Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, 2000). Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV. It has been approved in combination with IFN alpha-2a or IFN alpha-2b for the treatment of HCV infection. Therapies using ribavirin and IFN require 48 weeks of treatment—
nearly a whole year. The cure rate of patients completing a course of treatment with
the most advanced IFN + ribavirin therapies is about 55%. However, because of the
severe side effects and long duration of therapy, many patients are non-compliant
and, thus, do not receive the complete course of therapy to cure the disease.
Moreover, given the low success rate of interferon and ribavirin combination
treatment, many patients endured the severe side effects in vain.

In light of the fact that HCV infection had reached epidemic levels worldwide and
has tragic effects on the infected patient, at the time the present application was
filed, there was a strong need to provide new effective pharmaceutical agents to
treat HCV that have low toxicity to the host and that can shorten the duration of
treatment.

The present application specifically claims (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl
nucleosides of the following formula:

![Chemical Structure Image]

wherein

R^1 and R^7 are independently H, a monophosphate, a diphosphate, or a
triphosphate; and

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

The Applicant has demonstrated that compounds of this formula have high levels of
activity against HCV, low toxicities and other favorable characteristics.
Contrary to Opponent's arguments, the present invention is novel and involves inventive step for at least the following reasons:

A. The Opponent's cited references do not disclose or suggest the compounds claimed in the present application;

B. Neither the Opponent's cited references, nor any other teachings in the prior art, enabled the synthesis of the claimed (2'R)-2'-deoxy-2'-fluoro (down)-2'C-methyl (up) nucleosides; and

C. Neither Opponent's cited references, nor any other teachings in the prior art, demonstrated or suggested that the claimed (2'R)-2'-deoxy-2'-fluoro (down)-2'C-methyl (up) nucleosides would be useful, e.g., as anti-HCV therapeutics.

It is submitted that none of the prior art documents impeach the novelty or inventiveness or patentability of the invention as contained in the present application. The submissions of Applicant herein below may be read in this regard and be treated as a reply on merits.

In addition, the Applicant has also invented novel and inventive prodrugs of the compounds claimed in the present application. The Applicant claimed the invention relating to such prodrugs, including sofosbuvir, the active ingredient in Sovaldi®, in a separate application being Indian Patent Application No. 3658/KOLNP/2009.

Sovaldi® offers a cure rate of about 90% when taken as prescribed, and has shortened treatment duration and reduced debilitating side effects, enabling more people to complete treatment. This revolutionary product was approved by the Central Drug Standard Control Organization (CDSCO) on January 13, 2015. To date, the applicant has signed a licensing and technology transfer agreement with the following 11 Indian pharmaceutical companies: Biocon, Cadila Healthcare, Cipla, Hetero Labs, Mylan Laboratories, Ranbaxy Laboratories, Sequent Scientific, Strides Arcolab, Natco Pharma Ltd., Aurobindo Pharma Ltd., and Laurus Labs Pvt. Ltd. The agreement allows these companies to manufacture and distribute generic
sofosbuvir in 91 developing countries, including India. Eight licensees have launched or are in the process of launching generic sofosbuvir and other companies are expected to follow soon. The drug has thus been made readily available for the patient population at reasonably affordable prices.

Consistent with the overwhelming success of this product, patents with claims corresponding to the claims of this application have been granted in the following 18 countries and regions:

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None of the prior art documents cited by the Opponent discloses or suggests the compounds of the present invention and, as such, these documents cannot impeach the novelty or inventiveness of the invention as contained in the instant application. The submissions of the Applicant herein below may be read in this regard and be treated as reply on merits.

**GROUNDs:**

6. **Ground I: Lack of Novelty**

The averments made in **Ground I (paragraph 1)** regarding anticipation are factually and legally incorrect, and are furthermore misleading, and hence denied. Regarding novelty, for an invention to be anticipated by a single reference, the invention must be fully and identically described in that reference. The structural and functional differences between the claimed invention and the prior art cannot be ignored. In order for an invention to be held to be anticipated all the same elements of the invention must be found in the same situation and united in the same way to perform an identical function. Furthermore, the reference must enable those skilled in the art to practice the claimed invention without undue experimentation or undue burden.
I. WO2002/057287 (WO’287)

As per the Opponent, claims 1-10 of present application are anticipated by WO02/057287 ("WO’287") (Annexure 1 to Opponent’s submission). As per the Opponent, WO’287 discloses a Markush structure that is drawn to several nucleoside compounds and the compounds as claimed in claims 1 to 5 and in claim 6 and 7 are known and encompassed within the basic chemical structure of the WO’287 application.

Applicant’s Response

In response, Applicant respectfully disagrees with Opponents assertions. The compounds of WO’287 are structurally very different compounds than the nucleoside compounds of present application. Applicant submits that a careful analysis of WO’287 reveals that the compounds of the present application are not at all anticipated by the cited reference.

Firstly, it is to be noted that the compounds disclosed and taught by WO’287 are purine analogue compounds, particularly, pyrrolo[2,3-d]pyrimidine compounds unlike the compounds of the present application.

Secondly, all the exemplified or promising compounds of WO’287 either have a 2'-hydroxy (down) – 2'-methyl (up) or 2'-hydroxy (up) – 2'-methyl (down) substitution pattern at 2'-position of sugar in pyrrolo[2,3-d]pyrimidine compounds. There is no disclosure or teaching of compounds with 2'-methyl (up) 2'-fluoro (down). Further, WO’287 describes a general method for preparation of compounds of the present invention in scheme 1 which is reproduced herein below. The synthetic scheme does not teach fluorination at 2'-position of pyranose ring in order to have 2'-fluoro (down) and 2'-C-methyl (up). Actually, there is not a single example for the preparation of a compound with 2'-fluoro (down) and 2'-C-methyl (up) even with pyrrolo-pyrimidine as a base. The only teaching from WO’287 is to have a 2'-hydroxy (down) and 2'-methyl (up) or 2'-methyl (down) and 2'-hydroxy
(up) that too in purine based nucleoside compounds more specifically pyrrolo[2,3-d]pyrimidine compounds.

\[
P_g^1 \text{O} \quad \text{OR} \quad \text{OH} \quad \xrightarrow{[\text{O}]} \quad \text{PGO} \quad \text{O} \quad \text{OR} \quad \text{OH} \quad \xrightarrow{\text{R}^1 \text{MgX}} \quad \text{PGO} \quad \text{O} \quad \text{OR} \quad \text{OH} \quad \xrightarrow{\text{X} = \text{Cl}, \text{Br}, \text{or I}}
\]

\[\text{Pg} = \text{protecting group} \quad R = \text{lower alkyl}\]

\[
P_g \quad \text{O} \quad \text{OR} \quad \text{OH} \quad \xrightarrow{\text{HX}} \quad \text{PGO} \quad \text{O} \quad \text{OR} \quad \text{OH} \quad \xrightarrow{\text{X} = \text{Cl}, \text{Br}, \text{or I}}
\]

\[\text{R}^9 \quad \text{X} \quad \text{M} \quad \text{R}^{11} \quad \xrightarrow{\text{M} = \text{Li}, \text{Na}, \text{or K}} \quad \text{X} = \text{Cl}, \text{Br}, \text{or I}\]

In addition, please note that the illustration shown on p. 6 of Opponent's brief (figure 2) does not appear in WO'287. It is a hypothetical example concocted by the Opponent and was not made, described, or even suggested in WO'287. Further, WO'287 does not describe how to make a 2'-deoxyribonucleoside compound with a 2'-fluoro (down)-2'-C-methyl (up) substitution pattern at 2'-carbon of ribose sugar moiety or provide any data indicating that such a compound has anti-flaviviridae activity, let alone anti-HCV activity. Still further, the WO'287
fails to provide any guidance or suggestion as to compounds having the particular 2'-fluoro (down)-2'-C-methyl (up) substitution pattern of the instant invention.

In view of the comments above, Applicant submits that WO'287 fails as a novelty-destroying reference and that the presently pending claims are novel. Accordingly, the instant ground is liable to be rejected.

7. **Ground II: Obviousness – Lack of Inventive Step**

The averments made in *Ground II (paragraph II)* regarding lack of inventive step are factually and legally incorrect, misleading and should be rejected.

The Opponent presents several references and alleges “[i]t was known that modification at the 2' position of the ribose sugar ring yielded compounds with excellent therapeutic activity.” The Opponent contents that Matsuda et al. teaches a nucleoside with a methyl group at the 2' (up) position and a hydroxyl group at the 2' (down) position, and that hydroxyl and fluorine were known to be bioisosteres (e.g., as evidenced by Bioisosteres in Medicinal Chemistry, published by Maybridge MedChem). The Opponent also contends Hertel et al. evidences that “the presence of fluoro group in down configuration at 2'-position of the sugar molecule of nucleoside analogues is already well established” and that “such compounds have been demonstrated by the author for their anti-viral activity.” Based on these contentions, the Opponent concludes it would have been obvious to make a nucleoside with 2-deoxy-2'-fluoro (down)-2'-C-methyl (up) substitution, and that Middleton allegedly teaches reagents for doing so, such as the fluorinating reagent DAST. As explained below, this is not correct, and the Opponent's arguments are based on impermissible hindsight. The Opponent's averments in Ground II are therefore wrong and hereby denied.

I. **Matsuda et al.**

As per the opponent, Matsuda et al. (Annexure 2 to Opponent's submission) “discloses the synthesis of 2'-deoxy-2'-(S)-methyl cytidine and their use in anti-
leukemic." Thus, according to the Opponent, "the presence of methyl group at 2'-position in up configuration is already known ...."

Applicant's Response

In response, Applicant respectfully disagrees with the Opponent's assertions. Matsuda et al. discusses the synthesis of 2'-deoxy-2'-(S)-methylcytidine (compound 7) along with compounds 13-15 shown below:

Matsuda et al. also discusses the inhibitory activity of these compounds against mouse leukemic cell line L1210 cells. The compounds disclosed in Matsuda et al. differ from the presently claimed compounds, e.g., Matsuda et al. does not disclose or suggest compounds with 2'-deoxy-2'-fluoro (down)-2'-methyl (up) substitution. In fact, Matsuda et al. does contain any reference to fluorinated nucleosides or processes for making such compounds. Matsuda et al. also lacks any suggestion that the (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides of the present application's claims would have anti-Flaviviridae, e.g., anti-HCV activity. In fact, Matsuda et al. does not mention any type of antiviral activity, but rather focuses only on anti-leukemic activity. In this regard, Matsuda et al. teaches that 2'-deoxy-2'-methyl compound 7 was the most active against the mouse leukemic cell line tested (page 3969-70). The skilled artisan would also understand that an anti-leukemic (or anti-cancer) agent would be acting as DNA and that natural DNA nucleosides have a hydrogen in the 2' (down) position. The skilled artisan would understand that a nucleoside with anti-HCV (or anti-Flaviviridae) activity would be acting on RNA and that natural RNA nucleosides have a hydroxyl in the 2' (down) position. Thus, the Opponent's bioisostere argument about replacing a 2' (down) hydroxyl
group in a Matsuda et al. compound with a fluorine atom clearly relies on impermissible hindsight, as it is premised on selecting and modifying a compound that the reference teaches is not the most active in order to arrive at a compound with a type of biological activity that the reference does not discuss.

Therefore, Matsuda et al. does not provide the basis for an inventive step rejection in view of above comments.

II. Hertel et al.

As per the Opponent, Hertel et al. (Annexure 3 to Opponent's submission) "discloses the synthesis of 2-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2,2'-difluoro-D-ribofuranosyl nucleoside analogues and their use as anticancer and antiviral agents." As per the Opponent, "the presence of fluoro group in down configuration at 2'-position of the sugar molecule of nucleoside analogues is already well established" in view of Hertel et al.

Applicant's Response

In response, Applicant respectfully disagrees with the Opponent's assertions. Hertel et al. describes the synthesis of 2-deoxy-2,2-difluoro-D-ribofuranosyl nucleosides, which lack the (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) substitution required by the present application's claims. Hertel et al. does not disclose or suggest nucleosides with the 2' substitution pattern required by the present claims, and it also does not teach how to make such compounds. For example, Hertel et al. does not teach how to install both a methyl group and a fluorine atom at the 2' position, let alone how to do so with the specific stereochemistry required by the present application's claims.

Furthermore, Hertel et al. contains no suggestion that the presently claimed compounds would have anti-Flaviviridae, e.g., anti-HCV activity. Hertel et al. discusses research done pursuant to a program "initiated with hopes of finding compounds of potential value as anticancer and/or antiviral agents" (abstract) and "with hopes of finding some unique biological activity" (page 2406). Hertel et al.
does not teach that any of the compounds disclosed therein actually have any particular type of antiviral or anticancer activity, let alone anti-\textit{Flaviviridae}, or anti-HCV, activity. Further, Hertel et al. contains no suggestion that replacing a hydroxyl group (i.e., OH) in a Matsuda et al. compound with a fluorine atom would give a nucleoside with anti-\textit{Flaviviridae} activity, let alone with anti-HCV activity.

Therefore, Hertel et al. does not provide the basis for an inventive step rejection in view of above comments.

III.\hspace{1em} \textbf{Middleton}

As per the Opponent, Middleton (Annexure 4 to Opponent's submission) "discloses the use of fluorinating agent such as DAST and dialkylaminosulfur trifluorides to replace hydroxyl group of alcohols with a fluorine group." As per the Opponent, the use of DAST as a fluorinating agent was already known much before the priority date of the present patent application.

\textbf{Applicant's Response}

In response, Applicant respectfully disagrees with the Opponent's assertions. Middleton does not discuss the use of DAST to fluorinate tertiary alcohols on nucleoside sugar rings, nor does it disclose or refer to (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up)-substituted nucleosides. The Opponent engages in oversimplification when asserting that, because DAST had been shown to fluorinate certain alcohols, it was therefore known how it would react with very different substrates. Rather, even if DAST had been shown to successfully fluorinate, e.g., certain straight chain alcohols, one skilled in the art could not have predicted that DAST would work to fluorinate a sterically hindered tertiary alcohol at the 2' position of a nucleoside's sugar ring. The Opponent's argument is based on impermissible hindsight gained from Applicant's present application, which was the first publication teaching the synthesis of a (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleoside using DAST.
Therefore, Middleton does not provide the basis for an inventive step rejection in view of above comments.

IV. Bioisosteres in Medicinal Chemistry, published by Maybridge MedChem

The averments on pages 10-11 of the opposition petition are wrong and hereby denied. As per the Opponent, “substitution of hydroxyl group with fluorine is the most commonly employed classical bioisosteric replacement.” The Opponent further contends that Bioisosteres in Medicinal Chemistry published by Maybridge MedChem (“Maybridge MedChem”) (Annexure 5 to Opponent’s submission) discloses that replacement of a hydroxyl group with fluorine extends biological half-life and eliminates the formation of toxic metabolites.

Applicant’s Response

In response, Applicant respectfully disagrees with the Opponent’s assertions.

As a preliminary matter, the Opponent’s argument relies on assumptions that the Opponent makes across the entire field of medicinal chemistry without showing that it is appropriate to do so. For example Maybridge MedChem discusses a variety of drugs and other biologically active chemicals that are very different from the compounds of the present application in terms of both chemical structure and biological function. Maybridge MedChem does not specifically address nucleosides or nucleotides. The Opponent’s contention that an artisan would have applied teachings regarding structurally different compounds that act through very different biological mechanisms so as to arrive at the presently claimed compounds depends on oversimplifications that one skilled in the art would not have made.

Contrary to the Opponent’s argument, literature available as of the present application’s filing date, including references relied on by the Opponent, indicated that fluorine could potentially be an isostere for either a hydrogen atom (H) or a hydroxyl group (OH). See, e.g., Maybridge MedChem at 2-3 (“Despite the fact that fluorine has a greater size then hydrogen, several studies have demonstrated it as a reasonable hydrogen mimic. ... The replacement of hydrogen by fluorine is thus an
extensively used technique in medicinal chemistry ...") The present application also states that "[f]luorine is known to be capable of forming a hydrogen bond but unlike a hydroxyl group, which can act both as a proton receptor and proton donor, fluorine acts only as a proton acceptor" (page 45 of original PCT application).

Further, certain fluorinated nucleosides had been reported to have anti-cancer (e.g., gemcitabine) and/or anti-hepatitis B virus (anti-HBV) activity. Based on these reports, one skilled in the art would have expected fluorine to act as an isosteric replacement for a hydrogen atom and not for a hydroxyl group. Consistent with this expectation, a recent study has confirmed, using one of the claimed compounds, that the 2' (down) fluorine atom does not act as an isosteric replacement for hydroxyl in the context of the present invention. The 2' (down) fluorine atom does not engage in the same type of bonding with the NS5B enzyme that a 2' (down) hydroxyl group does; rather, the fluorine atom appears to disrupt such interactions. See Appleby et al., Structural Basis for RNA Replication by the Hepatitis C Virus Polymerase, Science 2015 347:771-775 at 774 (Exhibit J).

Even further, the references upon which the Opponent relies demonstrate that there would have been uncertainty about the result of substituting a hydroxyl group with a fluorine atom in a nucleoside, given the dramatic effects that introduction of a fluorine atom can have on molecule. Thus, an artisan would not have had a reasonable expectation that replacing a hydroxyl group with a fluorine atom would result in a compound with the desired activity.

V. **No Motivation to Combine: No Expectation of Success**

The Opponent's argument is devoid of any explanation as to why one skilled in the art would have selected any of the foregoing references or would have been motivated to combine any of them to arrive at the presently claimed invention. Thus, the Opponent fails to establish a prima facie case of lack of inventive step. Rather, in hindsight the Opponent has attempted to identify in scientific literature the discrete structural components of the presently claimed compounds, as well as discrete chemical reagents that may be used to make them according to the
Applicant's own novel methods. However, such is insufficient where there is no evidence that an artisan would have selected any of the foregoing references or any combination thereof, no evidence that an artisan would have been motivated to select and combine particular portions in the disclosure of each reference to arrive at the claimed invention, and no evidence that the artisan would have had any reasonable expectation that the presently claimed compounds would have anti-
*Flaviviridae*, e.g., anti-HCV, activity and low toxicity. Accordingly, the Opponent's inventive step argument wholly fails to establish that the presently claimed invention lacks inventive step.

Furthermore, the combination of references discussed above would not have taught a skilled artisan how to make the claimed compounds. In fact, the United States Patent and Trademark Office ("USPTO") has repeatedly rejected arguments very similar to those made by the Opponent with respect to synthetic methods. For example, in Interference No. 105,871, Idenix Pharmaceuticals, Inc., et al. argued that DAST could have been routinely used to replace a hydroxyl group with a fluorine atom in a compound from related work published by Matsuda et al. so as to make a (2'R)-2'-deoxy-2'-fluoro (down)-2'C-methyl (up) nucleoside. See Exhibit H at 7-14. The PTAB rejected such arguments:

Specifically, Dr. Dahma [Idenix's expert witness] testifies that the literature taught fluorinating the sugar at the 2' position of a deoxy-arabino nucleoside or arabinonucleoside with the reagent DAST. (FFs 11-13). According to Dr. Dahma, because these reactions include replacing an OH group with a fluorine and inverting the stereochemistry so that the fluorine is in the "down" position, those in the art would have considered these reactions to be the same as the reactions needed to make 2'-F-2'Me-ribonucleoside within Count 1. Dr. Dahma also testifies that even though the nucleoside fluorinations with DAST reported
in the literature as of December 2001 were fluorinations of secondary alcohols, fluorinations of tertiary alcohols with DAST were also known. (FFs 15-17.)

Clark [Applicant] opposes Sommadossi's [Idenix's] argument, relying on the opinion of its witness, Dr. Marquez. According to Dr. Marquez, the evidence presented by Dr. Dahma does not show that those in the art would have considered using DAST to synthesize a 2'-F-2'-'Me-nucleoside because it would have been too unpredictable. Dr. Marquez testifies that those of skill in the art would have been aware of the risks of producing elimination and anhydro products when using DAST and would have understood that DAST had not been shown to produce a tertiary fluorine on the 2' carbon of the sugar of a nucleoside. (FFs 26.) In support, Dr. Marquez cites to correspondence between Idenix personnel and to the advice of consultants hired by Idenix, which were critical of the proposed schemes. (FFs 27-33.)

Clark also argues that Sommadossi’s own diligence period attests to the lack of knowledge about how make a compound within the scope of Count 1 at the time of Sommadossi’s asserted conception. (Clark Opp. 9, Paper 460, at 3:17-4:4.) Clark argues that six Ph.D. level chemists at Idenix, as well as other researchers, with the help of two consultants (Dr. Fleet (see Storer Deposition, Exh. 1644, 73:22-24 (describing Dr. Fleet as a “world expert on carbohydrate chemistry”) and Dr. Coe (see id., 74:23-24 (describing
Dr. Coe as an “expert in organofluorine chemistry”), worked for over three years to make a 2'-F-2'Me-ribonucleoside. (Clark Opp., Paper 460, at 9:5-9.) Clark also notes that at least one member of the Idenix team (Dr. Griffon and Claire Pierra, see Storer Decl., Exh. 1429, at ¶ 35) attended a four-day training course in fluorination chemistry to gain the necessary knowledge and, further, that Sommadossi was only able to actually reduce to practice an embodiment of the Count after the publication of a synthesis pathway in the application that became the Clark patent. (Clark Opp. 9, Paper 460, at 9:6-7 and 3:17-22.) According to Clark, this effort was not routine and demonstrates the lack of skill of any artisan at the time, as well as an incomplete conception by the Sommadossi inventors by their asserted conception dates.

We are persuaded by Clark's argument. Though Dr. Dahma presents evidence to show that each step of the synthesis of a 2'-F-2'Me-ribonucleoside would have been known to those in the art, the skepticism shown by Dr. Coe, who was consulted for his expertise, and in the communications between Drs. Storer and Stewart support Dr. Marquez's opinion that those of skill in the art would not have had the necessary skill.

In addition, we are persuaded that the length of time Idenix personnel spent trying to synthesize a 2'-F-2'Me-ribonucleoside does not exemplify routine experimentation. Sommadossi argues that it is improper to look to the activities of specific people to show what was known by a skilled artisan at the time
because such analysis "is premised on the false assumption that those efforts were made by the hypothetical person instead of real people with imperfect awareness of the relevant art." (Sommadossi Reply 9, Paper 464, at 3:20-23.) According to Sommadossi, if there is an operative method of making a compound in the art, it is irrelevant that the actual inventor tried and failed, even many times, to make it. (Sommadossi Reply 9, Paper 464, at 3:20-4:10.)

Sommadossi's argument does not persuade us to ignore the evidence of the Idenix personnel's extraordinary effort. To make a determination of what the hypothetical ordinarily skilled artisan would have been able to do, we look to evidence of not only what information was publically available, but also evidence of what actual artisans did with that knowledge.

Both Drs. Dahma and Marquez agree that a hypothetical person skilled in the art of synthesizing a compound of the count would have an advanced education (Ph.D. or master's degree) and additional experience in the chemical aspects of drug discovery (i.e., synthetic organic chemistry). (See Dahma Decl., Exh. 1281, ¶ 16; Marquez Decl., Exh. 2001, ¶ 70.) The members of the Idenix team were all employed as chemists and several had doctoral degrees. (See, e.g., Storer Decl., Exh. 1429, ¶ 2 (testifying that he has a D.Phil. degree in chemistry); Substitute Declaration of Jean-Francois Griffon, Exh. 1471, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Adel Moussa, Exh. 1428, ¶ 2 (testifying
that he has a Ph.D. degree in organic chemistry; Substitute Declaration of Alistair Steward, Exh. 1241, ¶ 2-3 (testifying that he has a Ph.D. degree in organic chemistry.) Sommadossi does not argue that they were not at least ordinarily skilled artisans. On the record before us, we have no reason to exclude them as representative of ordinarily skilled artisans at the time. Thus, the evidence of the effort exerted by the Idenix team to eventually synthesize a 2'F-2'Meribonucleoside is informative of what the hypothetical skilled artisan could do.

Furthermore, the evidence of the effort exerted by the Idenix team shows that it was not just one chemist who was unable to synthesize a compound within Count 1 with routine experimentation, but a team of chemists, even after they had consulted with others considered to be experts and had sought additional training. From this record it is reasonable to find that if after all of this effort, a compound within the scope of the count could not be synthesized easily, a hypothetical person of ordinary skill would not have known how to synthesis such a compound either.

Id. at 8-21.

For this additional reason, the combination cannot render the claimed invention obvious.
ADDITIONAL ARGUMENTS REGARDING INVENTIVE STEP

The Applicant submits its additional reply under Sections 7.2 and 7.3 as below:

7.2 Changes in Substituents at the 2’ Position of Nucleosides Result in Large Changes in Activity or Toxicity.

The particular substitution pattern of the claimed compounds is unique, and imparts unexpectedly high activity and low toxicity to them. In this regard, Applicant re-submits Table 1, below, which shows activity (EC$_{90}^2$) and cytotoxicity (CC$_{50}^3$) of various 2’-substituted nucleosides:

Table 1. Activity and Cytotoxicity Comparison of 2’-Substituted Cytidine Analogs

<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>HCV Activity EC$_{90}$ (μM)</th>
<th>Clone A CC$_{50}$ (μM)</th>
<th>Hep G2 CC$_{50}$ (μM)</th>
<th>BxPC3 CC$_{50}$ (μM)</th>
<th>CEM CC$_{50}$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Compound 1" /></td>
<td>&lt;1</td>
<td>&lt;0.1</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Compound 2" /></td>
<td>5.66</td>
<td>&gt;100</td>
<td>400</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

$^2$ EC$_{90}$ refers to effective concentration to achieve 90% inhibition (see, e.g., ‘6087 description of FIG. 1).

$^3$ CC$_{50}$ refers to the concentration required to reduce the number of non-virus-infected cells by 50% (see, e.g., ‘6087 Example 5 (Toxicity)).
<table>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>HCV Activity EC&lt;sub&gt;90&lt;/sub&gt; (μM)</th>
<th>Clone A CC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
<th>Hep G2 CC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
<th>BxPC3 CC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
<th>CEM CC&lt;sub&gt;50&lt;/sub&gt; (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 3" /></td>
<td>Cannot determine: Toxic to cells</td>
<td>&lt;50</td>
<td>200</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 4" /></td>
<td>9.73</td>
<td>10.47</td>
<td>40</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 5" /></td>
<td>4.5</td>
<td>&gt;100</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

"C" represents cytosine.

This table is instructive for at least the following reasons.

First, it shows that the data for Compound 5<sup>4</sup> (present invention) is unexpectedly better than that of the compared compounds. For example, the 2'-fluoro (down)-2'-hydrogen (up) compound (Compound 2) shows HCV activity but is also toxic in certain cell lines. As noted above, Compound 2 (i.e., FdC) has also demonstrated mitochondrial toxicity. See Exhibit F at Table 5. The 2'-fluoro (up)-2'-hydrogen (down) compound (Compound 3) is too toxic to test for anti-HCV activity. The 2'-difluoro compound (Compound 1) is more active than Compound 2 but also very toxic. Finally, the 2'-methyl (up)-2'-hydrogen (down) compound (Compound 4) has activity but is also toxic against certain cell lines.

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<sup>4</sup> Table 1's Compound 5 corresponds to the '6087 application's Compound 3-6/Compound 4-6, i.e., (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine.
Second, these data demonstrate the high degree of unpredictability when varying the substituents at a nucleoside's 2' position. There is no clear trend in the data. Compound 5, therefore, has a very unexpected and surprising activity and toxicity profile.

Third, if one attempted to discern some trend from the foregoing data, it would suggest that a 2'-fluoro (down)-2'-methyl (up) substitution pattern would cause toxicity. Both Compound 2 (2'-fluoro (down)) and Compound 4 (2'-methyl (up)) show significant cytotoxicity against the cell lines tested. Thus, one of ordinary skill in the art would not predict the very low toxicity observed for Compound 5.

In addition, the learned Controller may refer to the experimental data already disclosed in the specification (see pages 66-71 and 87-94), which clearly indicates that 2'-deoxynucleosides with 2'-fluoro (down)-2'-C-methyl (up) substitution patterns are non-toxic, highly active and have other favorable characteristics as compared to the nucleoside compounds of the prior art. For example, Tables 1 to 9 of the present application compare the activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (Compound 3-6/Compound 4-6 in '6087) with the activities of 2'-C-methylcytidine and 2'-C-methyladenosine.

![Chemical Structure](image)

(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine \(\text{(Compound 3-6/4-6)}\)
Tables 1 and 2 in ’6087 demonstrate that (2’R)-2’-deoxy-2’-fluoro-2’-C-methylcytidine has unexpectedly superior activity compared to 2’-C-methylcytidine in several HCV replicon assays. Tables 6 and 9 also demonstrate that (2’R)-2’-deoxy-2’-fluoro-2’-C-methylcytidine has unexpectedly lower toxicity, compared to 2’-C-methylcytidine and 2’-C-methyladenosine in cytotoxicity and human bone marrow cell assays. Table 8 further demonstrates (2’R)-2’-deoxy-2’-fluoro-2’-C-methylcytidine's PK parameters in Rhesus monkeys following a single oral dose. (2’R)-2’-deoxy-2’-fluoro-2’-C-methylcytidine's unexpected properties could not have been predicted and, thus, could not have been obvious from the compounds disclosed in the references upon which the Opponent relies.

Applicant asserts that, from the data presented above in Table 1 and in the specification, it is clear that the 2’-fluoro (down)-2’-methyl (up) substitution pattern present in the nucleosides of the present application unexpectedly imparts therapeutic activity against HCV while at the same time imparting no toxicity to the host.

In view of above, the compounds of instant invention are novel and not obvious to one skilled in the art.

7.3 The Prior Art Did Not Enable the Synthesis of 2’-Fluoro (down)-2’-Methyl (up) Nucleosides.

As noted above, none of the cited references describe how to make the compounds of the present application. The same is true of the prior art as a whole. Rather,
Applicant's application first published on 13 January 2005 provided the first report of how to synthesize a 2'-fluoro-(down)-2'-methyl-(up) nucleoside.

Applicant has prevailed in contested proceedings with Idenix et al. in other countries—in particular Norway, the UK, and the United States. One issue central in these proceedings was whether the prior art would have enabled an artisan to make the claimed compounds without undue or overly burdensome experimentation. In addition to the lack of teaching in the prior art, these tribunals have considered the attempts of actual scientists in the field, specifically those at Idenix and affiliated institutions (i.e., the applicants for WO'121). Evidence of Idenix's failed attempts to make such compounds over a period of several years was first made available in U.S. Patent Interference No. 105,871, where Idenix's witnesses admitted that the first time Idenix successfully made a 2'-fluoro-(down)-2'-methyl-(up) nucleoside was only after Gilead's application published in 2005 and they repeated a procedure as written therein. See Exhibit G at 106-107; see Exhibit C at 9-10. Idenix's multi-year struggle illustrates that the prior art would have been insufficient to enable the synthesis of 2'-fluoro-(down)-2'-C-methyl-(up) nucleosides prior to Gilead's application.

Further in this regard, the Oslo District Court panel, which included a technical judge who was a professor of chemistry, issued a decision on 21 March 2014 (Exhibit B) which, in part, discussed how difficult it was to make 2'-fluoro (down)-2'-C-methyl (up) nucleosides prior to the publication of Gilead's application. The Oslo District Court wrote:

[T] he skilled person will be faced with a number of choices that have to be made in order to be able to produce or synthesise [a 2'-fluoro-2'-methyl nucleoside]. Firstly, a choice needs to be made between the sugar route and the nucleoside route. Thereafter, starting materials need to be chosen. Many alternatives will be available in respect of both route alternatives,
and the choices will not be perceived as obvious. Moreover, a fluorination reagent needs to be selected. This also involves numerous alternatives. Even if one starts out from the most precise and restrictive part of the description, as well as the alternative claims, there are several options. One may for example choose both natural and synthetic bases. Finally, one needs to select reaction conditions and solvents, etc., for the various reactions. The Court notes that minor variations in chemical processes may have a major impact and be decisive in terms of whether or not one succeeds in bringing about the desired compound.

Exhibit B at page 32 (emphasis added). The Court then gave its judgment on whether the art was enabling, taking in account whether Idenix made any 2'-fluoro-2'-C-methyl nucleosides before the priority date of the present application:

[T]he skilled person will, in order to carry out the invention, have to find an overall solution that will depend on the sum total of a number of partial solutions. The Court is of the view that the skilled person would not be able to carry out the invention without a considerable amount of trial and error. This conclusion is also supported by the fact that Idenix itself would not appear to have been able to produce the compound until at a much later date.

Id. at page 33. The Oslo District Court concluded that the Gilead patent (equivalent to '6087) was valid and the Idenix patent based on WO2004/002999 was invalid.

The USPTO reached a similar conclusion: Gilead was the first to invent (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides. See Exhibits C, D, E and H. In
reaching this conclusion, the USPTO considered Idenix's repeated failed attempts to make such compounds prior to the publication of Gilead's application as evidence that the prior art was not enabling. For example, the USPTO stated:

In addition, we are persuaded that the length of time Idenix personnel spent trying to synthesize a 2'-F-2'Me-ribonucleoside does not exemplify routine experimentation. Sommadossi [Idenix] argues that it is improper to look to the activities of specific people to show what was known by a skilled artisan at the time because such analysis "is premised on the false assumption that those efforts were made by the hypothetical person instead of real people with imperfect awareness of the relevant art." (Sommadossi Reply 9, Paper 464, at 3:20-23.) According to Sommadossi, if there is an operative method of making a compound in the art, it is irrelevant that the actual inventor tried and failed, even many times, to make it. (Sommadossi Reply 9, Paper 464, at 3:20-4:10.)

Sommadossi's argument does not persuade us to ignore the evidence of the Idenix personnel's extraordinary effort. To make a determination of what the hypothetical ordinarily skilled artisan would have been able to do, we look to evidence of not only what information was publically available, but also evidence of what actual artisans did with that knowledge.

Both Drs. Dahma and Marquez agree that a hypothetical person skilled in the art of synthesizing a compound of the count would have an advanced education (Ph.D. or master's degree) and additional experience in the
chemical aspects of drug discovery (i.e., synthetic organic chemistry). (See Dahma Decl., Exh. 1281, 16; Marquez Decl., Exh. 2001, ¶ 70.) The members of the Idenix team were all employed as chemists and several had doctoral degrees. (See, e.g., Storer Decl., Exh. 1429, ¶ 2 (testifying that he has a D.Phil. degree in chemistry); Substitute Declaration of Jean-Francois Griffon, Exh. 1471, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Adel Moussa, Exh. 1428, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry; Substitute Declaration of Alistair Steward, Exh. 1241, ¶ 2-3 (testifying that he has a Ph.D. degree in organic chemistry.) Sommadossi does not argue that they were not at least ordinarily skilled artisans. On the record before us, we have no reason to exclude them as representative of ordinarily skilled artisans at the time. Thus, the evidence of the effort exerted by the Idenix team to eventually synthesize a 2'-F-2'Me-ribonucleoside is informative of what the hypothetical skilled artisan could do.

Furthermore, the evidence of the effort exerted by the Idenix team shows that it was not just one chemist who was unable to synthesize a compound within Count 1 with routine experimentation, but a team of chemists, even after they had consulted with others considered to be experts and had sought additional training. From this record it is reasonable to find that if after all of this effort, a compound within the scope of the count could not be synthesized easily, a hypothetical person of
ordinary skill would not have known how to synthesis such a compound either.

Exhibit H at pages 20-21. The USPTO also stated "[w]e find it informative that Idenix’s research team in Montpellier, France, repeatedly attempted without success to synthesize a 2’-methyl (‘up’) 2’-fluoro (‘down’) nucleoside during the interval between December, 2002 and September, 2004." Exhibit C at 14 (emphasis added); see also id. at pages 14-19.

Testimony by Dr. Victor E. Marquez on this point was also important. For example, in a declaration submitted to the USPTO (Exhibit I), Dr. Marquez described, based on his review of Idenix’s internal documents, that Idenix employed a team of Ph.D. chemists, as well as consultants specializing in carbohydrate and fluorination chemistry, all of whom were unable to make the (2’R)-2’-deoxy-2’-fluoro (down)-2’-C-methyl (up) nucleosides for a period of several years. Dr. Marquez noted that these chemists tried numerous potential chemical routes and many different reagents in attempts to make a (2’R)-2’-deoxy-2’-fluoro (down)-2’-C-methyl (up) nucleosides. All of these attempts failed. It was only after the publication of the Gilead patent application (i.e., the Pharmasset PCT corresponding to ‘6087) that Idenix researchers were purportedly finally able to synthesize compounds of this type, thereby illustrating that the prior art was not enabling. Exhibit I at paragraphs 21-35.

In summary, the Applicant requests the Controller to withdraw the novelty and inventive step rejections because (A) none of the cited references describe or suggest the claimed compounds, (B) the prior art did not teach how to make the claimed compounds, as illustrated by Idenix’s difficulties, and (B) the claimed compounds have unexpectedly high activity and low toxicity not suggested by the prior art. Thus, it is Applicant’s position that the (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl nucleosides of the present invention remain novel and inventive in view of the cited reference.
8. **Ground III: Not Patentable under Sections 2(1)(i), 3(d) or 3(e) of the Act**

I. **Section 2(1)(i)**

As per the Opponent, claims 1-10 do not constitute an "invention" under the Act because they are not novel, not inventive and lack industrial application.

**Applicant's Response**

In response, Applicant respectfully disagrees with Opponent's assertions. The Applicant submits that Section 2(1)(j) of The Patents Act sets forth definitions and not the substantive criteria for patentability. Thus, Section 2(1)(j) does not provide a proper basis for rejection. Additionally, the Applicant has explained above that the present application claims compounds that are novel and possess inventive step, and that are useful for the treatment of HCV infection. Accordingly, the Opponent's argument regarding Section 2(1)(j) should be dismissed.

II. **Section 3(d)**

The averments made in paragraph III(b) regarding Section 3(d) are factually and legally incorrect, and are furthermore misleading, and hence denied. As per the Opponent, the subject matter of claims 1-7 are not patentable under Section 3(d) of the Act. The Opponent alleges that the set of claims are drawn to nucleoside analogs and such compounds are derivatives of compounds already known in the prior art unless they differ significantly with regard to efficacy. Also, as per the Opponent, the glycosylation process of claims 8 and 9 is not patentable because it is merely use of a known glycosylation process.

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5 Applicant presumes that the Opponent's reference to Section "2(i)(j)" is intended to refer to Section 2(1)(j), and Applicant has responded accordingly herein.
Applicant's Response

In response, the Applicant respectfully disagrees. It is submitted that the provisions of Section 3(d) are not applicable to the present case as detailed under:

a) New Form: The compounds of the present invention are a new chemical entity, and are not related to any known substance in a way that would fall within Sec. 3(d).

b) Mere Discovery: The present invention cannot be held to be a "mere discovery" within the meaning of Sec. 3(d). In fact, the present invention relates to a new chemical entity.

c) Known therapeutic efficacy: Without prejudice, even if it is assumed that Sec. 3(d) is applicable in present case, the Opponent has failed to point out known efficacy of any other known substance against which any comparable data is to be submitted in the present case. There is no known substance over which the present invention can be deemed to be lacking in efficacy. In fact the efficacy of the compounds of the present invention is significantly enhanced and different over any other known medicine for treatment of Hepatitis C. The reliance on section 3(d) is misplaced and untenable. Opponent has completely failed to discharge its onus of proof in respect of Sec. 3(d).

It is submitted that Sec. 3(d) does not apply to all pharmaceutical and chemical inventions, and in particular does not apply to new chemical entities (NCE). It is submitted that Sec. 3(d) was designed to make a higher bar of innovation for patentability of new salts, esters, and other derivatives (second generation compounds) of known substances (e.g. pharmaceuticals) unless they differ significantly in properties with regard to efficacy, to avoid alterations being made to the FORM of such substances and thus extending market exclusivity of known
substances. It is not meant to create a higher bar for new substances by deeming all new compounds to be merely derivatives of known compounds.

The claims of the present application do not contravene Section 3(d). As explained above, the claimed compounds are novel and inventive NCEs whose properties would have been unpredictable prior to the Applicant’s teachings in the present application. In particular, the presently claimed compounds have a unique and novel (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) substitution pattern, and they have both high potency and low toxicity as compared to comparative compounds. See Sections 12.3 and 12.2, above, discussing data for (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine and comparative compounds. They are not “new forms of known substances,” such as salts, esters, ethers, polymorphs, pure forms, particle sizes, isomers, complexes, or combinations of the type targeted by Section 3(d). The Patent Office should reject Opponents’ suggestion that Section 3(d) can be used to prevent patenting every new compound by calling it a derivative of some known chemical core, despite the new compound's novelty and inventiveness in the unpredictable chemical arts.

The Applicant also respectfully submits that Section 3(d) is inapplicable to the presently pending process claims, which are directed to glycosylation methods for making the novel compounds of claim 1. Section 3(d) excludes from the meaning of “inventions,” inter alia, “the mere use of a known process … unless such known process results in a new product or employs at least one new reactant.” Claims 14 and 15 are directed to processes that both result in a new product and employ at least one new reactant. The “new product” is a nucleoside as claimed in claim 1, which, as explained above, is a novel compound. Examples of the “new reactant” are the protected 2-deoxy-2-fluoro (down)-2-C-methyl (up) compound 1-4 recited in claim 14 and the protected 2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleoside recited in claim 15, both of which are novel reactants.
In the light of the above, the Applicant submits that the claimed compounds and processes are completely novel and inventive. Thus, Section 3(d) cannot be applied to the claims of the instant application.

III. **Section 3(e)**

As per the Opponent, claim 10 is not patentable under Section 3(e) because purportedly it is directed to a composition that “is a mere admixture of known substances, which result only in aggregation of the properties of the individual components and do not demonstrate any synergistic activity.”

**Applicant’s Response**

In response, Applicant respectfully disagrees with Opponent's assertions. Claim 10 is directed to “[a] nucleoside as claimed in any of the Claims 1 to 7 as and when used for the preparation of a pharmaceutical composition or medicament.” As explained above, the compounds of Claims 1 to 7 are novel, inventive and have utility. Accordingly, claim 10 is directed to said novel and inventive compounds when used for the preparation of a pharmaceutical composition or medicament, which is also novel and inventive. In any case, the Opponent merely repeats conclusory language from Section 3(e) but fails to establish the grounds pleaded.

9. **Ground IV: Insufficient or Unclear Description**

As per the Opponent, the claims are not supported by the specification for several reasons. For example, the Opponent alleges that the initial application was filed with claims drawn to several hundred compounds, but Applicant has confined itself to fewer compounds in a manner that is not prescribed in law. The Opponent also contends that the specification does not disclose the best method of performing the invention, insufficiently discloses how to prepare the claimed compounds, and does not teach the claimed compounds have efficacy in treatment of HCV. The Opponent further alleges that the specification discloses insufficient information regarding specific pharmaceutically acceptable salts, glycosylation methods, and methods for employing a nucleoside in a pharmaceutical preparation or a medicament.
To the extent they are not irrelevant and/or moot in light of the amendments submitted herewith, the Opponent's averments regarding insufficient or unclear description are factually and legally incorrect for at least the reasons explained below, and are furthermore misleading, and hence denied.

**Applicant's Response**

In response, the Applicant respectfully disagrees. As presently amended, the '6087 claims are directed to (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides having cytosine or uracil bases, and their corresponding 5' mono-, di-, and triphosphates. An applicant is within its own right to amend the claims so long as the requirements of Section 59 of the Patents Act, 1970 are met. Applicant has sought amendments, which are permissible under Section 59, and has followed the correct process before the IPO for claim amendments. Admittedly, Applicant has limited the scope of original claims and such amendments are permissible within the meaning of Section 59.

The present specification provides general schemes and procedures for preparing (2'R)-2'-deoxy-2'-fluoro (down)-2'-methyl (up) nucleosides, e.g., Schemes 1 and 2 and accompanying descriptions on pages 72-76 (original PCT application). The specification also contains working examples of (2'R)-2'-deoxy-2'-fluoro (down)-2'-methyl (up) nucleosides, such as (2'R)-2'-deoxy-2'-fluoro-2'-methylcytidine and its hydrochloride salt, including detailed synthetic procedures and characterization data for both intermediates and final compounds. See Schemes 3-6 and accompanying descriptions on pages 77-87 (original PCT application). The specification further provides biological data for (2'R)-2'-deoxy-2'-fluoro-2'-methylcytidine and its corresponding 5' triphosphate, as well as for comparative compounds, such as:

i) Antiviral activity in HCV replicon assays (Tables 1 and 2, Figs. 1A and 1B);

ii) Potency in NS5B polymerase assay (Table 3);

iii) Cytotoxicity (Table 6);
iv) Mitochondrial toxicity (Table 7);

v) Human bone marrow toxicity (Table 9);

vi) *In vivo* toxicity in female Swiss mice (Fig. 2);

vii) Pharmacokinetic parameters in Rhesus monkeys (Table 8, Fig. 3); and

viii) Antiviral activity against viruses including Rhinovirus, West Nile virus, Yellow Fever virus, and Dengue virus (Tables 4 and 5).

For example, Tables 1 to 3, 5, 6, 7 and 9 on pages 90 to 94 include activity and other biological data for of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (Compound 3-6/Compound 4-6) as compared with 2'-C-methylcytidine and 2'-C-methyladenosine. Table 4 summarizes the antiviral activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine against a variety of viruses, and Table 8 provides pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-last}, T_{1/2}, and Bioavailability) in Rhesus monkeys following a single oral dose of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. Table 9 compares the human bone marrow toxicity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine against that of 2'-C-methylcytidine and AZT. The foregoing data support that compounds of the present application have good anti-HCV activity and low toxicity as compared to comparative compounds.

In view of above, the Applicant submits that the claims of the present application are described with sufficient clarity to enable a person skilled in the art to put the claimed invention to practice. The data in the patent specification as filed, in combination with the information provided in the description, allow a skilled person to put the invention into effect across the entire scope claimed.

---

6 Lower IC_{50} values indicate higher potential toxicity. Thus, Table 9 shows that (2'R)-2'-deoxy-2'-fluoro-2'-methylcytidine was significantly less toxic to the tested human bone marrow cells compared to 2'-C-methylcytidine and AZT.
10-**Ground V: Section 8 Requirements**

It is denied that the Applicant has failed to furnish information as required under Section 8. It is submitted that claims similar to those presented here in 6087/DELNP/2005 have been granted in numerous countries (see Form 3 details):

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Australia</td>
<td>2004253860</td>
</tr>
<tr>
<td>Canada</td>
<td>2527657</td>
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<tr>
<td>China</td>
<td>200480019148.4</td>
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<tr>
<td>Colombia</td>
<td>1214</td>
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<tr>
<td>Indonesia</td>
<td>P0028288</td>
</tr>
<tr>
<td>Israel</td>
<td>172259</td>
</tr>
<tr>
<td>Israel (Divisional)</td>
<td>210367</td>
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<tr>
<td>Japan</td>
<td>4958158</td>
</tr>
<tr>
<td>Japan (Divisional)</td>
<td>5266357</td>
</tr>
<tr>
<td>Korea</td>
<td>200883703</td>
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<tr>
<td>Mexico</td>
<td>275935</td>
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<td>Malaysia</td>
<td>138477</td>
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<td>0333700</td>
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<tr>
<td>New Zealand</td>
<td>543867</td>
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<td>Philippines</td>
<td>1-2005-502136</td>
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<tr>
<td>Russia</td>
<td>2358979</td>
</tr>
<tr>
<td>Singapore</td>
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<td>2005-09521</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1333956</td>
</tr>
</tbody>
</table>
Exemplary claim sets of the Granted Patent in some of these countries have been already submitted to the Indian Patent Office on 30 June 30 2014 and 23 July 23 2014.

Most of the information required under Section 8 of the Indian Patents Act at this stage of the prosecution have been provided, and remaining information shall be provided accordingly in due time.

**11. Conclusion**

In view of the above submissions, it is clear that the subject application claims compounds that are novel, inventive and patentable. The Opponent has failed to make out or substantiate any of alleged Grounds I-V. The entire opposition is frivolous and vexatious and has been filed merely to harass this Applicant. None of the prayers prayed for by the Opponent are tenable, and the same deserve to be rejected outright and the opposition should be dismissed with heavy costs. As such, the representation filed by the Opponent is frivolous and ought to be dismissed *in limine*.

**PRAYER**

In the above premises, the Applicant prays that –

i) the representation filed by Opponent under Section 25(1) be rejected by the Ld. Controller of Patents and Indian Application No.6087/DELNP/2005 be allowed to proceed to grant;

IPO DELHI 07-08-2015 17:16
ii) the applicant be allowed to file evidence as may be necessary to comply with the provisions of the Patents Act, 1970;

iii) Costs of delays in grant of the patent and for engaging in this representation be awarded to this Applicant;

iv) Any other relief or reliefs as the Controller may deem fit may be granted in favour of the Applicant.

Dated this 07th day of August, 2015.

(SANJEEV K. TIWARI & AMRISH TIWARI)
K&S PARTNERS
ATTORNEYS FOR THE APPLICANT

To,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI.
We Claim:

1. A nucleoside or its pharmaceutically acceptable salt of the structure:

\[
\begin{align*}
\text{Base} & \\
\text{R} & \text{R}^{1} \quad \text{C} \quad \text{R}^{7} \\
\text{X} & \\
\text{R}^{2} \quad \text{O} & \text{N} \quad \text{O}
\end{align*}
\]

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

\[
\begin{align*}
\text{R}^{4} \quad \text{R}^{3} \quad \text{N} \quad \text{O}
\end{align*}
\]

X is O; R\(^{1}\) and R\(^{7}\) are independently H, a monophosphate, a diphosphate, or a triphosphate; and

R\(^{3}\) is H and R\(^{4}\) is NH\(_{2}\) or OH.

2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R\(^{7}\) is H and R\(^{1}\) is a monophosphate, a diphosphate, or a triphosphate.

3. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R\(^{7}\) is H and R\(^{1}\) is a diphosphate or a triphosphate.

4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R\(^{7}\) is H and R\(^{1}\) is a triphosphate.

5. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R\(^{1}\) and R\(^{7}\) are H.
6. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:

![Chemical Structure](image)

7. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula:

![Chemical Structure](image)

8. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula:

![Chemical Structure](image)
9. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

![Chemical Structure](image)

10. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:

![Chemical Structure](image)

11. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

![Chemical Structure](image)
12. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

![Chemical Structure 1]

13. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

![Chemical Structure 2]

14. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:

![Chemical Structure 3]
wherein R is C1-C4 lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C1-C10 alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH2-C1-C10 alkyl, CH2-C1-C10 alkenyl, CH2-phenyl, CH2-biphenyl, CH2-naphthyl, CH2O-C1-C10 alkyl, CH2O-phenyl, CH2O-biphenyl, CH2O-naphthyl, SO2-C1-C10 alkyl, SO2-phenyl, SO2-biphenyl, SO2-naphthyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

15. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:

```
  O
 / \/
O-CH3
 / \/
PgO PgO
```

wherein, each Pg is independently a protecting group selected from among C(O)-C1-C10 alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH3, CH2-C1-C10 alkyl, CH2-C1-C10 alkenyl, CH2-phenyl, CH2-biphenyl, CH2-naphthyl, CH2O-C1-C10 alkyl, CH2O-phenyl, CH2O-biphenyl, CH2O-naphthyl, SO2-C1-C10 alkyl, SO2-phenyl, SO2-biphenyl, SO2-naphthyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

16. A nucleoside as claimed in any of the Claims 1 to 13 as and when used for the preparation of a pharmaceutical composition or medicament.

Dated this 27th day of December, 2005

[Amrish Tiwari]
Of K & S Partners
Attorney for the Applicant(s)
We Claim:

1. A nucleoside or its pharmaceutically acceptable salt of the structure:

   ![Chemical Structure]

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

   ![Pyrimidine Base]

   X is O; R¹ and R⁷ are independently H, a monophosphate, a diphosphate, or a triphosphate; and

   R³ is H and R⁴ is NH₂ or OH.

2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R⁷ is H and R¹ is a monophosphate, a diphosphate, or a triphosphate.

3. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R⁷ is H and R¹ is a diphosphate or a triphosphate.

4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R⁷ is H and R¹ is a triphosphate.
5. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein $R^1$ and $R^7$ are H.

6. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:

```
\[
\text{NH}_2
\]
```

7. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

```
\[
\text{NH}_2
\]
```

8. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

```
\[
\text{NH}_2
\]
9. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

710. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:
11. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

[Chemical structure image]

12. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

[Chemical structure image]

13. The nucleoside as claimed in claim 1, or its pharmaceutically acceptable salt, having the formula

[Chemical structure image]
814. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:

wherein R is C₁-C₄ lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C₁-C₁₀ alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₂-C₁-C₁₀ alkyl, CH₂-C₁-C₁₀ alkenyl, CH₂-phenyl, CH₂-biphenyl, CH₂-naphthyl, CH₂O-C₁-C₁₀ alkyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, SO₂-C₁-C₁₀ alkyl, SO₂-phenyl, SO₂-biphenyl, SO₂-naphtyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

915. A method of synthesizing the nucleoside as claimed in claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:
wherein, each Pg is independently a protecting group selected from among C(O)-C_{1}-C_{10} alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH_{3}, CH_{2}-C_{1}-C_{10} alkyl, CH_{2}-C_{1}-C_{10} alkenyl, CH_{2}-phenyl, CH_{2}-biphenyl, CH_{2}-naphthyl, CH_{2}O-C_{1}-C_{10} alkyl, CH_{2}O-phenyl, CH_{2}O-biphenyl, CH_{2}O-naphthyl, SO_{2}-C_{1}-C_{10} alkyl, SO_{2}-phenyl, SO_{2}-biphenyl, SO_{2}-naphtyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylsiloxanylidene).

____

1016. A nucleoside as claimed in any of the Claims 1 to 137 as and when used for the preparation of a pharmaceutical composition or medicament.
JUDGMENT

Rendered: 21 March 2014 by the Oslo District Court

Case Nos.: 12-155575TVI-OTIR/01 and 13-170456TVI-OTIR/01

Judge: District Court Judge Iger Kjersti Dørstad

Lay judges: Professor Hans Einar Krokan
             Professor Jesper Wengel

Subject-matter of the case: Invalidation of Norwegian patent

V.

1. Idenix Pharmaceuticals Inc
   Counsel: Attorney Arne Ringnes
   Of counsel: Attorney Harald Ludvig
   Joachim Irgens-Jensen and Associate Ellen Kristina Rognlien

2. Centre National de la Recherche Scientifique

3. Universita Degli Studi Di Cagliari

4. L'Université Montpellier II

Disclosure to the general public is not subject to any restrictions

True translation certified.
2 April 2014

Knut Hogne Engedal
Government-authorised translator
English – Norwegian • Norwegian – English
Idenix Pharmaceuticals Inc

Counsel: Attorney Arne Ringnes
Of counsel: Attorney Halrad [sic]
Irgens-Jensen and Associate Ellen
Kristian [sic] Rognlien

v.

Gilead Pharmasset LLC

Counsel: Attorney Are Stenvik
Of counsel: Attorney Gunna [sic]
Sørlie and Attorney Elin Moen
The present proceedings concern a dispute as to the validity of the two Norwegian patents NO 330 755 and NO 333 700, cf. Section 52, cf. Sections 2 and 8, of the Norwegian Patents Act.

The defendants in the two cases that have been consolidated for a joint hearing are each the holder of one Norwegian patent. Both of the disputed patents pertain to chemical compounds that are suitable for use in pharmaceutical products, especially for the treatment of Flaviviridae infections, such as hepatitis C virus infections.

The present proceedings have their origin in a disagreement between the parties to the case as to who are the rightful inventors of chemical substances of the pattern 2'-methyl-up, 2'-fluorine-down nucleosides with a natural N-bonded base. The parties also disagree on which of them first disclosed the invention in a patent application with a valid priority sequence.

Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II are joint holders of NO 330 755 (hereinafter referred to as "NO 755"). Defendant No. 1, Idenix Pharmaceuticals Inc, was founded in 1998 and is headquartered in Massachusetts, United States. It is a pharmaceuticals company engaged in research on, and development of, antiviral pharmaceutical products, including antiviral nucleosides for the treatment of, inter alia, HIV, HBV (hepatitis B) and HCV (hepatitis C). The company has collaborated with the three other defendants, all of which are universities or research institutions, in research on, and development of, antiviral pharmaceutical products. The said parties will be jointly referred to as "Idenix". Idenix Pharmaceuticals Inc. is the sole claimant with regard to the validity of the other patent.

Gilead Pharmasset Inc. is the holder of the other Norwegian patent, NO 333 700 (hereinafter referred to as "NO 700"), and is the defendant in the case concerning the validity of the said patent. A company within the same group, Gilead Sciences Europe Ltd., is the claimant in the case concerning the validity of patent NO 755. Both companies will be jointly referred to as "Gilead". Gilead was founded in California in 1987 and is a pharmaceuticals firm with a product portfolio encompassing several disease categories, including, inter alia, HIV/AIDS, hepatitis, serious respiratory diseases, cardiovascular diseases and cancer.

The patent history
There has, as mentioned, been a race between the parties to arrive first at the invention and be the first to secure the rights by way of a patent.

Idenix first applied for a patent in the United States. Reference has been made to four US applications, but the case has been restricted to application US 60/392,350 ("US 350"). The said application was filed
on 28 June 2002. If this priority is valid, Idenix will be first in time. Gilead has disputed that Idenix can claim priority based on the said application.

Gilead applied for a patent in the United States on 30 May 2003. The application is designated as US 60/474,368 ("US 368"). If Idenix cannot claim priority from its application US 350, this application [US 368] will be first in time. Idenix has disputed that Gilead can claim priority from the said application.

Idenix filed a PCT application on 27 June 2003. It has subsequently been extended to include Norway. If Gilead cannot claim priority from its application US 368, Idenix' PCT application will be first in time. It is not contested that Idenix can claim formal priority from the said application.

Idenix’ applications US 350 and PCT became available to the public on 8 January 2004.

Gilead filed a PCT application on 21 April 2004, i.e. after Idenix’ applications had been published. It is not contested that Gilead can claim formal priority from the said application.

Idenix filed Norwegian patent application NO 20050465 ("NO 465") on 27 January 2005.

Gilead filed Norwegian patent application NO 20056221 ("NO 221") on 28 December 2005.

Norwegian patent NO 330 755 was granted to Idenix on 4 July 2011.
Norwegian patent NO 333 700 was granted to Gilead on 26 August 2013.

Schematically, the time sequence may be presented as follows:

Procedural history
Case No. 12-155575TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 330 755, was brought by Gilead Sciences Europe Ltd. by way of a Writ of Summons to the Oslo District Court, dated 28 September 2012. The Notice of Intention to Defend from the four defendants Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L’Université Montpellier II, which was filed in a timely manner, is dated 20 November 2012.

True translation certified.
2 April 2014

Knut Hogne Engedal
Government-authorised translator
English – Norwegian + Norwegian – English

IPO DELHI 07-08-201
Case No. 13-170456TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 333 700, was brought by Idenix Pharmaceuticals Inc. by way of a supplementary pleading to the Oslo District Court, dated 6 September 2013. The Notice of Intention to Defend from Gilead Pharmasset LLC, which was filed in a timely manner, is dated 1 October 2013. Both parties requested that the cases be consolidated for a joint hearing, despite the short time left before the scheduled main hearing. None of the parties requested postponement of [the main hearing] for reasons of necessary preparation of the case. Both parties did, on the contrary, state that the case concerned the same or corresponding issues, and that it would neither be necessary to allocate additional time for the preparation of the case, nor to schedule more time for the main hearing, for purposes of explaining the case properly. It was decided, against this background, to consolidate the cases for a joint hearing.

A number of supplementary pleadings have been submitted in the present proceedings. Besides, one written submission pursuant to Section 9-9, Sub-section 3, of the Norwegian Dispute Act has been filed by each of the parties in relation to the priority issues raised in these proceedings. A planning meeting has been held, as well as several preparatory meetings. The main hearing of the case was conducted over nine days during the period from 7 to 19 November 2013. Fourteen witnesses gave testimony, ten of whom were expert witnesses called by the parties. There was disclosed such documentation as is reflected in the court record. The Court was set with two expert lay judges, at the request of both parties. The judgment is not rendered within the statutory time limit. This is partly because the case has been very wide in scope and has raised complex issues. In addition, one of the members of the Court has been on sick leave for a protracted period of time.

Gilead has, in the main, invoked the following:

In Case 12-155575TVI-OTIR/01:
Gilead argues that patent NO 330 755 ("NO 755") is invalid.
NO 755 can neither derive valid priority from the cited priority document US 60/392,350 ("US 350"), nor from any of the other US priority documents. This can be concluded on a number of grounds, each of which are sufficient, in themselves, for the priority claim to be set aside.

Firstly, there is no formal priority. Not all inventors of US 350 had assigned the right to the invention, including the priority right, prior to the filing of the patent application, i.e. before the filing of international application PCT/IB2003/003246 (published as WO 2004/002999, hereinafter referred to as "WO '999"), which led to NO '755.

Secondly, there is no substantive priority either. US 350 contains no clear and direct disclosure of the chemical compounds in respect of which protection is claimed under NO 755. Neither does US 350 describe any process for the production of the chemical compounds in respect of which protection is claimed under NO 755, nor did the prior art include any process that enabled a skilled person to produce the said compounds without undue burden or experimentation.
Nor did US 350 disclose any information that made it plausible to the skilled person that the alleged effect is achieved by any of the chemical compounds falling within the scope of the patent claims in NO 755.

When the application date, 27 June 2003, is adopted as the priority date, i.e. the date of the filing of the PCT application, the invention was anticipated by Gilead's patent application NO 20056221, which derives valid priority from US 60/474,368 (hereinafter referred to as “US 368”). This [application] was filed on 30 May 2003, i.e. before the defendants filed their EPC application.

It is argued, irrespective of which priority date is adopted, that NO 755 is invalid for the following reasons, each of which are sufficient, in themselves, for the patent to be revoked:

- NO 755 discloses no information that would have enabled the skilled person to identify, without undue burden or experimentation, chemical compounds which fall within the scope of the patent claims, and which can be used in the treatment of Flaviviridae infections.
- NO 755 discloses no process for the production of the chemical compounds in respect of which protection is claimed. Nor did the prior art include any process that enabled the skilled person to produce the said compounds without undue burden or experimentation.
- NO '755 discloses no information that made it plausible for the skilled person that the alleged effect is achieved by any the chemical compounds that fall within the scope of the patent claims in NO 755.
- Neither the dependent patent claims, nor the alternative patent claim, add anything that might justify upholding the patent.

In Case 13-170456TVI-OTIR/01:
Gilead argues that patent NO 333 700 (NO 700) is valid in its entirety.
The arguments [outlined] in following pertain to all patent claims.

NO 700 derives valid priority from US 368, filed on 30 May 2003. The patent applicant, Pharmasset, Ltd. (Barbados), had validly acquired the right to the invention in US 368, including the priority right, prior to the filing of the patent application, i.e. before the filing of international application PCT/US04/012472 (published as WO 2005/003147 A2), which led to NO 700, on 21 April 2004. WO 999 cannot derive valid priority from US 350. Hence, Idenix' application cannot be deemed to have been filed before the PCT application date of 27 June 2003. When the correct priority dates are adopted, none of the publications invoked by Idenix can be cited against NO 700.
Moreover, Gilead will argue that NO 700 is valid irrespective of which priority dates are adopted. Even if the contents of WO 999 and/or US 350 are deemed to have been known within the meaning of Section 2, Sub-section 2, of the Norwegian Patents Act, NO 700 meets the novelty and inventive step requirements under Section 2, Sub-section 1.

Each of the following grounds are sufficient, in themselves, for concluding that the cited publications do not anticipate the invention:

- The publications disclose no process for the production of the chemical compounds protected by NO 700. Nor was any production process that enabled the skilled person to produce these chemical compounds without undue burden or experimentation available from other sources.
- The publications disclose no information that made it plausible to the skilled person that the alleged effect is achieved by exercising the invention.

The invention in NO 700 also meets the inventive step requirement, i.e. it differs essentially from what could be inferred from US 350, WO 999 and other prior art. The patented invention exhibits beneficial properties.

Gilead has prayed for the following relief:

In Case 12-15557STVI-OTIR/01:

1. Norwegian patent NO 330 755 to be declared invalid.
2. Idexis Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L’Université Montpellier II to be ordered to pay the legal costs of Gilead Sciences Europe Ltd.

In Case 13-170456TVI-OTIR/01:

1. The Court to find in favour of Gilead Pharmasset LLC.
2. Idexis Pharmaceuticals Inc. to be ordered to pay the legal costs of Gilead Pharmasset LLC.

Idexis has, in the main, invoked the following:

In Case 12-15557STVI-OTIR/01:

The defendants, Idexis Pharmaceuticals, Inc., Centre National de la Recherche Scientifique, Universita Degli Studi di Cagliari and l’Université Montpellier II, argue that Claims 2-22 of their patent 330 755 (the “755 Patent”) shall be upheld as valid in the form of new Claims 1-21 as shown in the principal claims set out in Exhibit 1a. Alternatively, in the event that the Court finds, contrary to expectation, the said claims to be invalid, the Court is requested to rephrase the patent claims in conformity with the alternative patent claims set out in Exhibit 1b.
Gilead asserts that patent application NO20056221 prevents novelty for the Idenix Patent. Gilead claims priority from the US application filed on 30 May 2003. However, this claimed priority is invalid, thus implying that Gilead can only claim priority from the filing of the PCT application on 21 April 2004. Consequently, Gilead's patent application NO20056221 does not qualify as prior art, irrespective of whether Idenix' claimed priority in respect of NO 755 is valid, because Idenix' PCT application has an earlier filing date, i.e. 27 June 2003.

Besides, Gilead cannot claim priority from US 368 for the following reasons: It follows from Section 6 of the Norwegian Patents Act, which needs to be interpreted in accordance with the Paris Convention and European case law, that those inventors holding a right of priority must have assigned such right to the applicant filing the PCT application, in the form of a written document signed by both parties, before such PCT application was filed. Gilead has failed to substantiate any valid assignment from those holding the priority right to Pharmasset, Ltd. (Barbados) prior to 21 April 2004. Instead, the priority right was assigned to Pharmasset, Inc. (Georgia).

The NO 755 patent meets the prerequisite in Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act, for the description to be sufficiently clear to enable the skilled person to carry out the invention on the basis thereof. A skilled person would on 28 June 2002 and 27 June 2003 have been able to synthesise the compounds in respect of which protection is claimed, based on the information disclosed in the patent and his or her general knowledge of the art. He [or she] could have done this by only conducting routine experimentation.

The skilled person would, based on his or her general knowledge of the art, have been familiar with appropriate reagents for purposes of achieving fluorination, including diethylaminosulfur trifluoride (DAST) and Deoxo-Fluor. The skilled person would also know how to get to the appropriate precursor for achieving the correct stereochemistry.

The defendants maintain that it is not a legal prerequisite for the description with regard to the product claims in Claims 1 and 2 of Exhibit 1a and Claims 1 and 2 of Exhibit 1b to be sufficient to enable the skilled person to test the activity of the compounds. However, methods for the testing of the antiviral activity of the compounds were available to the skilled person. As far as anti-HCV testing is concerned, assays based on the HCV replicon system constituted common general knowledge in the art as at the priority date. Alternatively, in vitro assays for RNA polymerase activity, which are described in the patent, were available.

As far as testing of activity against WNV, YFV, dengue fever, etc., is concerned, routine cell-based assays for viral infections were available, such as assays for the calculation/reduction of plaque. Moreover, assays for cell protection/cytopathic effect, including neutral red [dye] uptake (neutral "red dye update [sic]") assay, were available to the skilled person. These
assays are described in the patent, and were well known, in routine use, as well as available, on 28 June 2002.

Nor is there any doubt that the invention does in fact exhibit technical effect and is susceptible of industrial application. Gilead discusses a "credibility test" i.e. that there is a requirement for the application in itself, in view of the common general knowledge of the skilled person as at the application date, to make the effect "plausible". However, such credibility test is only relevant to the assessment of inventive step. The Norwegian Industrial Property Office has correctly concluded that the invention has inventive step, and Gilead has not denied that such is the case. In the event that a credibility test is inherent in the technical effect requirement, this is nothing more than a requirement that the relevant type of object is likely to exhibit technical effect. Nucleoside analogues, which have long been known to exhibit antiviral effect, meet this basic requirement. Since Gilead's arguments with regard to credibility are not only legally untenable, but also lack any basis in the facts, the defendants have submitted evidence that substantiates the credibility of the invention, although this is not a legal requirement. In the event that the legal standard for documentation of the technical effect that has been invoked by Gilead is to be applied, Gilead's own patent NO 700 shall also be declared invalid, because they have not complied with such standard either.

Alternatively, it is argued that even if the Gilead Patent, NO 700, is deemed to have valid priority from US 368, of 30 May 2003, the defendants' patent NO 755 have better priority, since their priority from US 350 is valid.

The true inventors who were entitled to the right of priority, i.e. Sommadossi, Gosselin and Storer, had validly assigned the right to claim priority to Idenix (Cayman), Ltd. and Centre National de la Recherche, the applicants under the PCT application, before the PCT application was filed. Reference is made to priority application US 350, application PCT/IB2003/003246, employment agreements with the inventors and declarations of assignment.

Moreover, the invention disclosed in the Norwegian patent is the "same invention" as the one disclosed in the US 350 application, cf. Section 6 of the Norwegian Patents Act and Article 4A of the Paris Convention. A skilled person would derive the invention directly and unambiguously from Formula IX on pp. 26-27/91-92 and Formula IV on pp. 57-58/105 of the 350 application.

In Case 13-170456TVI-OTIR/01:
Idenix Pharmaceuticals, Inc. argues that the Gilead Patent, NO 700, shall be declared invalid in its entirety due to lack of novelty and inventive step over applications PCT 346, NO 465 and US 350, which applications the defendants' patent is based on.

As mentioned, application PCT 246, which corresponds to the defendants' Norwegian patent application—NO 465, has earlier priority than the Gilead Patent, NO 700. The same applies to the defendants'
priority application US 350. The subject-matter of Claims 1-12, 14, 15 and 19-60 of the Gilead Patent is disclosed in Idenix' PCT application and Norwegian application. The subject-matter of the same claims of the Gilead Patent is disclosed in Idenix' 350 application. The descriptions in the defendants' PCT application, Norwegian application and priority application are all sufficient. Consequently, the said claims of the Gilead Patent lack novelty, cf. Section 2, Sub-section 1, cf. Sub-section 2; third sentence, of the Norwegian Patents Act.

Both the defendants’ application PCT 246 and priority application US 350 became available to the public on 8 January 2004. None of these were examined by the Norwegian Industrial Property Office at the time of the granting of the Gilead Patent, NO 700. Based on the description of 2’Me-up/2’F-down compounds in the said prior art, the compounds in respect of which protection is claimed in the Gilead Patent would have been obvious to the skilled person, irrespective of whether the Idenix citations meet the requirement for sufficient description in Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act. Any allegedly “unexpected effect”, which according to European case law is only a secondary indicator of patentability, cannot change this.

Correspondingly, the method and the pharmaceutical preparation claimed in the Gilead Patent, NO 700 (Claims 13 and 16-18) are obvious in view of the 2’Me-up/2’F-down compounds disclosed in the defendants’ application PCT 246 and in priority application US 350, when taking the common general knowledge of the skilled person into consideration.

Idenix has prayed for the following relief:

In Case 12-155575TVI-OTIR/01:

1. Norwegian patent NO 330 755 to be upheld with the claims set out in Bundle 23, pages 10,558 – 10,561.
3. Gilead Sciences Europe, Ltd. and Gilead Pharmasset LLC to be ordered to pay the legal costs of Idenix Pharmaceuticals, Inc., Centre National de la Recherche [sic] Scientifique, Università Degli Studi Di Cagliari and L’Université Montpellier II.

In Case 13-170456TVI-OTIR/01:

1. Norwegian patent NO 333 700 to be declared invalid.
2. Gilead Pharmasset LLC to be ordered to pay the legal costs of Idenix Pharmaceuticals, Inc.
Technical background
Hepatitis is a disease caused by certain hepatitis viruses, including hepatitis C virus, which primarily affect the liver. Hepatitis C virus was first described in 1989. Hepatitis C virus is a positive-sense, single-stranded RNA virus. RNA is, like DNA, a macromolecule comprised of long chains of “building blocks” called nucleotides. Hepatitis C virus belongs to the Hepacivirus genus, which again belongs to the Flaviviridae family. The Flaviviridae family also includes, inter alia, yellow fever virus, West Nile virus, dengue fever virus and the virus causing tick-borne encephalitis (acute inflammation of the brain). Hepatitis C virus is transmitted via blood or other bodily fluids.

Most patients (about 85%) infected by hepatitis C virus do not show any symptoms, or only specific symptoms, during the acute phase. Hepatitis C virus will in many cases not show any symptoms for the first few years, not even for those who develop chronic infection after the acute phase. Chronic infection may result in cirrhosis of the liver, and evolve into liver failure, liver cancer or other fatal diseases. It is assumed that up to 130-180 million people are suffering from chronic hepatitis C virus infection worldwide, that 3-4 million people are infected each year and that about 350,000 people die each year of hepatitis C-related causes.

At present, there exists no vaccine against hepatitis C virus infection. The standard treatment of C virus infection involves administration of the active ingredients alpha interferon or pegylated alpha interferon and ribavirin. Other active ingredients are also used in some cases, such as the NS3/NS4a protease inhibitors telaprevir or boceprevir. Hepatitis C treatment with alpha interferon or pegylated alpha interferon and ribavirin typically lasts for 48 weeks, and involves frequent side effects, including bone marrow suppression, fatigue, flu-like symptoms, as well as neurological diseases and mental disorders. In general, only between 40 and 50% of patients with (genotype 1) hepatitis C virus infection achieve a sustained virologic response indicating that the treatment is effective. Those who are not cured, and who develop liver failure or liver cancer, will often need a liver transplant. This, as well as the large number of patients afflicted with the disease, has resulted in hepatitis C virus infection being one of the most widespread causes of liver transplants.

In the development of new treatment methods, extensive research has related to the hepatitis C virus replication process, which briefly summarised involves the following stages:

a) The hepatitis C virus enters a host cell;
b) the shell of the virus disintegrates and the RNA strand (the genetic material) of the virus is exposed; 
c) by using the information from the RNA strand, the host cell produces polymerase (a protein called NS5B), which is used for making new copies of the genetic material of the virus, and other proteins included in, inter alia, the virus particle;
d) the polymerase recognises and binds to so-called nucleotides, which are chemical substances that exist in the host cell, and incorporates the nucleotides into new RNA strands; and 
e) the virus builds a shell around the new RNA strand, and thereby makes a new virus particle that can leave the host cell and infect other cells.

Several strategies have been pursued with a view to preventing the replication of the hepatitis C virus. The inventions with which the present proceedings are concerned are nucleosides and nucleotides intended to influence what is referred to as stage (d) of the replication process above, and which thereby inhibit replication of the virus.

Nucleosides are chemical substances that serve as starting materials for the biological formation of nucleotides. Both nucleosides and nucleotides typically consist of a sugar ring (called ribose or deoxyribose), which is bonded with a base (nucleobase). The main difference is that nucleotides include one or more phosphate groups at the 5'-position, which are not included in nucleosides, as shown below.

![Chemical structure of nucleoside, nucleotide monophosphate, nucleotide diphosphate, nucleotide triphosphate]

Nucleotides are molecules that constitute “building blocks” of nucleic acids (DNA and RNA). In addition, the nucleotides participate in biological processes in the cells. The most common naturally occurring nucleobases in DNA and RNA are: (1) cytosine, (2) uracil and (3) thymine, all of which are termed pyrimidines, as well as (4) adenine and (5) guanine, which are termed purines. Thymine only occurs naturally in DNA, and uracil only occurs naturally in RNA, whilst the remaining three occur naturally in both DNA and RNA. There are also differences in the sugar ring, inasmuch as the DNA ring (2'-deoxyribose) does not include the OH-group at the 2'-down
position (at the bottom right of the sugar ring). The diagram below shows the building blocks of DNA and RNA:

**The components of nucleic acids**

<table>
<thead>
<tr>
<th>In DNA only</th>
<th>In both DNA and RNA</th>
<th>In RNA only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymine</td>
<td>Adenine</td>
<td>Guanine</td>
</tr>
<tr>
<td></td>
<td>Cytosine</td>
<td>Uracil</td>
</tr>
</tbody>
</table>

[Diagrams of nitrogen bases and sugar-phosphate structures]

The following requirements must be met in order for a nucleoside/nucleotide compound to prevent the replication of hepatitis C virus:

a) The compound must be recognised by the hepatitis C virus polymerase (NS5B);

b) it must be incorporated into new RNA strands instead of the nucleotides that occur naturally in the cells; and

c) the compound must have properties that result in it preventing the completion of replication, after it has been incorporated into new RNA strands.

Ribavirin, which forms part of the current standard treatment of hepatitis C virus infection, was synthesised in 1970. It was first marketed in 1980, and has been used in the treatment of hepatitis C virus infection since 1998. Ribavirin is a nucleoside analogue that influences the replication process as described above. Ribavirin does not work specifically on hepatitis C virus, but is active against a number of DNA and RNA viruses.

**Disputed patent NO 755 (the “Idenix Patent”)**

As mentioned, the disputed patent concerns chemical compounds that have turned out to be suitable as pharmaceutical products, especially in the treatment of *Flaviviridae* infections, such as hepatitis C virus infection. The patent claims pertain, according to their wording, to a group of 2'-fluorine substituted nucleoside/nucleotide compounds of the general formula:
A number of alternatives are specified for the substituents $R^1$ and $R^2$. Base* may be a "purine or pyrimidine base", which is defined in the patent as encompassing a large number of individual bases, both natural and non-natural bases.

$X$ may, for example, be oxygen (O). Several alternatives are specified for $R^{12}$, including methyl (CH$_3$), whilst $R^{13}$ can only be fluorine.

Idenix has requested patent limitation in connection with these proceedings. Idenix has limited the patent to Patent Claims 2–22. Alternatively, Idenix has moved for the patent to be upheld on the basis of a new claim that corresponds to Claim 5 of the alternative set of claims filed with the EPO on 4 July 2013.

Gilead has not objected thereto, and the parties have requested the Court to base its assessment on the new claims. The Court adheres to this, although it refrains, against the background of the outcome of the case, from ruling on the limitation.

The new claims are worded as follows:

Patent Claim (1a) Patent No 755

1. Compound, characterised in having Formula (IX):

or a pharmaceutically acceptable salt thereof, where
R1 and R2, independently, are H; phosphate; straight-chain, branched, or cyclical C1-10 alkyl; CO-C1-10 alkyl; CO-aryl; CO-C1-10 alkoxy(C1-10)alkyl; CO-aryloxy(C1-10)alkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents chosen from fluoride, chlorine, bromine, iodine, hydroxyl, amino, C1-10 alkylamino, arylamino, C1-10 alkoxy, aryloxy, nitro, cyano; sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; C1-10 alkylsulfonyl; arylsulfonyl; ar(C1-10 alkyl) sulfonyl; or an amino acid chosen from α, β, γ or δ glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in D or L configurations;

X is O;

Base* is a purine or pyrimidine base;

R12 is C(Y3)3;

Y3 is H; and

R13 is fluorine;

wherein aryl in each case means phenyl, biphenyl or naphthyl.

2. Compound according to claim 1, characterised in that R1 and R2 are H.

Alternative Patent Claim (1b) Patent NO 755

Compound, characterised in having Formula (IX):

![Chemical Structure Diagram](image)

or a pharmaceutically acceptable salt thereof, where
R1 and R2, independently, are H; phosphate; straight-chain, branched, or cyclical C1-10 alkyl; CO-C1-10 alkyl; CO-aryl; CO-C1-10 alkoxyc(1-10)alkyl; CO-aryloxy(C1-10)alkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents chosen from fluorine, chlorine, bromine, iodine, hydroxyl, amino, C1-10 alkylamino, arylamino, C1-10 alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate; C1-10 alkylsulfonyl; arylsulfonyl; ar(C1-10 alkyl)sulfonyl; or an amino-acid chosen from α, β, γ or δ glycine, alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan, proline, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartate, glutamate, lysine, arginine and histidine in D or L configurations;

X is O;

Base* is cytosine, uracil, guanine, adenine, or thymine;

R12 is C(Y3)3;

Y3 is H; and

1 is fluorine;

wherein aryl in each case means phenyl, biphenyl or naphthyl.

Disputed patent NO 700 (the “Gilead Patent”)
The Gilead Patent also concerns certain nucleoside and nucleotide compounds that can be used in the treatment of Flaviviridae infections, especially hepatitis C. According to Patent Claim 1, filed on 30 March 2012, the patent pertains to compounds of the general formula:

```
    R1 O
      |   Base
    X   |
      |  R2 O
      |   |
      |  CH3
      |  F
```

The thick lines in the above formula show the three-dimensional shape of the molecule, and indicate that the bonds between the atoms are pointing towards the viewer. For this reason, some atoms and atom groups are designated as “up” and some as “down”, as illustrated in the diagram below:
Another way of illustrating the three-dimensional shape is to use unbroken and broken [lines to represent] bonds, respectively, as in the following [diagram]:

The compounds disclosed in Claim 1 are N-nucleosides/nucleotides, i.e. compounds in which the nitrogen atom of the base is bonded with the carbon atom at the 1'-position on the sugar ring. More specifically, the patent claim pertains to compounds wherein Base is of the following formula:

The characterising features invoked in respect of Gilead's invention include, inter alia, the 2'-position on the sugar ring having been substituted with F (fluorine) at the 2'-down-position and CH₃ (methyl) at the 2'-up-position, as well as Base being cytosine or uracil bonded from a nitrogen atom of the base (i.e. N-bonded). One embodiment of the invention is shown on page 33 of the application as filed, and is illustrated in Example 1 and Example 2 (wherein the base is cytosine):
The comments of the Court
The Court has full jurisdiction over the issue of the validity of patents. Reference is made to Section 52, Sub-section 1, of the Norwegian Patents Act, from which it follows that a patent may be invalidated by a court decision if it has been granted in spite of the fact that the requirements under Sections 1 – 2 are not complied with (1); or it relates to an invention the description of which is not sufficiently clear to enable a person skilled in the art to carry out the invention on the basis thereof (2); or after a request for patent limitation, the patent has been amended in such a way that the scope of protection has been extended (5).

Although the courts of law also have full jurisdiction over the specific discretionary assessment, the Supreme Court has stated in two cases concerning decisions to reject patent applications that the courts of law shall exercise restraint in their judicial review of the discretionary technical assessments of the Norwegian Industrial Property Office. Reference is made to the Swingball Judgment, published on p. 603 onwards of the 1975 volume of the Norsk Retstidende court reporter, and the Biomar Judgment, HR-2008-1991-A.

The invalidity action with regard to NO 755
The Court will first examine Gilead’s argument that patent NO 755 is not valid because the description is not sufficiently clear to enable it to be carried out by a skilled person.

_Gilead has, in the main, invoked the following in relation thereto:_
The application that forms the basis for the disputed patent contains no embodiment examples illustrating the patented invention and does not contain information that would have enabled the skilled person to identify, without undue burden or experimentation, chemical compounds within the scope of the patent claims that can be used for the treatment of Flaviviridae infections. Nor does the application contain any information that would have enabled a skilled person to produce and make use of the therapeutically active compounds without undue burden or experimentation. It describes no process for the production of the chemical compounds in respect of which protection is claimed. Nor did the prior art include any process that enabled the skilled person to produce the said compounds without undue burden or experimentation.

The disputed patent encompasses an enormous number of different compounds as the result of the many alternatives specified for the various substituents, without disclosing any information that would have enabled the skilled person to choose between them.

Furthermore, the description neither discloses sufficient information concerning how to conduct and interpret suitable tests, for purposes of distinguishing the alleged pharmaceutical product candidates, nor provides any guidance with regard to synthesis routes or reaction conditions that would enable the skilled person to produce the patented compounds.
Neither the dependent patent claims, nor the alternative patent claim, add anything that might justify 
upholding the patent.

*Idenix has, in the main, invoked the following:*
The skilled person would be able to produce the compounds in the patent claims without undue burden by 
using information from chemical literature and the patent documents, as well as starting materials, reagents, 
techniques and equipment that are available to the public, together with his or her own expertise and 
knowhow, as well as routine experiments. As at the priority date of NO 755, the synthesis for nucleoside 
analogues, with both natural and non-natural bases, had been known for a long time. Both suitable starting 
materials and synthesis strategies were available. The same was the case with a number of methods for 
testing the antiviral effect of different compounds in relation to various viruses within the *Flaviviridae* 
family. Some of these are discussed in the patent, cf. p. 45 and pp. 180–183, whilst others, such as for 
example the HCV Replication System, formed part of the common general knowledge of the skilled person.

A skilled person would on 28 June 2002 and 27 June 2003 have been able to synthesise the compounds in 
respect of which protection is claimed, based on the information disclosed in the patent and common 
general knowledge in the art. The skilled person could have done this by only conducting routine 
experimentation. The skilled person would have been familiar with appropriate reagents for purposes of 
achieving fluorination, including diethylaminosulfur trifluoride (DAST) and Deoxo-Fluor. The skilled 
person would also know how to get to the appropriate precursor for achieving the correct stereochemistry. 
Reference is made to the expert opinions, incl. appendices, and the witness testimony of Professors Meier 
and Sydnes.

It is not a legal prerequisite for the description with regard to the product claims in Claims 1 and 2 of 
Exhibit 1a and Claims 1 and 2 of Exhibit 1b to be sufficient to enable the skilled person to test the activity 
of the compounds. However, methods for the testing of the antiviral activity of the compounds were 
available to the skilled person. As far as anti-HCV testing is concerned, assays based on the HCV replicon 
system constituted common general knowledge in the art as at the priority date. Alternatively, in vitro 
assays for RNA polymerase activity were available. This is described in the patent. As far as testing of 
activity against WNV, YFV, dengue fever, etc., is concerned, routine cell-based assays for viral infections 
were available, such as assays for the calculation/reduction of plaque. Moreover, assays for cell protection/cytopathic effect, including neutral red uptake assay, were available to the skilled person. These assays are 
described in the patent, and were well known, in routine use, as well as available, on 28 June 2002. 
Reference is made to the expert opinion, incl. appendices, and the witness testimony of Dr DeFrancesco.

*The Court* will base its assessment on Section 8, Sub-section 2, third sentence, of the Norwegian Patents 
Act, which is worded as follows:

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*True translation certified.*

2 April 2014

Knut Høgne Engedal

*Government-authorised translator*

*English – Norwegian • Norwegian – English*
The description shall be sufficiently clear to enable a person skilled in the art to carry out the invention on the basis thereof.

The requirement with regard to the clarity of the description is a substantive prerequisite for patentability. The reasoning behind such requirement is, firstly, that the invention shall be made available to the public and clarify the scope of the exclusive right. If the requirement is not met, the patent may be declared invalid, cf. Section 52, Sub-section 1, No. 2, of the Norwegian Patents Act.

The parallel provision of the European Patent Convention ("EPC") is Article 83. It is worded as follows:

*The European patent application shall disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.*

The said provision stresses that the description shall not only be clear, but also "complete". The same wording is used in Art. 5 PCT. The former Norwegian patents acts used the wording "clear and complete". Although the wording of the current act is different, it follows from the preparatory works that one did not intend to affect any amendment to the substance [of the legislation], cf. the NOU 1963:6 Green Paper, page 185. Reference is made, furthermore, to the NOU 1976:49 Green Paper, page 110, in which it is concluded that Art. 5 PCT, which we have noted corresponds to Art. 83 EPC, does not occasion any amendment to Section 8, Sub-section 2, of the Norwegian Patents Act.

There is a presumption that Norwegian law is in conformity with the EPC. This is a key factor of interpretation. It must be concluded, when read in the context of the legislative history of the provision, that the contents of Section 8, Sub-section 2, third sentence, of the Norwegian Patents Act are the same as the contents of Art. 83 EPC. Consequently, the description shall not only be clear, but also complete. This can also be reasonably inferred from the requirement that the skilled person shall be able to exercise ["carry out"] the invention on the basis of the description.

Neither the preparatory works of the Act, nor case law, provide further guidance with regard to the requirements for the description. It can nonetheless be concluded, against the background of case law and literature relating to Art. 83 EPC, that one must be able to directly derive the information necessary to carry out the invention, either from the description or from common general knowledge in the art. One must, on the basis of the said information, be able to solve the problem intended to be solved by the invention. One must be able to produce and make use of the invention. Claims 1 and 2 are product claims. Hence, the question is whether the skilled person can make the product. In order to make the product, the starting materials and the active ingredient need to be identified. The Court also refers, in relation hereto, to the decision of the EPO Technical Boards of Appeal in Case T 0412/93:

True translation certified.
2 April 2014

Knut Hogne Engedal
Government-authorised translator
English – Norwegian • Norwegian – English
Whether this product claim can stand for the purposes of Article 83 depends on whether what is claimed can be identified, and whether a reliable method existed for making it using the teaching of the patent and common general knowledge available at the priority.

Moreover, the EPO has concluded that everything of critical importance to understanding the invention shall be disclosed in the description. It is not sufficient to refer to publications, etc., in which it is disclosed, cf. T 276/99.

One shall be able to carry out [the invention] without undue burden or experimentation. The EPO has put it as follows:

- It must be possible to reproduce the invention on the basis of the original application documents without any inventive effort and undue burden. (T 629/05)

Some experimentation and a reasonable amount of trial and error can be accepted, but the EPO has stated the following:

- Where the skilled person can only establish by trial and error whether or not his particular choice of numerous parameters will provide a satisfactory result, this amounts to an undue burden. (T 32/85)

The EPO has stated the following with regard to experimentation:

They should quickly give a reliable picture of how the products can be produced or manufactured (T 475/88).

It is not necessary to show all steps leading to the compound, and there is no requirement that the invention can be carried out with only a small number of non-disclosed steps. However, the requirement is that each of these steps are perceived by the skilled person as sufficiently clear to make a detailed description thereof seem superfluous. Reference is made to the EPO Technical Boards of Appeal:

Furthermore, there is in the Board’s opinion, no requirement in the European Patent Convention that where it is not explicitly described how a claimed invention is to be carried out this must be practicable with the aid of only a few additional non-disclosed steps. The only essential requirement that must be fulfilled is rather that everyone of these additional steps must be so apparent to the skilled person that, in the light of his common general knowledge, a detailed description thereof is superfluous. (T 721/89)

The skilled person must be able to know that he has achieved the outcome, and hence there must be a method for verifying whether the invention has been realised.
It is the technical solution defined in the patent claims that shall be capable of being carried out on the basis of the description and common general knowledge in the art. The parties agree that the Court may for purposes of the present case restrict its assessment to the new patent claims. The Court bases [its assessment] on the arguments invoked by the parties, but, as the Court will revert to, [the Court] refrains from ruling on whether or not the patent limitation request is admissible.

It follows from EPO case law that any doubt as to whether or not the invention can be carried out without "undue burden" shall be resolved in favour of the patent holder.

**Review of the patent description**

the Idenix Patent, NO '755, pertains to chemical compounds that are suitable for use in pharmaceutical products, especially for the treatment of *Flaviviridae* infections such as hepatitis C virus infections.

The patent describes a very large number of nucleosides and nucleoside derivatives. According to the description, these nucleosides are branched at the 1'-, 2'-, 3'- or 4'-position and may feature β-D- or β-L-configuration. The nucleosides may contain a number of different bases and may in the 2'-, 3'- and/or 5'-position contain a biologically decomposable entity, typically a natural or synthetic D- or L-amino acid.

The description includes numerous detailed embodiments. A number of these include formulas with high chemical variability. Application NO 465 uses the term "Principal Embodiments" to designate the first six groups specified. Sub-embodiments are specified under each of these groups. Some of these are termed "preferred" and some are termed "even more preferred" or "especially preferred". The Court finds the use of these designations to be purely incidental and void of guidance. After the six principal embodiments, [the description] specifies four forms designated as "particular aspects" of the invention. Some additional embodiments are also specified, one of which is termed "another preferred embodiment", cf. application NO 465, page 42.

The said designations are not included in the description of patent NO 755 as granted. Apart from that, the contents are virtually identical. The description starts out by discussing the main formulas. The formulas are discussed anew from page 54 of the patent. This is termed "Active Compound" in the US application, and is the active part of the pharmaceutical product and thus also the key aspect of the invention. A total of 23 formulas are discussed. The patent describes a number of variants under each of these. It would appear that the grouping into the six main groups continues, although the designation "Main Group" is not used.

All of the formulas are presented with the following wording:
A compound of the Formula (...) or [its] pharmaceutically acceptable salt or prodrug [thereof], or stereoisomer, tautomer or polymer form thereof are described...
The designations "sub-embodiment groups" or "preferred embodiment", etc., are not used in the patent description either, unlike in the application, subject to certain exceptions to which the Court will revert.

**Formula (I)** is discussed from page 19 and from page 54 of the patent description. The diagram discloses 2'-branched ribonucleosides with OR substituents in the 2', 3'- and 5'-position and with a synthetic/non-natural purine base with three variable substituents. The formula encompasses a very large number of chemical compounds; probably much more than one billion. The number must in reality be considered infinite since the definition of the variable substituents includes substance classes and substituents with unlimited scope for variation. One specifically described compound is identified in relation to this formula. Although the said variant represents a limitation, this description also allows for a very large number of alternative choices.

This first embodiment is of no direct relevance in relation to the invention as currently claimed, i.e., in relation to the revised principal and alternative claims, since the variant with 2'-fluorine-down is not included.

**Formula (II)** is discussed from page 19 and from page 56 of the patent description. This diagram also discloses ribonucleosides with OR substituents, "2'-OR-down, with non-natural pyrimidine bases. Likewise, this formula encompasses a very large number of chemical compounds, probably much more than one billion. The embodiment is narrowed down in one "specifically described" form, but such [form] is also likely to encompass about 1,000 embodiments.

Nor is this second embodiment of any direct relevance in relation to the compounds currently claimed as the invention, as it does not include the variant with 2'-fluorine-down either.

**Formulas (III), (IV) and (V) are discussed from page 21 and from page 57 of the patent description. In application NO 465, these formulas were designated as the "third principal embodiment". In addition to compounds with oxygenous sugar rings, [the formulas] also allow for other nucleosides, for example carbocyclic nucleosides (X=CH₂), thionucleosides (X=S) or unsaturated nucleosides (X*=CH). In the same way as with Formulas (I) and (II), the number of chemical compounds encompassed by the description is infinitely large as the result of very considerable scope for structural variation in the base and substituent groups. The base may be chosen from a large number of bases outlined in some detail. However, it would appear to the Court that the potential choices are limited to non-natural or synthetic bases. The natural N-bonded purine and pyrimidine bases are not included. As an example, reference is made to Diagram (E) on pages 22 and 58. The diagram as presented includes cytosine (if Y² = O, W¹ = N, Y¹ = NH₂, X² = H, W⁴ = CH), uracil (in the enol form if Y² = O, W¹ = N, Y¹ = OH, X² = H, W⁴ = CH), and thymine (in the enol form if Y² = O, W¹ = N, Y¹ = OH, X² = CH₃, W⁴ = CH). Consequently, even though natural bases are encompassed at the outset,
such natural bases are specifically excluded at the bottom of page 28 and at the top of page 29 of the patent description. The same is evident from the middle of page 64. The Court is of the view that this will be perceived by the skilled person as a deliberate choice. In other words, it is not perceived as an oversight or unintentional error that it would be appropriate for the skilled person to rectify.

In Formula (IV), fluorine (F) is listed as one of many available choices for the $R^7$ substituent (2'-down position). Fluorine is disclosed as one of four halo substituents. Halo is included at the bottom of a listing of a very large number of alternatives, cf. pages 30 and 66 of the patent. Given the structure of the description, the Court is of the view that the skilled person will not perceive fluorine as having been highlighted, and the available choices will also here be perceived as infinite in number.

A further three embodiments are described under these three formulas. Thereafter, one additional embodiment is described under Formula IV, which is designated Formula (IV(a)), cf. page 68 of the patent. Fluorine is therein specified as the preferred $R^7$ substituent, i.e. in position 2'-down. Formula (IV(a)) is not specified as "an especially preferred embodiment" in the patent, as was the case in the application. The said limited embodiment also encompasses a large number of chemical compounds, when considered against the background that there is very considerable scope for variation with regard to Base, $R^1$ and $R^2$.

The Court is of the view that none of these embodiments are of direct relevance in relation to the revised patent claims either, inasmuch as Base, and not Base*, is specified with regard to all of them. The Court is of the understanding that the term Base as used in the patent does not include the natural bases.

Formulas (VI) and (VII) are discussed from page 30 and from page 69 of the patent description. In application NO 465, these formulas were designated as the “fourth principal embodiment”.

These formulas include miscellaneous branched nucleosides, including a very large number of chemical compounds with different bases. At first, one embodiment is disclosed under both of Formulas (VI) and (VII). Thereafter, eight compounds are disclosed under Formula (VI), four under Formula (VII) and an additional 15 compounds under Formula (VI). Hence, a very large number of chemical compounds are encompassed.

These formulas are not of appreciable relevance in relation to the amended patent claims. Given how these formulas are presented on pages 69 to 71, the natural N-bonded bases are not included. Given how the range of bases is disclosed on pages 71 onwards, it would appear that natural bases are also included. Fluorine and methyl might be an option under some of the outlined alternatives, but it would be very difficult for the skilled person to deduce the invention from what is disclosed here. Indeed, the parties have not focused on these formulas.
Formulas (VIII), (IX) and (X) are discussed from page 32 and from page 111 of the patent description. In application NO 465, these formulas were designated as the “fifth principal embodiment”.

These formulas include three classes of nucleosides in which the base is designated as Base*. Base* is defined in the patent as “a purine or pyrimidine base as defined herein”. It follows from the definition of purine or pyrimidine base on page 128 that the natural pyrimidine (cytosine, thymine and uracil) and purine (adenine and guanine) bases fall within the scope of the term Base*. However, Base* is not limited to the natural bases. According to the definition, a large number of non-natural bases are also included, thus implying that the total number of available base choices is very large here as well.

The first discussion of Formulas (IX) and (X), cf. page 32 and page 111, mentions fluorine as one out of a very large number of alternatives for the R₁³ substituent (2'-down position). The number of available choices for R₁³ must be characterised as infinite. Fluorine is listed as the last alternative, and the Court is of the view that the skilled person would not perceive fluorine as being highlighted here in any way as a preferred choice. The description also offers up a very large number of available choices with regard to X, R₁, R₂, R₁², CH₃ (methyl up) is one of these alternatives, but it is not highlighted.

Following discussion of these three formulas, a “first aspect of the present invention” is mentioned, characterised by Formula (IX). R₁³ is therein limited to fluorine, whilst R₁² is limited to C(Y₃)₃, cf. page 113. Thereafter, “a preferred embodiment” is disclosed, in which X=O and Y₃=H. Furthermore, “a second preferred embodiment” is disclosed, in accordance with the first aspect, in which R¹ and R²=H. As mentioned, the base is specified as Base*, which also includes natural bases. Consequently, this embodiment encompasses the invention as currently accentuated by the limited patent claims. Reference is made to page 114 of the patent. It is noted that the said presentation of a limited version of Formula (IX) was not included in this part of the Norwegian application as originally worded in NO 465.

Thereafter follows a description of a number of nucleosides with formulas from (XI) to (XXII). These formulas are not assumed to be of any relevance to the invention, as now sought protected with the pattern 2'-fluorine-down, 2'-methyl-up and a natural base. The Court therefore does not examine this part of the patent in further detail. However, it is noted that these formulas also allow for a very large number of available choices for the various substituents. An infinite number of chemical compounds fall within the scope of this part of the patent description as well.

After discussion of Formulas (XI) to (XXII), the patent reverts to Formula (IX) on its page 123. In the corresponding part of application NO 465, page 118, the designation “a preferred embodiment” is used. The patent description of NO 755 does not use the said designation. The substituents are described in the same manner as in the preceding discussion of Formula (IX) on pages 111 and 112. In addition, there is a
sub-embodiment in which \( R^1, R^2 \) and \( R^3 \) are specified as H when \( X \) is O and \( Y^3 \) is H. According to the said description of the formula, the chemical compound will be limited to 2'-fluorine-down, 2'-methyl-up, with only the base being variable. The base shall be a purine or pyrimidine base, but it could be either natural or non-natural.

**Description and exemplification of syntheses**

The description states that the nucleosides can be synthesised (produced) through “a number of processes known in the literature”. It is noted that synthesis of the disclosed nucleosides can be achieved, in particular, by either alkylation of suitable modified sugar, followed by glycosylation (the sugar route), or by glycosylation followed by alkylation of nucleosides (the nucleoside route).

Thereafter, a number of general synthesis routes to different branched nucleosides are presented, without experimental data. All of the descriptions include general protection and deprotection steps, and references to known and relevant monographs and publications are included.

For 1'-C-branched nucleosides, the sugar route is described by two general examples. The first example includes nucleophilic attack on lactone intermediate, followed by activation and coupling with base (Diagram 1). The second example uses D-fructose as starting material. Following conversion into psicofuranose intermediate, this is coupled with base (Diagram 2). For 2'-C-branched derivatives, the sugar route is described first, including nucleophilic attack on 2-keto-sugar derivative followed by coupling with base (Diagram 3). Thereafter, it is described how the nucleoside route can alternatively be used with 2'-ketonucleoside as intermediate (Diagram 4). The corresponding general synthesis path is described for 3'-C-branched nucleosides (Diagram 5 and Diagram 6). A sugar route that includes oxidation of C5 followed by attack on electrophilic alkyl reagent is described for 4'-C-branched nucleosides. These descriptions are followed by a general description of synthesis of 2'/3'-prodrug derivatives (alkylation of hydroxy group with amino acid).

This is followed by a number of examples of specific experimental synthesis procedures. These are typical literature procedures for illustration of the preceding disclosures. The same applies to Diagrams 7 and 9, which describe synthesis of nucleoside intermediates that were also known from the literature.

None of these examples address the synthesis of fluorine substituted nucleosides.

**Common general knowledge in the art**

It is a statutory requirement that the description is sufficiently clear to enable a skilled person to carry out the invention. The EPC uses the term a person skilled in the art. Consequently, it is not necessary for the description to include what is normally known or
understood by persons skilled in the art. This is termed common general knowledge in the art. The skilled person shall be representative of the general, average professional level.

Idenix has, in its Notice of Intention to Defend of 20 November 2012, provided the following description of the skilled person:

The "skilled person" will for purposes of the present case be a team in possession of the knowledge and experience of, for example, a synthetic organic chemist who is familiar with the synthesis of nucleosides and nucleoside analogues, a medicinal chemist who is familiar with structure-activity relationships for nucleosides and nucleoside analogues, as well as a virologist who is familiar with assays for determining antiviral activity, especially with regard to Flaviviridae virus, in addition to structure-activity relationships. Each of the members of the team may have experience, knowledge and abilities that overlap with the knowledge of other members. Each of the members of the team will have appropriate education and experience, such as a Ph.D. degree within a relevant field, as well as no less than two years' experience.

Gilead has not objected directly to this, and the Court will base its assessment on the above description.

The next question is what shall be deemed to have been known to the skilled person for purposes of the assessment to be performed herein. The Court adopts the premise that the skilled person within the meaning of Section 8 will not be in possession of the same knowledge as would be assumed for purposes of the inventive step assessment under Section 2. This follows from case law from the EPO, and also follows from the purpose of the said [statutory] provisions. The patent description shall disclose the invention in such a way as to make it understandable to the ordinary person skilled in the art. Information available from textbooks and key articles that are normally read by persons skilled in the art will be assumed to form part of common general knowledge in the art. Patent documents and other sources that are more specialised will not be included, although such information is taken into consideration for purposes of inventive step assessments.

The skilled person is assumed to be capable of drawing on common general knowledge in the art, in addition to the information in the patent. The skilled person is also presumed to be capable of rectifying errors in the description on the basis of common general knowledge in the art. Textbooks and general technical literature form part of common general knowledge in the art. However, information which can only be obtained after a comprehensive search is not to be regarded as part of the common general knowledge, cf. T 206/83, T 634/90. The burden of proof is on whoever asserts that something forms part of common general knowledge in the art.

The application date will be of decisive importance in assessing what information the skilled person could have inferred from his or her common general knowledge. The Court will base such assessment on the date of the European application, i.e. 27 June 2003.
As at the said date, the skilled person knew, first of all, that nucleosides could be produced by either the so-called sugar route or the so-called nucleoside route. This is also, incidentally, specified in the patent. Many examples of successful introduction of a fluorine substituent on the sugar ring, including in the 2'-position, had been published, and it had been documented that both the sugar route and the nucleoside route were viable in this context. Reference is made, in particular, to the article Fluorinated Nucleosides; Pankiewicz, published in 2000 (the “Pankiewicz Citation”). The following is stated at the beginning of the said article:

The objective of this chapter is not to present a list of known fluorinated nucleosides but rather to show the development of the field. Since some early-synthesized 2'-deoxy-2'-fluoro nucleosides showed promising therapeutic potential (mainly antiviral and anticancer), the synthesis of new generations of 2'-fluorinated nucleosides flourished in hope of new drug discovery. Thus, more than 77% of fluorinated nucleosides synthesized to date contain fluorine atom(s) at C-2' of the sugar.

The skilled person was also familiar with the use of protecting groups, for example via knowledge of the monographs of Greene and Kocienski. Besides, the skilled person was familiar with the article Alkyl Addition Reaction of Pyrimidine 2'-Ketonucleosides, Matsuda, et al, published in 1988 (the “Matsuda Citation”). The said [article] describes synthesis of 2'-methyl-up, 2'-hydroxy-down and 2'-methyl-down, 2'-hydroxy-up nucleosides with pyrimidine bases. Consequently, the skilled person would be able to identify these derivatives as potential starting materials for the synthesis of 2'-methyl-up, 2'-fluorine-down nucleosides with pyrimidine bases.

Moreover, the skilled person was familiar with 2-keto carbohydrates and the alkylation thereof with C-nucleophiles into starting materials for potential syntheses of 2-methyl-up, 2-fluorine-down intermediates with a view to subsequent coupling with base into corresponding nucleoside derivatives.

The Court further assumes that the skilled person was familiar with potential stereochemical challenges in the coupling of activated carbohydrates with bases, and with heterogeneous reactivity and synthesis strategy across different bases, e.g. between pyrimidine and purine bases. The skilled person would also be aware of the need for making use of completely heterogeneous reaction types in the synthesis of N- and C-nucleosides via the so-called sugar route.

The skilled person would be aware that a decisive step in the syntheses of 2'-methyl-up, 2'-fluorine-down nucleosides would be the introduction of fluorine into the desired stereochemical configuration. The skilled person was familiar with a number of different reagents for the replacement of a hydroxy group with a fluorine atom. Moreover, the skilled person was familiar with potential stereochemical challenges and with potential undesired side reactions when attempting the introduction of fluorine substituents.

The skilled person knew, for example, about DAST (diethylaminosulfur trifluoride) and the closely related Deoxo-Fluor (di-2-(methoxy)ethylamino(sulfur trifluoride)) as reagents.
in the replacement of a hydroxy group with a fluorine atom. The skilled person also knew that DAST had been used successfully for the introduction of fluorine substituents in the 2'-position on the sugar ring of nucleosides, via both the sugar route and the nucleoside route.

The Court has not registered any disagreement between the parties with regard to the conclusion that the [knowledge] outlined above formed part of common general knowledge in the art as at the priority date. The disagreement concerns, in particular, issues relating to the introduction of a fluorine substituent in the synthesis of the relevant 2'-methyl-up, 2'-fluorine-down nucleosides.

The respective expert witnesses called by the parties would also appear to, partly, hold highly diverging opinions, precisely with regard to issues relating to the introduction of a fluorine substituent in the synthesis of the relevant nucleosides. Idenix’ expert witness Dr Meier stated, inter alia, the following in his report:

*These two reagents (note: DAST and Deoxy-Fluor*) were used previously by several scientists also in nucleoside chemistry and therefore was a routine reaction.*

He further stated that:

*Taking the arguments above together, a person skilled in the art could routinely and predictably convert the 2'-OH of a 2'-Me-up nucleoside into a 2'-F-derivative with a simultaneous inversion of stereochemistry to form a 2'-F-down-2'-methyl-up nucleoside analog as shown below.*

On the other hand, Gilead’s expert witness Dr Marquez stated the following:

*This is because fluorination reactions often have surprising or unpredictable outcomes. This can be especially true when one is trying to synthesize a compound with different chemical features from those known in the art, for example a nucleoside with a new substitution pattern on the sugar ring.*

He further stated that:

*Accordingly, it is my opinion that an artisan as of June 27, 2003 could not have predicted whether particular methods known in the literature for making fluorinated compounds would have worked to make the compounds of the Idenix Claims.*

The Court is of the view that it follows from the abovementioned article by Pankiewicz that the skilled person knew that the necessary protection of hydroxy groups could be achieved with different protecting groups. Reference is made to Diagrams 5, 8 and 11, in which trityl and silyl protecting groups are used. The Court is of the view that the skilled person would, in 2003, be aware that
the introduction of fluorine in the C2 position of carbohydrates, as implied by the sugar route, could be complex. This is evidenced by the following quote from the Pankiewicz Citation:

> Although, the introduction of a fluorine atom at C-2 of the carbohydrate by nucleophilic displacement reaction is rather difficult, the similar reaction at C-3 is not.

The Court also notes that common fluorination reagents such as, for example, DAST, Deoxo-Fluor, hydrogen fluoride and ammonium fluoride, are used in precisely such nucleophilic substitution reactions. The fact that the sugar route might involve challenges is also illustrated by a number of synthesis problems described in the Pankiewicz Citation under the synthesis of a sugar coupling reagent for the production of FMAU (2'-deoxy-2'-fluoro-arà-A), cf. Diagram 4 and text in the 2nd column.

Besides, it follows from the Pankiewicz Citation that it was known that ribo-configured 2'-fluorine-substituted pyrimidine nucleosides could be produced from 2,2'-anhydrous intermediate.

The skilled person would also be aware that an anhydrous intermediate could not be formed in respect of the natural purine nucleosides, thus implying that it would probably be necessary, as far as the nucleoside route was concerned, to make use of different synthesis strategies in the production of, respectively, pyrimidine and purine nucleosides with 2'-fluorine substituent.

The Court is of the view that the skilled person would be aware that the nucleoside route could be difficult. For purposes of the synthesis of 2'-methyl-up-2'-fluorine-down nucleosides because of, inter alia, steric and inductive effects and the potential for undesired side reactions. This can be illustrated by the following quote from the Pankiewicz Citation:

> The direct displacement of a good leaving group at C-2' in ribo configuration with fluorine attacking from the β-face had not been considered to be successful due to the steric hindrance provided by the aglycone positioned above the sugar face. Also, the inductive effects from the aglycone and the lactol ring oxygen make the substitution at the C-2' position difficult.

This quote concerns direct synthesis of 2'-F-up derivatives, but the necessity of the presence of a 2'-C-methyl-group at C2' might be expected to induce steric challenges in connection with the incorporation of a fluorine atom into the C2' atom. The same could not be excluded in connection with the sugar route.

The Court is of the understanding that Dr Meier, unlike Dr Marquez, believed that a replacement from OH to F would not result in a conformational change on the sugar ring. The Court is of the view that the presence of a 2'-C-methyl-group might entail new and not hitherto described
inductive and conformational conditions on the sugar ring, and that these might influence fluorination reactions. This might happen both when using the nucleoside route and [when using] the sugar route.

The skilled person would be aware that there did not exist many examples, if any at all, of the introduction of fluorine at the C2'-position of nucleosides by way of the replacement of a tertiary hydroxy group with a fluorine atom. Moreover, the skilled person would be aware that insertion of a fluorine atom into the carbon atom at the 2'-position; the neighbouring atom of the glycosidic centre, might be expected to influence the chemical and enzymatic stability of the glycosidic bond, as well as the preferred conformation of the furanose ring. This is supported by the Pańkiewicz Citation.

Furthermore, the Court assumes that the skilled person would be aware that it was known that structure-activity relationships (SAR), relating to the anti-HCV activity of ribonucleosides, are complex. Hence, only a small number of ribo-configured nucleosides were known to exhibit antiviral activity. The Court concludes, as a result thereof, that there was no general acceptance in professional circles that 2'-hydroxy ribonucleosides, and the corresponding 2'-fluorine ribonucleosides, would exhibit uniform antiviral activity. It is noted, in support thereof, that it was known that 2'-H-up, 2'-fluorine-down nucleosides of guanine and adenine, unlike the corresponding 2'-methyl-up, 2'-hydroxy-down nucleosides, were inactive in "replicon assay". The Court is of the view that this would lead the skilled person away from choosing 2'-methyl-up, 2'-fluorine-down nucleosides on the basis of the description in the patent.

Further details of the assessment of the Court

As mentioned, the notionally skilled person, as defined above, shall be able to both identify the product and produce it based on the reviewed description and common general knowledge in the art. Although Section 8 of the Norwegian Patents Act only refers to the description, it is assumed in case law and legal theory that the patent claims shall also be taken into consideration. Reference is made to “Patentoven med kommentarer” ["The Annotated Danish Patents Act"] by Lindgreen, Skhovsbo [sic], Thorsen, 2012, page 220. As far as identification of the product is concerned, the Court is of the view that the skilled person gets somewhat more guidance from the patent claims subsequent to the limitation thereof. This applies, in particular, to a limitation to the alternative claims referred to as 1b). The original claims were much broader in scope. The patent claims cannot be amended in such a way as to grant a patent on anything not encompassed by the application as filed. Such might be the case even if an amendment takes the form of a limitation. However, Gilead has not invoked any arguments in relation thereto, and hence the Court does not perform any assessment as to whether the limitation would have been lawful.

The patent is very broad in scope. The description encompasses billions, or even an infinite number, of chemical compounds. Moreover, the structure of the description is not particularly good or clarifying. A number of the diagrams are featured several times. An example is Formula IX, which the Court considers to be the only formula of direct relevance to the invention. A variant of this formula is repeated after the other formulas have been.
discussed, without any explanation being provided in relation thereto. Application NO 465 includes principal embodiments and sub-embodiments, preferred and especially preferred embodiments, etc. However, this terminology does not appear to have been consistently applied, and in many cases it would seem that the terms have been used almost randomly. Indeed, this [terminology] is abandoned in NO 755.

The compounds in respect of which protection is now claimed, and which constitute the "invention" under the limited patent claims, is a compound featuring methyl up and fluorine down, as well as a natural N-bonded base. This invention is disclosed in a variant of Formula (IX). However, the said compound is not specifically highlighted, as it is one of an infinite number of compounds described at the same level of detail. The question is therefore whether the skilled person would have identified such compound without extensive trial and error. The compound has, as mentioned, been rendered more visible after the limitation.

However, it is not sufficient for the skilled person to be able to identify the compound. He or she must also be able to produce it, based on the description and common general knowledge in the art. Neither the original patent claims, nor the amended ones, provide the skilled person with any guidance in this respect.

As far as the production process, or synthesis, is concerned, this is described in the form of a presentation of general synthesis paths. Corresponding descriptions can be found in earlier patent descriptions, cf. WO 121 and WO 282. Diagram 7 on page 157 has been added to [the descriptions from] WO 121 and WO 282, but this covers simple acylation of a 3'-hydroxy group, and is a synthesis known from the literature. Consequently, the said description does not provide the skilled person with any guidance on top of what he or she would already know from his or her general knowledge of the art.

Even if one were to assume that the skilled person has identified the "correct" formula; in this case a sub-embodiment of Formula IX, the skilled person will be faced with a number of choices that have to be made in order to be able to produce or synthesise the substance. Firstly, a choice needs to be made between the sugar route and the nucleoside route. Thereafter, starting materials need to be chosen. Many alternatives will be available in respect of both route alternatives, and the choices will not be perceived as obvious.

Moreover, a fluorination reagent needs to be selected. This also involves numerous alternatives: Even if one starts out from the most precise and restrictive part of the description, as well as the alternative claims, there are several options. One may for example choose both natural and synthetic bases. Finally, one needs to select reaction conditions and solvents, etc., for the various reactions.

The Court notes that minor variations in chemical processes may have a major impact and be decisive in terms of whether or not one succeeds in bringing about the desired compound.
As noted, the skilled person will here have to make a number of choices in respect of which no guidance is provided by the description. Matsuda and Pankiewicz are key citations that the skilled person is assumed to be familiar with. Despite this, the skilled person would not be able to find answers in common general knowledge in the art either, with regard to all of the choices that have to be made.

In other words, the skilled person will, in order to carry out the invention, have to find an overall solution that will depend on the sum total of a number of partial solutions. The Court is of the view that the skilled person would not be able to carry out the invention without a considerable amount of trial and error.

This conclusion is also supported by the fact that Idenix itself would not appear to have been able to produce the compound until at a much later date. It follows from Table 1 that a number of attempts had been made.

The Court refers, in particular, to attempts made by Griffon. Idenix has argued that the Court must disregard his unsuccessful attempts because his professional qualifications were inadequate. The Court finds it difficult to evaluate Griffon’s qualifications on the basis of the disclosures made in the main hearing. The Court notes, however, that he formed part of a professional circle. It is also noted that he did write articles together with other skilled persons. It would seem likely, on the other hand, that Griffon alone did not possess all qualifications expected from the skilled person under Section 8 of the Norwegian Patents Act. It is assumed, as noted above, that we are here concerned with a type of invention that is usually made in cooperation between persons from several professions. Hence, the notional skilled person will be a team of persons holding different qualifications. However, it is concluded that Griffon did not operate alone, but was instead part of a research team that was working on this for Idenix.

Idenix has also argued that the Court needs to disregard Griffon’s attempts for the particular reason that he used the incorrect reagents. However, the Court is of the view that the said conclusion is not obvious. Hence, the Court does not agree with Idenix’ argument that the silyl protecting group (TIPDS) used by Griffon was necessarily the “incorrect” protecting group. Reference is made to the Pankiewicz Citation, in which the following is stated:

*Interestingly, this work demonstrated the usefulness of the silyl protection in the reaction with DAST.*

It is noted, in this context, that Griffon included Deoxo-Fluor reaction on 3’,5’-di-O-tetraisopropylsiloxanyl-protected starting materials. Deoxo-Fluor and DAST are closely related reagents that work through the same mechanism. As mentioned, the skilled person would know from the Pankiewicz Citation that DAST and silyl protecting groups can work together. Against that background, the attempt made by Griffon in cooperation with Chappe must be considered well founded, also as far as the use of a silyl protecting group is concerned.
The Court does not place decisive weight on the fact that Griffon, or the team to which he has belonged, did not succeed in producing the compound. As mentioned, however, the Court considers this to be an argument, in addition to what has otherwise been mentioned, in favour of concluding that the description is incomplete. Both parties have described how there was a race in research circles to arrive first at the invention. It is therefore assumed that Idenix also put a major focus on precisely this field.

The Court has also considered the deliberations of the Norwegian Industrial Property Office. However, it is not evident from the disclosed correspondence that the Norwegian Industrial Property Office has conducted an assessment as to whether the description was sufficiently clear to enable the invention to be carried out within the entire scope of the claims. The Court refers, in this context, to "Patentloven med kommentarer" ["The Annotated Danish Patents Act"], by Lindgreen, Skchovsbo [sic], Thorsen (2012), page 221. It is there stated that the said grounds for opposition are almost always included in connection with an opposition because such issue has not normally been considered in connection with the deliberations before the Danish Patent and Trademark Office. The Court assumes that the same will often be the case in Norway.

The Court concludes, based on the above, that the description in patent NO 4755 is not sufficiently clear and complete as to enable a skilled person, as at the application date of 27 June 2003, to carry out the invention without undue burden or experimentation. This applies with regard to both Claims 1 and 2 of the claims included in Bundle 23, pages 10,558 – 10,561, and Claims 1 and 2 of the alternative claims included in Bundle 23, pages 10,562 – 10,565. The other claims are dependent claims, and thus cannot be upheld either.

Consequently, Norwegian patent NO 330 755 shall be declared invalid pursuant to Section 52, Sub-section 1, No. 2, of the Norwegian Patents Act.

**Technical effect**
Against the background that the Court has concluded that the disputed patent is invalid, it is not necessary for the Court to further address the issues relating to technical effect.

**The validity of the Gilead Patent NO 333 700**
Idenix Pharmaceuticals, Inc. has moved for patent 333 700 (the "Gilead Patent"), which was granted to the defendant's associate Gilead Pharmasset LLC on 26 August 2013, to be declared invalid, under reference to the said patent describing the same modified fluorinated nucleoside analogues for the treatment of *Flaviviridae* infections as the defendants' patent NO 330 755 (the "Idenix Patent").

*Idenix has, in the main, invoked the following:*
The Gilead Patent has been granted without Idenix' patent application having been examined by the Norwegian Industrial Property Office. During the deliberation of Gilead's patent application NO 20056221 (which resulted
In patent 333 700), neither Idenix' PCT application, nor the US 350 application, was taken into consideration as prior art. Hence, there is no reason for the Court to exercise restraint when it comes to declaring the patent invalid due to lack of inventive step in relation to Idenix' PCT application.

Idenix has earlier priority in respect of its patent than does Gilead in respect of its [patent]. Consequently, it is Idenix' patent application that prevents the Gilead Patent from meeting the novelty requirement, and not the reverse.

'Idenix' US 350 application and PCT application both represent prior art in relation to the Gilead Patent. Gilead claims priority from the US patent application referred to as US 368. That [application] was filed on 30 May 2003, i.e. after the filing of Idenix' priority application US 350, but before the filing of Idenix' PCT application. Gilead's PCT application was filed on 21 April 2004, i.e. after both the filing and the publication of Idenix' 350 application and PCT application.

Idenix maintains that Gilead's claimed priority from the 368 application is invalid, whilst Idenix' own priority from the 350 application is valid. Hence, Idenix enjoys the best priority. Gilead is only able to claim priority from its PCT application of 21 April 2004, which was filed after Idenix' PCT application and the US 350 application had been made available to the public.

This implies that both documents are relevant prior art for purposes of the assessment of both novelty and inventive step under Section 2, Sub-section 1, cf. Sub-section 2, first sentence, of the Norwegian Patents Act. Most of the claims in the Gilead Patent lack novelty in relation to both of these documents. Under any circumstance, all of the claims in the Gilead Patent lack inventive step in relation to these citations. Hence, the patent must be declared invalid pursuant to Section 52 of the Norwegian Patents Act.

In the event that the Court holds the priority claimed by Gilead to be valid, Gilead's priority date will precede the date on which Idenix' PCT application and the 350 application were made available to the public. However, Idenix' valid priority from 28 June 2002 implies that Idenix' PCT application and Norwegian application remain relevant prior art for purposes of assessing the novelty of the Gilead Patent, cf. Section 2, Sub-section 2, second sentence, of the Norwegian Patents Act.

In the event that the Court concludes that Idenix' Norwegian application and PCT application do not enable the skilled person to carry out the invention, these documents will nonetheless be of relevance to the inventive step assessment, since the applications were published before Gilead filed its PCT application. It is argued that the solution in the Gilead Patent would have been obvious to the skilled person, based on Idenix' applications. Reference is made, in particular, to the statement from Dr Meier that the selection of bases does not result in any novel invention. Consequently, the compounds, the approach and the pharmaceutical production process in the Gilead Patent were obvious in relation to US'350 and PCT'246. Hence, the patent lacks inventive step and is therefore invalid.
Gilead has, in the main, invoked the following:

NO '700 meets all patentability requirements, and the patent has been validly granted. None of the publications invoked by Idenix constitute prior art in relation to NO '700. NO '700 derives valid priority from US '368, and hence qualifies for priority from 30 May 2003. US '350 does not constitute prior art because the document did not become available to the public until 8 January 2004, i.e. after Gilead’s priority date. WO '999 does not constitute prior art because the application was filed on 27 June 2003, which is also after the priority date of NO '700. Idenix cannot derive valid priority from US '350, and hence Idenix’ PCT application cannot be deemed to have been filed on the date of the filing of US '350.

Furthermore, Gilead argues that NO '700 is valid irrespective of which priority dates are adopted. Even if the contents of WO '999 and/or US '350 are deemed to have been known for purposes of Section 2, Sub-section 2, of the Norwegian Patents Act, NO '700 meets the novelty and inventive step requirements under Section 2, Sub-section 1.

It is argued that neither US '350, nor WO '999, anticipates the invention protected by NO '700, because these publications do not describe any process for the production of the chemical compounds encompassed by the patent claims in NO '700. Nor was any production process that enabled the skilled person to carry out the invention without undue burden or experimentation available from any other sources. Moreover, the publications contain no information that made it plausible to the skilled person that the alleged effect would be achieved from any of the chemical compounds encompassed by the patent claims in NO '700.

The invention in NO '700 also meets the inventive step requirement. Even if US '350 and WO '999 were deemed to have been known prior to the application date, the patented invention differs essentially from what could be inferred from the [said] publications. It is mentioned, in relation thereto, that the patented invention exhibits properties that are superior to those of US '350 and WO '999, as well as to those of other prior art. As far as Process Claim 13 is concerned, reference is made, in particular, to the fact that the compound with Structure 1-4 was not previously known, whether from US '350, WO '999 or other prior art. Nor was it obvious for the skilled person to synthesise the compound with Structure 1-4 from generally available starting materials. The description on page 124 of WO '999, to which Idenix refers, does not pertain to the production of a compound with such a structure.

The Court has above concluded that the Idenix Patent, NO 755, shall be declared invalid because it is not described sufficiently clearly and completely to enable the skilled person to carry out the invention without undue burden or experimentation. The Court has based such assessment on Idenix’ PCT application, as it was the principal argument of Idenix that [such application] should form the basis [for the said assessment]. Consequently, the Court has not ruled on whether Idenix could have claimed valid priority from the filing of the US application referred to as US 350.
First, the Court examines the validity of the Gilead Patent, NO 700, based on priority from the PCT application. It is not disputed that the company enjoys priority from that date, i.e. from 21 April 2004. Idenix' applications US 350 and PCT246/WO 999 had been published by the said date. These were published on 8 January 2004. Consequently, both the novelty requirement and the inventive step requirement must be examined on the basis that the skilled person had knowledge of these documents. As far as the requirements applicable to the notional skilled person are concerned, reference is made to the observations previously made under the assessment of the Idenix Patent. It is assumed that the same qualification requirements shall apply here, although with the skilled person being expected to also have knowledge of patent applications published within the field.

The Court is of the understanding that patentability can in theory be forestalled by an application that has been made available to the public, despite such application not meeting the description requirement under Section 8 of the Norwegian Patents Act. This must depend on a specific assessment as to what had been made public. The question is, in other words, what information was communicated by Idenix' applications, i.e. what the skilled person could infer from these documents.

A solution having been previously described is not sufficient to prevent novelty. It is necessary for [such solution] to have been described is such a way as to enable the skilled person to carry it out, i.e. an "enabling disclosure". The EPO has concluded that the requirement as to the contents of the description corresponds to the novelty requirement, cf. T 206/83 (1987). In other words, an invention is held to be novel if it was not described in such manner in a previous publication as to enable the skilled person to carry out the invention on the basis of such description. The publications are required to contain a plausible description that is sufficiently clear to enable the skilled person to carry out the invention on the basis thereof, without undue burden or experimentation.

The Court refers to the observations made above under the assessment of Idenix' patent application. Unlike Idenix' PCT application, there is an unequivocal core to the Gilead Patent, NO 700, i.e. derivatives of 2'-methyl-up, 2'-fluorine-down nucleosides. It describes cytosine nucleoside without scope for variations, and thereafter describes, inter alia, stereochemical aspects and basic methods for the production of nucleosides. It is also noted that Idenix' applications that had been published by the application date of Gilead PCT did not contain the revised claims currently invoked. Hence, disclosure of the 2'-methyl-up, 2'-fluorine-down pattern was even weaker than at present.

The Court is of the view that Idenix' application fails to disclose any process that enables the skilled person to carry out the invention. This is also different in NO 700. Biological test methods are included there, and the sections on synthesis direction contain synthesis schemes pertaining to both the sugar route and the nucleoside route. These general synthesis schemes specify starting materials and synthesis steps to 2'-methyl-up, 2'-fluorine-down nucleosides. Furthermore, the patent contains synthesis examples to render the
general synthesis schemes specific. Experimental data are included, with all necessary details and characterisation data. The actually executed synthesis examples encompass both the sugar route and the nucleoside route, and both pyrimidine and purine bases, including the natural bases cytosine and adenine. Finally, the description contains extensive data to render the general biological experiment descriptions specific and to verify technical effect (antivirus activity).

The Court concludes, against this background, that the novelty requirement is met in relation to Idenix’ patent applications.

In order for the inventive step requirement to be met, the invention shall differ essentially from what was known from before, cf. Section 2, Sub-section 2, of the Norwegian Patents Act. The Court refers to what was mentioned under the assessment of the novelty requirement. The Court finds, especially against the background of the synthesis description, that the Gilead Patent, NO 700, differs essentially from what could be inferred from Idenix’ applications. Reference is also made, in this context, to the attempts made by Griffon and his team. These are described above. The Court has, as mentioned, concluded that Idenix failed, despite extensive research activity, to carry out the invention. It is not disputed that the invention can be carried out against the background of the description in the Gilead Patent. The Court concludes, against this background, that NO 700 exhibits the necessary inventive step in relation to Idenix’ published patent applications.

It is noted that the Court has not performed any assessment in relation to any other citation, since no arguments have been invoked in such regard. Only Idenix’ applications have been invoked as preventing novelty and inventive step. Consequently, these proceedings have not been structured around a thorough review of the Gilead Patent. The issue of the validity of the said patent was raised shortly before the main hearing, and the parties have devoted little attention thereto in these proceedings.

Consequently, the Court finds in favour of Gilead with regard to the claim for Norwegian patent NO 700 to be declared invalid.

The priority issues
The above implies that it is not necessary for the Court to rule of the issue of priority in relation to the US applications.

Legal costs
Gilead Sciences Europe Ltd. has prevailed with all of its claims in Case No. 12-155575TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 330 755. Gilead Pharmasset LLC has prevailed with all of its claims in Case No. 13-170456TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 333 700.

True translation certified.
2 April 2014

Knut Hogne Engedal
Government-authorised translator
English – Norwegian • Norwegian – English

IPO DELHI 07-08-201
The issue of legal costs is governed by Section 20-2 (1) of the Norwegian Dispute Act. The main rule is that a party is entitled to full compensation for its legal costs from the opposite party if the former has prevailed in the action. The Court has considered the statutory exemption provisions, but does not find these to be applicable to the present proceedings.

The amount shall be determined pursuant to Section 20-5 of the Norwegian Dispute Act. The main rule is that the prevailing parties are entitled to compensation for all of their necessary costs in relation to the case. In assessing whether costs have been necessary, weight is placed on whether it was reasonable to incur them in view of the importance of the case.

Gilead Sciences Europe Ltd. and Gilead Pharmasset LLC were both represented by the same counsel in the case. Attorney Stenvik has submitted a specification of legal costs in conformity with the statutory requirements. According to the said specification, the total cost claim in respect of both cases is NOK 14,736,373. NOK 8,069,625 is in the form of legal fees, NOK 2,247,521 is in the form of disbursements that are subject to VAT, NOK 1,839,941 is in the form of disbursements that are not subject to VAT and NOK 2,579,286 is in the form of VAT on the disbursements that are subject to VAT and on the legal fees.

Attorney Stenvik has apportioned, on a discretionary basis, 5% of the total fees to Case No. 13-170456TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 333 700. He has apportioned the remaining 95% to Case No. 12-155575TVI-OTIR/01, which is the invalidity action pertaining to Norwegian patent NO 330 755.

A preliminary cost specification was submitted in Court, with the opposite party being given the opportunity to comment thereon. Attorney Stenvik has submitted two revised specifications, the last of which was received by the Court on 13 December 2013. These specifications have also been forwarded to the opposite party, which has been given the opportunity to comment thereon. No comments have been received. The cost specification from the other party is for a similar amount.

The Court notes that both parties to the proceedings have incurred high costs, and the Court has assessed whether the legal cost claims from the parties that prevailed in the case exceed what has been necessary to conduct the proceedings in a proper manner. The Court notes that the case is extensive in scope. A number of preparatory meetings have been held. The main hearing lasted for 9 full days. The case has been complex and numerous experts have been involved in the proceedings from both sides. In part, these experts have diverged in their views. Although the Court has not been in doubt about the conclusion reached by the Court, the [case] has raised many, and in part highly complex, issues that have not previously been addressed by the judicial system. The case has also included an examination of foreign law.

Both parties have been represented by two lawyers acting as of counsel in addition to their counsel, two of whom from each side have been very experienced patent lawyers charging high hourly rates. The Court finds, against the background of the scope and complexity of the case, that this has been necessary. It is noted that the case has been very well prepared and

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True translation certified. 2 April 2014

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presented by the attorneys on both sides. Finally, reference is also made to the very considerable financial interests that the case represents for both parties.

The Court finds, based on an overall assessment, that the costs for which compensation is claimed have been necessary and that it was reasonable to incur these in view of the importance of the case. Liability for the legal costs is allocated across the two cases in conformity with the discretionary apportionment made by Attorney Stenvik. The opposite party has not submitted any comments in relation thereto, although it has apportioned its costs in a ratio of 90% - 10%. The Court has no comments in relation to the apportionment made by Attorney Stenvik.

Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L’Université Montpellier were the defendants in Case No. 12-155575TVI-OTIR/01. The Court found against them in all respects in the said case. Hence, these parties shall be jointly and severally liable for 95% of the costs, which amounts to a total of NOK 13,999,554.

Idenix Pharmaceuticals Inc. was the claimant in Case No. 13-170456TVI-OTIR/01. The Court also found against it in all respects in this case, and hence Idenix Pharmaceuticals Inc. shall be liable for 5% of the costs, which amounts to a total of NOK 736,819.

The court fees shall be paid by those parties that did not prevail in the case, in accordance with an invoice to be issued by the Court.

In addition, those parties that did not prevail in the case are ordered to pay the costs associated with the expert lay judges, based on the same apportionment. The amount of the costs associated with the expert lay judges will be specified in a separate ruling.

The judgment is rendered unanimously.
CONCLUSION OF THE JUDGMENT

In Case 12-155575TVI-OTIR/01:

1. Norwegian patent NO 330 755 is declared invalid.

2. Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II are ordered to pay, jointly and severally, the legal costs of Gilead Sciences Europe Ltd. in the amount of 13,999,554 – thirteen million nine hundred and ninety nine thousand five hundred and fifty four – Norwegian kroner within 2 – two – weeks of service of the present judgment.

3. Idenix Pharmaceuticals Inc., Centre National de la Recherche Scientifique, Universita Degli Studi Di Cagliari and L'Université Montpellier II shall in addition pay, jointly and severally, the costs apportioned to Gilead Sciences Europe Ltd. in relation to the Court and the expert lay judges. The amount of these costs is to be specified in a separate ruling.

In Case 13-170456TVI-OTIR/01:

1. The Court finds in favour of Gilead Pharmasset LLC.

2. Idenix Pharmaceuticals Inc. is ordered to pay the legal costs of Gilead Pharmasset LLC in the amount of 736,819 – seven hundred and thirty six thousand eight hundred and nineteen – Norwegian kroner within 2 – two – weeks of service of the present judgment.

3. Idenix Pharmaceuticals Inc. shall in addition pay the costs apportioned to Gilead Pharmasset LLC in relation to the Court and the expert lay judges. The amount of these costs is to be specified in a separate ruling.

True translation certified.
2 April 2014

Knut Hogne Engedal
Government-authorised translator
English – Norwegian • Norwegian – English

IPO DELHI 07-08-20
Court adjourned

[Signature]
Inger Kjersti Dørstad
District Court Judge

[Signature]  [Signature]
Hans Einar Krokan  Jesper Wengel

Guidance notes on the right of appeal in civil actions are appended.
UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

JEREMY CLARK
Junior Party
(Application No. 11/854,218)

v.

RICHARD STORER, GILLES GOSELIN, JEAN-PIERRE SOMMAOSSI,
and PAOLA LACOLLA
Senior Party
(US 7,608,600 B2)

Interference No. 105,981 (JGN)
Technology Center 1600

Decision on Motions - Bd.R. 125

Before RICHARD E. SCHAFER, DEBORAH KATZ, and JOHN G. NEW,
Administrative Patent Judges.

NEW, Administrative Patent Judge.
I. INTRODUCTION

This interference is before a merits panel for a decision on non-priority motions. The interference involves Junior Party Jeremy Clark’s ("Clark") US Appl. No. 11/854,218 (the "218 application") and Senior Party Richard Storer, Gilles Gosselin, Jean-Pierre Sommadossi, and Paola LaColla’s ("Storer") US Patent 7,608,600 B2 (the "600 patent"). Declaration at 1. The subject matter of the interference is generally related to a method of using a class of 2'-fluoro, 2'-methyl (or halomethyl) nucleosides with a uracil or cytosine base for the treatment of a host infected with the hepatitis C virus ("HCV"). An important aspect of the nucleosides is the position of the fluorine moiety (F) in the "down" position as shown in the image below. Count 1 of the interference is Storer claim 1 or Clark claim 164 and recites:

1. A method for the treatment of a host infected with a hepatitis C virus, comprising administering to the host infected with a hepatitis C virus an effective amount of a compound having the formula:

![Nucleoside structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

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1 Paper No. 1
R¹ is H; mono-, di- or triphosphate; acyl; an amino acid ester; a carbohydrate; a peptide;
or a pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein R¹ is H or phosphate;
R² is H; acyl; an amino acid ester; a carbohydrate; a peptide; or a pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein R² is H;
Base* is selected from the group consisting of adenine, N⁶-alkylpurine, N⁶-acylpurine, N⁶-benzylpurine, N⁶-halopurine, N⁶-vinylpurine, N⁶-acetylenic purine, N⁶-acyl purine, N⁶-hydroxyalkyl purine, N⁶-alkylaminopurine, N⁶-thioalkyl purine, N²-alkylpurine, N²-alkyl-6-thiopurine, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, 6-azacytosine, 2- and/or 4-mercaptopurine, uracil, 5-halouracil, 5-fluorouracil, C⁵-alkylpyrimidine, C⁵-benzylpyrimidine, C⁵-halopyrimidine, C⁵-vinylpyrimidine, C⁵-acetylenic pyrimidine, C⁵-acyl pyrimidine, C⁵-hydroxyalkyl purine, C⁵-amidopyrimidine, C⁵-cyanopyrimidine, C⁵-iodopyrimidine, C⁶-iodo-pyrimidine, C⁵-Br-vinyl pyrimidine, C⁵-Br-vinyl pyrimidine, C⁵-nitropyrimidine, C⁶-amino-pyrimidine, N²-alkylpurine, N²-alkyl-6-thiopurine, 5-azacytidinyl, 5-azaurnacilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, guanine, hypoxanthine, 2,6-diaminopurine, and 6-choropurine;
R¹² is C(Y³); and
Y³ is independently H or F.
or

* Base
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1 164. A method for the treatment of hepatitis C infection, which
2 comprises:
3
4 administering to a mammal in need thereof an antivirally
effective amount of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl
5 nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the
6 structure:
7
8
9
10
11 wherein R¹ and R⁷ are independently H, a monophosphate, a
diphosphate, a triphosphate, a H-phosphonate, an alkyl, an alkyl
12 sulfonyl, or an arylalkyl sulfonyl; and
13
14
15 R⁴ is NH₂ or OH.
16
17 Declaration at 3.
18
19 Before us are the following motions:
20
21 1. Clark Substantive Motion ¹ to deprive Storer of the benefit of its US
22    Appl. No. 60/392,350.
23 2. Clark Substantive Motion ² to deprive Storer of the benefit accorded
   with respect to Count 1 of its U.S. Appl. No. 60/466,194.

² Paper No. 389
³ Paper No. 390
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3. Clark Substantive Motion 3\textsuperscript{4} to deprive Storer of the benefit accorded with respect to Count 1 of its U.S. Appl. No. 60/470,949.

4. Clark Substantive Motion 10\textsuperscript{5} to deprive Storer of the benefit accorded with respect to Count 1 of U.S. Appl. No. 10/6018,907.


6. Clark Substantive Motion 5\textsuperscript{7} to substitute Clark’s proposed count 2 or, alternatively, Clark’s proposed count 3, for Count 1.


8. Clark Substantive Motion 9\textsuperscript{9} for judgment against Storer’s US Patent No. 7,608,600 B2 on the ground of unpatentability under 35 U.S.C. §§ 102(e) or 103 as being either anticipated by, or obvious over, Clark’s US Appl. No. 10/828,753.

9. Clark Miscellaneous Motion 18\textsuperscript{10} to exclude evidence.

\textsuperscript{4} Paper No. 391
\textsuperscript{5} Paper No. 392
\textsuperscript{6} Paper No. 154
\textsuperscript{7} Paper No. 162
\textsuperscript{8} Paper No. 155
\textsuperscript{9} Paper No. 156
\textsuperscript{10} Paper No. 427
10. Storer Substantive Motion 5\textsuperscript{11} to substitute proposed count B for Count 1.

11. Storer Substantive Motion 11\textsuperscript{12} for judgment against Clark on the grounds of unpatentability of all of Clark's involved claims as anticipated under 35 U.S.C. § 102(e) and/or 103.

12. Storer Contingent Motion 14\textsuperscript{13} to add a new claim to the interference.

13. Storer Contingent Motion 15\textsuperscript{14} to add an application to the interference.

14. Storer Miscellaneous Motion 16\textsuperscript{15} to exclude evidence.

We address these motions in the order presented above.

\textsuperscript{11} Paper No. 157
\textsuperscript{12} Paper No. 158
\textsuperscript{13} Paper No. 327
\textsuperscript{14} Paper No. 328
\textsuperscript{15} Paper No. 425
II. CLARK MOTIONS

A. Clark Substantive Motion

Clark Substantive Motion 1 seeks to deny Storer benefit for Count 1 of its US Appl. No. 60/392,350, filed June 28, 2002 (the “S1” application) pursuant to 37 C.F.R. § 41.208(3). Clark Subs. Motion 1, Paper 389 at 1. As challenger of Storer’s accorded benefit, Clark must demonstrate that the S1 application does not constitute a constructive reduction to practice of Count 1. Bd.R. 42,201; SO ¶ 208.4.2. Clark argues that the S1 application does not describe, enable or provide a credible utility of any of the 2’-fluoro-2’-methyl nucleosides that constitute the subject matter of Count 1.

1. Enablement of the compounds of Count 1

The first paragraph of 35 U.S.C. § 112 requires that the specification of a patent must enable a person skilled in the art to make and use the claimed invention. In re Wands, 858 F.2d 731, 735 (Fed. Cir. 1988). However, a patent

\[\text{\footnotesize {\cite{Note1}}\text{In addition to Clark’s arguments set forth in the main body of this decision, Clark continues to argue that, despite the panel’s prior decision (see Paper No. 350), interference estoppel should apply in this interference and that the Board should therefore reject Storer’s attempts to argue issues that Storer raised, or could have raised, in the 871 interference: Motion at 8-9. Clark’s attention is directed to the Federal Circuit’s recent decision in AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc., 759 F.3d 1285, 1296-97 (Fed. Cir. 2014), holding that, because an interference action under 35 U.S.C. § 146 was pending in the district court, the Board’s decision lacked requisite finality for purposes of estoppel. We therefore decline to address this argument further.}}\]
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1 need not disclose what is already well known in the art at the time of invention.
2 See Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730
3 F.2d 1452, 1463 (Fed. Cir. 1984).
4 Clark seeks relief on the basis that Storer’s S1 application does not
5 constitute a constructive reduction to practice of the subject matter of Count 1, i.e.,
6 it does not include a described and enabled anticipatory embodiment that falls
7 within Count 1. Count 1 is recited supra, and relates to methods of treating HCV
8 infections with members of a genus of nucleosides, all of which possess a fluorine
9 atom at the “down” position of the 2’ carbon atom on the ribose ring. Both parties
10 agree that the S1 application provides no explicit disclosure or example of how
11 such an embodiment of Count 1 can be synthesized. See Clark Subs. Motion 1,
12 Paper 389 at 12; Storer Opp. 1, Paper 402 at 12; see also Ex. 1194, pp. 97-99, 101,
13 110, 121-122; 130. Failure to synthesize a single embodiment of the compounds
14 recited in Count 1 would effectively prevent practice of the methods recited in the
15 S1 application.
16 The question therefore devolves onto whether Clark, as challenger, can
17 show, by a preponderance of the evidence, that a person skilled in the art, upon
18 reading the Specification of the S1 application, and being knowledgeable
19 concerning the prior art in the field of nucleoside synthesis, would not have been
20 able to synthesize the 2’-fluoro (“down”) nucleosides of Count 1 without undue
21 experimentation. See Wands, 858 F.2d at 736-37; see also Alcon Research Ltd. v.
22 Barr Laboratories, Inc., 745 F.3d 1180, 1188 (Fed. Cir. 2014).
Whether synthesis would require undue experimentation is a "conclusion reached by weighing many factual considerations... includ[ing] (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims"). In re Wands, 858 F.2d 731, 737 (Fed.Cir. 1988).

With respect to the first Wands factor, the quantity of experimentation necessary for a skilled artisan to arrive at the invention, Clark argues that an artisan attempting to synthesize a compound recited in Count 1 would have been required to engage in an extensive and undue amount of experimentation. Clark Subs.


Clark points to the findings of the panel in the related 105,871 interference, which found that the Idenix team members had diligently attempted to make a 2'-fluoro-2'-methyl nucleoside as a high priority target for several years. Clark Subs.

Motion 1, Paper 389 at 11. Clark observes that, during this interval, the Idenix team members were employed as chemists, several of whom hold doctoral degrees, but were nevertheless uniformly unsuccessful in synthesizing the target nucleoside. Id. Furthermore, argues Clark, Idenix also consulted outside experts, including individuals to whom Dr. Richard Storer, one of the Senior Party, referred to as an "expert in organofluorine chemistry" and a "world expert in carbohydrate chemistry" for advice on how to make a 2'-fluoro-2'-methyl nucleoside. However,
argues Clark, Storer alleged it was successful only after Clark’s C2 application was
published and Idenix scientists followed a procedure described therein. Clark
Subs. Motion 1, Paper 389 at 15-16. Furthermore, argues Clark, documents
produced by Storer show that Idenix chemists and/or consultants tried or
considered trying numerous different fluorinating reagents when unsuccessfully
attempting to synthesize a 2’-fluoro-2’-methyl nucleoside during the interval 2002-

Clark rejects the argument of Storer, and its technical expert Dr. Masad J.
Damha,\textsuperscript{17} that one skilled in the art as of June 28, 2002 would “immediately see,”
based on the prior art, that the fluorinating reagent N, N-Diethylamino sulfur
trifluoride (Et$_2$NSF$_3$ or “DAST”) could be readily used to make a 2’-fluoro-2’-
methyl nucleoside from a nucleoside substituted at the 2’ position with a tertiary
alcohol (OH) because DAST was a well-known and predictable reagent for
fluorinating nucleosides, including those with tertiary alcohols at the 2’ position.

\textsuperscript{17} Storer’s expert witness is Dr. Masad J. Damha. Dr. Damha is currently James
McGill Professor of Chemistry at McGill University, Montreal, Canada, where he
has been a faculty member since 1992. Ex. 1132, ¶ 2. He has also received a
number of distinguished awards and is the author of approximately 150 papers and
book chapters in peer-reviewed journals, many of which address the synthesis of
nucleoside analogs. Id., ¶ 7. Dr. Damha has also consulted for pharmaceutical
companies in the United States and Canada and has presented lectures and
conference presentations at academia and industry on synthesis and applications of
nucleosides, oligonucleotides and their analogs. Id., ¶ 9. Upon review of his
curriculum vitae, we find that Dr. Damha is therefore qualified to opine as an
expert on the subject matter of this interference.
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20, ll. 11-3; Storer Contingent Responsive Motion 14, p. 18-19, ll. 6-16; Ex. 1132,18 ¶ 64, 69-76). Clark points out that Dr. Damha admitted, on cross-examination, that none of the references on which he relied for this contention actually show fluorination of a tertiary alcohol at a nucleoside’s 2’ position using DAST. Id. (citing Ex. 1194, p. 125, ll. 4-18; Ex. 2145,19 ¶ 96; Ex. 1148,20 pp. 10761-10770; Ex. 1160,21 pp. 65-96; Ex. 1161,22 pp. 574-578).

Storer argues that the S1 application provides precursor molecules and guidance that would have enabled one skilled in the art to synthesize a 2’-methyl (“up”) 2’-fluoro (“down”) nucleoside without undue experimentation. Storer Opp. 1, Paper 402 at 4-5. Storer points to compound 17 of Exhibit 1140, Akira Matsuda et al., Alkyl addition reaction of pyrimidine 2’-Ketonucleosides: Synthesis of 2’-Branched-Chain Sugar Pyrimidine Nucleosides (Nucleosides and Nucleotides, LXXX), 36(3) CHEM. PHARM. BULL. 945-953 (1988) (“Matsuda”). Storer contends that a skilled artisan would have recognized that compound 17 of Exhibit 1140 was a precursor to the claimed compound. Id. at 4-5 (citing Ex. 1200, ¶ 91; Ex. 2139, at 110-112, ll. 25-7; Ex. 1144, p 949; Ex. 2001, ¶ 323). Compound 17 of Matsuda is reproduced below:

18 Paper No. 679  
19 Paper No. 400  
20 Paper No. 345  
21 Paper No. 309  
22 Paper No. 310
Compound 17 of Matsuda depicts 2'-hydroxy-2'-methyl cytidine.

Storer argues that a skilled artisan, when looking at the structure of the claimed compound, would necessarily have recognized the need for a fluorinating reagent for synthesis and that replacement of a hydroxyl (OH) group with fluorine (deoxyfluorination) was a well-known organic transformation, as cited in such reference texts such as Richard C. Larock, **COMPREHENSIVE ORGANIC TRANSFORMATIONS: A GUIDE TO FUNCTIONAL GROUP PREPARATIONS** (2nd ed.) (1999) ("Larock 1999") (Ex. 1199). Storer Opp. 1, Paper 402 at 5 (citing Ex. 1200, ¶ 89; Ex. 2139, p. 100-101, ll. 22-15; Ex. 1248, p. 90, ll. 13-19, p. 91, ll. 14-21, Ex. 1200, ¶ 79; Ex. 2139, p. 127, ll. 4-7; Ex. 1199, at 689 to 690 (Chapter 8, "Halogenation of Alcohols").

Storer also points out that Larock teaches the use of DAST in the deoxyfluorination of a "variety of chemical compounds with success" and argues that, by 2002, DAST was known as "the most convenient and powerful reagent for deoxyfluorination" reactions. Storer Opp. 1, Paper 402 at 5-6 (citing Ex. 2014, p. 5-6) (citing Ex. 2014, p. 5-6) (citing Ex. 2014, p. 5-6).

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23 Paper No. 549
24 DAST is a nucleophilic fluorinating agent and acts by displacing the hydroxyl group and inverting the position of the methyl group. Thus, a 2'-hydroxy ("up") –
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259; Ex. 1200, ¶ 82; Ex. 1223,25 p. 2357; Ex. 2139, pp. 126-127, ll. 17-3).
Therefore, argues Storer, a skilled artisan would have appreciated that DAST could
have been used to transform the hydroxyl group of known nucleosides, such as
Matsuda Compound 17, into the 2′ ("down") fluorinated nucleosides recited in
Count 1. *Id.* at 6 (citing Ex. 1200, ¶ 85). Accordingly, contends Storer, the prior
art disclosed information that would have enabled a skilled artisan to synthesize a
2′-methyl ("up") 2′-fluoro ("down") nucleoside within the scope of Count 1. *Id.*
(citing Ex. 1200, ¶¶ 74-99).

By way of example, Storer points out that an Idenix scientist, Jingyang
Wang, synthesized the compound, using DAST, on her first attempt without the
benefit of Clark’s publication. Storer Opp. 1, Paper 402 at 6 (citing Ex 1232,26 ¶¶
17-20; Ex. 1233,27 p. 70, ll. 5-11; see also Ex. 123128). Storer argues that is also
informative that Clark, a chemist without a Ph.D., was allegedly able to make a 2′-
methyl (up)-2′-fluoro (down) nucleoside in just a few months using DAST. *Id.*
(citing Ex. 1246,29 p. 40, ll. 2-3; Ex. 1247,30 ¶¶ 32, 39, 41).

2′ methyl ("down") cyclic sugar may become a 2′-methyl ("up") -2′-fluoro
("down") cyclic sugar. See, e.g., Ex. 2014.
25 Paper No. 527
26 Paper No. 535
27 Paper No. 536
28 Paper No. 534
29 Paper No. 547
30 Paper No. 548
Consequently, argues Storer, the synthesis of a 2′-fluoro-2′-methyl nucleoside would not have required undue experimentation by one skilled in the art.

We find it informative that Idenix’s research team in Montpellier, France, repeatedly attempted without success to synthesize a 2′-methyl ("up") 2′-fluoro ("down") nucleoside during the interval between December, 2002 and September, 2004. See, generally, Exs. 2128; 2129. Regular progress reports and correspondence of the Montpellier team during this interval demonstrate that synthesis of a 2′-fluoro-2′-methyl nucleoside during this interval was considered to be a high-priority result. Exs. 2026-2044; see, e.g., Ex. 2037, p. 3 (report dated July, 31, 2003: stating that synthesis of a 2′-fluoro-2′-methyl nucleoside with the fluoro substituent in the "down" position "still a high priority").

During this interval, Idenix scientists also corresponded with consultants Dr. George Fleet and Dr. Paul Coe in an attempt to effect a synthesis of the desired compound. See, e.g., Ex. 203431 ("Prioritized Summary of Idenix Meeting with G.W. J. Fleet held on 10th May 2004"); Ex. 2038 (communication from Dr. Coe to Dr. Storer entitled "Thoughts on your synthesis problems"). Dr. Richard Storer, one of the inventors of the S1 application, describes Dr. Fleet as "an expert in carbohydrate chemistry" and "one of the best in the world" and describes Dr. Coe as "an expert in organofluorine chemistry." Ex. 213132, pp. 35, 74. Both consultants suggested possible schemes for the synthesis of a 2′-fluoro-2′-methyl nucleoside.

31 Paper No. 74
32 Paper No. 625
nucleoside with the fluorine substituent in the "down" position. Ex. 2034; Ex. 2038. In the latter communication, Dr. Coe related that:

[In our experience and indeed in that of manner [sic] other[,] particularly the de-Clerc group[,] the most viable routes to fluoro nucleosides are by sugar/base condensation methods the anomer problem notwithstanding, for the very reasons you have discovered, in that leaving groups generated in situ[,] e.g.[,] in DAST reactions are readily attacked by the pyrimidine ring nucleophiles or elimination and/or participation of the blocking groups. Further migrations of groups can readily occur.

Ex. 2038, p. 1.

Idenix personnel also attended a "Scientific Update Course" entitled "Making and Using Fluoroorganic Molecules" in April, 2003, and submitted a report summarizing the course content. Ex. 2039.

Nevertheless, despite these consultations, the Montpellier team was never able to successfully synthesize a 2'-fluoro-2'-methyl nucleoside with the fluorine substituent in the "down" position. Dr. Jean-François Griffon,33 leader of the Montpellier group, testified that he attempted at least seven different synthetic schemes, including several suggested by Dr. Coe, and in some cases employing DAST, without success. Ex. 2128, ¶¶ 8-64; Ex. 2132, p. 57. As Dr. Griffon reported in an email to Dr. Storer on March 4, 2003: "As I told you last week at the end of the Summary Meeting, the compound I obtained after treatment with

33 By the standard we determined infra, we find that Dr. Griffon qualifies as a person skilled in the art. See Ex. 2152 (Paper No. 542).
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1 DeoxoFluor\textsuperscript{34} and deprotection was not the (very!) expected Fluoro derivative but
2 the 2'-methylene derivative.\textsuperscript{7} Ex. 2029, p. 1. A diagram in the accompanying
3 report documents the failure of this synthetic scheme, the end product having a 2'-
4 methylene group rather than the desired 2'-methyl-2'-fluoro groups:

5 \begin{center}
6 Illustration from Ex. 2029 indicating synthesis of an undesired 2'-methylene
7 nucleoside (6b) rather than a 2'-(down) fluorination (6a).
8
9 \textit{Id.}, p. 3
10 \end{center}

Furthermore, attempts by the Montpellier team to use DAST in the synthesis
of a 2'-fluoro-2'-methyl nucleoside produced similar failures, as this diagram from
an Idenix summary of results indicates:

\textsuperscript{34} Deoxo-Fluor\textcopyright is, like DAST, a nucleophilic organic fluorinating agent. \textit{See},
e.g., R.P. Singh and M.S. Jean'ne, \textit{Recent advances in nucleophilic fluorination
reactions of organic compounds using deoxofluor and DAST}, 17 SYNTHESIS 2561-
2578 (2002).
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Uracil Nucleosides

Illustration from Ex. 2041 indicating synthesis of an undesired 2'-methylene nucleoside via DAST reaction.

Ex. 2041, p. 2. The difficulties experienced by Idenix in synthesizing a 2'-fluoro-2'-methyl nucleoside are expressed in a November 11, 2014 email from Dr. Storer stating: __

When we get this information together we'll decide what, if anything, we will do in house and how it it [sic] fits with what anyone else knows. A lot of things which look simple on paper in related systems have been tried and don't work in this series. Having to make the tertiary fluoride is very different to having to make a secondary.

Ex. 2044, p. 1 (emphasis added).

With respect to the testimony of Jingyang Wang who allegedly synthesized the desired compound in a single attempt in January, 2015, at Idenix's research facility in Cambridge, Massachusetts, we note that, prior to beginning her synthesis, Ms. Wang had received the reports from the Montpellier group as well as intermediate compositions synthesized at Montpellier. Ex. 1233, pp. 99-101.

Consequently, Ms. Wang was not, as Storer seems to suggest, attempting synthesis of a 2'-fluoro-2'-methyl nucleoside *ab initio*, but rather had the hindsight benefit of the Montpellier group's efforts. *Id.*
Similarly, Storer’s expert, Dr. Damha, points in his Declaration to what he
terms Scheme A, of which the first step is disclosed by the S1 application. Ex.
1132, ¶ 67; see also Ex. 1003, p. 120. Scheme A of Dr. Damha’s declaration is
reproduced below:

Scheme A

Scheme A shows a sequence of two steps by which a 2' -keto group is
replaced by a 2'-hydroxyl (up) - 2' -methyl (down) nucleoside which
is in turn replaced by DAST with a
2'-methyl (up)-2'-fluoro (down) nucleoside.

Ex. 1132, ¶ 67. The intermediate form 2 in Scheme A also corresponds to Matsuda
compound 17. Id., ¶ 69, fn. 5. According to Dr. Damha:

A person skilled in the art as of June 28, 2002 could therefore simply
look at the 2'-F-2'-methyl-ribonucleoside species disclosed in the
'350 Application, and synthesize it without undue experimentation
using: (i) the starting materials and reagents disclosed in the '350
Application and known in the art [i.e., Matsuda compound 17], and
(ii) the then-existing routine DAST chemistry. It is well known that all
organic reactions produce by-product(s). As of June 28, 2002, it
would not have been a surprise to a person skilled in the art that
DAST fluorination might lead to elimination, rearrangement, or other
by-products. However, just like all other organic reactions, the DAST
fluorination does not need to be perfect to be useful in organic
synthesis, as separation and purification techniques were well-known
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Id., ¶ 76. However, Dr. Damha’s opinion is not borne out by the fact that this very
reaction was attempted by the Montpellier group and was not successful: attempts
to fluorinate compound 17 with DAST yielded a 2’-methylene nucleoside. See Ex.
2041, p. 2. Such a result is supported by Dr. Coe’s suggestion that “leaving groups
generated in … DAST reactions are readily attacked by the pyrimidine ring
nucleophiles or elimination and/or participation of the blocking groups.” Ex. 2038,
p. 1. The use of other fluorinating agents yielded similarly unsuccessful results.
See, e.g., Ex. 2029, p. 3 (using DeoxoFluor® as the fluorinating agent).

We therefore find, based upon the proffered evidence, that a high amount of
experimentation is necessary to synthesize a 2’-fluoro-2’-methyl nucleoside with
the fluoro moiety in the “down” position requiring at least two years of a high
priority experimentation by persons skilled in the art, including multiple
consultations with experts at the top of their fields and additional formal training.

With respect to the second Wands factor, the amount of direction or
guidance presented, Clark argues, and Storer does not contest, that the S1
application provides no explicit explanation or example describing synthesis of a
2’-fluoro “down” nucleoside as embodied in Count 1. See Clark Subs. Motion 1,
Paper 389 12; Storer Opp. 1, Paper 402 at 12. Clark also argues that no synthesis
of a 2’-fluoro-2’-C(H/F), nucleoside, including any 2’-fluoro-2’-methyl
nucleoside, had been reported in the available art as of the S1 application’s June
28, 2002 filing date. Clark Subs. Motion 1, Paper 389 at 9 (citing Ex. 2001, ¶¶
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1. 137, 231; Ex. 2005, p. 22, ll. 4-8; Ex. 1194, 35 p. 91, ll. 12-16). Rather, argues
3. published on January 13, 2005 (subsequent to the S1 application’s June 28, 2002
4. filing date), was the first reported synthesis of a 2′-fluoro-2′-methyl nucleoside, an
5. embodiment of Count 1. Id. at 9-10 (citing Ex. 2001, ¶¶ 137, 162; Ex. 2003; ¶¶
6. 221, 222; Ex. 2005, p. 22, ll. 4-8; Ex. 2013, 36 cover page (item 43), ¶ [0294]-
7. [0035]).
8. Furthermore, argues Clark, the S1 application’s failure to disclose any
9. specific starting materials or conditions under which such a compound could be
10. made cannot be rectified by reliance on the prior art for all of the required
11. teachings. Id. (citing Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1366
12. (Fed. Cir. 1997); also citing Ex 2005, pp. 24-25, ll. 13-10, 26, ll. 2-5). Clark
13. contends that Storer and its expert, Dr. Damha, argue that the S1 application
14. discloses “starting materials” and reagents (e.g., methyl lithium) for making 2′-
15. fluoro-2′-methyl nucleosides, and that an artisan purportedly would have
16. “immediately identified” operative methods for making such compounds by
17. reacting DAST with a 2′-methyl-2′-hydroxy nucleoside. Clark Subs. Motion 1,
19. However, Clark relates, Dr. Damha, on cross-examination, admitted that: (1)
20. no such methods are found in the S1 application; (2) the S1 application does not
21. discuss any fluorinating reagents, including DAST; (3) the S1 application does not

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1 disclose intermediate Compound 2 and final Compound 3 shown in Dr. Damha's
2 "Scheme A’; (4) nothing in Scheme 4 of the S1 application suggests isolating the
3 intermediate Compound 2 needed for the Damha "Scheme A" route, which has a
4 methyl group “down” and a hydroxyl group “up” at the 2’ position (the opposite 2’
5 stereochemistry from the compounds in Scheme 4); and (5) contrary to his
6 declaration, the S1 application does not “explicitly disclose” the reagent methyl
7 lithium. Clark Subs. Motion 1, Paper 389 at 14 (citing Ex. 1194, pp. 97, ll. 5-8, 98,
8 ll. 11-17, 98-99, ll. 22-17, 101, ll. 15-16, 110, ll. 14-24, 121-122, ll. 19-11, 130, ll.
9 7-16).

10 Clark also argues that Dr. Damha’s opinion relies on references not
11 mentioned in the S1 application, and he did not consider whether the S1
12 application would have guided an artisan to such literature. Clark Subs. Motion 1,
13 Paper 389 at 14 (citing Ex. 1194, pp. 102, ll. 12-17, 133-135, ll. 24-2).
14 Storer responds that the S1 application provides adequate guidance for
15 synthesizing compounds within Count 1. Storer Opp. 1, Paper 402 at 9-10. Storer
16 argues that the fluorination reagent DAST was known to the skilled artisan for
17 substituting fluorine for a hydroxyl group with inversion. Id. at 10. Therefore,
18 argues Storer, recognizing that inversion will occur, a skilled artisan would have
19 known to start with a nucleoside having a similar structure to that defined by Count
20 1, but with a 2’-OH (up) group, in order to obtain the desired 2’-F (down) structure
21 of the compounds within Count 1. Id. at 12. (citing Ex. 1200, ¶ 90).
Storer points out that Clark’s expert, Dr. Stanislaus Wnuk, agreed that a skilled artisan would have recognized Matsuda Compound 17 as a potential precursor to the subject matter of count 1, which is depicted at paragraph 323 of his Declaration. Storer Opp. 1, Paper 402 at 12 (citing Ex. 2001). Storer points out that Matsuda Compound 17 differs from the claimed compound in that the configuration at the 2’-position is inverted with a 2’-OH (up) instead of a 2’-fluoro (down). Id. at 12-13 (citing Ex. 1200, ¶92; Ex. 2139, pp. 107-108, ll. 18-6).

Further, alleges Storer, both parties’ experts agree that the synthesis of the compound of Count 1 would have been essentially a one-step reaction of Matsuda Compound 17 with DAST. Id. at 13 (citing Ex. 1200, ¶94; Ex. 2139, p. 156, ll. 2-12). Store contends that the synthesis of Matsuda Compound 17 is the same as the product of the first steps of Scheme 4 of the S1 application which is reproduced, in part, below:

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37 Clark’s expert witness, Dr. Stanislaus F. Wnuk received his Ph.D. in organic chemistry from Adam Mickiewicz University in Poznan, Poland in 1983 and is currently Professor of Chemistry at Florida International University, a position he has held since 1997. Ex. 2001, ¶¶8-9. He is the author of over 120 publications, more than 80 of which pertain to nucleosides or nucleotides, with approximately 30 of those relating to fluorinated nucleosides or nucleotides. Id., ¶12. He has also received a number of research and teaching awards. Id., ¶11. Upon review of his curriculum vitae, we find that Dr. Wnuk is sufficiently qualified as an expert to opine on the synthesis of fluorinated nucleosides.
The initial reaction steps of Scheme 4 depicts synthesis of Compound 17 of Matsuda, where R^6 is methyl, R^1 and R^2 are protective groups, and the base is uracil.

Id. (citing Ex 1132, ¶¶ 65, 66; Ex. 1003, p. 120). Storer points out that the intermediate compound (2′-keto) of Scheme 4 is the starting material of Matsuda Compound 17, wherein R^1 and R^2 form protecting groups and the Base is uracil.

Id. (citing Ex. 1132, ¶¶ 65-66; Ex. 1003, p. 120; Ex 1144, pp. 945-953).

As such, contends Storer, the specification of the S1 application teaches the starting materials and methods for making Matsuda Compound 17, which is a precursor to the claimed compound. Storer Opp. 1, Paper 402 at 13. Storer concludes that the S1 application therefore provides a skilled artisan with the starting materials and guidance for making the compounds within Count 1 without undue experimentation. Id. (citing Ex. 1200, ¶ 97).

We agree with Clark that the S1 application provides no explicit explanation or guidance as to how to synthesize a 2′-flouro “down” nucleoside as embodied in Count 1. Moreover, we have related supra how the Idenix team identified such a molecule as a high-priority target, but failed to synthesize such a compound for approximately two years subsequent to the submission of the S1 application.

Moreover, we have related how the Idenix team attempted the very syntheses that
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1 Storer's expert Dr. Damha states would be suggested by the disclosures of the S1 document, but were unable to successfully synthesize the target molecule. We therefore find that the S1 application provides little in the way of direction or guidance as to how to synthesize a 2'-fluoro-2'-methyl nucleoside with the fluoro moiety in the "down" position.

6 The third Wands factor enquires into the presence or absence of working examples of the invention. It is uncontested by the parties that there were no examples of such a molecule reported in the art prior to submission of the S1 application. Clark Subs. Motion 1, Paper 389 at 9. Clark contends, and Storer does not contest, that the S1 application lacks a single, specific example teaching how to synthesize any nucleoside having a fluorine atom substituent on the ribose ring. Clark Subs. Motion 1, Paper 389 at 12-13 (citing Ex. 2001, ¶¶ 138, 186, 202, 214, 230, 249; Ex. 2049, pp. 1-5297, ll. 1-21, Figs. 1-4). Additionally, argues Clark, the S1 application lacks any working example that an artisan could have modified, without extensive experimentation, to make a compound falling within either of Count 1's chemical formulae. Id. at 13 (Ex. 2001, ¶¶ 138-141, 186, 202, 214, 229, 230, 235, 248, 249; Ex. 2049, pp. 1, ll.1-5297, Figs. 1-4; Ex. 2005, pp. 23-24, ll. 18-3).

With respect to the fourth Wands factor, the nature of the invention, Clark contends that Count 1 is directed to methods for treating HCV infection using certain 2'-fluoro-2'-C(H/F)3 nucleosides, including certain 2'-fluoro-2'-methyl nucleosides. Clark Sübs. Motion 1, Paper 389 at 9 (citing Ex. 2001, ¶¶ 45-50; Ex. 2049, pp. 1-5297, ll. 1-21, Figs. 1-4).
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2003, 38 ¶ 26, 28, 31-33, 40-42; Ex 2012, 39 p. 2:8-17; Ex. 2098, 40 col. 2221, ll. 9-52). According to Clark, because such compounds were not commercially available as of June 28, 2002, it would have been necessary for an artisan to make a compound falling within one of Count 1's chemical formulae. Id. (citing Ex. 2001, ¶ 136; Ex. 2005, p. 20, ll. 23-26).

Storer does not contest Clark's characterization of the nature of the invention, but responds that the nature of the invention is such as to require a high level of skill in the art, so much so that a skilled artisan would have been familiar with the methods for synthesizing nucleosides of the type within Count 1.

We find that the nature of the invention, as recite in Count 1 is best characterized as the administration of a genus of nucleosides used in the treatment of viruses, particularly those of the family Flaviviridae (which includes HBV and HCV41). We also find that, as of the time of filing of the S1 application, although organic fluoridation mechanisms were generally well-known in the art a 2'-fluoro-2'-methyl nucleoside with the fluoro substituent in the "down" position had not yet been synthesized.

With respect to the fifth Wands factor, the state of the prior art, Clark argues that no synthesis of a 2'-fluoro-2'-C(H/F), nucleoside, including any 2'-fluoro-2'-methyl nucleoside, had been reported in the available art as of S1’s June 28, 2002 filing date. Clark Subs. Motion 1, Paper 389 at 9 (Ex. 2001, ¶¶ 137, 231; Ex.

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38 Paper No. 47
39 Paper No. 55
40 Paper No. 137
41 See, e.g., Clark Subs. Motion 1, Paper 398 at 2

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2005, p. 22, II. 4-8; Ex. 1194,42 p. 91, II. 12-16). Rather, argues Clark, its US Appl. Pub. No. 2005/0009737 A1 (the "C2 application"), published on January 13, 2005 (subsequent to the S1 application's June 28, 2002 filing date), was the first reported synthesis of a 2'-fluoro-2'-methyl nucleoside. Id. at 9-10 (citing Ex. 2001, ¶¶ 137, 162; Ex. 2003, ¶¶ 221, 222; Ex. 2005, p. 22, II. 4-8; Ex. 2013,43 cover page (item 43), ¶ [0294]-[0035]). Storer argues that the specification of the S1 application, when viewed in light of the prior art, discloses sufficient information to enable a skilled artisan to synthesize a 2'-methyl (up)-2'-F (down) nucleoside without undue experimentation. Storer Opp. 1, Paper 402 at 4. According to Storer, and as argued supra, a skilled artisan would have readily recognized that a well-known precursor to the nucleoside, such as Matsuda Compound 17, could have been transformed in a single step to a nucleoside within the scope of the count. Id. (citing Ex. 1132, ¶ 25; Ex. 1144,44 p. 949; Ex 1115,45 pp. 40-45). Storer argues that compounds that were one reaction step away from the compounds of Count 1, such as 2'-methyl (down)-2'-OH (up) nucleosides, were well known by June 2002. Id. (citing Ex. 1132, ¶ 25; Ex. 1144, p. 949; Ex. 1115, pp. 40-45).

Reviewing the evidence before us, we find, with respect to the prior art, that certain methods of organic fluoridation were well-known at the time of invention, but that synthesis of a 2'-fluoro-2'-methyl nucleoside had not yet been reported in

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43 Paper No. 56
44 Paper No. 293
45 Paper No. 269

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The prior art. See Ex. 1132, ¶ 33. The fluorinating agent DAST was well-known in
the prior art to be useful in the fluorination of nucleosides and nucleoside analogs.
For example, Johanna Wachtmeister et al., *Synthesis of 4-substituted carbocyclic
2,3-dideoxy-3-C-hydroxymethyl nucleoside analogues as potential anti-viral
agents*, 55 *TETRAHEDRON* 10761 (1999) ("Wachtmeister") teaches the use of
DAST in the fluoridation of certain carbocyclic nucleoside analogs in which the
oxygen in the five-member ribose ring is replaced with a carbon atom and
fluoridation takes place at the C-4 position. Ex. 1148, p. 10763. Similarly, P.
Herdewijn et al., *Synthesis of nucleosides fluorinated in the sugar moiety. The
application of diethylaminosulfur trifluoride to the synthesis of fluorinated
nucleosides*, 8(1) *NUCLEOSIDES AND NUCLEOTIDES* 65 (1989) ("Herdewijn")
teaches using DAST for, *inter alia*, fluoridation of nucleosides at the 2'-position.
Ex. 1160, pp. 65-96. A. Van Aerschot et al., *2',3'-difluoro- and 3'-azido-2'-fluoro
substituted dideoxypyrimidines as potential anti-HIV agents*, 98(12) *BULL. SOC.
CHIM. BELG.* 937 (1989) ("Van Aerschot") teaches the use of DAST to produce
various 2'-fluoro-nucleoside analogs. Ex. 1151, 46 pp. 938-941. Hiroyuki
Hayakawa et al., *Diethylaminosulfur trifluoride (DAST) as a fluorinating agent of
pyrimidine nucleosides having a 2',3'-vicinal diol system*, 38(5) *CHEM. PHARM.
BULL.* 1136 (1990) ("Hayakawa") teaches that although "participation of the base
moiety often thwarts the desired introduction of a fluorine atom ... appropriate
modification of the base and/or sugar moieties allowed the desired
fluorodehydroxilation to occur, giving 5'-, 3'-β, and 2'-α-fluorinated

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uracil nucleosides in good yields." Ex. 1152, p. 1136. Consequently, we find that
it was well-known in the prior art that DAST could be employed in the 2′-flouridation of nucleosides and nucleoside analogs.

Dr. Damha cites these prior art references, among others, as demonstrating
that:
The fluorinating reagent, DAST, may be used to prepare a 2′-F-ribonucleoside in a single step from an "arabinonucleoside" (compound 2 of Scheme A, above). As of June 28, 2002, DAST had routinely been used in the nucleoside field to install a fluoro group at the 2′-position of nucleosides, often with an unprotected nucleobase, in a single step under very mild conditions.

Ex. 1132, ¶ 71: However, Dr. Damha admits that none of these references teaches using DAST to convert a tertiary alcohol at a nucleoside 2′ position to a tertiary fluoride at the nucleoside 2′ position:

Q. [Ms. Austin] I just want to make sure the record is clear. So just maybe a yes or a no, did any of these references describe using DAST to convert a tertiary alcohol at a nucleoside 2′ position to a tertiary fluoride at the nucleoside 2′ position?

A. [Dr. Damha] No.

Ex. 1194, p. 125. And Dr. Wnuk opined in response that "I believe it is an oversimplification to assert that, because DAST had been used to fluorinate certain
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...secondary and tertiary alcohols with inversion of stereochemistry, it was therefore well-known that it would react similarly with significantly different substrates." Ex. 2145, ¶ 96.

We consequently find, with respect to the fifth Wands factor, that although DAST was well-known in the prior art as fluoridating agent for nucleosides and nucleoside analogs, the prior art did not teach, or explicitly suggest, the use of DAST in the fluoridation of a tertiary alcohol to convert a tertiary alcohol at a nucleoside 2' position to a tertiary fluorine at the nucleoside 2' "down" position.

We further find that, although organic fluoridation techniques were well-known in the art at the time the S1 application was filed, fluoridation of tertiary alcohols to produce a 2' "down" tertiary fluorine was not taught or suggested by the prior art.

The sixth Wands factor is the relative level of skill of those in the art. The parties largely agree that the level of skill in the art is very high and on the

47 In a secondary alcohol, the carbon atom binding the hydroxyl group is attached directly to two alkyl groups, which may be the same or different. In a tertiary alcohol, the carbon atom binding the hydroxyl group is attached directly to three alkyl groups, any combination of same or different. By way of example, Matsuda compound 17:

![Matsuda compound 17](image)

is a tertiary alcohol because the 2' carbon binding the hydroxyl group is bound to three carbons: the 1' and 3' ring carbons and the carbon of the methyl (Me) group.
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qualifications of a person of ordinary skill. See Ex. 1132, ¶ 14; Ex. 2001, ¶¶ 60-61.
We therefore find that a person possessing the ordinary level of skill in this art, as
of the time of invention, would hold a doctoral degree in the field of organic,
synthetic, or medicinal chemistry with at least a year's experience in the field of
nucleoside synthesis or relevant drug discovery. Alternatively, that artisan could
hold a master's degree in one of those same fields with at least three years of
practical experience in the field of nucleoside synthesis or relevant drug discovery.

With respect to the seventh Wands factor, the predictability or
unpredictability of the art, Clark argues that the fluorination chemistry involved in
attempting to synthesize 2'-fluoro ("down") 2'-C(H/F), ("up") nucleosides was
unpredictable at the time of Idenix's attempts to do so, because there was no
precedent in the literature for making such a substitution on tertiary carbons of the
ribose ring. Clark Subs. Motion 1, Paper 389 at 12 (citing Ex. 2001, ¶¶ 154-159,
231; Ex. 2005, p. 22, ll. 12-17, Ex. 2007, pp. 19, ll. 4-12, 22, ll. 5-18; Ex. 2022,48
pp. 65-96; Ex. 2023,49 pp. 574-78; Ex. 2024,50 pp. 2315-16; Ex. 2025,51 pp. 251-
54; Ex. 1194, pp. 91, ll. 12-16, 92, ll. 3-93:18, 125, ll. 4-18). Clark maintains that
the prior art demonstrated that attempted fluorination reactions (including those
involving DAST) could fail, resulting in unfluorinated elimination and/or
rearrangement products, or products with incorrect stereochemistry. Id. (citing Ex.

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49 Paper No. 63
50 Paper No. 64
51 Paper No. 65

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1. 2001, ¶ 156, 231; Ex. 2014, 52 p. 259, ll. 15-20; Ex. 2015, 53 pp. 7570-7571, ll. 18-4; Ex. 2016, 54 pp. 2563 (left col, ll. 11-14, Scheme 5), 2564 (Scheme 9); Ex. 2017, 55 pp. 1090-91; Ex. 2018, 56 pp. 554-55; Ex. 2139, 57 pp. 156-157, ll. 15-3).

Clark argues further that the documents that produced by Storer in the related 105,871 Interference demonstrate that DAST treatment of tertiary and secondary alcohols failed to produce fluorinated products. Clark points out that Dr. Paul Coe, an expert in organofluorines expressed skepticism regarding the use of DAST; and Dr. Richard Storer stated that “[a] lot of things which look simple on paper in related systems have been tried and don’t work in this series. Having to make the tertiary fluoride is very different to [sic] having to make secondary.”

Id. (citing Ex. 2001, ¶ 157, 158, 174; Ex. 2007, pp. 15-17, ll. 15-2; 20, ll. 3-8; Ex. 2029, p. 2 (numbered p. 1); Ex. 2035, p. 3 (numbered p. 2); Ex. 2038, pp. 1-3, 5-10; Ex. 2041, 58 p. 1; Ex. 2042, 59 p. 1; Ex. 2043, 60 pp. 38, 40; Ex. 2044, 61 p. 1; Ex. 2139, pp. 146, ll. 9-22, 147, ll. 14-23).

Storer responds that deoxyfluorination with DAST was highly predictable. Storer Opp. 1, Paper 402 at 7 (citing Ex. 1200, ¶¶ 100-131). According to Storer, 52 Paper No. 57
53 Paper No. 58
54 Paper No. 59
55 Paper No. 60
56 Paper No. 61
57 Paper No. 368
58 Paper No. 81
59 Paper No. 82
60 Paper No. 83
61 Paper No. 84
the references that Clark and its expert, Dr. Wnuk, rely on in support of their argument that fluorination with DAST was unpredictable are Exhibit 2018, Krzysztof W. Pankiewicz et al., A synthesis of 9-(2-deoxy-2-fluoro-β-D- arabinofuranosyl) adenine and hypoxanthine. An effect of C3'-endo to C2'-endo conformational shift on the reaction course of 2'-hydroxyl group with DAST, 57 J. Org. Chem. 553-59 (1992) ("Pankiewicz") and Exhibit 1152, Hiroyuki Hayakawa et al., Diethylaminosulfur trifluoride (DAST) as a fluoridating agent of pyrimidine nucleosides having a 2',3'-vicinal diol system, (38(5) Chem. Pharm Bull. 1136-39 (1990) ("Hayakawa"). Storer argues that Clark relies upon these references to demonstrate that using DAST in the preparation of fluorinated nucleosides may result in a "rearrangement product" and an "unfluorinated 2'-cyclo derivative." Id. (citing Storer Motion 1, p. 12, ll. 6-11; Ex. 2001, ¶ 156; Ex. 2145, ¶ 98). However, argues Storer, both Pankiewicz and Hayakawa teach that DAST deoxyfluorination of a nucleoside with a 2'-OH (up) proceeded with inversion to form a nucleoside with a 2'-F (down) in over 80% yields without any alleged rearrangement or unfluorinated products reported. Id. (citing Ex. 1152, p. 1139; Ex. 2018, p. 559; Ex. 2139, p. 149-150, ll. 10-11. Ex. 1248, p. 87, ll. 2-11).

Storer also disputes that Exhibit 2015 teaches that fluorination with DAST may proceed with double inversion resulting in a "product with unexpected stereochemistry" as Clark and its expert suggest. Storer Opp. 1, Paper 402 at 8 (citing Clark Motion 1, p 12, ll. 6-11; Ex. 2001, ¶ 156). Exhibit 2015 is Lak S.

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62 Paper No. 61
63 Paper No. 301
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1 Jeong et al., *Unanticipated retention of configuration in the DAST fluorination of Deoxy-4'-thiopyrimidine nucleosides with “up” hydroxyl groups*, 35(41)

2 *TETRAHEDRON LETTERS*, 7569-72 (1994) (“Jeong”). According to Storer, the title of the article explains that the double inversion was not the norm. *Id.* According to Storer, Jeong teaches that the double inversion was a result of the sulfur atom in the thiofuranose ring, which is not present in the compounds of Count 1. *Id.*

(citing Ex. 2139, p. 136, ll. 8-12).

8 Storer also points to Exhibits 2014, 2016, and 2017, which Clark and its expert rely upon to argue that deoxyfluorination with DAST may result in an “unfluorinated dehydration product,” a “rearrangement product,” or an “elimination product.” Storer Opp. 1, Paper 402 at 9 (citing Storer Motion 1, p. 12, ll. 6-11; Ex. 2001, ¶ 156). According to Storer, none of the DAST reactions relied upon by Clark was performed on a nucleoside. *Id.* Nevertheless, argues Storer, Exhibit 2014 teaches that “diethylaminosulfur trifluoride (DAST) appears to be the most convenient and powerful reagent for deoxyfluorination,” and Exhibit 2016 teaches that “Deoxy-Fluor ... and DAST ... are widely used in one-step reactions for the introduction of fluorine into organic compounds.” *Id.* (quoting Ex. 2014, p. 259; Ex. 2016, p. 2561). Moreover, argues Storer, Dr. Wnuk agreed that the latter statement describes the state of the art for fluorination in 2002. *Id.* (citing Ex. 2139, p. 139, ll. 13-21).

Having reviewed the parties’ arguments, and the proffered evidence, we find that the art, with respect to fluoridation of tertiary alcohols, was highly unpredictable, as evidenced by Idenix’s repeatedly unsuccessful attempts to
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synthesize its high-priority target nucleoside, and as further evinced by the
statements of Dr. Coe and Dr. Storer. See Ex. 2038, p. 1; Ex. 2044, p. 1.

In summary, having reviewed the Wands factors argued by the parties,64 we
find that (1) synthesis of a 2'-fluoro-2’-methyl nucleoside with the fluoro moiety in
the “down” position required at least two years of a high-priority experimentation
by persons skilled in the art, including multiple consultations with experts at the
top of their fields and additional formal training; (2) the S1 application provides
little in the way of direction or guidance as to how to synthesize such a compound;
(3) the S1 application provides no explicit example of a 2’-fluoro-2’-methyl
nucleoside, nor was an example provided by the relevant art as of the S1
application’s filing date; (4) the invention is characterized as the administration of
a genus of nucleosides used in the treatment of viruses, particularly those of the
family Flaviviridae (which includes HBV and HCV) and an embodiment of the
count requires a 2’-fluoro (“down”) 2’-methyl nucleoside; (5) although organic
fluoridation techniques were well-known in the art at the time the S1 application
was filed, fluoridation of tertiary alcohols to produce a 2’ “down” tertiary fluorine
was not taught or suggested by the prior art; (6) the level of skill in the art was
highly sophisticated: a person possessing the ordinary level of skill in this art, as of
the time of invention, would hold a doctoral degree in the field of organic,
synthetic, or medicinal chemistry with at least a year’s experience in the field of
nucleoside synthesis or relevant drug discovery; and (7) the art, at least with
respect to fluoridation of tertiary alcohols to produce a tertiary fluorine in the 2’

64 Neither party argued the eighth Wands factor, the breadth of the claims.
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"down" position, was highly unpredictable. We therefore find that Wands factors 1, 2, 3, 5, and 7 strongly indicate that a person skilled in the art would not arrive at the claimed invention without undue experimentation. We therefore conclude that the S1 application does not enable any species of Count 1, all of which require a fluorine atom in the 2'-"down" position.

A party is accorded benefit of the date of an earlier application if its earlier application constitutes a constructive reduction to practice of the count. Bd.R. 41.201. Clark, as the party challenging Storer's accorded benefit of the S1 application, must therefore demonstrate that the S1 application does not provide a constructive reduction to practice of Count 1. SO ¶ 208.4.2. Constructive reduction to practice means a described and enabled anticipation under 35 U.S.C. 102(g)(1) in a patent application of the subject matter of Count 1. Bd.R. 41.201.

Thus, even if the S1 application does not describe and enable the full scope of Count 1, Storer cannot be deprived of the filing date of the S1 application if the S1 application describes a single embodiment or species that meets all of Count 1's limitations.

Neither party disputes that all of the species of the genus contemplated within the scope of Count 1 require a fluorine atom in the "down" position and a C(H/F)₃ moiety in the "up" position at the 2'-carbon of the sugar ring. We have found that the analysis of the factors set forth in Wands compel the conclusion that, at the time the S1 application was filed, a person skilled in the art would not have been able to synthesize any of the 2'-fluoro ("down") nucleosides of Count 1 without undue experimentation. We therefore conclude that the S1 application
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1 does not enable a single species of Count 1 and, consequently, the S1 application is
2 not a constructive reduction to practice of Count 1. Because we find this issue to
3 be dispositive of the motion, we do not reach Clark’s other arguments. Clark
4 Substantive Motion 1 to deny Storer the accorded benefit of its S1 application is
5 granted.
6
7 B. Clark Substantive Motions 2 and 3
8 Clark Substantive Motion 2 seeks to deprive Storer of the benefit accorded
9 with respect to Count 1 of its U.S. Appl. No. 60/466,194 (the “S2 application”) 
11 Motion 3 seeks to deprive Storer of the benefit accorded with respect to Count 1 of
12 its US Appl. No. 60/470,949 (the “S3 application”) filed May 14, 2003. Clark
13 Subs. Motion 3, Paper 391 at 1.
14 Clark argues that although Storer was accorded benefit of the S2 and S3
15 applications when the present interference was declared, Storer has not relied upon
16 either in any of its motions in the present interference. Clark Subs. Motion 2,
17 Paper 390 at 9; Clark Substantive Motion 3, Paper 391 at 9. According to Clark,
18 that constitutes an admission by Storer that the S2 and S3 applications are
19 unrelated to the subject matter in dispute between the parties. Clark Subs. Motion
20 2, Paper 390 at 9; Clark Substantive Motion 3, Paper 391 at 9.
21 Clark argues that Count 1 of the interference pertains to a method for
22 treating HCV infection. Clark Subs. Motion 2, Paper 390 at 10; Clark Subs.
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1 Motion 3 Paper 391 at 10 (citing Declaration,\textsuperscript{65} p. 3, ll. 16-17; Ex. 2001, ¶¶ 45-50; Ex 2003, ¶¶ 26, 28, 29, 31-33; 40-42; Ex. 2012,\textsuperscript{66} p. 2:8-17; Ex. 2098, col. 2221, ll. 9-52). However, argues Clark, the S2 and S3 applications are deficient because it fails to mention HCV or methods for treating HCV infection, as required by Count 1. \textit{Id.} (citing Ex. 2001, ¶¶ 256-261; Ex. 2003, ¶¶ 140-141, 145-147; Ex. 2050,\textsuperscript{67} pp. 1-36, Figs. 1-3). According to Clark, the S2 and S3 applications disclose processes for chemically synthesizing certain prodrugs of antiviral nucleosides. \textit{Id.} (citing Ex. 2001, ¶¶ 58, 59; Ex. 2003, ¶¶ 49, 136-137; Ex. 2050, pp. 1, ll. 3-6, 6-9, ll. 24-9).

Clark also argues that Count 1 requires certain compounds, specifically, certain 2'-fluoro-2'-C(H/F)\textsubscript{3} nucleosides, which the S2 and S3 applications fail to disclose. Clark Subs. Motion 2, Paper 390 at 10; Clark Subs. Motion 3, Paper 391 at 10 (citing Ex. 2001, ¶ 256-261; Ex. 2050, pp. 1-36, Fig. 1-3). Therefore, argues Clark, as of the filing dates of the S2 and S3 applications, an artisan would not have believed that S2 and S3’s applicants were in possession of any compound(s) falling within either of Count 1’s chemical formulae, or any_method(s) for treating HCV infection involving such compound(s). Clark Subs. Motion 2, Paper 390 at 11; Clark Subs. Motion 3, Paper 391 at 13 (citing Ex. 2001, ¶¶ 256-261).

Clark also argues that the S2 and S3 applications fail to provide an enabling anticipation of Count 1 because it does not teach an artisan as how to make any

\textsuperscript{65} Paper No. 1
\textsuperscript{66} Paper No. 55
\textsuperscript{67} Paper No. 112
nucleoside falling within the scope of Count 1, or teach how to treat HCV infection
using any such nucleoside, without undue experimentation. Clark Subs. Motion 2,
Paper 390 at 11; Clark Subs. Motion 3, Paper 391 at 13 (citing Ex. 2001, ¶¶ 256-
261; Ex. 2003, ¶¶ 136-147; Ex. 2050, pp. 1-36, Fig. 1-3).

Storer argues only that Clark has failed to establish that it is entitled to the
relief requested. Storer Opp. 2, Paper 403 at 2; Storer Opp. 3, Paper 403 at 2
Storer does not provide substantive argument and does not direct us to evidence to
contradict Clark’s arguments.

We have reviewed the disclosures of the S2 and S3 applications. For the
reasons stated with respect of the S1 application, we agree with Clark that the S2
and S3 applications do not describe either the genus of Count 1 or an embodiment
that meets all the limitations of that count. Clark Substantive Motions 2 and 3 to
deprive Storer of the benefit accorded with respect to Count 1 of its S2 and S3
applications are granted.

C. Clark Substantive Motion 7

Clark’s Substantive Motion 7 seeks judgment against Storer on the grounds
that involved claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 of
Storer’s involved US Patent No. 7,608,600 B2 (the “’600 Patent”) are unpatentable
under 35 U.S.C. § 112, 1st paragraph for lack of enablement and written
description. Clark Subs. Motion 7, Paper 154 at 1. To prevail, Clark must
demonstrate that the Specification of the ’600 patent does not support the full
scope of the claimed subject matter.
Claim 1 of the '600 patent has been recited supra as part of Count 1 and we do not repeat it here. As we have related, Clark argues that the salient limitation of Storer claim 1, for purposes of enablement, is the fluorine atom in the 2' "down" position, thus:

Ex. 1001-2, col. 2221, ll. 14-24. Storer's involved dependent claims 2-12, 17, 18, 20, 33, 34, 36, 38, and 49 all depend from claim 1 and all claim a fluorine atom in the 2' "down" position. Ex. 1001-2. Storer's involved claims 51-57, 62, 64, and 76-85 all depend from independent claim 50, which also claims a fluorine atom in the 2' "down" position, as do all of the involved claims depending from it. Id.

Storer's '600 patent issued from Storer's S4 application, which claims priority benefit of the S1 application. See Ex. 1001, p. 1. Clark argues that, as of June 27, 2003, the filing date of the S4 application, there was no available prior art reporting synthesis of a 2'-fluoro-2'-C(H/F)₃. Clark Motion 7, paper 154, at 9, citing Wnuk Decl., Ex. 2001, ¶ 136, 137. Clark argues further that the prior art as of 27 June 2003 would not have taught an ordinarily skilled artisan how to make the recited nucleoside without undue experimentation. Id. at 10.

Storer does not argue or direct us to evidence of art available prior to the June 27, 2003 filing of the S4 application that reporting or describing synthesis of
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the recited nucleosides. Accordingly, because we have found supra that the S1
application does not enable a nucleoside as recited in Count 1, we find that the
specification of the '600 patent does not enable Storer's involved claims. We
therefore conclude that the involved claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57,
62, 64, and 76-85 of '600 patent are unpatentable under 35 U.S.C. § 112, 1st
paragraph, for lack of enablement. Clark Substantive Motion 7 for judgment
against the involved claims of Storer's '600 patent is granted.

D. Clark Substantive Motion 10

Clark next moves to deprive Storer of the benefit accorded with respect to
Count 1 of US Appl. No. 10/608,907, filed June 27, 2003 (the "S4" application).
Motion at 1. Clark contends that the S4 application S4 lacks enablement, written
description, and utility for subject matter anticipating Count 1. Clark Subs. Motion
10, Paper 392 at 1. Storer has opposed. Storer Opp. 10, Paper 405. Clark has

Because we have determined supra that Storer's involved claims -12, 17, 18,
20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 are unpatentable under 35 U.S.C. §
112, first paragraph, for lack of enablement, we need not reach this motion.

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68 We note that all of the remaining claims of the '600 patent similarly-recite a
fluorine atom in the 2' "down" position and may likewise be unpatentable under 35
U.S.C. § 112, first paragraph, for the same reasons. Storer may wish to seek re-
examination of these claims.
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E. Clark Substantive Motion 5
Clark next moves to substitute its proposed count 2 or, alternatively, its proposed count 3, for Count 1. Clark Subs. Motion 5, Paper 192 at 1. Clark’s Proposed Count 2 is simply its Count 164 of its '218 application. Id. However, because we have already determined that Storer’s involved claims are unpatentable, we sua sponte remove Storer’s unpatentable claim 1 from the count and reformulate Count 1 as Clark’s claim 164. We therefore need not reach Clark’s Substantive Motion 5.

F. Clark’s Substantive Motion 8
Clark’s Substantive Motion 8 seeks judgment against Storer on the ground that all of Storer’s involved claims, claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 of Storer’s ’600 patent are unpatentable under 35 U.S.C. § 101, for lack of utility and, accordingly under 35 U.S.C. § 112, 1st paragraph, for lack of enablement. Clark Subs. Motion 8, Paper 155 at 1.
Our decision on Clark’s Substantive Motion 7 that Storer’s involved claims are unpatentable under 35 U.S.C. § 112, 1st paragraph, for lack of enablement is dispositive of the patentability of Storer’s claims. Therefore, it is unnecessary for us to reach this motion. Clark’s Substantive Motion 8 is consequently dismissed.

G. Clark Substantive Motion 9
Clark Substantive Motion 9 seeks judgment against Storer on the ground that all of Storer’s involved claims, claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62,
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64, and 76-85 of Storer’s ’600 patent are unpatentable under 35 U.S.C. §§ 102(e) or 103 as being either anticipated by; or obvious over, Clark’s US Appl. No. 10/828,753 (the “C2 application”), filed April 21, 2004. Clark Subs. Motion 9, Paper 156 at 1.

Our decision on Clark’s Substantive Motion 7 that Storer’s involved claims are unpatentable under 35 U.S.C. § 112, 1st paragraph, for lack of enablement is dispositive of the patentability of Storer’s claims. Therefore, it is unnecessary for us to reach Clark Substantive Motion 9.

H. Clark Miscellaneous Motion 18

Clark has moved to exclude the following Storer Exhibits: 1132, 1175-76, 1177, 1200, 1201, 1228, 1229, 1231, 1232, and 1233. Clark Misc. Motion 18, Paper 427 at 1.

1. Storer Exhibit 1132

Clark argues that Storer Exhibit 1132, the Declaration of Masad J. Damha, Ph.D., (the “Damha Declaration”) is inadmissible under SO ¶ 105.6 because it is an affidavit without an original signature. Clark Misc. Motion 18, Paper 427 at 1. According to Clark, Dr. Damha, Storer’s declarant, testified at his deposition that he did not sign a paper copy of Exhibit 1132 in ink, but instead inserted a digital image of his signature. Id. (citing Ex. 1194, p. 26, ll. 14-24). Furthermore, argues Clark, there is no original copy of Exhibit 1132 with a handwritten original
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1 signature that could have been retained or made available on demand, which is also
2 in violation of SO ¶ 105.6. Id. (citing Ex. 1194, pp. 26-27, ll. 25-4).
3 Alternatively, argues Clark, paragraphs 61-81 of the Damha Declaration
4 should be excluded under Federal Rule of Evidence 702 because Dr. Damha’s
5 opinions expressed in these paragraphs are not based on sufficient facts or data.
6 Clark Misc. Motion 18, Paper 427 at 2. According to Clark, when opining that it
7 would have been trivial for an artisan to make 2’-fluoro-2’-methyl nucleosides, Dr.
8 Damha did not take into account Storer’s own documents from the prior
9 ‘871 interference (e.g., Ex. 2029, Ex. 2035, Ex. 2041, Ex. 2042, and Ex. 2043).
10 Storer responds that Dr. Damha verified during his deposition that he
11 personally inserted his digital signature into his Declaration. Storer Opp. 18, Paper
12 29 at 1 (citing Ex. 1194, p. 26, ll. 19-24. Therefore, argues Storer, although Dr.
13 Damha did not handwrite his signature on a paper copy of his declaration, he did
14 verify that he personally electronically signed the declaration. Id. Storer submits
15 that the Board should accept this as sufficient. Id.
16 Storer also argues that Clark did not timely object to Exhibit 1132 at the
17 deposition and also failed to request a conference call with the Administrative
18 Patent Judge managing the interference to seek authorization to belatedly object to
19 Exhibit 1132. Storer Opp. 18, Paper 29 at 1 (citing 37 C.F.R. § 41.155(a)).
20 Dr. Damha has affirmed that the digital signature is a reproduction of his
21 own signature and that the declaration was his own. We therefore decline to
22 exclude the Exhibit on this ground.
More substantially, we agree with Storer that whether Dr. Damha examined the '871 interference documents prior to forming his opinion on whether a person of ordinary skill could have synthesized 2'-fluoro-2'-methyl nucleoside compounds is a question of the probative weight of the opinion testimony and not one of admissibility. We held, supra, that Dr. Damha was qualified as an expert. He may express his opinions on matters relevant to this interference. Federal Rule of Evidence 702 states that a "witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if ... the testimony is based on sufficient facts or data." Fed. R. Evid. 702(b).

We therefore decline to exclude Exhibit 1132.

Clark next argues that Storer Exhibits 1175 and 1176, which comprise two emails to the Patent Trial and Appeal Board concerning the '871 interference, with copies to Administrative Patent Judge New, discuss Storer's allegations of inequitable conduct and request authorization to move for additional discovery in the present interference, are inadmissible in their entirety because they are irrelevant under Rule 402, as well as confusing and a waste of time under Rule 403. Clark Misc. Motion 18, Paper 427 at 3.

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69 Paper No. 458
70 Paper No. 459
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Storer was not authorized to file a motion asserting inequitable conduct and has not raised the issue in any of its substantive or contingent motions considered herein. Because this evidence is unrelated to any of the matters before us we decline to address the admissibility of Exhibits 1175 and 1176 as an evidentiary matter. However, because the exhibits are extraneous to this proceeding we order that they be expunged from the record. Bd.R. 7(a) & 122(c)(1)(iii).

3. Storer Exhibit 1177

Storer Exhibit 1177\textsuperscript{71} is a copy of an order (Docket No. T-1156-12) from Federal Court of Canada, regarding the litigation with respect to the Canadian versions of Storer's involved patent and Clark's involved application in that venue. Clark seeks exclusion of Exhibit 1177 on substantially the same grounds that it seeks exclusion of Exhibits 1175 and 1176. Clark Misc. Motion 18, Paper 427 at 4.

Storer has not raised, in any of its substantive or contingent motions, any argument that relies upon this Exhibit and, having reviewed the Exhibit, we can discern no purpose for it to be included in this proceeding. Because the exhibit appears to be extraneous to this proceeding, we decline to consider it as an evidentiary matter and order that it be expunged from the record of this proceeding. Bd.R. 7(a) & 122(c)(1)(iii).

\textsuperscript{71} Paper No. 460
4. Storer Exhibit 1200

Clark next seeks exclusion of Exhibit 1200, the Second Declaration of Dr. Damha. Clark Misc. Motion 18, Paper 427 at 5. According to Clark, Dr. Damha failed to consider relevant information. Clark argues that Dr. Damha did not take into account the Storer Documents when forming his view that it would have been trivial for an artisan to make 2'-fluoro-2'-methyl nucleosides as of June 28, 2002. *Id.* (citing Ex. 1244, pp. 26-40, ll. 19-15). Clark argues further that Dr. Damha testified that such evidence was not important and that there was not "any chance" that it could have affected his opinions, despite the Board having previously found it significant. *Id.* (citing Ex. 1244, pp. 31-40, ll. 15-15).

We have related *supra*, with respect to Storer's Exhibit 1132, why the credibility of Dr. Damha's opinion testimony is a probative question on the merits of Storer's substantive motions. The issue is one of the weight of the testimony rather than one of admissibility. We employ the same reasoning here. Clark's motion to exclude Exhibit 1200 is denied.

5. Storer Exhibit 1201

Storer Exhibit 1201 is the Second Declaration of Raffaele De Francesco, Ph.D. According to Clark, Dr. De Francesco opines on an artisan's ability to perform high throughput testing of compounds for activity against hepatitis C virus ("HCV") using an HCV replicon assay during the 2000-2003 timeframe. Clark Misc. Motion 18, Paper 427 at 5 (citing Ex. 1201, ¶¶ 82, 95-101). Clark argues that Dr. De Francesco's opinions are based on unpublished techniques allegedly
used in his own labs. Because the reaction conditions and experimental processes
for these screening experiments were not published, argues Clark, they were not
available to the artisan to utilize, test or publicly critique. Clark Misc. Motion 18,
Paper 427 at 5-6 (citing Ex. 2171, ¶ 128). Therefore, contends Clark, De
Francesco's testimony regarding his non-public activities within his laboratory
does not provide any insight whatsoever into any issue pending in this. Motion at
6:

Storer did not oppose Clark's motion to exclude Exhibit 1201. Nevertheless,
we are not persuaded by Clark's arguments. As we have related supra, with
respect to Storer's Exhibits 1132 and 1200, the credibility of Dr. De Francesco's
opinion testimony is a probative question on the merits of Storer's motions. The
issue is one of weight and not one of admissibility. We employ the same reasoning
here. Clark's motion to exclude Exhibit 1201 is denied.

6. Storer Exhibit 1228 and 1229

Storer Exhibit 1228\textsuperscript{72} is the transcript of the deposition of Stanley Moncrief
Lemon and Storer Exhibit 1229\textsuperscript{73} is the transcript of the deposition of Jeffrey Scott
Glenn, both taken on Tuesday, July 31, 2012. Clark Misc. Motion 18, Paper 427 at
7. Clark argues that both transcripts are inadmissible as hearsay under Rule 802,
and under SO ¶¶ 157.1 and 157.3, because they are transcripts of depositions taken
in the prior 105,871 interference. \textit{Id.} Clark contends that if Storer wanted to rely

\textsuperscript{72} Paper No. 531
\textsuperscript{73} Paper No. 532
on the testimonies of Drs. Lemon and Glenn, it should have submitted a new
declaration from both individuals in the present case, thereby making them subject
to cross-examination in this interference. *Id.*

Storer points out that Clark has failed to demonstrate that Storer relies on
Exhibits 1228 and 1229 to prove the truth of any statements therein. Storer Opp.
18, Paper 429 at 7, 8. Storer points out that Clark has not directed the Board to any
statements in either Exhibit that Storer relies on to prove the truth of an asserted
matter. *Id.* Finally, Storer argues that that Clark was a party to the prior 105,871
interference and that Clark cross-examined both deponents during their respective
depositions. *Id.* (citing Exs. 1228; 1229). Moreover, contends Storer, Clark
submitted the Declarations of Drs. Lemon and Glenn, which was the basis for the
deposition as Exhibit 2167. *Id.* Therefore, argues Storer, Clark is not prejudiced
by the introduction of Exhibits 1228 into evidence. *Id.*

We agree that Storer has not relied upon Exhibits 1228 and 1229 in support
of any of its arguments in its substantive or contingent motions. Accordingly, we
can discern no purpose for it to be included in this proceeding. We decline to
consider it as an evidentiary matter and order that it be expunged from the record
of this proceeding. Bd.R. 7(a) & 122(c)(1)(iii).

7. Storer Exhibits 1231, 1232, and 1233

Storer Exhibit 1231 is the laboratory notebook by Jingyang Wang, an
employee of Idenix Pharmaceuticals, Inc., one of the Storer real parties-in-interest.
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1. Clark contends that Exhibit 1231 is inadmissible under Rules 402, 403, 802, and
2. 901(a), and SO ¶¶ 152.2.2 and 157.1. Clark Misc. Motion 18, Paper 427 at 7.
3. We considered Exhibits 1232 and 1233 with respect to our conclusion that
4. the S1 application did not enable the embodiments of a 2′ fluoro “down”
5. nucleoside within the scope of Count 1. Clark prevailed upon that issue
6. notwithstanding the consideration of these exhibits. Exclusion of the exhibits
7. would not influence the outcome of our review. It is therefore unnecessary for us
8. to consider the admissibility of the exhibits.

8. Summary

For the reasons set forth above, Clark’s Miscellaneous Motion 18 is denied.

III. STORER MOTIONS

A. Storer Substantive Motion 5

Storer moves to substitute proposed Count B for Count 1 and to be accorded
benefit of the S1 application. Motion at 1. All of the species encompassed by
Storer’s proposed Count B and disclosed in the Genus Disclosure of Storer’s
involved application have a fluorine atom in the 2′ “down” position. See Storer
Subs. Motion 5, Paper 157 at App’x 8-2 (“R7 is F”, “[F is shown in the 2′ “down”
position of the above formula]”). We have related supra that the claims of Storer’s
involved application fail to provide an enabling disclosure for any of the
embodiments of the nucleosides within the scope of its involved claims. All of
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those claims are characterized by a fluorine in the 2′ “down” position. As a result
of our determination we removed Storer’s claim 1 as an alternative of the count.
Storer’s proposed Count B broadens the species substituents at other positions of
the nucleotide but includes the fluorine in the 2′ “down” position. Thus, Storer’s
proposed Count B is unsuitable as a vehicle for determining priority in this
interference for the same reasons that Storer’s Claim 1 was unsuitable. We
therefore deny Storer’s Substantive Motion 5.

B. Storer Substantive Motion 11

Storer next argues that Clark’s involved claims are unpatentable under 35
U.S.C. § 102(e)(2) and/or 35 U.S.C. §§ 102(e)(2)/103(a) over Storer’s ’600 patent.
Storer Subs. Motion 11, Paper 158 at 1. —Storer does not challenge that the Clark
‘218 application has an effective filing date of May 30, 2003, the date Clark’s ’368
provisional application was filed. Id.

Storer argues that its ’600 patent, which it cites as prior art under 35 U.S.C.
§ 102(e), has an effective filing date of June 28, 2002, the filing date of its S1
application, which precedes the May 30, 2003, filing date of Clark’s ’368
application. Storer Subs. Motion 5, Paper 157 at 2. Therefore, argues Storer, the
’600 patent is prior art to the Clark claims. Id.

We have related supra why we Storer’s involved claims are not supported
by an enabling disclosure of an embodiment having a 2′-fluoro “down” nucleoside.
For the same reason, the earlier S1 application fails to provide an enabling
disclosure for nucleoside with the fluorine in the down position. —Storer is not

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entitled to the benefit of the June 28, 2002, filing date of the S1 application.

Storer’s ‘600 patent is not prior art for Clark’s ‘638 application. We therefore
deny Storer’s Substantive Motion 11.

C. Storer Contingent Responsive Motion 14

Storer Contingent Responsive Motion 14 seeks to add a new claim, claim 14
to the interference if any of Clark Substantive Motions 7, 8, or 9 are granted.

Storer Cont. Motion 14, Paper No. 327 at 1.

Because we have granted Clark Substantive Motion 8, we now address

Storer Contingent Motion 14.

Storer Claim 14 recites:

virus, comprising administering to the host infected with a hepatitis C
virus an effective amount of a compound of the formula:

\[
\text{Base}
\]

or a pharmaceutically acceptable salt thereof, wherein:

Base is selected from the group consisting of thymine, cytosine, 5-
fluorocytosine, 5-methylcytosine, 6-azapyrimidine, 6-azacytosine, 2-
and/or 4 mercaptopyrimidine, uracil, 5-halouracil, 5-fluorouracil, C5-
alkylpyrimidine, C5'-benzylpyrimidine, C5'-halopyrimidine, C5-
vinylpyrimidine, C5'-acylenic pyrimidine, C5'-acyl pyrimidine, C5-

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amidopyrimidine, C₅-cyanopyrimidine, C₅-iodopyrimidinè, C₆-iodopyrimidine, C²-Br-vinyl pyrimidine, C₆-Br-vinyl pyrimidine, C₅-nitropyrimidine, C₅-aminopyrimidine, 5-azacytidinyl, 5-azauracilyl;

R² is F;

R¹ is H; phosphate; monophosphate, diphosphate; triphosphate; a stabilized phosphate prodrug; acyl; lower acyl; alkyl; lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; benzylsulfonyl; a lipid; a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein R¹ is H or phosphate;

R² is phosphate; monophosphate; diphosphate; triphosphate; a stabilized phosphate prodrug; acyl; lower acyl; alkyl; lower alkyl; sulfonate ester; alkyl or arylalkyl sulfonyl; methanesulfonyl; benzylsulfonyl; a lipid; a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein R² is H or phosphate; and wherein each Y³ is H.

Motion App’x at 2-1-2. We note that all of the embodiments of Storer’s proposed claim 14 possess a fluorine atom in the 2’ “down” position.

Responsive motions may be filed to cure a claim defect raised on a notice of requested relief or a substantive motion. Bd.R. 41.121(a)(2). However, we have related supra why the S1 application fails to enable a fluorine atom in the 2’ “down” position of any of the embodiments of the nucleoside species within the scope of count 1. Storer’s proposed claim 14 fails to cure this defect of the Storer claims corresponding to Count 1. We therefore deny Storer’s Contingent Responsive Motion 14.
D. Storer Contingent Miscellaneous Motion 15

Storer Contingent Motion 15 seeks the addition to this interference of Storer
Cont. Motion 15, Paper 328 at 1. Storer's proposed Claim 14 is the sole claim
pending in the '534 application. Id. The '534 application claims the benefit
accorded the S1 and S4 applications. Id. at 2.

When Storer was authorized to file the contingent responsive motion to add
Storer's new claim 14, Storer was also required to file a contingent miscellaneous
motion to add the new continuation application with the new claim to the
interference. See Order Responsive Motion Bd.R. 41.121(a)(2), Paper 326, at 3:1-
3. Storer Contingent Miscellaneous Motion 15 serves that purpose. Storer Cont.
Motion 15, Paper 328 at 1:

Because we have denied Storer's Contingent Responsive Motion 14 to add
its new claim 14, we do not reach Storer's Contingent Motion 15 to add the '534
application to the instant interference.

E. Storer Miscellaneous Motion 16

Storer seeks to exclude the following Exhibits, in full or in part: Storer
Exhibits 1194, 1243, 1244, and exclusion of Clark Exhibits 2088, and 2100. Storer
Misc. Motion 16, Paper 425 at 1-5.
Storer Exhibit 1194 is the deposition of Dr. Damha, taken on April 15, 2014. Storer argues that the questions posed by Clark’s counsel at page 81, lines 9 to page 85, lines 14 were beyond the scope of Dr. Damha’s direct testimony given in Exhibit 1132 and/or were irrelevant as to whether one of ordinary skill in the art as of June 28, 2002 would have been able to synthesize a 2′-fluoro-2′-methyl-nucleoside at issue. Storer Misc. Motion 16, Paper 427 at 1. Specifically, Storer argues that Dr. Damha did not, in his Declaration, address Idenix’s post-June 28, 2002 efforts to synthesize a 2′-fluoro-2′-methyl-nucleoside, which was the subject of the questions posed by Clark’s counsel in the disputed pages. *Id.* at 1-2.

Clark responds that, first, impeachment evidence is always relevant and within the scope of permissible cross-examination. Clark Opp. 16, Paper 430 at 1 (citing Fed. R. Evid. 611(b); 702).

Second, Clark denies that, in the disputed questions in Exhibit 1194, the questions exceeded the scope of Dr. Damha’s direct testimony. Clark Opp. 16, Paper 430 at 3. Clark contends that the questions went to the bases for the opinions proffered in Exhibit 1132 and, specifically, whether those opinions took into account Idenix’s synthesis efforts. *Id.*

Third, Clark points out that Storer’s counsel did not object to the questions posed by Clark’s counsel pp. 82, ll.11-13; 82, ll. 15-18; 82, ll. 20-21; 82, l. 23; 82, l. 25; 83, ll. 3-4; 83, ll. 6-7; and 85, ll. 10-13 of Exhibit 1194, and to which Dr. Damha at pp. 82, l. 14; 82; l. 19, 82, l. 22; 82, l. 24; 83, l. 2; 83, l. 5; 83, l. 8; and
85, l. 14, respectively, responded. Clark Opp. 16, Paper 430 at 3 (citing Ex. 1194).

Therefore, argues Clark, these questions and answers should not be excluded: *Id.*

We are not persuaded by Storer’s arguments. In the disputed passages of Exhibit 1132, Dr. Damha is questioned repeatedly whether, in arriving at his opinion that one of ordinary skill in the art would be aware of “a method for preparing a 2’-F-2’-methyl-ribonucleoside of the ’350 Application and within the scope of Claim 38 of the Storer Patent,” he had been made aware of, or considered, any of Idenix’s efforts to synthesize the compound during the interval between 2002 and 2005. For example, during the Dr. Damha’s deposition, he responded to the questions as below:

Q. So you’re not aware that in the prior interference Idenix put forth its story about how its chemists tried to make 2’-fluoro-2’-methyl nucleosides during the 2002 to 2005 time period?

MR. KINTON: Same objection. Beyond the scope.

A. No.

Q. So then you couldn’t have considered any of Idenix’s story about its attempt to make those compounds in forming your opinions?

A. None whatsoever.

Q. And did you consider any Idenix documents about trying to make 2’-fluoro-2’-methyl nucleosides when you formed your opinion?

A. No.

Q. Did you consider any Idenix lab notebooks when forming your opinion?
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A. On how to make these compounds, no.

Q. What about Idenix's meeting minutes?

A. No.

... 

Q. Did you ever ask to see such information when forming your opinions?

A. No.

Q. Why not?

MR. KINTON: Objection. Irrelevant.

Ex. 1194, p. 82, ll. 3-24; p. 83, ll. 6-10. These, and the other disputed passages, all inquire whether Dr. Damha had reviewed, or had knowledge of, any documents concerning Idenix's research efforts between 2002 and 2005. Dr. Damha responded in the negative to this entire line of questioning:

Q. Do you think what Idenix actually tried in terms of attempting to make a 2'-fluoro-2'-methyl nucleoside might be important when forming your opinion?


A. No, not at all. I formed my opinion on literature and knowledge that I have gained as a nucleoside nucleic acid chemist. And in fact, having used procedures that are directly applied to the synthesis of the 2'-methyl-2'-fluoro compounds.

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Ex. 1194, pp. 84-85, ll. 22-9. Thus, this line of questioning by Clark inquires as to
the materials that formed the basis for Dr. Damha’s opinion expressed in his
Declaration. As such, it is neither beyond the scope of Dr. Damha’s declaration,
nor is it irrelevant. Moreover, Clark is entitled to attempt to impeach the
credibility of Storer’s expert on cross-examination. FRE 611(b). Storer’s motion
to exclude the cited passages of Storer’s Exhibit 1194 is consequently denied.

2. Storer Exhibit 1243

Storer Exhibit 1243\textsuperscript{74} is the transcript of the deposition of Dr. De Francesco.

Storer moves to exclude certain passages in the Exhibit, viz., page 81, lines 12-13
and 21-22 and page 82, lines 6-8 as exceeding the scope of Dr. De Francesco’s
direct testimony in his Declaration (Ex 1201). Storer Misc. Motion 16, Paper 427
at 3. According to Storer, Dr. De Francesco did not address in his declaration the
disclosure in Exhibit 1093 of the bases for particular compounds, including
Formula (IV), which was the subject of the questions posed by Clark’s counsel.

Clark responds that, first, Dr. De Francesco’s testimony in the contested
passages is admissible because Clark’s counsel’s questions were within the scope
of Dr. De Francesco’s direct testimony in his Declaration or, alternatively, went to
a matter affecting Dr. De Francesco’s credibility. Clark Opp. 16, Paper 430 at 4
(citing FRE 611(b), 702).

We are not persuaded by Storer’s arguments. In his Declaration, Dr. De
Francesco opined:

\textsuperscript{74} Paper No. 544
The '350 and '907 applications state that the compounds of the invention exhibit antiviral activity against *Flaviviridae* viruses such as HCV, and can be used to treat infections by those viruses. Ex 1003, at 44:3-4, 57:15-19; Ex 1002, at 46:3-4, 58:4-9. As of June 28, 2002 and June 27; 2003, persons skilled in the art would have believed that the Relevant Compounds could have anti-HCV activity because: (i) the Relevant Compounds are nucleoside analogs, and it was known at the time that certain nucleoside analogs exhibit antiviral activity due to interference with viral polymerases required for replication of viral genetic material (referred to herein as "genome replication"), as described in ¶39-40;

(ii) it had been shown experimentally at the time that certain 2'-modified nucleosides exhibit anti-*Flaviviridae* activity, in particular against BVDV and YFV, as described in ¶41-46;

(iii) persons skilled in the art would have believed that nucleoside analogs that exhibit activity against BVDV are likely to also exhibit activity against HCV, and that nucleoside analogs that exhibit activity against BVDV and YFV are highly likely to also exhibit activity against HCV, as described in ¶47-67;

(iv) as of June 27, 2003, it had been experimentally shown that certain 2'-modified nucleosides exhibit anti-HCV activity, as described in ¶68-70; and

(v) there were no specific reasons to doubt anti-HCV activity of the Relevant Compounds, as described in ¶71.

Ex. 1201, ¶ 21. In the contested passages of Exhibit 1243, Dr. De Francesco states:

Q. Would you turn back to page 57 of the '350 application, which is Exhibit 1003?

...
A. Uh-huh.

Q. And could you identify for me what the base is for that formula?

MR. FRIEBEL: Objection, beyond the scope of his declaration.

A. (Perusing.) No. Sorry. This is — I think this is beyond my — it would require a better understanding of chemistry than I have.

Q. So you have no idea what the base would be?

MR. FRIEBEL: Same objection.

A. (Perusing.) I didn't review these as part of my opinion because I don't think this was requested to me. Tentatively, I would say it's one of the group — must be one of the group of bases described in the previous pages, I guess.

Q. So we were talking about the compounds at pages 1551 previously. Would that be previous pages?

MR. FRIEBEL: Same objection, beyond the scope of his original — of his second declaration.

A. (Perusing.) Yeah, I believe herein means one of the bases described in pages 48, 49 to 54, but I'm not sure. I mean, again, I'm not a chemist, so I don't — it's a tentative answer.

Ex. 1243, pp. 81-82, ll. 7-16.

Determining the scope of cross-examination is within the sound discretion of the administrative tribunal. See, e.g., Guise v. Dep't of Justice, 330 F.3d 1376, 1379 (Fed. Cir. 2003). Dr. De Francesco has explicitly declared that he has studied Storer Exhibit 1003, the '350 application, as part of the preparation for giving his
expert opinion. Ex. 1243, ¶ 10. Because Dr. De Francesco places no limiting
language on this statement in his Declaration, we assume that he has reviewed the
total document and that questions concerning the contents of the document on
cross-examination are not beyond the scope of his Declaration. Therefore, the
contents of the '350 application are within the scope of his Declaration. The line
of questioning in the disputed passages goes to the basis for the formation of that
opinion, although his statements ("it would require a better understanding of
chemistry than I have") may undermine his credibility as an expert witness with
respect to the chemistry of nucleoside bases. Nevertheless, the credibility of a
witness' opinion, and the probative weight we consequently ascribe to that
testimony, is a substantive issue and not one of admissibility. We consequently
deny Storer's motion to exclude the contested passages of Exhibit 1243.

3. Storer Exhibit 1244

Storer Exhibit 1244 is the Second Deposition of Dr. Damha, taken on June
20, 2014. Storer moves to exclude certain passages in the Exhibit, viz., page 26,
line 19 to page 29, line 25; page 33, line 11 to page 36, line 2; and page 36, line 18
to page 40, line 15 as exceeding the scope of Dr. Damha's direct testimony in his
Declaration (Ex. 1200). Storer Misc. Motion 16, Paper 427 at 4. Specifically,
Clark contends that Dr. Damha did not address, in his Declaration, Idenix's post-
June 28, 2002 effort in synthesizing a 2'-fluoro-2'-methyl nucleoside, the subject
of the questions posed by Clark's counsel in the contested passages. Id.
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1. In response, Clark repeats the argument that it made with respect to Ex. 1195
2. *supra:* that the testimony that Storer seeks to exclude is relevant to determining
3. whether Dr. Damha's direct testimony in Exhibit 1200 should be given any weight,
4. and whether it is relevant to assessing Dr. Damha's credibility, particularly with
5. regard to Dr. Damha's opinions about whether an artisan could have made 2'-
6. fluoro-2'-methyl nucleosides without undue experimentation. Clark Opp. 16,
7. Paper 430 at 5. Clark also contends that Dr. Damha's alleged failure to consider
8. Idenix's extended efforts to synthesize the compounds affects his credibility as an
9. expert witness. *Id.*
10. We agree with Clark. As we related *supra,* the lines of questioning objected
11. to by Storer inquire as to the materials that formed the basis for Dr. Damha's
12. opinion, as expressed in his Declaration and the extent of Dr. Damha’s knowledge
13. of Idenix's efforts at synthesis of 2'-fluoro-2'-methyl nucleosides. Moreover,
14. Clark is entitled to attempt to impeach the credibility of Storer's expert in cross-
15. examination. FRE 611(b). As such, it is neither beyond the scope of Dr. Damha’s
16. declaration, nor is it irrelevant. Storer's motion to exclude the cited passages of
17. Storer's Exhibit 1194 is denied.
18.
19. 4. Clark Exhibit 2088
20. Clark Exhibit 208876 is the Declaration and curriculum vitae of Dr. Jean-
21. Pierre Sommadossi, one of the inventors of Storer's '600 patent. Storer Misc.
22. Motion 16, Paper 427 at 5. Storer argues that although Exhibit 2088 refers to

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1 Exhibit 1 (a copy of Tables 4 and 5 from Chapter Two of B.N. Fields et al., Fields Virology, Lippincott-Raven, Philadelphia (3rd ed. 1996)) at 3, ¶ 11.), Exhibit 2088 does not in fact contain an Exhibit 1. Id. Therefore, argues Storer, Exhibit 2088 is incomplete and should be excluded under Federal Rule of Evidence 106. Id.

2 Storer also argues that Clark relies on Exhibit 2088, and particularly ¶ 15, to prove that one cannot predict a compound’s activity against another virus without testing it. Storer Misc. Motion 16, Paper 427 at 5 (citing Clark Substantive Motion 87, at 11, ll. 13-14). Consequently, argues Storer, Clark Exhibit 2088 is an out-of-court statement made by a declarant who has not testified in this proceeding and the statement is offered to prove its truth. Id. Therefore, Storer contends, Exhibit 2088 is also inadmissible as impermissible hearsay. Id. (citing FRE 802).

3 As an initial matter, Federal Rule 106 is not an exclusionary rule. Federal Rule 106 states: “If a party introduces all or part of a writing or recorded statement, an adverse party may require the introduction, at that time, of any other part—or any other writing or recorded statement—that in fairness ought to be considered at the same time.” Fed. R. Evid. 106. Storer has not requested completion of the record, and we therefore consider any such request waived.

5. Clark Exhibit 2100

Clark Exhibit 210078 is a document of the European Patent Office (“EPO”), purportedly reporting of a consultation by the EPO with applicant/representative

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1. Idenix Pharmaceuticals, Inc., the real party-in-interest in the instant interference, with respect to EPO Application No. 03 761 744.6. Storer argues that Clark relies on Exhibit 2100 to prove that Exhibit 1002's Formula (IX) does not provide for R1 to be di- or triphosphate and thus does not describe certain Storer claims. Storer Misc. Motion 16, Paper 427 at 5-6. As such, contends Storer, Exhibit 2100 constitutes impermissible hearsay and should be excluded. Id. at 6.

8. We do not see the relationship of Exhibit 2100 to the dispositive issue with respect to Storer's involved claims, viz., the enablement of a 2'-fluoro "down" nucleoside. Accordingly, we can discern no purpose for it to be included in this proceeding. We decline to consider it as an evidentiary matter and order that it be expunged from the record. Bd.R. 7(a) & 122(c)(1)(iii).

14. 6. Summary
15. For the reasons set forth above, Storer's Miscellaneous Motion 16 is denied.

17. IV. CONCLUSION
18. For the reasons set forth above:
1. Clark Substantive Motion 1 to deprive Storer of the benefit of its US Appl. No. 60/392,350 is GRANTED.

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2. Clark Substantive Motion 2 to deprive Storer of the benefit accorded with respect to Count 1 of its U.S. Appl. No. 60/466,194 is GRANTED.

3. Clark Substantive Motion 3 to deprive Storer of the benefit accorded with respect to Count 1 of its U.S. Appl. No. 60/470,949 is GRANTED.

4. Clark Substantive Motion 10 to deprive Storer of the benefit accorded with respect to Count 1 of US Appl. No. 10/608,907 is DISMISSED.

5. Clark Substantive Motion 7 for judgment against Storer's US Patent No. 7,608,600 B2 on the grounds of unpatentability under 35 U.S.C. § 112, 1st paragraph for lack of enablement and written description is GRANTED.

6. Clark Substantive Motion 5 to substitute its proposed alternate count 2 for the present Count 1 of the interference is DISMISSED.


8. Clark Substantive Motion 9 for judgment against Storer's US Patent No. 7,608,600 B2 on the ground of unpatentability under 35 U.S.C. §§ 102(e) or 103 as being either anticipated by, or obvious over, Clark's US Appl. No. 10/828,753 is DISMISSED.

9. Clark Miscellaneous Motion 18 to exclude evidence is DENIED. We sua sponte order that Storer Exhibits 1175, 1176, 1177, 1228, and 1229 be expunged.

10. Storer Substantive Motion 5 to substitute proposed count B for Count 1 is DENIED.
11. Storer Substantive Motion 11 for judgment against Clark on the grounds of unpatentability of all of Clark's involved claims as anticipated under 35 U.S.C. § 102(e) and/or 103 is DENIED.

12. Storer Contingent Motion 14 to add a new claim is DENIED.

13. Storer Contingent Motion 15 to add an application to the interference is DISMISSED.

14. Storer Miscellaneous Motion 16 to exclude evidence is DENIED. We sua sponte order that Clark Exhibit 2100 be expunged.

15. Party Clark shall be designated Senior Party for any further proceedings according to the Redeclaration issued herewith.

IT IS SO ORDERED
Interference 105,981
Clark v. Storer

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

RICHARD STORER, GILLES GOSSELIN, JEAN-PIERRE SOMADOSSI,
and PAOLA LACOLLA
Junior Party
(US 7,608,600 B2)

v.

JEREMY CLARK
Senior Party
(Application No. 11/854,218)

Interference No. 105,981 (JGN)
Technology Center 1600

JUDGMENT - REQUEST FOR ADVERSE
Bd.R. 127(b)(4)

Before RICHARD SCHAFER, DEBORAH KATZ, and

NEW, Administrative Patent Judge
I.

On January 16, 2015, a merits panel of the Board entered a decision on then-Senior Party Richard Storer, Gilles Gosselin, Jean-Pierre Sommadossi, and Paola LaColla’s ("Storer") and then-Junior Party Jeremy Clark’s ("Clark") substantive motions.\(^1\) Paper No. 687. The panel concluded, *inter alia*, that Storer’s US Appl. No. 60/392,350 (the "350 application"), for which Storer had been accorded priority benefit, failed to enable any of the 2’-fluoro-2’-C-methyl nucleosides that are required by the count. *Id.* at 35–36. The panel consequently granted Clark’s motion 1 to deprive Storer of the benefit accorded with respect to Count 1 of the ‘350 application. *Id.*

As a result, the interference was redeclared with Storer as the Junior Party, Clark as the Senior Party, and with Clark’s involved claims 164 and 165 and Storer’s involved claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 corresponding to the new Count 2. Paper No. 688. A scheduling order for the priority phase was also entered on January 16, 2015. Paper No. 689. Storer’s priority motion was due on February 27, 2015. Paper 689, Appendix. Rather than filing its priority motion, Storer contacted the Board via email to indicate that it did not intend to file a priority motion. See Paper No. 692.

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\(^1\) On January 16, 2015, the Board also entered an order for Storer to show cause why, in view of the Board’s decision on the parties’ substantive motions, judgment should not be entered against it. Paper 690. Storer timely responded. Paper No. 691. Although the panel finds Storer’s response to the order to show cause to be insufficient, Storer’s response to the order to show cause played no role in the entry of this judgment.
II.

As Senior Party, Clark is entitled to the presumption under Bd.R. 207(a)(1) that it is the prior inventor. See also Bd.R. 201, definition of senior party. As the Junior Party, Storer therefore bears the burden of establishing a date of inventorship prior to Clark’s accorded benefit date of May 30, 2003. See Bd. Rs. 121(b) and 208(b). By declining to file a priority motion and forgoing the opportunity to prove an earlier date of invention, Storer has effectively abandoned the contest. Storer’s abandonment of the contest is construed as a request for adverse judgment.

See Bd.R. 127(b)(4).

It is therefore—

ORDERED that judgment on priority be entered against Junior Party Storer for the subject matter of count 2;

FURTHER ORDERED that claims 1-12, 17, 18, 20, 33, 34, 36, 38, 49-57, 62, 64, and 76-85 of Storer’s involved U.S. Patent No. US 7,608,600 B2 be CANCELED, 35 U.S.C. 135(a); and

FURTHER ORDERED that a copy of this judgment be entered in the administrative records of Storer’s involved US 7,608,600 B2 patent and Clark’s involved US Appl. No. 11/854,218.

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As was in effect on March 15, 2013. See Pub. L. 112-29, § 3(n), 125 Stat. 284, 293 (2011).
FURTHER ORDERED that if a party seeks judicial review, the party must file a notice with the Board (37 C.F.R. § 41.8(b)) within seven days of initiating judicial review.


NOTICE: “Any agreement or understanding between parties to an interference, including any collateral agreements referred to therein, made in connection with or in contemplation of the termination of the interference, shall be in writing and a true copy thereof filed in the Patent and Trademark Office before the termination of the interference as between the said parties to the agreement or understanding.” 35 U.S.C. 135(c); see also Bd.R. 205 (settlement agreements).
cc (via electronic transmission):

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UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT TRIAL AND APPEAL BOARD

Patent Interference 105,871 (RPG)
Technology Center 1600

JEREMY CLARK,

Patent 7,429,572,
Junior Party,

v.

JEAN-PIERRE SOMMADOSSI, PAOLO LACOLLA, RICHARD STORER, and
GILLES GOSSELIN,

Application 12/131,868,
Senior Party

Before: SALLY G. LANE, RAE LYNN P. GUEST, and DEBORAH KATZ,
Administrative Patent Judges.

GUEST, Administrative Patent Judge.

DECISION ON MOTIONS

IPO DELHI 07-08-2015 17:17
Introduction

The interference is before a merits panel for a decision on non-priority motions.

The interference involves a Clark patent and a Sommadossi patent application. Paper 1.

The subject matter of the interference is generally related to a class of 2'-methyl, 2'-fluoro nucleosides with a uracil or cytosine base. Count 1 (Paper 1, p. 8) reads: A compound of the formula:

![Chemical structure](image)

...or a pharmaceutically acceptable salt thereof, wherein:

1. \(X\) is \(\mathrm{O}\);
2. \(R^1\) is \(\mathrm{H}\), a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl;
3. \(R^2\) is \(\mathrm{H}\), a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and
4. Base is a pyrimidine represented by the following formula:

![Chemical structure](image)

wherein,

1. \(R^3\) is \(\mathrm{H}\); and
2. \(R^4\) is \(\mathrm{NH}_2\) or \(\mathrm{OH}\).
1. **Real parties in interest**
   
   The real party in interest for Clark is Gilead Pharmasset LLC. Paper 8.

2. **Motions before the panel**
   
   Clark has filed 5 motions. Sommadossi has filed a total of 5 motions, but withdrew Sommadossi Substantive Motion 5. Paper 39. The following motions of Clark are before the Board:

3.   - Clark Substantive Motion 1 for benefit to Clark’s Provisional Application 60/474,368 (Clark’s C1 Application);

4.   - Clark Substantive Motion 2 to deny Sommadossi’s accorded benefit to Sommadossi US Application 10/608,907 (Sommadossi’s S4 Application);

5.   - Clark Substantive Motion 3 for judgment by repose under 35 U.S.C. § 135(b)(1) and 135(b)(2);

6.   - Clark Substantive Motion 6 for judgment based on unpatentability of Sommadossi’s involved claims under 35 U.S.C. §§ 101 and 112, first paragraph; and

7.   - Clark Miscellaneous Motion 7 to exclude evidence.

8. The following motions of Sommadossi are before the Board:

9.   - Sommadossi Substantive Motion 1 for benefit to Sommadossi’s Provisional Application 60/392,350 (Sommadossi’s S1 Application);

10.  - Sommadossi Responsive Motion 6 to substitute proposed Counts C or D for Count 1;
• Sommadossi Miscellaneous Motion 7 to amend the specification of
the involved application to clarify a cross-reference to Sommadossi
US Application 10/608,907 (Sommadossi’s S4 Application); and
• Sommadossi Miscellaneous Motion 8 to exclude evidence.

Pursuant to 37 C.F.R. § 41.125(a) (2007), we exercise discretion to consider
the motions in the order discussed below: See also Berman v. Housey, 291 F.3d
1345, 1351 (Fed. Cir. 2002).

I. Clark Substantive Motion 3

- Sommadossi’s involved claims are barred under 35 U.S.C. § 135(b)

Clark Substantive Motion 3 (Paper 34) seeks judgment that Sommadossi’s
involved claims are barred by repose under 35 U.S.C. § 135(b)(1) over Clark’s
involved patent or, alternatively, under 35 U.S.C. § 135(b)(2) over Clark’s US

Sommadossi has opposed. Paper 70.

Clark has replied. Paper 83.

This motion is a threshold motion, in that if the motion is granted as to all of
Sommadossi’s involved claims then Sommadossi would lack standing to continue
in the interference. Bd. R. 201.

As the moving party, Clark has the burden to show that it is entitled to the
relief requested. Bd. R. 208(b).

A. Repose under 35 U.S.C. § 135(b)(1)

Findings of fact

Clark’s involved patent, US 7,429,572 (hereinafter the ‘572 patent), issued
on 30 September 2008. Ex. 2009. Thus, the “critical date,” under 35 U.S.C.
§135(b)(1), by which Sommadossi must have filed claims to the same or
substantially the same subject matter as claimed in the ‘572 patent is 30 September
2009.
Sommadossi’s involved claims are claims 44, 45, 48, 52, 53, 57, 58, 63, 64, 72, 78, 80, 91, 92, 95, 96, 99, 100, 103, 104, 131, 133-138, and 151-154 of US. Application 12/131,868 (hereinafter the “‘868 application” or “S5”). Paper 1.


Claims 44-130 were filed in a preliminary amendment with the application on 2 June 2008. Claims 44 and 45 were the sole independent claims. Claims 44 and 45 are directed to a compound having a general formula with various certain constituents. Of relevance for deciding this motion, claims 44 and 45 each included a limitation that “R^7 is halo, F, Cl, Br or I.” Claims 59 and 60, which depended from claims 44 and 45, were also presented in the preliminary amendment and limited R^7 to F. Ex. 2018.

In response to a restriction requirement, some claims were cancelled and claims 131-150 were added on 14 December 2011. Claim 131 was the sole independent claim added and included a limitation that R^7 is halo, F, Cl, Br or I. Claim 132 was presented, which depended from claim 131, and limited R^7 to F. Ex. 2020.

An office action dated 3 March 2011 rejected all the pending claims under 35 U.S.C. § 112, second paragraph as being indefinite on two basis. Regarding the first basis, the Examiner stated that “[t]he claims should not define the variables [R^1 and R^2] as that which is [optionally] ‘capable of’ providing the groups, but which do provide the groups.” Accordingly, the Examiner suggested more favorable language. The second basis is that the variable R^7 uses the term “halo” or alternatively specific halogens, namely “F, Cl, Br or I.” Ex. 2021, p. 3.

Claims 44, 45 and 131 were amended on 27 May 2011 to delete “halo” from the R^7 options and to amend the language of variables R^1 and R^2 from including a “pharmacologically acceptable leaving group which when administered in vivo is
capable of providing a compound wherein \([R^1 \text{ or } R^2, \text{ respectively}]\) is H or phosphate” to the language that the Examiner suggested was more favorable, i.e. a "pharmaceutically acceptable leaving group which when administered in vivo provides a compound wherein \([R^1 \text{ or } R^2, \text{ respectively}]\) is H or phosphate.” Ex. 2022 (underlining added to emphasize the amended language); Ex. 2021, p. 3.

After a second office action dated 16 August 2011 based on prior art rejections, an amendment was filed 20 September 2011. In the amendment, claims 44, 45 and 131 were amended to limit \(R^7\) to F, claims 59, 60 and 132 were cancelled, and claims 151-154 were added. Claim 153 is independent. Ex. 2024.

In the amendment, Sommadossi states that the rejection under 35 U.S.C. § 102(e) "is moot in view of the above amendments to the claims, in which \(R^7\) has been amended to recite ‘F’ in each of the independent claims (claims 44, 45 and 131).” Ex. 2024 at 12.

The claims of the 20 September 2011 amendment are Sommadossi’s involved claims.

The claims of the 2 June 2008 preliminary amendment were filed before the critical date.

The claims of the 14 December 2011 amendment, 27 May 2011 amendment, and 20 September 2011 amendment were all filed after the critical date.

**Analysis**

35 U.S.C. § 135(b)(1) reads as follows:

(1) A claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made prior to one year from the date on which the patent was granted.

This statute acts to bar a party from claiming patented subject matter more than one year from the issuance of a patent.
A claim to the same or substantially the same subject matter as a claim of an issued patent is barred by §135(b)(1) unless timely presented. Thus, 135(b)(1) acts as a statue of repose placing a time limit on a patentee’s exposure to an interference proceeding. *Regents of Univ. of Calif. v. Univ. of Iowa Res. Found.*, 455 F.3d 1371, 1376 (Fed. Cir. 2006). A claim to the same or substantially the same subject matter filed after one year from the date on which the patent was issued, the “critical date,” is barred unless the “later filed claim does not differ from an earlier [pre-critical date] claim in any ‘material limitation,’” *In re Berger*, 279 F.3d 975, 981-82 (Fed. Cir. 2002) (quoting *Corbett v. Chisholm*, 568 F.2d 759, 765-66 (CCPA 1977)). What is to be considered is whether “all material limitations of the copied claim necessarily occur in the prior claims” or, in other words, whether “all material limitations of the copied claim are present in, or necessarily result from, the limitations of the prior claims.” *Berger*, 279 F.3d at 982 (claims are missing a particularly recited limitation of the copied claim); *see also Corbett*, 568 F.2d at 766 (earlier claims missing particular squeezing step).

We agree with Clark (Paper 34, 2:3-9) that “[w]hen an applicant adds limitations in response to an examiner’s rejection, and those limitations result in allowance, there exists a well established presumption that those limitations are necessary to patentability and thus material” *Adair v. Carter*, 668 F.3d 1334, 1339 (Fed. Cir. 2012) (citing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 734 (2002); *Corbett*, 568 F.2d at 765; *Parks v. Fine*, 773 F.2d 1577, 1579 (Fed. Cir. 1985) (“The insertion of this limitation to overcome the examiner’s rejection is strong, if not conclusive, evidence of materiality.”)). *See also Berger*, 279 F.3d at 982 (holding that a limitation added during prosecution to avoid the prior art is a “material limitation”). However, this presumption may be rebutted with explanation and supporting evidence that the limitation is not a material one.

It is with this understanding that we address Sommadossi’s involved claims.
understood the claim to have the same meaning, i.e., reciting the same leaving
groups, before and after the amendment. Paper 70, 5:18-24 (citing Raz v. Davis,
2011 WL 4568986, *9 (BPAI 2011)). Sommadossi reasons that the in vivo
conditions of the claim are not specified, such that any leaving groups “capable of
providing” a compound, necessarily “provide” the compound when the in vivo
conditions to do so are met. Id., 6:7-17. Sommadossi notes that the current claim
does not require the leaving group “provides” the compound under all in vivo
conditions, but that the language means “it provides under at least one set of in
vivo conditions. Id., 7:5-13. Sommadossi directs us to the identical testimony of
Drs. Trost and Damha to support this contention. Id., 6:7-17.

Clark responds that the “two expressions have manifestly different
meanings” in that “while something that ‘provides’ necessarily is ‘capable of
providing,’ the converse is not true.” Paper 83, 2:20-21. Clark argues that
“capable of providing” means under at least one in vivo condition, while
“provides” means under any, i.e. all or every, in vivo condition. Id., 2:15-20.
Clark cites to no evidence to support its interpretation of the claim language. Id.,
2:9-23.

We find Sommadossi’s position that the amended language of the R¹ and R²
variable has the same meaning in the context of the claims to be persuasive. We
note that the Examiner’s phrasing of the rejection supports this position. The
Examiner stated that “[t]he claims should not define the variables [R¹ and R²] as
that which is [optionally] ‘capable of’ providing the groups, but which do provide
the groups.” Ex. 2021, p. 3. We take this comment by the Examiner to suggest
that the change in language as proposed by the Examiner did not alter the meaning
of the claim itself but rather put the language into a more acceptable and definite
form. In other words, Sommadossi has sufficiently rebutted Clark’s argument that
the R¹ and R² option of “a leaving group which when administered in vivo provides
Claims 44 and 45

Here, current claims 44 and 45 were amended in the current S5 application in only two ways. The first we do not consider an additional limitation at all. Claims 44 and 45 originally stated “wherein $R^7$ is halo, F, Cl, Br or I.” At the same time, claims 59 and 60, which directly depended from claims 44 and 45, respectively, recited “wherein $R^7$ is F.” Thus, the amendment of claims 44 and 45 changing “wherein $R^7$ is halo, F, Cl, Br or I” to read “wherein $R^7$ is F” and the concurrent deletion of claims 59 and 60 is no more than the rewriting of claims 59 and 60 in independent form as claims 44 and 45. Thus, the subject matter of original claims 59 and 60, i.e., “wherein $R^7$ is F,” clearly demonstrates that a ‘2-fluoro-sugar constituent of the formula of claims 44 and 45, respectively, was initially claimed subject matter of the S5 application.

The second change in claims 44 and 45 is the change of variables $R^1$ and $R^2$ from optionally constituting “a leaving group which when administered in vivo is capable of providing a compound wherein $R^1$ and $R^2$ is H or phosphate” to optionally constituting “a leaving group which when administered in vivo provides a compound wherein $R^1$ and $R^2$ is H or phosphate” (underlining added to show amended language). This change was indisputably made in response to a 35 U.S.C. § 112, second paragraph rejection based on indefiniteness.

Clark argues that the change is presumptively a “material limitation” within the meaning of Corbett and Berger. Paper 34, 9:5-10 and 18-22. Under the reasoning in Adair, we agree with Clark that there is a rebuttable presumption that the change in language is a material one. Thus, the issue before us is whether the differences in language between the pre- and post-critical date claims are material differences.

Sommadossi contends that the change does not render the current claim language to be a “material limitation” because the skilled artisan would have
a compound wherein $R^1$ and $R^2$ is H or phosphate” is a “material limitation” missing from the earlier claim.

Thus, we determine that Sommadossi may rely upon original claims 44 and 45 for purposes of avoiding the bar of 35 USC 135(b), and Clark Substantive Motion 3 is denied at least with respect to claims 44 and 45 under 35 U.S.C. § 135(b)(1). Because at least involved claims 44 and 45 of Sommadossi are not barred, the remainder of the arguments under 35 U.S.C. § 135(b)(1) do not present a threshold issue that might deprive Sommadossi of standing in the interference.

B. Repose under 35 U.S.C. § 135(b)(2)

Findings of fact

Clark also argues that all the involved claims are barred by 35 U.S.C. § 135(b)(2).


Clark relies upon claims 10 and 25 of the ‘737 application as being the same or substantially the same subject matter as Sommadossi’s involved claims. Paper 30, 18:20-19:5.

Published claim 10 and published claim 25 are independent claims that recite the identical compound “or its pharmaceutically acceptable salt or prodrug,” but published claim 25 was directed to “a pharmaceutical composition” comprising...
the compound, or salt or prodrug thereof, in “a pharmaceutically acceptable

On January 4, 2007, Clark replaced published claim 25 with an entirely new
claim reciting “[a] pharmaceutical composition comprising the nucleoside of claim
10 or its pharmaceutically acceptable salt or prodrug and a pharmaceutically
acceptable carrier.” Ex. 1170, at 25-26. Accordingly, this amendment did not
change the scope for published claim 25.

In an Office Action dated March 30, 2007, independent claims 10 and, now
dependent, claim 25 of the ‘753 application were rejected under 35 U.S.C. § 112,
first paragraph on the basis that the Specification was not enabled for “making
prodrugs of the claimed compounds” and under 35 U.S.C. § 112, second paragraph
on the basis that certain parenthetical phrases and the phrase “optionally
substituted” were indefinite. Ex. 1172, at 6 and 9.

On September 12, 2007, Clark replaced claim 10 with a new claim reciting
“[a] (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) of claim 6 or
its pharmaceutically acceptable salt thereof wherein R1 and R7 are H.” Ex. 1173, at
6-7. Clark also deleted “or prodrug” from claim 25. Ex. 1173, at 9.

After the September 12, 2007 amendment, claim 6 did not recite a prodrug
of the compound, and the R1, R3, R4, and R7 constituents were limited beyond that
of published claim 10. Ex 1173 at and 2-3 and 6-7.

In the September 12, 2007 amendment, Clark states that the 35 U.S.C. § 112,
first paragraph rejection should be withdrawn because “the term ‘prodrug thereof’
does not appear in the presently amended claims.” Ex. 1173 at 26.

In the September 12, 2007 amendment, Clark states that the 35 U.S.C. § T12,
second paragraph rejection should be withdrawn because “the term ‘optionally
substituted’ . . . [does] not appear in the presently amended claims.” Ex. 1173 at
26.
In an Office Action dated February 26, 2008, the Examiner noted that the 35 U.S.C. § 112, first and second paragraph rejections were overcome by applicant’s amendments. Ex. 1174 at 2.

Analysis

Section 135(b)(2) reads:

A claim which is the same as, or for the same or substantially the same subject matter as, a claim of an application published under section 122(b) of this title may be made in an application filed after the application is published only if the claim is made before 1 year after the date on which the application is published.

Sommadossi directs us to no particular claim sets filed prior to 13 January 2006 upon which it relies. Paper 70, 12:13-26:7.

Sommadossi’s contends that Clark is not eligible for repose under § 135(b)(2) because Clark’s involved claims of the ‘572 patent are materially different from the published claims of the ‘737 publication. Paper 70, 12:13-17:23 (citing Ryan v. Young, 2008 WL 577435 (BPAI Mar. 4, 2008) and Steffel v. Schofield, 2011 WL 1576590, at *8 (BPAI Apr. 25, 2011)).

In particular, Sommadossi argues that claims 10 and 25 of the ‘737 patent were materially changed, after publication, in response to an Office Action rejection dated March 30, 2007. We find that there is sufficient evidence to support the position that claims 10 and 25 were successfully amended to overcome certain 35 U.S.C. § 112, first and second paragraph rejections. Clark does not oppose these findings.

Clark contends that Ryan was improperly decided because (1) it is not supported by the statute or legislative history, (2) it bars an applicant from moving for repose under 35 U.S.C. § 135(b)(2) without an issued patent, and (3) it transmutes the “material difference” test against the party who should be protected by repose. Paper 30, 18:2-8; Paper 83, 5:4-14.
We need not reach Clark's arguments regarding the *Ryan* decision because Sommadossi's involved claims only recite the compound or "a pharmaceutically acceptable salt thereof" and do not encompass a "prodrug." Thus, Sommadossi's allegedly "copied" claims are materially different in scope from Clark's published claims because they lack a limitation to a prodrug. Accordingly, Sommadossi's claims are not directed to the same or substantially the same subject matter as claim 10 or claim 25 of the '737 publication by virtue of the fact that they are materially narrower claims.

Accordingly, Clark has not met the burden of establishing that Sommadossi's claims are barred under 35 U.S.C. § 135(b)(2) because Clark has not shown that it is eligible for repose based on claims 10 and 25. Accordingly, we deny Clark Substantive Motion 3 with respect to 35 U.S.C. § 135(b)(2).

Since not all of Sommadossi's involved claims are barred under either 35 U.S.C. § 135(b)(1) or § 135(b)(2), we exercise our discretion to dismiss the remainder of the motion as its consideration does not aid in resolution of the priority dispute before us and is not consistent with securing the just, speedy and inexpensive determination of the interference. Bd. R. 125(a).

**Decision on Clark Substantive Motion 3**

Upon consideration of Clark Substantive Motion 3, and for the reasons given, it is

ORDERED that Clark Substantive Motion 3 is *denied-in-part* and

*dismissed-in-part.*

**II. Clark Substantive Motion 6**

For judgment based on some of Sommadossi's involved claims for being unpatentable under 35 U.S.C. § 101 and 112, first paragraph

Clark Substantive Motion 6 (Paper 35) seeks judgment against Sommadossi on the grounds that some, but not all, of Sommadossi's involved claims are

Sommadossi has opposed. Paper 71.

Clark has replied. Paper 86.

Clark has not challenged all of Sommadossi's involved claims. Paper 35, 3:8-13. Even if Clark prevailed on its motion, some of Sommadossi's involved claims would remain and the interference would continue. Accordingly, we dismiss the motion as its consideration does not further resolution of the priority dispute that is the subject matter of the interference. Bd. R. 125(a).

Decision on Clark Substantive Motion 6
Upon consideration of Clark Substantive Motion 6, and for the reasons given, it is

ORDERED that Clark Substantive Motion 6 is dismissed.

III. Sommadossi Responsive Motion 6

To substitute Count C or Count D for Count 1

Sommadossi Responsive Motion 6 (Paper 41) is responsive to Clark Motion 6 (Paper 37) which we dismissed. Accordingly we need not and do not reach Sommadossi Responsive Motion 6.

Decision on Sommadossi Responsive Motion 6
Upon consideration of Sommadossi Responsive Motion 6, and for the reasons given, it is

ORDERED that Sommadossi Responsive Motion 6 is dismissed as moot.

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Sommadossi Responsive Motion 6 was filed incorrectly numbered as Sommadossi Responsive Motion 18. Paper 41. Clark was ordered to respond as Opposition 6, and Sommadossi was ordered to respond as Reply 6. Paper 66. Accordingly, we will refer to this Motion as Sommadossi Responsive Motion 6.
IV. Clark Motion I

For benefit to Clark's Provisional Application 60/474,368

Clark Substantive Motion 1 (Paper 32) seeks to be accorded benefit for
Count 1 of US Provisional Application 60/474,368, filed May 20, 2003
(hereinafter “C1” or “the '368 Application”).

Sommadossi has filed an Opposition. Paper 68.

Clark has replied. Paper 85.

As the moving party, Clark has the burden to show that it is entitled to the
relief requested. Bd. R. 208(b).

Findings of Fact

Count 1 is as noted supra at Page 2 and will not be repeated here for brevity.
Count 1 is limited to certain constituents for X, R¹, R², R³, and R⁴. Paper 1, p. 8.
Count 1 is directed to a class of 2'-methyl, 2'-fluoro nucleosides with a
uracil or cytosine base. Id.

The application that became Clark’s involved patent was filed April 21,
2009, cover page.

Clark’s involved application includes a cross-reference to Clark’s C1
application. Ex. 2009, col. 1, ll. 7-10.

Clark’s involved patent and Clark’s C1 application both recited Jeremy C.
Clark as the sole inventor. Ex. 2009, cover page; see Exs. 2006 and 2007
(indicating the inventorship of Clark’s C1 application was corrected to recite only
Jeremy C. Clark as the sole inventor).

Clark’s C1 application discloses a compound referred therein as “beta-D-2'-
methyl-2’fluoro-2’-deoxycytidine,” “2'-methyl-2'-fluorocytidine” and “Compound
6,” which has the chemical structure reproduced below (hereinafter referred to as
“Compound 6”).
Compound 6 is encompassed by the scope of Count 1.

Clark’s C1 application discloses a scheme and procedure for preparing the above-described compound. Paper 32, 6:6-17; Ex. 2005, 32:17-34:25.


Applicable Law

In an interference, for a party to be accorded benefit for the purpose of priority, the party must establish that its “benefit” application constitutes a constructive reduction to practice of the subject matter of the count. Our applicable rule puts it this way (italics in original) “Constructive reduction to practice means a described and enabled anticipation under 35 U.S.C. 102(g)(1) in a patent application of the subject matter of the count.” 37 C.F.R. § 41.201 (definition of constructive reduction to practice); Hunt v. Treppschuh, 523 F.2d 1386, 1389 (CCPA 1975) (an application need only disclose a single enabled embodiment within the scope of the count to constitute a constructive reduction to practice of the invention of the count); see also Weil v. Fritz, 572 F.2d 856, 9 865 n.16 (CCPA 1978). “[T]he § 112, first paragraph, requirements need only be met for an
2005, 34:17-30) and its associated description teaches a specific procedure for
making Compound 6 such that the skilled artisan could make Compound 6 with
only routine, if any, experimentation. Ex. 2001, ¶ 88-91. Dr. Marquez further
testifies that Clark’s C1 application discloses what appears to be data confirming
that Compound 6 has antiviral activity. Id., ¶¶ 101-105.

Sommadossi filed an Opposition, but does not substantively contest Clark’s
motion. Paper 68. Rather, Sommadossi concedes that “neither party disputes the
proofs offered by Clark are sufficient” and the “[m]any of these same proofs are in

Decision on Clark Substantive Motion 1

Upon consideration of Clark Substantive Motion 1, and for the reasons
given, it is

ORDERED that Clark’s Substantive Motion 1 is granted.

FURTHER ORDERED that benefit is accorded to Clark for Clark’s

V. Clark Substantive Motion 2

To deny Sommadossi the accorded benefit of
Sommadossi’s Application 10/608,907

Clark Substantive Motion 2 (Paper 33) seeks to deny Sommadossi benefit
for Count 1 of US Application 10/608,907, filed June 27, 2003 (hereinafter “S4” or
“the ’907 Application”).

Sommadossi has opposed. Paper 69.

Clark has replied. Paper 82.

As the moving party, Clark has the burden to show that it is entitled to the
relief requested. Bd. R. 208(b).
Background of Motion

Clark seeks relief on the basis that (1) Sommadossi's S4 application does not constitute a constructive reduction to practice of the subject matter of Count 1 (i.e., does not include a described and enabled anticipatory embodiment that falls within Count 1) and that (2) Sommadossi's involved application fails to properly cross-reference Sommadossi's S4 application and thus is not entitled to benefit under 35 U.S.C. § 120.

Count 1 is as noted supra at Page 2 and will not be repeated here for brevity.

Count 1 is directed to a class of 2'-methyl, 2'-fluoro nucleosides with a uracil or cytosine base. Paper 1, p. 8.

Sommadossi's S4 application describes a preferred genus of Formula (IX) which is a 2'-methyl, 2'-fluoro nucleoside having the following structure:

![Formula IX](image)

wherein X=O, R^{13} is fluoro, R^{12} is CH_3, R^1 and R^2 is H, and Base* is "a purine or pyrimidine base." Ex. 3002, 100:6-29.

The S4 application includes a list of "purine" and "pyrimidine" bases that recites cytosine and uracil among other natural and synthetic bases. Ex. 3002, 104:15-32. The S4 application does not include a preference for a cytosine or uracil base.

Clark contends that this disclosure is insufficient to provide written descriptive support to an embodiment of Count 1, is not enabled, and lacks a credible utility. Paper 33. As discussed below, we conclude that Clark has shown
a lack of enablement for an embodiment of Count 1 and thus we need not and do not reach the utility and description issues raised by Clark.

**Analysis**

Enablement is a question of law involving underlying factual inquiries. See *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997).

"Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). The specification need not explicitly teach those in the art to make and use the invention; the requirement is satisfied if, given what they already know, the specification teaches those in the art enough that they can make and use the invention without "undue experimentation." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003).

Whether undue experimentation is required is a "conclusion reached by weighing many factual considerations... includ[ing] (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.").

*In re Wands*, 858 F.2d 731, 737 (Fed.Cir.1988).

Accordingly, we discuss each of the *Wands* factors below.

**Nature of the invention and breadth of the count**

There does not appear to be a dispute that the nature of the invention at issue is the synthesis of a nucleoside compound with a methyl constituent in the "up" 2'-position and a fluoro constituent in the "down" 2'-position. Paper 33, 9:19-10:2; Paper 69, 9:23-10:8 (indicating the need for "stereochemical control").
Level of Skill in the Art

Both Clark and Sommadossi agree that the level of skill in the art of nucleoside chemistry is high. Paper 33, 2:5-23; Paper 69, 8:21-23.

Clark presents evidence that the ordinary artisan would not have had expertise or experience with fluorination reactions, and would require some guidance. Paper 33, 10:3-5; Ex. 2001, ¶ 214. According to Clark's expert, fluorination chemistry is "considered a specialized field" and the ordinary chemist engaged in drug discovery did not have experience or expertise. Id.

Sommadossi does not dispute Clark's experts regarding the skilled artisan's general familiarity with fluorination reactions. Rather, Sommadossi argues that expertise with fluorination would not have been required. Paper 69, 9:21-23. This argument appears to be supported on cross-examination of Clark's expert witness:

Q. And now, other chemists, organic chemists can follow your publication and do the same. Is that right?

A. If they are interested in the field of fluorine chemistry or fluoro nucleosides, they might.

Ex. 2065, Marquez Tr. 64:22-65:3.

Accordingly, while fluorination reactions may be rare in nucleoside organic chemistry, the skilled artisan in nucleoside chemistry would likely be capable of performing a fluorination reaction in the manner described in the literature at the time of the invention.

State of the prior art

Sommadossi presents evidence of a scheme, "Scheme 1," that "could have been used" at the time of the invention to prepare a 2'-fluoro, 2'-methyl nucleoside. Ex. 1101, ¶ 95.
There appears to be no dispute that fluorinating agents and certain fluorinating reactions used in "Scheme 1," namely the DAST reagent, were known in the art as of June 27, 2003. Ex. 2001 ¶ 210-212; Ex. 1101, ¶ 100.

However, there also does not appear to be a dispute that Clark’s published patent application on January 13, 2005, after the filing date of Sommadossi’s S4 application, was the first reported scheme for the synthesis of 2’-fluoro, 2’-methyl nucleosides in the art. Paper 33, 10:10-11; Ex. 2001, ¶ 219; Ex. 1191, 158:6-159:10; Ex. 2008.

Clark’s published application describes the DAST reaction of Sommadossi’s Scheme 1. Ex. 1004, 49:44-49; Ex. 1101, ¶ 101.

**Predictability of the art**

Clark argues that fluorination chemistry can be unpredictable, especially for nucleoside molecules, such as that for Count 1. Paper 33, 10:5-7. Clark relies on the testimony of Dr. Marquez, whose qualifications to testify are discussed supra. In fact, Dr. Marquez testifies that “attempted fluorination reactions could result in products with the wrong stereochemistry, products resulting from undesired rearrangements or products in which no fluorination occurred.” Ex. 2001, ¶ 217.

Sommadossi argues that the DAST reaction had been extensively studied and that “replacement of hydroxyl groups by fluorine with DAST usually precedes with complete inversion of configuration” such that the conversion of hydroxy to fluoro in the 2’ position would have been “routine.” Paper 69, 10:2-8.

**Quantity of experimentation necessary**

Neither party discusses the quantity of experimentation that may be necessary to synthesize a 2’-methyl, 2’-fluoro nucleoside given the disclosure of Sommadossi’s S4 application.
Clark presents evidence that the experimentation would be a “trial-and-error process” that would require determination of “appropriate starting materials, reagents and chemical transformations.” Paper 33, 10:7-10; Ex. 2001, ¶217. 

*Amount of direction or guidance presented and presence or absence of working examples*

It is not disputed that Sommadossi’s S4 application does not include any working examples of 2’-methyl, 2’-fluoro nucleosides with a uracil or cytosine base. Admitted fact 55, Paper 33, 8:23-9:3; Paper 69, 9:9-11, Appx. 2-11; see generally Ex. 3002.

Sommadossi’s S4 application does not appear to describe any schemes or procedures for preparing a 2’-methyl, 2’-fluoro nucleoside with a uracil or cytosine base. Paper 33, 9:11-12; Paper 69, 9:12-18; see generally Ex. 3002.

Sommadossi’s S4 application does not appear to describe “fluorinating starting materials, fluorinating reagents, or compounds that could be fluorinated.” In particular, Sommadossi’s S4 application does not appear to describe DAST as a known or desirable fluorinating reagent. Paper 33, 9:20-22; Ex. 3002; Ex. 2001, ¶220; Ex. 1168, 156:21-157:15; Ex. 1169, 178:5-17.


Clark’s expert, Dr. Marquez, indicates that the scheme for making 2’-hydroxy, 2’-methyl described in Sommadossi’s S4 application would not be directly useful for fluorination via the DAST reaction that was known in the art because it would have been expected to result in the opposite stereochemistry. Paper 82, 4:3-15; Ex. 2001, ¶220. We credit Dr. Marquez’s testimony, which is supported by the description of the DAST reaction in Scheme 1, proposed by Sommadossi’s experts, having the opposite stereochemistry as that of the 2’-
hydroxy, 2'-methyl scheme described in Sommadossi’s S4 application. Compare Ex. 3002, 124:4-5 and 125:14-15 (showing a hydroxyl in the “down” 2'-position) and Ex. 1101, ¶ 100 (showing a hydroxyl in the “up” 2'-position).

Discussion

Sommadossi correctly points out that the absence of working examples is not dispositive of a lack of enablement. Paper 69, 9:9-11 (citing In re Strahilevitz, 668 F.2d 1229, 1232 (CCPA 1982) and Martin v. Johnson, 454 F.2d 746, 750 (CCPA 1972)). Yet, in considering the Wands factors discussed above, we determine that, having only the disclosure provided by Sommadossi’s S4 application, i.e., only the structure of a 2’-methyl, 2’-fluoro nucleoside, it would have required undue experimentation for the skilled artisan to synthesize the compound.

“Although the knowledge of one skilled in the art is indeed relevant, the novel aspect of an invention must be enabled in the patent.” Automotive Techs. Int’l, Inc. v. BMW of N. Am., Inc., 501 F.3d 1274, 1283 (Fed. Cir. 2007). “[O]mission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required.” Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

Here, the novel aspect appears to be the presence of a fluorine in the “down” 2’-position of a nucleoside. We agree with Clark that Sommadossi’s S4 application is so void of an explanation as to how to synthesize a 2’-fluoro, 2’-methyl nucleoside with the fluorine in the “down” position that the skilled artisan would have to rely on the prior art for all of the teachings necessary to make a compound of such a structure.
Moreover, Sommadossi’s “Scheme 1” appears to be similar to Clark’s own scheme for synthesis of a 2’-methyl, 2’-fluoro nucleoside, which was not prior art at the time of Sommadossi’s S4 application. We are persuaded that the skilled artisan could not have relied upon the synthesis of the 2’-hydroxy, 2’-methyl compound described in Sommadossi’s S4 application as a starting point for Sommadossi’s “Scheme 1” and nothing in Sommadossi’s S4 application would have instructed the skilled artisan to the DAST technique and the inverse stereochemistry used in Sommadossi’s “Scheme 1.” Accordingly, Sommadossi’s S4 application is not enabling for an embodiment encompassed by Count 1.

... We need not reach a decision on whether Sommadossi’s S4 Application has proper cross-reference under 35 U.S.C. § 120.

**Decision on Clark Substantive Motion 2**

Upon consideration of Clark Substantive Motion 2, and for the reasons given, it is

**** ORDERED that Clark’s Substantive Motion 2 is granted.****

FURTHER ORDERED that Sommadossi’s S4 application, US Application 10/608,907, fails to describe an embodiment within the scope of Count 1.

FURTHER ORDERED that benefit accorded to Sommadossi in the Declaration (Paper 1, page 10) as to Sommadossi’s S4 application 10/608,907, filed June 27, 2003 is vacated.

**VI. Sommadossi Substantive Motion 1**

**For benefit to Sommadossi’s Provisional Application 60/392,350**

Sommadossi Substantive Motion 1 (Paper 25) seeks to accord Sommadossi benefit for Count 1 of US Provisional Application 60/392,350, filed June 28, 2002 (hereinafter “S1” or “the ‘350 Application”).

Clark has opposed. Paper 72.
Sommadossi has replied. Paper 79.

As discussed above, we determine that Sommadossi was not entitled to benefit with respect to Count 1 of its intervening S4 Application. On this basis, priority benefit to Sommadossi’s earlier filed S1 Application is not appropriate for the same reasons.

Decision on Sommadossi Substantive Motion 1

Upon consideration of Sommadossi Substantive Motion 1, and for the reasons given, it is

ORDERED that Sommadossi Substantive Motion 1 is denied.

FURTHER ORDERED that Sommadossi is denied benefit to Sommadossi’s S1 application, US Provisional Application 60/392,350, filed June 28, 2002.

FURTHER ORDERED that party Clark shall be designated senior party for any further proceedings according to the Redeclaration issued herewith.

VII. Sommadossi Miscellaneous Motion 7

For authorization to amend the Specification of Sommadossi’s involved application 12/131,868 to recite a cross-reference to its earlier filed application 10/608,907

Because priority to Sommadossi’s earlier filed application 10/608,907 (S4 Application) was denied due to lack of enablement of an embodiment within the count, and we do not reach a decision on Clark’s contention that Sommadossi’s S4 Application lacked proper cross-reference under 35 U.S.C. § 120, Sommadossi’s Miscellaneous Motion 7 is moot.

2 Sommadossi Miscellaneous Motion 7 was filed incorrectly numbered as Sommadossi Miscellaneous Motion 19. Paper 58. It was ordered that these incorrectly numbered motion papers would hereinafter be stylized as Sommadossi Miscellaneous Motion 7, Clark Opposition 7, and Sommadossi Reply 7. Paper 66. Accordingly, we will refer to this Motion as Sommadossi Miscellaneous Motion 7.
Decision on Sommadossi Miscellaneous Motion 7

Upon consideration of Sommadossi Miscellaneous Motion 7, and for the reasons given, it is

ORDERED that Sommadossi Miscellaneous Motion 7 is dismissed as moot.

VIII. Clark Miscellaneous Motion 7

To exclude evidence

Clark Miscellaneous Motion 7 (Paper 95) seeks to exclude from evidence all or portions of the following exhibits: 1013, 1088, 1101, 1136, 1145, 1146, 1147, 1152, 1168, 1206, 1207, and 2065.

Sommadossi has opposed. Paper 97.

Clark has replied. Paper 102.

As the moving party, Clark has the burden to show that it is entitled to the relief requested. Bd. R. 208(b).

Conduct during Cross-Examination

Clark argues that pages 171:22-178:23 of Ex. 1168 (Deposition of Dr. Trost) is inadmissible under Rules 611(b) and 611(c) because it consists of deposition testimony obtained through the improper use of leading questions on re-direct, as well as questions on re-direct that were outside the scope of cross-examination.

Paper 95, 8:11-9:3. Clark also argues that pages 39:20-40:6, 171:3-8, and 202:12-203:9 of Ex. 1207 (Deposition of Dr. Marquez of September 26, 2012) are inadmissible under FRE 611(a) because these portions of Ex. 1207 consist of Dr. Marquez’s responses to questions that improperly mischaracterized his prior testimony. Id., 10:8-11:10.

Clark also argues that pp. 174:15-16 of Ex. 2065 (Deposition of Dr. Marquez of July 27, 2012) is inadmissible under Rule 611(a). Our decision does not rely on the portions of Ex. 1168, 1207, and 2065 raised by Clark as allegedly being improper. Accordingly, this portion of the motion is dismissed as moot.

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Cumulative exhibits/Duplicity

Clark contends that these exhibits are inadmissible under FRE 403 as cumulative and a "waste of time." E.g., Paper 95, 1:17. According to Clark, Exhibits 1013 (Declaration of Dr. Lemon) and 1088 (Declaration of Dr. Glenn) are substantially identical testimony, at times verbatim. Paper 95, 1:13-24, 2:13-15, 3:5-13. Likewise, according to Clark, Exhibits 1101 (Declaration of Dr. Damha) and 1136/1152 (Declarations of Dr. Trost) are substantially identical testimony, at times verbatim. Id., 3:20-4:15, 5:1-24. According to Clark, Exhibits 1145 (Declaration of Dr. Lemon) and 1146 (Declaration of Dr. Glenn) are likewise substantially identical testimony, at times verbatim. Id., 6:21-7:14. Clark argues that certain paragraphs of Exhibits 1147 are substantially identical in content to certain paragraphs of Exhibit 1136. Id., 7:15-23. Clark also argues that Exhibit 1152 (Declaration of Dr. Trost), which is supplement evidence to Ex. 1136 (Declaration of Dr. Trost) is inadmissible for the same reason as Ex. 1136. Id., 7:24-8:10. Clark also argues that Ex. 1206 is an unsigned version of Ex. 2094 and Ex. 1207 is an unsigned version of Ex. 2093 and, thus, duplicative. Id., 9:10-10:7. Finally, Clark argues that repetitive questioning of Dr. Marquez in Ex. 2065 is cumulative and improper. Id., 11:11-12:15. Among other arguments, Sommadossi responds that the duplicative testimony reflects the fact that two experts with difference experience and backgrounds have the same opinion. Paper 97, 1:5-24, 4:14-5:6.

We decline to exclude the evidence solely on the basis that it is cumulative or duplicative. The evidence Clark argues to be duplicative is not excessive and appears to be used to reinforce other similar evidence. To the extent that the presentation of testimony that is verbatim identical cast doubt on the veracity of the testimony, we choose to consider this as an issue of credibility, not admissibility. We deny this portion of the motion.
Relevance

Clark argues that the declaration testimony of Dr. Lemon (Ex. 1013) and Dr. Glenn (Ex. 1088) directed to "the availability of various procedures for testing compounds as of December 14, 2001, are irrelevant to determining any issue in the interference" because "evidence regarding whether it would have been possible to test compounds for pharmacological activity does not establish utility and confuses the issues of enablement and utility." Paper 95, 2:1-12 and 22-4.

This argument is moot in light of the fact that our decision did not reach the issue of utility in any application or rely on the portion of the testimony of Dr. Lemon and Dr. Glenn raised by Clark. We dismiss as moot this portion of the motion.

Timeliness

Clark argues that Ex. 1136 (Declaration testimony of Dr. Trost) is inadmissible under Standing Order ¶ 7.2 for being served on Clark on June 22, 2012, over two weeks after the June 5, 2012, deadline for serving evidence in support of Sommadossi Substantive Motion T. Paper 95, 6:1-13.

It appears that Ex. 1136 was filed in support of Sommadossi Responsive Motion 6. This motion was dismissed. Accordingly, we did not rely upon Ex. 1136. This portion of the Motion is dismissed as moot.

Decision on Clark's Miscellaneous Motion 7

Upon consideration of Clark's Miscellaneous Motion 7, and for the reasons given, it is ORDERED that Clark's Miscellaneous Motion 7 is dismissed-in-part and denied-in-part.
IX. Sommadossi Motion 8

To exclude evidence

Sommadossi Miscellaneous Motion 8 (Paper 93) seeks to exclude from evidence all or portions of the following exhibits: 2025, 2054, 1167/1190, and 1168/1191.

Clark has opposed. Paper 99.

Sommadossi has replied. Paper 101.

As the moving party, Sommadossi has the burden to show that it is entitled to the relief requested. Bd. R. 208(b).

Exhibit 1167/1190

Sommadossi argues that page 97, ll. 6-15 of Ex. 1167/Ex. 1190 (Dr. Glenn’s Deposition Testimony with and without and errata sheet) should be excluded from evidence because Clark’s counsel’s questioning went beyond the scope of Dr. Glenn’s declaration (Ex. 1088). Paper 93, 4:1-24. According to Sommadossi, this testimony addressed “the meaning of the phrases ‘capable of providing’ and ‘providing.’” Id., 4:9-10.

We note that Clark did not rely on Dr. Glenn’s testimony regarding the meaning of the terms “capable of providing” and “providing.” Paper 83, 2:7-23.

In fact, we note above that Clark relies on no evidence that the terms “capable of providing” and “providing” have different meanings.

Accordingly, we did not consider this testimony in rendering our decision on that issue supra. Thus, this portion of the Sommadossi Motion is dismissed as moot.

Exhibits 2025 and 2054

Sommadossi argues that Ex. 2025 (Lalezari article) should be excluded for lack of authentication and as inadmissible hearsay under F.R.E. 901 and 802. Paper 93, 1:6-3:8. According to Sommadossi, this article was submitted as
evidence that Clark’s “Compound 6” “has been shown to be effective against HCV
in human clinical trials.” Id.

Sommadossi also argues that Ex. 2054 (Sommadossi declaration submitted
in Interference 103,906) as inadmissible hearsay under FRE 802. Id., 3:9-23.

According to Sommadossi, this testimony was directed to whether “one cannot
predict a compound’s activity against another virus without testing it.” Id.

We credit the largely uncontested testimony of Dr. Marquez as to the skilled
artisan’s understanding of disclosure in Clark’s C1 application as evidence of the
activity of Compound 6. We do not find it necessary to consider Ex. 2025 or Ex.
2054 to support a finding of utility in Clark’s C1 application. Accordingly, we do
not consider this testimony in rendering our decision on that issue supra. Thus,
this portion of the Sommadossi Motion is dismissed as moot.

Exhibit 1168/1191

Sommadossi also argues that page 188, l. 25 to page 190, l. 19 of Ex
1168/Ex 1191 (Dr. Trost’s Deposition Testimony with and without an errata sheet)
should be excluded from evidence because the re-cross questions posed by Clark’s
counsel went beyond the scope of Sommadossi’s counsel’s redirect examination.

Paper 93, 4:1-24. According to Sommadossi, Clark relied on this testimony in its
Opposition 6 as evidence that Sommadossi’s schemes “were created by
Sommadossi in hindsight by copying Clark’s procedures.” Id.

We do not reach Sommadossi Responsive Motion 6 and as a consequence,
Clark Opposition 6. According this portion of the Motion is dismissed as moot.

Decision on Sommadossi Miscellaneous Motion 8

Upon consideration of Sommadossi Miscellaneous Motion 8, and for the
reasons given, it is

ORDERED that Sommadossi Miscellaneous Motion 8 is dismissed.

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Inhibition of hepatitis C replicon RNA synthesis by \(\beta\)-D-2'-deoxy-2'-fluoro-2'-C-methylcytidine: a specific inhibitor of hepatitis C virus replication

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\(\beta\)-D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine (PSI-6130) is a cytidine analogue with potent and selective anti-hepatitis C virus (HCV) activity in the subgenomic HCV replicon assay. 90% effective concentration (EC\(_{90}\))=4.6 ±2.0 \(\mu\)M. The spectrum of activity and cytopathicity profile of PSI-6130 was evaluated against a diverse panel of viruses and cell types, and against two additional HCV-1b replicons. The S282T mutation, which confers resistance to 2-C-methyl adenosine and other 2'-methylated nucleosides, showed only a 6.5-fold increase in EC\(_{90}\). When assayed for activity against bovine diarrhoea virus (BVDV), which is typically used as a surrogate assay to identify compounds active against HCV, PSI-6130 showed no anti-BVDV activity. Weak antiviral activity was noted against other flaviviruses, including West Nile virus, Dengue type 2, and yellow fever virus. These results indicate that PSI-6130 is a specific inhibitor of HCV. PSI-6130 showed little or no cytoxicity against various cell types, including human peripheral blood mononuclear and human bone marrow progenitor cells. No mitochondrial toxicity was observed with PSI-6130. The reduced activity against the RdRp S282T mutant suggests that PSI-6130 is an inhibitor of replication RNA synthesis. Finally, the no-effect dose for mice treated intraperitoneally with PSI-6130 for six consecutive days was \(\leq\)100 mg/kg per day.

Keywords: antiviral activity, HCV, PSI-6130

Introduction

Hepatitis C virus (HCV), an important member of the Flaviviridae, is the leading cause of liver transplantation in the United States. Nearly 500,000 people in the United States are estimated to be infected, and an estimated 170 million people worldwide are HCV carriers (Poynter et al., 2000; Alter et al., 1999). The current standard of care is a combination of pegylated interferon and ribavirin (Di Bisceglie et al., 2002; Collier & Chapman, 2001; Alter et al., 1999). Because of the adverse effects associated with both interferon and ribavirin (Di Bisceglie et al., 2002; Collier & Chapman, 2001; Alter et al., 1999), there is a need for more potent anti-HCV compounds with fewer adverse effects.

The lack of cell-based assays for HCV has hindered the discovery and development of therapies to treat HCV infection. However, surrogate models such as the HCV RNA replicon that replicates in human hepatoma cells has facilitated the identification of candidate anti-HCV drugs (Lohmann et al., 1999; Blight et al., 2000). Nucleoside analogues, which inhibit viral encoded polymerases, have a proven track record as therapies for viral infections caused by herpes viruses, HIV and hepatitis B virus (De Clercq, 2004). The HCV RNA-dependent RNA polymerase NS5B protein (RdRsp) is considered to be essential for HCV replication and therefore is an ideal...
therapeutic target for nucleoside analogues (Yamashita et al., 1998; Lohmann et al., 1998; Lohmann et al., 1997; Ishii et al., 1999; Blight et al., 2000).

Recently, several 2'-modified nucleoside analogues with activity against HCV have been identified (Yamashita et al., 1998; Lohmann et al., 1998; Lohmann et al., 1997; Ishii et al., 1999; Blight et al., 2000). These compounds are phosphorylated to the corresponding 5'-triphosphate which in turn inhibits the HCV RdRp. Of these compounds the valine ester of β-d-2'-C-methylecytidine (NM283, valopicitabine) is currently undergoing Phase II clinical trials in HCV-infected individuals (Pietra et al., 2005). Here we describe the in vitro results of studies with β-d-2'-deoxy-2'-fluoro-2'-C-methylecytidine (PSI-6130; Figure 1), a new, potent and specific anti-HCV compound, which shows little or no toxicity in vitro and in vivo.

Materials and methods

Chemistry

PSI-6130 (Figure 1) was synthesized according to the methods of Clark et al. (2005). 2'-C-Methylcytidine and 2'-C-methyladenosine were synthesized in our laboratories following published procedures (Elledrup et al., 2004; Clark et al., 2005). Interferon-α2a (Roferon-A) was obtained from Hoffmann-La Roche Inc., Nutley, NJ, USA.

Virology

Viruses and cells. The HCV subgenomic replica-RNA-containing Huh 7 cells (Clone A cells; Apathe, LLC, St. Louis, MO, USA) and the full length HCV replicon RNA-containing Huh 7 cells, 21-S, kindly provided by Dr Ralf Bartenschlager (Johannes-Gutenberg University Mainz, Mainz, Germany), were maintained in exponential growth in Dulbecco’s modified Eagle’s medium (high glucose and no pyruvate) containing 10% fetal bovine serum, 1x nonessential amino acids, 100 U/ml of penicillin, 100 µg/ml of streptomycin, 0.292 mg/ml of glutamine and 500 µg/ml of G418. Madin–Darby bovine kidney (MDBK) cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% horse serum and 100 µg/ml of penicillin-streptomycin. HepAD38 cells (a gift from Dr Brent Korba) were maintained in Dulbecco’s modified Eagle’s/F12 medium (DMEM/F12; Gibco/Invitrogen Technologies, Carlsbad, CA, USA) supplemented with 10% heat inactivated fetal bovine serum, 50 µg/ml of penicillin, 50 µg/ml of streptomycin, 100 µg/ml of kanamycin and 0.3 µg/ml of tetracycline in a humidified 5% CO₂ atmosphere at 37°C. The cytopathic NADL strain of bovine diarrhea virus (BVDV) was kindly provided by Dr Ruben Donis, University of Nebraska. The New Guinea strain of Dengue type 2 virus (DV) and the New York strain of the West Nile virus (WNV) were provided by Drs N Karabatsos and R Lanciotti, respectively, of the Centers for Disease Control and Prevention, Atlanta, GA, USA. The 17D strain of yellow fever virus (YFV), CEM and HepG2 cells (HB-8065) were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA).

Generation of NSSB 52B2T mutant replicon. Clone A cells were seeded into six-well plates at 2.4×10⁶ cells/well in the presence of 1 mg/ml G418 and 5 µM of 2'-C-Me-adenosine in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum, 1x nonessential amino acids, 100 U/ml of penicillin, 100 µg/ml of streptomycin and 0.292 mg/ml of glutamine. After 10 days, cells became confluent. Cultures were then split with a one to five dilution into fresh medium and the concentration of compound was increased to 10 µM. On day 21, the concentration was increased to 20 µM. On day 34, cell death was first noted, and small colonies of cells resistant to the inhibitor and the antibiotic became visible. The medium was renewed as needed, and on day 47, resistant colonies were isolated and transferred to a 24-well plate. Resistant colonies were then expanded and characterized. RNA was isolated from a representative clone using the RNeasy 96 kit (Qiagen, Valencia, CA, USA), reverse transcribed and amplified. The resulting DNA was sequenced using primers specific for NSSB to identify any mutations present in the NSSB polymerase gene. The only mutation found in the NSSB of the resistant clone was
the substitution of serine 282 with threonine (S282T), consistent with Migliaccio et al. (2003).

**HCV replicon assay.** The HCV replicon assay was performed as previously described by Stryver et al. (2003b). Briefly, clone A cells were added to a 96-well plate at 1,000 cells/well in 50 μl of medium without G418. Test compounds in 50 μl (two-fold serial dilutions) were added immediately after seeding. Plates were incubated at 37°C in a 5% CO₂ atmosphere for 4 days. Replicon RNA was extracted and amplified in a single-step multiplex RT-PCR protocol as described by Stryver et al. (2003b). Antiviral activity was determined by subtracting the average threshold RT-PCR cycle of the test compound from the average threshold RT-PCR cycle of the no-drug control (ΔCt_{test}). A ΔCt of 3.3 equals a 1-log reduction (equal to the 90% effective concentration [EC_{90}]) in replicon RNA levels. Cytotoxicity of test compounds was also determined by calculating the ΔCt for ribosomal RNA (ΔCt_{rRNA}).

**BVDV assay.** Cells were seeded in a 96-well plate at 5×10^3 cells/well and incubated for 72 h at 37°C in a humidified 5% CO₂ atmosphere. The cells were then infected with the cytopathic NADL strain of BVDV at a virus dilution of 10^{-2} and incubated for 45 min. Cell monolayers were washed three times with medium. Fresh medium containing serial dilutions of test compounds or ribavirin (positive control) was added to cultures, and medium containing no drug was added to the no-drug controls. After 72 h incubation, supernatant was collected and viral RNA was extracted using the QIAamp Viral RNA Mini Kit (Qiagen). Viral load was determined by quantitative RT-PCR using primers specific for the NADL strain of BVDV, (Stryver et al., 2003b).

**DV, WNV and YFV assays.** Antiviral activity against DV, WNV and YFV was determined using the neutral red dye uptake assay described by McManus (1976). A known positive control compound was included in each assay. Ribavirin was used as the positive control in the DV virus assays, and 6-azauridine was the positive control for the WNV and YFV assays.

**HIV assay.** The assay was performed using a modification of the assay described by Schinazi et al. (1990 & 1992). Briefly, primary human peripheral blood mononuclear (PBMC) cells were isolated from sero-negative donors and activated with phytohemagglutinin A (1 μg/ml). Cells were infected with HIV-1 (HIV-1_FAI (Centers for Disease Control and Prevention)) at a multiplicity of infection of 0.1. At 1 hr post-infection, compounds were added in duplicate at concentrations of 0.1, 1.0, 10, and 100 μM. 3'-Azido-3'-deoxythymidine (AZT) was used as a positive control. After incubating for 6 days at 37°C in a humidified 5% CO₂ atmosphere, 1 ml of culture supernatant was centrifuged and the virus pellet resuspended in 100 μl of a buffer containing 0.05 M Tris, pH 7.8, 0.5% Triton X-100, 0.8 M NaCl, 0.5 mM phenylmethylsulfonyl fluoride, and 20% glycerol. Ten microliters of solubilized virus were added to 75 μl of reverse transcriptase reaction mixture (0.06 M Tris at pH 7.8, 0.012 M MgCl₂, 0.006 M dithiothreitol, 0.006 mg/ml poly rA·oligo dT₁₂₋₁₈ [Amersham Bioscience, Piscataway, NJ, USA], 96 μg/ml dATP [Sigma-Aldrich, St. Louis, MO, USA] and 1 μM [³H]-thymidine-5'-triphosphate [87.0 Ci/m mole; Perkin Elmer, Boston, MA, USA]) and incubated at 37°C for 2 h. The reaction was stopped and the reaction product precipitated by the addition of 10% trichloroacetic acid (100 μl) containing 0.05% sodium pyrophosphate. The precipitate was collected using a Packard FilterMate Cell Harvester (Packard, Meriden, CT, USA) and counted in a Packard Direct Beta Counter. The 50% effective concentration was determined using the method of Belenk'kii and Schinazi (1994).

**HBV assay.** The HBV quantitative-PCR assay with HepAD38 cells was performed as previously described (Stryver et al., 2002; Hassan et al., 2003). HepAD38 cells replicate HBV under conditions that can be regulated with tetracycline (Ladner et al., 1997). HepAD38 cells were seeded into 96-well plates at 5×10⁶ cells/well in 200 μl of medium and incubated at 37°C in a humidified 5% CO₂ atmosphere. On day two, medium was removed and the cells were washed with PBS. Compounds and controls were prepared in medium without tetracycline and added at 10 μM (final concentration) in duplicate. On day seven, HepAD38 cell supernatant was collected and stored for analysis. Supernatant containing extracellular HBV was extracted using DNeasy® 96 Tissue Kit (Qiagen, catalog #69582) in a 96-well format. DNA was eluted at 100 μl total volume and 5 μl was used for real time PCR in a 25 μl reaction. HBV primers were used at 22.5 pmol/reaction and probe was used at 5 pmol/reaction (Operon, Huntsville, AL, USA/Qiagen). Taqman® Universal PCR Master Mix was added at twice the concentration (Applied Biosystems, Foster City, CA, USA/Roche, Pleasanton, CA, USA).

**Cytotoxicity assay.** Human PBMC cells (5×10⁶ cells/well), CEM cells (2.5×10⁶ cells/well), HepG2 (5×10⁶ cells/well), Huh-7 (5×10⁶ cells/well) and Clone A cells (5×10⁶ cells/well) were seeded in 96-well plates in the presence of increasing concentrations of test compound and incubated at 37°C in a humidified 5% CO₂ atmosphere for 3–5 days. For each assay, 50 μl of twofold serial dilutions of test compound.
were added in to each well of a 96-well plate. Final concentrations of PSI-6130 ranged from 1 to 100 μM. A "no drug" (medium only) control and a "cells plus medium only" control were included. After 5 days incubation for PBM cells, 3 days incubation for CEM cells or 4 days incubation for all others, cell viability was determined using the CellTiter 96 AQ 
One Solution cell proliferation colorimetric assay (Promega, Madison, WI, USA). The absorbance (490 nm) was then read on an ELISA plate reader using the 'no drug' wells as blanks. Cytotoxicity was expressed as the concentration of test compound that inhibited cell growth by 50% (CC_{50}).

**Human bone marrow cytotoxicity assay.** Primary human bone marrow mononuclear cells were obtained from Cambrex Bioscience (Walkersville, MD, USA). CFU-GM assays were performed using a bilayer soft agar in the presence of 50 units/ml human recombinant granulocyte/macrophage colony-stimulating factor, whereas BFU-E assays used a methylcellulose matrix containing 1 unit/ml erythropoietin (Sommadossi & Carlisle, 1987). Cells were incubated in the presence of the compound for 14–18 days at 37°C with 5% CO₂. Colonies of greater than 50 cells were counted using an inverted microscope to determine 50% inhibition concentration (Sommadossi et al., 1992). Each experiment was performed in duplicate using cells from three different donors. 3'-Azido-3'-deoxythymidine (AZT) was used as a positive control.

**Mitochondrial toxicity assays.** HepG2 cells (5,000 cells/well) were seeded in 96-well, collagen-coated plates. Test compounds were added to the medium at selected concentrations and the plates were incubated at 37°C in a humidified 5% CO₂ atmosphere for 14 days. After incubation, the supernatant was removed and cellular nucleic acids were extracted using a RNeasy 96 kit (Qiagen). The mitochondrial cytochrome C oxidase subunit II (cox2) gene and ribosomal DNA (rDNA) were amplified from a 5 µl sample using a multiplex quantitative PCR protocol (Stuyver et al., 2002) and the ΔCt (mitochondrial DNA) and ΔCt (rDNA) for each sample were determined. The fold difference in mitochondrial DNA normalized for rDNA relative to control was calculated.

Lactic acid quantification was performed using the D-lactic acid/ t-lactic acid test kit (Boehringer Mannheim, Indianapolis, IN, USA / R-Biopharm, South Marshall, MI, USA/ Roche). The total amount of lactic acid produced for each sample was determined as well as the fold change in lactic acid production (% of lactic acid/ % of rDNA), following a 7 day incubation in the presence of various concentrations of PSI-6130, as described in the manufacturer's instructions.

**Evaluation of toxicity in mice.** Five groups of five six-week-old female Swiss mice (SWR/J; Charles River Laboratory, Wilmington, MA, USA) were dosed intraperitoneally (i.p.) with 0, 3, 3, 10, 33 or 100 mg/kg per day of PSI-6130 dissolved in pyrogen-free, sterile saline (0.85% NaCl, Sigma-Aldrich, St. Louis MO, USA). Animals were monitored daily for weight changes, general appearance and mortality up to 24 days post-treatment. The statistical significance of changes in animal weight was evaluated by one-way analysis of variance. A P-value of <0.05 was deemed statistically significant. These studies were conducted under the approval of the Institutional Animal Care and Use Committee (IACUC) of the Department of Veteran Affairs, Atlanta, GA, USA.

**Results**

**Inhibition of HCV RNA in replicon cells**

The results from the subgenomic HCV replicon assay with PSI-6130 are presented as EC_{50} values in Table 1. An EC_{50} value of 4.6 ±2.0 μM was determined for PSI-6130. Comparing the activity of PSI-6130 with that of 2'-C-methylcytidine (2'-C-MeC), 2'-C-methyladenosine (2'-C-Mea) and 2'-deoxy-2'-fluorocytidine (2'-F-C), we found that PSI-6130 was greater than fourfold more potent than 2'-C-MeC, half as active as 2'-C-Mea and showed similar activity to 2'-F-C (Table 1). The activity of PSI-6130 was also compared with that of 2'-C-MeC and 2'-C-Mea using the full length replicon 21–5. The EC_{50} values were lower for each of the compounds, but the relative potency was similar to what was seen with the Clone A subgenomic replicon (Table 1).

It has been demonstrated that candidate antiviral agents can indirectly alter replicon RNA levels by affecting cell growth rates (Stuyver et al., 2003a). To address this issue, we followed the level of HCV replicon RNA on a per cell basis over the course of 7 days in cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>Replicon</th>
<th>21-5 HCV</th>
<th>5282T</th>
<th>BVDV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI-6130</td>
<td>4.6±0.2</td>
<td>1.6±0.7</td>
<td>30.7±11.7</td>
<td>&gt;100</td>
</tr>
<tr>
<td>2'-C-MeC</td>
<td>21.9±4.3</td>
<td>6.6*</td>
<td>&gt;100</td>
<td>2.3±0.1</td>
</tr>
<tr>
<td>2'-C-Mea</td>
<td>2.1±0.27</td>
<td>0.6*</td>
<td>&gt;100</td>
<td>2.0±0.08</td>
</tr>
<tr>
<td>2'-F-Cytidine</td>
<td>6.5±1.6</td>
<td>ND</td>
<td>ND</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

*Single assay performed in duplicate. ND, not determined.
treated with PSI-6130. Cells were seeded in the presence or absence of PSI-6130 (5 μM and 25 μM) and incubated at 37°C. On days 3–7, cells were harvested and counted using the trypan blue exclusion method, followed by total cellular RNA isolation and quantification of replicon RNA. When the log_{10} change in HCV replicon RNA copy number was determined per cell, cells treated with PSI-6130 showed a significant and steady decrease in replicon copy number per cell compared to untreated control cells, which showed a slight increase in replicon copy number (Figure 2A). Interferon-α2a and ribavirin was used as a positive and negative control, respectively (Figure 2B). Compared to the "no drug" control, interferon-α2a significantly reduced the HCV replicon RNA copy numbers per cell (Figure 2B), whereas ribavirin reduced the replicon RNA copy number per cell only minimally (Figure 2B). These results indicate that PSI-6130 selectively inhibited replication of the HCV replicon.

Migliaccio et al. (2003) previously isolated a resistant replicon by passaging in the presence of 2'-C-MeA and identified a serine to threonine mutation at position 282 of the HCV RdRp that conferred a loss of sensitivity to 2'-C-MeA. In contrast to 2'-C-MeA and 2'-C-MeC, which were inactive against the S282T mutant, PSI-6130 showed only a 6.5-fold increase in EC_{50} (30.7 ± 11.7 μM) with the S282T mutant replicon (Table 1).

Prevention of PSI-6130 inhibition of HCV replicon replication

Using a real-time RT-PCR assay (Sneyers et al., 2003b), the ability of natural nucleosides to prevent the anti-HCV activity of PSI-6130 was explored to gain some insight as to the mechanism by which PSI-6130 is phosphorylated in replicon cells. These reversal studies were performed with exogenously added natural nucleosides. In these studies, 5 μM of PSI-6130 (the concentration of PSI-6130 that approximates the EC_{50} value) was incubated with natural ribo- or 2'-deoxyribonucleosides at a concentration of 50 μM (approximately 10-times the EC_{50} of PSI-6130). Cells were incubated at 37°C in a humidified 5% CO₂ atmosphere for 4 days and antiviral activity was determined by real time PCR as described in the Materials and methods. Of the natural nucleoside analogues tested, only 2'-deoxycytidine completely inhibited the antiviral activity of PSI-6130 (Table 2). Exogenous cytidine caused a partial reversal of antiviral activity whereas none of the other ribo- or

![Image](image-url)

**Figure 2. Effect of PSI-6130 (A), Ribavirin or Interferon (B) on HCV replicon RNA per cell**

**Table 2. Prevention of the anti-HCV activity of PSI-6130 by exogenously added nucleosides**

<table>
<thead>
<tr>
<th>Competing nucleoside (50 μM)</th>
<th>ΔCt ±SD</th>
<th>% Inhibition of HCV replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI-6130 control</td>
<td>3.39 ±0.11</td>
<td>90.4</td>
</tr>
<tr>
<td>Cytidine</td>
<td>0.74 ±0.87</td>
<td>40.0</td>
</tr>
<tr>
<td>Uridine</td>
<td>3.52 ±0.61</td>
<td>91.2</td>
</tr>
<tr>
<td>Adenosine</td>
<td>2.82 ±0.53</td>
<td>85.8</td>
</tr>
<tr>
<td>Guanosine</td>
<td>2.90 ±0.06</td>
<td>86.5</td>
</tr>
<tr>
<td>2'-Deoxyuridine</td>
<td>0.00 ±0.14</td>
<td>0.0</td>
</tr>
<tr>
<td>2'-Deoxyxuridine</td>
<td>3.38 ±0.01</td>
<td>90.3</td>
</tr>
<tr>
<td>Thymidine</td>
<td>4.59 ±0.14</td>
<td>95.8</td>
</tr>
<tr>
<td>2'-Deoxyadenosine</td>
<td>3.42 ±0.08</td>
<td>90.6</td>
</tr>
<tr>
<td>2'-Deoxyguanosine</td>
<td>3.42 ±0.17</td>
<td>89.3</td>
</tr>
</tbody>
</table>

ΔCt (the average threshold RT-PCR cycle of the test compound subtracted from the average threshold RT-PCR cycle of the no-drug control) of 3.3 equals a 1-log reduction or 90% inhibition.
2'-deoxyribonucleoside analogues were effective (Table 2). These results were quite different from those obtained with 2'-C-MeC where cytidine completely reversed the anti-HCV activity of the compound (data not shown). These results suggest that there are differences in the metabolic pathways of PSI-6130 and 2'-C-MeC even though both compounds are cytidine analogues.

Activity of PSI-6130 against other viruses

Like HCV, BVDV, WNV, YFV and DV are members of the Flaviviridae family of viruses. To demonstrate the specificity of PSI-6130 for HCV, we tested the compound for activity against these other flaviviruses. BVDV is typically used as an HCV surrogate to assess compounds for potential activity against HCV. Interestingly, unlike 2'-C-MeC and 2'-C-MeA that were active against the NADL strain of BVDV, giving EC concentrations of 2.4 μM and 1.5 μM, respectively; PSI-6130 was not active against this virus (EC >100 μM; Table 1). PSI-6130 had little or no activity against WNV (EC >46.3 μM), YFV (in two separate experiments EC >46.3 μM and 100 μM) and DV (EC >100 μM). PSI-6130 was also found to be inactive against HIV (EC >100 μM) and HBV (EC >100 μM).

Cytotoxicity and mitochondrial toxicity of PSI-6130

In standard 3-4 or 5-day cytotoxicity assays with Huh7, Clone A replicon cells, HepG2 cells, CEM cells and human PBM cells, PSI-6130 did not show significant toxicity in the MTT assay at concentrations up to 100 μM (Table 3). Bone marrow toxicity is the principal dose-limiting toxicity associated with a number of nucleoside antiviral drugs (Sommadossi et al. 1992; Sommadossi and Carlisle, 1987). Therefore, candidate antiviral nucleosides are typically evaluated in vitro for their haematopoietic toxicity potential. PSI-6130 showed inhibition of BU-E and CFU-GM growth at concentrations >80 μM, whereas 2'-C-methylcytidine inhibited these cells at twofold lower concentrations (Table 4). The AZT control was toxic and gave values similar to published results (Table 4).

As mitochondrial toxicity has been associated with several nucleoside analogues, the effect of PSI-6130 on mitochondrial DNA content was determined using HepG2 cells. In a 14-day mitochondrial toxicity assay, no significant effect on mitochondrial DNA content was observed when PSI-6130 was evaluated up to 100 μM (Table 5). In contrast, the positive control, 2',3'-dideoxy-cytidine, was toxic at a concentration less than 10 μM. In addition, the effect of PSI-6130 on lactate production, another measure of mitochondrial toxicity, was assessed. In a 7-day assay, no increase in lactate was noted at concentrations up to 33 μM, the highest concentration tested (data not shown).

Evaluation of toxicity in mice

Swiss mice (five animals/dose) were given single i.p. injections of PSI-6130 for six consecutive days (that is, days 0-5). The doses tested were 0, 3, 10, 33.3 and 100 mg/kg administered in 500 μl of sterile saline solution. Mortality and overall appearance (that is, ruffled fur, dehydration, etc.) of the mice were monitored daily and individual animal weights were determined on days 0, 1, 2, 3, 4, 5, 7, 9, 11, 14, 18, 21, 25, 28 and 30. As shown in Figure 3, there were no significant differences in the weight gain among the

Table 3. Cytotoxicity of PSI-6130 compared with other nucleoside analogues with anti-HCV activity

<table>
<thead>
<tr>
<th>Compound</th>
<th>Clone A</th>
<th>Huh7</th>
<th>HepG2</th>
<th>CEM</th>
<th>PBM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI-6130</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>2'-C-MeC</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>2'-C-MeA</td>
<td>30.5</td>
<td>50.2</td>
<td>31.2</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>2'-F-Cytidine</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

All experiments were performed in duplicate. CC_{50} concentration of compound that inhibits cell growth by 50%; ND, not determined; PBM, peripheral blood mononuclear.

Table 4. Effect of PSI-6130 and 2'-C-Methylcytidine on human bone marrow progenitor cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>BFU-E, μM</th>
<th>CFU-GM, μM</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSI-6130</td>
<td>83.6 ± 4.8</td>
<td>86.5 ± 6.4</td>
</tr>
<tr>
<td>2'-C-Methylcytidine</td>
<td>36.1 ± 6.0</td>
<td>33.7 ± 2.8</td>
</tr>
<tr>
<td>AZT</td>
<td>0.09 ± 0.01</td>
<td>2.9 ± 1.2</td>
</tr>
</tbody>
</table>

BFU-E, erythroid blast forming unit; CC_{50} concentration of compound that inhibits cell growth by 50%; CFU-GM, granulocyte macrophage colony forming unit.

Table 5. Fourteen day mitochondrial toxicity assay comparing PSI-6130 with 2'-C-Methylcytidine, 2'-C-Methyladenosine and 2'-F-Cytidine

<table>
<thead>
<tr>
<th>Compound</th>
<th>MitCoxII</th>
<th>rDNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dideoxycytidine</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>PSI-6130</td>
<td>&gt;100</td>
<td>71.80 ± 33.6</td>
</tr>
<tr>
<td>2'-C-Methylcytidine</td>
<td>32.5 ± 11.7</td>
<td>43.5 ± 9.5</td>
</tr>
<tr>
<td>2'-F-Cytidine</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

rDNA, ribosomal DNA; mitCoxII, mitochondrial cox2 DNA.
Swiss mice, five animals per dosing group, were injected intraperitoneally (i.p.) with PSI-6130 on day 0 to day 5 and changes in weight were monitored on the indicated days. ■, 0 mg/kg/day PSI-6130; ●, 3.3 mg/kg/day PSI-6130; x, 10 mg/kg/day PSI-6130; ▲, 33 mg/kg/day PSI-6130; □, 100 mg/kg/day PSI-6130. For clarity, standard deviations (s.d.) are shown only for the 0 mg/kg/day and 100 mg/kg/day treatment groups.

Discussion

Recently, several modified nucleoside analogues with potent inhibitory activity against the HCV NS5B polymerase have been described (Walker & Hong, 2002; Shim et al., 2003; Migliaccio et al., 2003; Lai et al., 2003; Eldrup et al., 2004; Devos, 2002; Carroll et al., 2003). These analogues can be divided into the following three classes: 2'-modifications of the ribose ring (methyl or O-methyl; Walker & Hong, 2002; Migliaccio et al., 2003; Eldrup et al., 2004; Carroll et al., 2003); 3'-modifications – mainly 3'-deoxy (Migliaccio et al., 2003; Lai et al., 2003) and 4'-modifications (Devos, 2002). Among the most potent compounds are β-D-2'-C-methyl-ctydine and 2'-C-methyl-ctydine. In a recent publication, the synthesis and anti-HCV activity of PSI-6130 was described (Clark et al., 2005). Because of the similar size and electronegativity of fluorine and oxygen, and because the hydrogen bonding characteristics of fluorine are similar to those of a hydroxy group, substituting fluorine would be expected to allow the molecule to have biological activity. In addition, the presence of a 2'-fluoro group should stabilize the glycosidic bond (Watanabe et al., 1983; Watanabe et al., 1979). In this present study, PSI-6130 was found to be both a potent and a selective inhibitor of HCV RNA replication in the HCV replicon assay system. Instead of using a surrogate virus for assaying compounds of anti-HCV activity, we assayed for anti-HCV activity using a subgenomic or a full length HCV replicon. EC₅₀ values of 4.6 ± 2.0 μM and 1.6 ± 0.6 μM were obtained for PSI-6130 with the subgenomic and full length replicon, respectively. Interestingly, little or no antiviral activity was observed when PSI-6130 was tested for activity using other members of the Flaviviridae family. This modest or lack of activity against other members of the flavivirus family, as well as HIV and HBV, suggest that PSI-6130, unlike 2'-C-MeC and 2'-C-MeA, is a specific inhibitor of HCV. The lack of significant antiviral activity seen with other flaviviruses, including BVDV, could be due to an inability of certain cells, for example, MDBK cells to phosphorylate PSI-6130. Alternatively, the RdRp of these viruses might be less...
susceptible to inhibition by the 5'-triphosphate of PSI-6130. Since the differential activity of PSI-6130 extends to a number of flaviviruses in different cell lines, it is more likely a result of target sensitivity brought about by the dual substitution of methyl and fluorne at the 2' position than levels of phosphorylation.

To gain insight into the mechanism of action of PSI-6130, inhibition studies were performed using exogenously added natural ribo- and 2'-deoxyribonucleosides to determine which nucleosides could prevent the anti-HCV activity of PSI-6130. The antiviral effect was prevented strongly by 2'-deoxyctydine. This would suggest that the compound is primarily phosphorylated by the host cell's deoxycytidine kinase and not by uridine-cytidine kinase. Although deoxyadenosine and deoxycytidine are substrates of cytosolic deoxycytidine kinase, PSI-6130 phosphorylation was not affected significantly by deoxyadenosine or deoxycytidine. This observation could be due to the poor binding affinity of deoxyadenosine and deoxycytidine for cytosolic deoxycytidine kinase. The weak inhibition of antiviral activity seen with cytidine could be the result of competition by cytidine which could be utilized as a weak substrate by deoxycytidine kinase (Sabini et al., 2003, Datta et al., 1989); competition of cytidine monophosphate or diphosphate with the corresponding phosphate derivatives of PSI-6130 with the cellular cytidate kinase and/or nucleoside diphosphate kinase or competition between cytidine 5'-triphosphate and PSI-6130 triphosphate for binding to the HCV RdRp. The reduced activity of PSI-6130 seen when the compound was tested against a replicon, which carried the S282T mutation in the RdRp, is consistent with PSI-6130 being an inhibitor of the NS5B enzyme. The mechanism of action studies with purified HCV RdRp, which will be published elsewhere, indicate that the 5'-triphosphate of PSI-6130 is an alternative substrate inhibitor of the enzyme. To date, no mutations in NS5B have been selected in the in vitro passing experiments with PSI-6130 (unpublished data) in the subgenomic replicon cells.

Studies were performed to assess the toxicity of PSI-6130 in vitro and in vivo. Cytotoxicity assays using several different cell types, including human bone marrow progenitor cells, indicated no toxicity associated with PSI-6130 at physiologically relevant concentrations. Mitochondria are often a target for nucleoside toxicity (Lewis & Dalakas, 1995). Mitochondrial toxicity can be determined by measuring the effect of a compound on mitochondrial DNA and the production of lactic acid in liver cells. In these studies, there was no detectable reduction in mitochondrial DNA or an increase in lactic acid production compared to untreated control cells, indicating that PSI-6130 did not produce any mitochondrial toxicity at the concentrations tested. Finally, the no-effect dose for mice treated i.p. with PSI-6130 was 100 mg/kg per day.

In summary, we describe the in vitro antiviral activity of the PSI-6130, PSI-6130 demonstrated potent and specific activity in the HCV replicon assay system. PSI-6130 showed little or no cytotoxicity and no mitochondrial toxicity. Prevention studies performed with natural nucleosides suggest that PSI-6130 is phosphorylated via the 2'-deoxy-cytidine salvage pathway. The details of the mechanism of action remain to be determined.

Acknowledgements

Dr Raymond F Schinazi is the principal founder, former director and consultant for Pharmasset Inc. His laboratory, which was responsible for some of the cytotoxicity and anti-HIV data as well as performing the mouse toxicity studies, received no funding for his participation in this work. John D Morrey and Justin L Julander were partially supported by contract N01-AI-30049 from the NIAID, NIH.

References


DATE FILED: 11/07/2013
DOCUMENT NO: 926

PATENT TRIAL AND APPEAL BOARD

Patent Interference 105,871 (DK)
Technology Center 1600

JEAN-PIERRE SOMMAOSSI,
PAOLO LACOLLA, RICHARD STORER, and
GILLES GOSSELIN,
Application 12/131,868,
Junior Party,

v.

JEREMY CLARK,
Patent 7,429,572,
Senior Party

DEPOSITION OF DR. ALISTAIR STEWART
Wednesday, June 19, 2013, 9:58 a.m.
Jones Day
100 High Street
Boston, Massachusetts 02110

Reported by:
MARYJO O'CONNOR, RPR/CSR
JOB NO. 62493

TSG Reporting - Worldwide 877-702-9580
Idenix EXHIBIT 1645
Interference 105,871

IPO DELHI 07-08-2015 17:18
Wednesday, June 19, 2013
9:58 a.m.

Deposition of DR. ALISTAIR STEWART,

held at Jones Day, 100 High Street, Boston,
Massachusetts, before MaryJo O'Connor, Registered
Professional Reporter, Certified Shorthand
Reporter, and Notary Public in the Commonwealth
of Massachusetts.
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THOMAS FRIEBEL, ESQ.
ALSO PRESENT: Maria Stahl, Esq.

Idenix Pharmaceuticals, Inc.
Stewart —

PROCEEDINGS

ALISTAIR STEWART,
called as a witness, having been duly sworn
by a Notary Public, was examined and
testified as follows:

EXAMINATION BY:

MR. KLINE:

Q. Good morning. Could you just please
state your name and address for the record,
please.

A. Sure. It's Alistair James Stewart,
28 Old Sudbury Road, Lincoln, Massachusetts,
01773.

Q. Doctor Stewart, I'm going to be
asking you questions today regarding issues in
this interference.

If at any time you don't understand
one of my questions, will you please say so and
I'll do my best to repeat or clarify the question
for you.

— Is that fair?

A. Yes.

Q. And just remember that all of your
answers need be to be in words because the court
Stewart

reporter can't transcribe gestures or nods, so just try to remember to always answer verbally.

A. Okay.

Q. And if you could just wait until I finish my questions before answering. Sometimes I may pause as I'm contemplating the question. So just let me finish it and I'll do my best to let you finish your answer before I ask the next question, that way the court reporter can't transcribe two people talking at once.

A. Okay.

Q. And your attorney may make objections today. Please understand that you're to answer my questions regardless of those objections unless specifically directed not to answer by your attorney.

A. Okay.

Q. And we'll take breaks probably every hour or so, but if at any time you need to take a break, just let me know and I'll do my best to get to a good stopping point to take a break.

The only rule is that if a question is pending, I'll just ask that at least you finish answering that question before you take a
break. Fair?
A. Okay.
Q. And you understand that this deposition is being transcribed by a court reporter and will be submitted to the board of patent appeals and interferences at the United States Patent and Trademark Office?
A. Yes.
Q. And do you understand that your testimony today is being given under oath and that you're obligated to tell the truth as if in a court of law?
A. Yes.
Q. Is there any reason you're unable to give truthful testimony today?
A. No.
Q. I'm required to read into the record certain guidelines that apply to this deposition, so if you'll just -- the first one is: "In accordance with Guideline 1, during this cross-examination please ask me rather than your counsel for any clarification, definitions, or explanations of any words, questions, or documents presented during this
Stewart

cross-examination."

Is that understood?

A. Yes.

Q. And the other one. "In accordance with

Guideline 4 you are not to engage in any private

off-the-record conference with your counsel
during this cross-examination or during any

breaks or recesses except for the purposes of

deciding whether to assert a privilege; is that

understood?

A. Yes.

Q. Let me just -- let's start with your

declaration, which is Idenix Exhibit 1241.

A. Thank you.

Q. Doctor Stewart, I first want you to

look at what's been placed in front of you as

Idenix Exhibit 1241, which I believe is actually

probably two copies. I understand that's the way

it was provided, but can you just turn to Page 45

of Idenix Exhibit 1241 and just confirm that

that's your signature?

A. Yes, it is.

Q. And did you sign and date this

declaration on May 30, 2013?
A. Yes, I did.

Q. Are there any corrections you wish to make to your declaration before we begin?

A. No.

Q. What did you do to prepare for your deposition today?

A. I spoke with Jones Day yesterday.

Q. For how long?

A. For three and a half hours at Idenix.

Q. And did you -- and who did you meet with?

A. I met with Mark Kafka, Tom Friebel both of Jones Day, and Maria Stall of Idenix Pharmaceuticals.

Q. And did you review any documents in preparing for your deposition?

A. I reviewed my declaration.

Q. The entire declaration?

A. Yes.

Q. With exhibits?

A. With two exhibits.

Q. Okay. Do you recall what exhibits those were?

A. One was -- no, but two exhibits were
Stewart

references listed in my declaration. I don't recall exactly which references.

Q. But they were attachments --

A. Exactly. Yes.

Q. -- or references referred to in your declaration?

A. Yes.

Q. Other than what your declaration or the exhibits referenced in the list of exhibits to your declaration, did you review any other documents in preparing for your deposition?

A. Sorry. Can you repeat the question?

Q. Sure.

Other than looking at your declaration itself or the -- well, if you look at Page 46, there is a list of exhibits to your declaration.

Other than looking at either the declaration or documents among this list of exhibits, did you look at any other documents in preparing for your deposition yesterday?

A. A training document of how to prepare for a deposition.

Q. And other than that, you didn't look
Stewart

Q. Going back to my previous comment, just let me finish my question before you answer.

A. All right. Doctor Stewart, you received a bachelor of science in chemistry from the University of Durham in 1999, correct?

Q. And you received your Ph.D. in organic chemistry from University of Oxford in 2003?

A. Yes.

Q. What was your thesis on?

A. My thesis was psicofuranosyl nucleosides -- yes, psicofuranosyl nucleosides with Professor Fleet.

Q. And so while you were working at -- or obtaining your Ph.D. at the University of Oxford, you were working with nucleosides?

A. Yes.

Q. And in obtaining your bachelor of science degree, did you ever work with nucleosides?

A. I had courses, organic chemistry
courses, which mentioned nucleosides and carbohydrate chemistry but no hands-on work.

Q. Your work on nucleosides in obtaining your Ph.D., were you actually in the lab synthesizing nucleoside compounds?

A. Yes.

Q. Approximately when did you begin working with the synthesis of nucleosides?

A. Approximately ninety -- December 1999.

Q. And other than nucleosides, did you work on the synthesis of any other types of compounds while obtaining your Ph.D. at the University of Oxford?

A. Yes. I worked on hydantoin compounds.

Q. Now, after receiving your Ph.D., what did you do?

A. I was offered a position at Idenix Pharmaceuticals and moved to Cambridge in September 2003 to start a position at Idenix.

Q. Now, I understand your first position at Idenix was as a research scientist I; is that correct?
Stewart

Q. And that was in September of 2003, correct?

A. Yes.

Q. And when you began at Idenix, just generally what were your responsibilities?

A. To synthesize intermediates for our medicinal chemistry group in Montpellier and to synthesize target compounds as directed by my supervisor, Adel Moussa.

Q. And when you began in September 2003, were you assigned to any projects for your work?

A. I was assigned to work on LDT.

Q. Okay. And what is LDT?

A. LDT is an L-nucleoside used for treatment of hepatitis B.

Q. And other than LDT, were you assigned to any other projects when you began in September of 2003 at Idenix?

A. I also worked on NM283.

Q. And that's when you began in September of 2003?

A. Yes.

Q. And what were you doing on NM283?
Stewart

MR. KAFKA: Objection. Beyond the scope of the declaration.

Q. Go ahead.

A. I was investigating new routes to NM283 to obtain a superior process.

Q. And all of this work from September 2003; I guess, even up to the current, have you always been located in Cambridge? At the Cambridge facility?

A. Yes.

Q. Was there any time during the time you worked at Idenix where you were working at any of the other facilities?

A. No. I visited Montpellier, however, I did not work there.

Q. So all of your — to the extent you did lab work, that was all done in Cambridge, correct?

A. Yes.

Q. And when you began in September of 2003, who did you report to?

A. Doctor Adel Moussa.

Q. Anyone else?

A. No. Other than -- Dick Storer was
Stewart

Doctor Adel Moussa's supervisor and the head of chemistry.

So by definition, I worked for him. But my direct supervisor was Doctor Adel Moussa.

Q. Did anyone report to you when you began in September of 2003?

A. No.

Q. At some point were you assigned other projects other than the work on the LDT and the NM283 project?

A. Can you clarify "at some point"?

Q. Well, what was the next project you were assigned after? I know you said when you started you worked on LDT and NM283. I'm just trying to --

A. I don't recall.

Q. Do you recall any other projects you worked on between 2003 and 2004 other than LDT and NM283?

A. I began work -- to the best of my recollection, I began work on the synthesis of 2'-C-methyl-2'-fluoro nucleoside in May 2004.

Q. And that's the next project you remember, recall, being assigned to?
Stewart

A. I worked on NM887 I believe in 2003.

Q. And what is NM887?

MR. KAFKA: Objection. Beyond the scope of the declaration.

A. NM887 is a prodrug of a nucleoside.

Q. Is it a -- I don't have to -- I believe you said a 2'-C-2'-methyl nucleoside; is that correct?

A. 2'-C-methyl-2'-fluoro nucleoside in May 2004.

Q. NM887 is not a 2'-C-methyl-2'-fluoro nucleoside, correct?

A. No, it is.

Q. It is?

A. Sorry. Can you repeat the question?

Q. NM887 is not a 2'-C-methyl-2'-fluoro nucleoside?

A. No.

Q. I'm just trying to -- so the first time you assigned to work on a 2'-C-methyl-2'-fluoro nucleoside was in May of 2004 at Idenix?

A. To the best of my recollection, yes.

Q. Now, in this May 2004 time frame, how
are assignments assigned to you?

A. From Doctor Adel Moussa. By Doctor Adel Moussa.

Q. And was there a particular group you were in at Idenix in Cambridge?

A. Yes.

Q. What was that group?

A. The process chemistry group.

Q. And what were the main tasks of the process chemistry group?

A. To develop new processes to compounds, to optimize processes to compounds, to provide intermediates to Montpellier to synthesize target compounds as directed by Adel Moussa.

Q. Were you also working on the scale-up of processes?

A. Yes.

Q. How much of your time was spent on scale-up in the 2003 to 2004 time frame versus synthesis of intermediates?

A. To the best of my recollection, 40 percent.

Q. And what was the other 60 percent
Stewart spent on?

A. Intermediates for Montpellier, synthesis of target compounds as directed by Adel Moussa, research of the literature.

Q. And what is your understanding of what the folks at Montpellier were doing?

A. They were synthesizing small amounts of target compounds of interest for biology studies.

Q. Now, when you were working on the synthesis of intermediates, was it your responsibility to come up with the process or the scheme for how to make the intermediate, or was that usually given to you by someone?

A. It could be either. We held regular group meetings to discuss targets, to discuss routes. So we were expected to provide ideas.

Q. And when you say "45 regular group meetings," how often would those occur?

A. I believe at least a month. Every month.

Q. And who would attend these meetings?

A. All members of the group; Adel Moussa, Jingyang Wang, Ben Mayes,
Stewart

Narayan Chaudhuri, Steve Mathieu, and Dick Storer
on the occasions that he was present in Cambridge
at that time.

Q. Are those all of the people who are
the members of the group at Idenix at the time to
the best of your recollection?

A. I believe Mark Latham may also have
been there at that time.

As to the other members, I don't
remember.

Q. Now, you said you began working on
the 2'-C-methyl-2'-fluoro compounds in May of
2004.

What do you recall about being
assigned that project?

A. I recall Adel Moussa approaching me
with a target compound to discuss routes to make
that compound.

Q. Okay. When you say "He presented you
with a target compound," did he give you
something in writing?

A. No, it was verbal. Verbal
discussion.

Q. It was a verbal discussion, okay.
Stewart

Did he tell you whether people at
other parts of Idenix were working on that
project?

MR. KAFKA: Objection. Calls for
hearsay.

A. I don't -- I don't know what -- I
don't know what he -- I don't remember.

Q. You don't remember him saying, "We've
been working on trying to make this compound in
Montpellier," for example?

A. No. I heard -- no, he didn't tell me
that at the time.

Q. Did you ever become aware that others
at Idenix were trying to synthesize
2'-'C-methyl-2'-'fluoro compounds?

A. Yes.

Q. When did you become aware of that?

A. From Dick Storer.

Q. When?

A. In -- at the same time. May 2004.

Q. Was Dick Storer at this meeting when
you were assigned the project?

A. No.

Q. That was just --
Stewart

A. To -- no.

Q. Who else was present when you were assigned this project?

A. Jingyang Wang, Ben Mayes, Adel Moussa, to the best of my recollection.

Q. I'm just trying to -- were you specifically assigned the task or was it given to the group?

A. It was given to Jingyang Wang and myself.

Q. You mentioned another discussion concerning this project with Dick Storer in May 2004?

A. Yes.

Q. Where was that conversation?

A. I don't recall. I recall that it was certainly verbal. I can't remember if it was a phone conversation or if he was at Idenix at that time. I don't remember.

Q. Well, what do you recall about that conversation?

A. He told me that Jean-Francois Griffon in Montpellier had been working on the compound and to contact him for information.
Stewart

I was also provided with a report from Jean-Francois Griffon of his work between, I believe, it was 2002 to 2004. And I was given that by Dick Storer.

Q. Okay. This report, which exhibit to your declaration is that?

A. I don't believe it is an exhibit in my declaration.

Q. Okay. Did you have an understanding at the time that you started working on this whether anyone at Idenix had actually successfully synthesized the target compound?

A. I had no understanding at that time.

Q. And was it your understanding that the reason you were being asked to work on it was because it hadn't been done yet?

A. No. I had no understanding of the reason I was working on the compound.

Q. Well, when you reviewed this report from J.F. Griffon, did you see any indication that the target compound had actually been successfully made by anyone at Idenix at that time?

A. No.
Stewart

Q. So based on your reading of that report, at least, there was no indication that anyone had successfully synthesized the target compound, correct?

A. According to that document, yes.

Q. And that report, it's your understanding described over two years of work?

A. Yes.

Q. Do you think that was two years of full-time effort?

MR. KAFKA: Objection. Calls for speculation.

A. I wasn't present in Montpellier. I have no knowledge of what Jean-Francois Griffon was working on.

Q. Is it your understanding that that was a significant part of the work being done by J.F. Griffon?

A. I don't know what his -- I'm not aware of his other responsibilities or his work in that detail.

Q. After being assigned the task of making a target 2'-C-methyl-2'-fluoro compound, what did you do first?
Stewart

A. I reviewed the literature for examples of fluorination and fluorinated nucleosides.

Q. Now, I've seen your lab notebook. It looks like the first experiment you did was sometime in November of 2004, correct?

A. Correct.

Q. Between the time you were assigned this task in May of 2004 and up through November when you began working in the lab, how much time did you spend on the project?

A. I don't recall.

Q. Days?

A. I don't recall to that level of detail. I know that I was communicating with Professor George Fleet in May 2004. I know I was reviewing the literature in that period of time as well to the best of my recollection.

Q. When you say you were "reviewing the literature," what did you do?

A. I use SciFinder Scholar, a program to look at chemical compounds to study the literature surrounding fluorinated compounds.

Q. What were the search terms you used?
A. I don't recall.

Q. In your searching -- and when did you start this searching?

A. I don't recall an exact date. It would have been -- can I consult my declaration?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. Can you repeat the question?

Q. When did you start your searching?

A. It was May -- probably the 9th of May 2004.

Q. And when you searched in May of 2004, did you find any literature describing a successful process for synthesizing the 2'-C-methyl-2'-fluoro compound?

A. Can you clarify "compound"?

Q. Did you find any literature describing a successful process for synthesizing any 2'-C-methyl-2'-fluoro nucleoside compound?

A. No.

Q. Now, what in your declaration led you to believe you started the searching in May of 2004?
S Stewart

A. On Page 34 Paragraph 88 there is an e-mail from Professor Fleet regarding erythorbic acid as a potential starting material for the synthesis of these compounds.

Q. Okay. But is that the result of a search you did for literature?

A. When I received the e-mail, I searched for erythorbic acids.

Q. What was the next literature search you did after May 2004, or May 9, 2004?

A. I don't recall.

Q. How many literature searches do you recall doing between May of 2004 up through November of 2004 on this project?

A. I don't recall an exact number.

Q. You didn't do any lab work between May 2004 or up through November 2004 on this project, correct?

A. Can I consult my declaration?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. No.

Q. Other than doing a literature search,
what work do you recall doing between May of 2004 up through November 2004 on the project?

A. I met with Professor George Fleet at Idenix to discuss the synthesis of the compound in May 2004.

Q. Right. Okay. So you met with him, and I think in your declaration it says it was on May 10, 2004, right?

A. Yes.

Q. So other than that May 10, 2004, meeting and a literature search, what else did you do between May 2004 up through November 2004 when you began your lab work?

A. I communicated with Professor Fleet on a -- via e-mail concerning schemes that were developed during the course of that meeting.

I communicated with my colleagues Jingyang Wang, Ben Mayes, Adel Moussa, together I believe with Narayan Chaudhuri an ongoing progress in terms of potential schemes to make the 2'-C-methyl-2'-fluoro nucleoside.

Q. I assume during this time you were working on other projects, right?

A. I don't recall.
Stewart

Q. You don't recall working on any other projects between May 2004 and November 2004?
A. I don't remember.
Q. But you can remember meeting with people to discuss this project?
A. Yes.
Q. You were working on the LDT project at this time, right?
A. I don't remember. I believe you are looking at my time sheet, and I'd need to look at that.

Q. Okay. Let's show you Idenix Exhibit 1380.

The first time sheet, I guess the second page, is that your time sheet for September 2004?
A. Yes.
Q. And it shows you were working only on LDT, right?
A. Not necessarily only on LDT. At the time we had an agreement with Novartis where we had to record the time we were working on LDT. So this is the time I was working on LDT, I would have worked for longer than nine
Stewart

hours on other projects in addition to this.

Q. Well, at least from your time sheet
that you filled out at the time, you did not
assign any work to any other task on any other
projects, right?

A. Yes.

Q. Okay. So as far as this time sheet
indicates, you didn't work on anything else at
that time, right?

A. As far as this time sheet indicates,
yes.

Q. Now, if you were working on this
project to make a 2'-C-methyl-2'-fluoro compound,
which of these project descriptions would it be
under?

A. Am I allowed to look at the rest of
the exhibit?

Q. If you need to.

A. I believe it's "Hep C Other."

Q. Now, in preparing your declaration,
did you look at your time sheets for any other
weeks between May 2004 up through November 2004?

A. No.

Q. So there is no record of what you
Stewart
were actually doing during that time, right, as
far as you're aware?

A. I believe there are copies of other
time sheets, but I don't recall having seen them.

Q. And in reviewing this declaration, or
in preparing your declaration, did you look at
any of the time sheets you had between May 2004
up through November 2004 other than this one
sheet you attached as an exhibit?

A. No.

Q. When you say this project required a
substantial part of your time between May 2004
and May 2005, and I just want to break it down
the part between May 2004 and November 2004.

What was the basis for saying it
required a substantial part of your time?

A. Ongoing discussion with
Professor Fleet, with my colleagues in the group
with schemes and we were meeting on a weekly to
discuss.

Q. What do you characterize as a
substantial part of your time in that time frame?

A. A substantial part of my time would
be -- I can't put a number on it. I couldn't
Stewart,

quantify "substantial part." At least over two
hours a day.

Q. So you were spending two hours a
day --

A. I said at least two hours. At least:
So it could be more than.

Q. So is it your testimony that you were
spending at least two hours a day between
May 2004 up through November 2004 on this
project?

A. Yes.

Q. Describe for me what you would do
other than when you were meeting with someone.
What would you do for two hours?

A. Literature searches to try and
identify relevant references.

Q. So six months of literature
references? Searches?

A. It could be.

Q. Is that your testimony? You spent
six months searching the literature on this
project?

A. Together with other tasks, yes.

Q. The other tasks, I want to just know
Stewart,

everything you did for these two hours a day that you're saying you spent on this project from May 2004 to November 2004.

A. Conversations with my colleagues.

Conversations with my supervisor for the targets in question. Possibly e-mail communication as well with colleagues in Montpellier, and communication with Professor Fleet.

Q. And you would work roughly how much a day? How many hours?

A. It would vary. It could be anything from 8 to 11 or 12, depending on the day.

Q. So you're saying you spent about 20 percent of your time on this project from May 2004 up through November of 2004?

A. Each day is not the same.

Q. Understood.

A. Each day I may have worked a longer period of time. I think 20 would be a minimum on a given day, but I don't recall exact details for that period of time.

Q. So what were you spending the majority of your time doing during this time?

A. I don't recall. I do not recall.
Stewart

don't remember whether it was --

Q. Can you -- sorry. Finished?

A. I was going to say I believe I was
working on other targets at that time in May. It
looked from my time sheet, it appears in
September I was working on LDT; but I don't
recall exactly which compound.

Q. Now, you spent I guess from May 2004
up through November 2004, whatever time you spent
on this project, is it fair to say that it did
not result in you actually trying to synthesize
the compound during that time frame?

A. Can you repeat the question? Between
May?

Q. Between May 2004 and November 2004,
you didn't actually attempt to synthesize a
2'-C-methyl-2'-fluoro nucleoside compound; true?

A. Yes. In the lab. Hands-on in the
lab.

Q. Right.

Were you given a time frame when you
were assigned this project as to when you should
try to come up with a compound?

A. As soon as possible.
Stewart

Q. So as soon as possible, but you didn't actually go in the lab to start the work for six months?

A. No. We had -- we were delayed in a collaboration with Professor Fleet owing to I believe issues with Oxford University in obtaining input from him at that time.

Q. Okay. What input from him did you need to begin synthesizing or attempting to synthesize the target compound?

A. The schemes that we had discussed, we were waiting for direction on which would be the best place to start from.

Q. From your research of the literature at the time, did you have an indication as to where would be the best place to start from?

A. Yes.

Q. And what did that literature tell you?

A. We knew that fluorination on secondary alcohol was proceeded with inversion of stereochemistry to introduce flourine.

Q. And when did you learn that?

A. Can I consult? Oh, when I was aware
of that. Prior to starting Idenix.

Q. So how did Doctor Fleet's work delay that start?

A. The schemes that we developed in collaboration with Professor Fleet in that May 2004 meeting, and we were waiting; ongoing, waiting for Sarah Jenkinson - at the time Sarah Barker - to start work on synthesis of the key starting materials. These are only obtained by reaction with cyanide which we were unable to use.

Q. When you began your work in 2004, did you consider any other schemes that did not require the synthesis of this key starting material from Doctor Fleet's lab?

A. Yes.

Q. But you didn't attempt any of them at that time?

A. I received an intermediate from Jean-Francois Griffon. I cannot recall the date. It may be listed in my declaration.

Q. If you received it and you would have done work on it, it would have been in your lab notebook?
Stewart

A. Yes.

Q. And your lab notebook does not begin until December 2004?

A. Yes.

Q. So is it fair to say that between May 2004 and November 2004, you didn't attempt with an intermediate received from Jean Griffon to try to synthesize a nucleoside, correct?

A. Yes.

Q. If you turn to your declaration, Paragraph 14, you refer to a Scheme A. Do you see that?

A. Yes.

Q. Where did that come from?

A. It arose from -- I received a scheme from Jones Day. This was a result of my revising of that scheme.

Q. So this was prepared in connection with this declaration, right? This Scheme A?

A. Yes.

Q. Okay. You never wrote this scheme down in the 2004 time frame anywhere, right?

A. I don't recall. Not this exact scheme, no.
Stewart

Q. Now, going back to Paragraph 5 of your declaration, you discuss your notebook pages and how you identify things. I just want to ask you just a couple of preliminary questions before we go.

A. Okay.

Q. When you would complete a reaction, what was your general practice as far as how to determine what compounds or compound you had synthesized?

A. I would analyze them by one or more techniques: NMR, HPRC analysis, on occasion mass spectrometry, and TLC analysis.

Q. And did you obtain the NMR spectra?

A. No.

Q. Who did that?

A. Jin Hong of Custom NMR Services.

Q. Did Cambridge have an NMR machine when you worked there?

A. No.

Q. So you did not personally run any NMR experiments on the compounds you synthesized?

A. No.

Q. What about mass spectrometry, did you
Stewart

perform that type of analysis on the compounds?

A. My colleague John Mao in our DMPK
group ran analysis for us.

Q. I'm sorry. Say that again? DMPK?

A. DMPK.

Q. What does that stand for?

A. Oh, gee. I have no idea. I can't

remember.

Q. Was he in Cambridge?

A. It's biochemistry I imagine is the

best.

Yes, he was.

Q. You also mentioned that you would use

TLC analysis to determine a compound, correct?

A. To determine if a new species had

formed, yes.

Q. And did you perform the TLC analysis?

A. Yes.

Q. Is that equipment you have in your

lab in Cambridge?

A. Yes.

Q. Did you ever use HPLC to determine

whether you had synthesized the compound?

A. Yes.
Q. Do you recall -- how does HPLC tell you whether you had synthesized a particular compound?

A. Retention -- the HPLC will lead to a peak with a retention time. The retention time may be identical to the starting material or may be different from the starting material.

Q. Did you perform HPLC yourself?

A. We had an open access spectrometer to submit the samples to.

Q. Okay. But did you personally perform the HPLC analysis?

A. I submitted the sample to the machine, yes.

Q. For this project to try to synthesize a 2'-C-methyl-2'-fluoro-nucleoside compound, did you use NMR to analyze compounds you were synthesizing?

A. Yes.

Q. Did you use TLC?

A. Yes.

Q. Did you use mass spectrometry?

A. On occasion.

Q. Did you use HPLC?
Stewart

A. Yes.

Q. When you say you used mass spectrometry on occasion, on what occasions would you decide to use mass spectrometry?

A. When we needed to confirm the molecular weights of a compound either in crude mixture or isolated compounds.

MR. KAFKA: I think this might be a good time to take a break.

MR. KLINE: Sure.

(Proceedings recessed at 10:51 a.m., and reconvened at 11:06 a.m.)

BY MR. KLINE:

Q. Doctor Stewart, just going back where we were before the break discussing the NMR analysis that was done for this project, while you were working on the project from I guess November 2004 up through, what was it, May of 2005? Is that fair?

A. Just --

Q. Who obtained the NMR spectra for the compounds you synthesized?

A. Just to clarify, I was working from May 2004 to May 2005. I think I believe you said
Stewart

November there, but I'm not sure if you were
speaking about NMR specifically.

Q. Well, you didn't do any NMR analysis
on this project before November 2004; true?

A. Yes.

Q. Okay. So let's start with November
2004 when you actually did some NMR analysis on
this project.

A. Yes.

Q. Okay. So starting in November 2004
up through when you completed your assignment on
this project described in your declaration, who
obtained the NMR spectra for the compounds you
synthesized?

A. Jin Hong of Custom NMR Services ran
the samples for Idenix.

Q. And I just want to walk through the
process you would go about for obtaining an NMR
spectra for a particular compound on this
project.

What was the name of Jin Hong's
company?

A. Custom NMR Services.

Q. Did Custom NMR Services pick up
Stewart

samples from you?

A. Yes.

Q. Was it on a set schedule?

A. No.

Q. How would they know to come pick up a sample?

A. To the best of my recollection, we telephoned her. We telephoned Custom NMR Services to arrange collection.

Q. And would you be responsible for contacting Custom NMR Services for the samples that you had prepared?

A. On occasion, yes.

Q. Who else would be involved in doing that?

A. It may have been Jingyang Wang. It may have been any member of the process chemistry group, or receptionist at that time.

Q. And who from Custom NMR Services picked up the samples?

A. Jin Hong.

Q. And what was Ms. Hong's title? Do you know?

A. I don't know.
Stewart

Q. Do you know if she performed the analysis?
A. Yes.

Q. And how would you provide the samples to Custom NMR Services?
A. We would either prepare an NMR tube containing the compound and the solvent of choice, or on occasion I believe we submitted the solid sample to her.

Q. And when you submitted the solid sample and it wasn't in an NMR tube, how was it given?
A. I believe it was in a vial.

Q. Now, did it ever occur that Custom NMR Services did not pick up your samples right away?
A. Yes.

Q. And what did you do then?
A. We would telephone to arrange collection.

Q. And if they couldn't come right away to pick it up, what would you do with the sample?
A. We would retain it in storage until collection.
Stewart

Q. Okay. And how would you store the samples?

A. It depended upon the compound. It would be either at room temperature or in a refrigerator or in a freezer.

Q. Did you provide Custom NMR Services with any paperwork in connection with each sample?

A. If we wanted a specific experiment to be run, yes. Or if we wanted a specific solvent to be used for the NMR analysis.

Q. Okay. And can you when you say a specific experiment, what are you referring to?

A. If we -- a standard experiment would be proton NMR, COSY - C-O-S-Y - spectra. If we wanted 13 carbon NMR or NOE, Nuclear Overhauser Experiments, we would request those.

Q. And when you talk about a specific solvent, what are you referring to?

A. It could be chloroform, dimethyl sulfoxide, deuterated methanol, deuterated water.

Q. Did you when you made a request for an NMR spectra to be performed, would you always
Stewart

specify the solvent to be used?

A. I don't recall. I believe so.

Q. Okay.

A. If issues with solubility were observed, we would be contacted by Jin Hong to inform us.

Q. And am I correct that when sending a sample out for NMR analysis, you would only specify the type of NMR spectra if it was anything something other than proton NMR?

A. We would still specify proton NMR, but we would list everything we wanted to be run on that sample.

Q. So was there a sample sheet which you would fill out for each sample?

A. I don't recall. I don't remember.

Q. How many of these did you fill out during the time you've been at Idenix?

A. It was a number of samples, but -- I don't know an exact number. It was a number of samples.

Q. But you can't remember what the paperwork involved?

A. No.
Stewart

Q. Did you identify the reaction performed in the sample?

A. No. We labeled either the NMR tube or the vial with the code corresponding to the laboratory notebook for that specific experiment.

Q. Did you identify the proposed structure of the product that was being sampled?

A. No.

Q. Did you provide any other data on the sample like melting point or any other indication to help the person?

A. No.

Q. So as far as you recall, it would just identify the specific experiment and the solvent?

A. On occasion temperature, if maybe low or high temperature reaction. I don't recall submitting a temperature NMR, but I know that was a service that was offered.

Q. When the samples were sent out, did Idenix or you keep a copy of the paperwork that you provided to Custom NMR Services with each sample?

A. I did not.
Stewart

Q. Did you keep a log of samples that were provided to Custom NMR Services?
   A. I did not.

Q. Do you know if Idenix did?
   A. I do not know.

Q. And you don't know if Idenix kept a copy of any paperwork for the samples provided to Custom NMR Services, correct?
   A. The spectra we received from Custom NMR Services we kept.

Q. But the transmittal of the samples, do you know if any of that paperwork was kept at Idenix?
   A. I don't know.

Q. After you submitted a sample to Custom NMR Services, what happened?
   A. We would be contacted if the sample had a problem with solubility. We would then be either faxed the spectra, or Jin Hong would return the spectra to Idenix.

Q. Okay. So sometimes you would receive a copy of the spectra by fax?
   A. I believe so, yes.

Q. And when you received a spectra by
Stewart

fax, that would have a fax header at the top?

   A. Yes.
   Q. And would it have, I guess, some
   information on the date or?
   A. I think the date was -- I don't think
   the fax machine had been programed, and I think
   the date was 1900 or -- just from memory.
   Q. And you're saying on other times she
   would physically give you the copy?
   A. She would leave it at reception.
   Q. Is there a procedure as to which one
   was more common?

   MR. KAFKA: Objection. Calls for
   speculation.
   Q. Well, based on your experience, was
   it more common to receive a fax, or did you
   receive it by hand?
   A. For my spectra, I believe it was more
   common to receive them by hand.
   Q. Even when you received a faxed
   version, would you also receive a follow-up
   version that was not faxed?
   A. I don't recall if we received -- I
   believe we did receive duplicates on occasion,
Stewart

fax and also by hand.

Q. And who retained the originals of these NMR spectra at Idenix?

A. I retained my spectra.

Q. And how did you retain them? Where did you keep them?

A. I kept them in binders which were assigned to me by Zaybell Escribano. And they were kept at Idenix until being sent to Iron Mountain for storage.

Q. As far as you're aware, are the originals of the NMR spectra performed on the compounds you prepared that are described in your notebook at Iron Mountain?

A. No.

Q. Where are they?

A. At Idenix.

Q. Okay. How do you know that?

A. During the course -- preparing my declaration, I obtained the spectra from Iron Mountain to Idenix.

Q. Did you attach any of those spectra to your declaration as an exhibit?

A. I don't recall. Can I consult my
Stewart

declaration?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. The spectra recorded in my lab
notebook but not -- the spectra themselves are
not an exhibit.

Q. So why do you recall the spectra from
Iron Mountain as opposed to just looking at your
lab notebook?

A. I did both. And the --

Q. Why did you feel you needed to call
back the originals?

A. I was requested to obtain all
information between 2002 to 2005, and the spectra
fell into that time period.

Q. Okay. But you're not relying on the
originals outside of what's in your lab notebook,
correct? For your declaration, correct?

A. No.

Q. Did you ever receive electronic
copies of the NMR spectra?

A. No. I don't believe so. Not
directly from Custom NMR Services.
Q. Okay. How soon after the NMR spectrum was acquired did you receive a fax?

A. Dependent on the analysis and also dependent on Jin Hong's availability at Custom NMR Services, it would be one to two days for routine analysis, and it could be up to three weeks for a more complex spectra.

Q. Okay. We'll get to that. Actually my question was actually a little more basic. Once she had completed the analysis, how soon would you receive a copy of the spectrum?

A. I don't know. I don't know when she completed the experiments on every turn.

Q. Now, when you talk about routine analysis of one to two days, what do you consider to be routine analysis?

A. Proton NMR.

Q. And what would be -- you said it can take, what, up to three weeks for complex experiments?

A. That would be COSY 13 carbon NMR and NOE experiments. Also HMBC or HMQC experiments.

Q. Your work on this project, do you
recall ever requesting any of these complex NMR experiments?

A. Yes.

Q. How often?

A. COSY regularly. Carbon 13 dependent on the experiment, not as regularly. NOE experiments rarely.

Q. And why were you requesting these non-routine analysis on these compounds?

A. To gain further information about the structure. To assign the structure.

Q. So the routine analysis was not sufficient to allow you to assign a structure for these types of compounds?

A. Not always.

Q. And why is that?

A. The stereochemistry of specific centers or the nature of the signals of the compound may overlap and did not allow full characterization.

Q. Have you ever performed any of these complex NMR experiments that you were just referring to?

A. Yes.
Q. Which ones have you performed personally?

A. COSY, Carbon 13, NOE, HMBC, HMQC.

Q. Based on your experience, how long once you've received a sample does it take to run the COSY process?

A. It's variable depending on the quality of the spectra you obtain. You may need to look into other solvents to get good resolution.

Q. Okay. But based on your experience, how long would it take?

A. It could be between -- dependent on the experiment, COSY could be up to three weeks. NOE could be up to three weeks. 13 carbon, depending on the quantity of sample, could be up to three weeks.

Q. Okay. But based upon your experience, what's the normal time it takes to run these experiments?

A. The COSY experiment could be run within a day. Carbon 13 could be I've heard probably three days. NOE experiments require significantly more time, and my experience was
Stewart

two weeks. For the compounds at that time. When I was running the experiments.

Q. Right.

If Custom NMR Services had any problems with your sample, would you be notified right away?

A. Yes.

Q. Do you recall that happening on this project?

A. No.

Q. And that's true for any of the samples you provided?

A. Yes.

Q. Do you know who whether Ms. Hong personally obtained the spectra you requested, or was it someone working under her direction or someone else at Custom NMR Services?

A. I don't know.

Q. Do you know what qualifications they had to acquire NMR spectra?

A. No.

Q. Do you know what type of NMR spectrometers they were using?

A. I believe it's listed on the spectra.
I believe they were Bruker spectrometers.

Q. Did Ms. Hong or others at Custom NMR Service's analyze the spectra to determine what compound was shown?

A. No.

Q. Were you responsible for analyzing the NMR spectra for the samples you provided?

A. Yes.

Q. Did Ms. Hong or her colleagues make handwritten comments on the NMR spectra?

MR. KAFKA: Objection. Calls for speculation.

A. I don't remember. I don't -- I don't believe so.

Q. Do you recall them ever like drawing chemical structures on the spectra?

A. No.

Q. Or labeling peaks?

A. No.

Q. Now, if you turn to Paragraph 6 of your declaration, you state -- and take whatever time you need to refresh yourself on this topic -- but you say "Occasionally I would request Ms. Hong to re-integrate a spectrum or to
Stewart provide an expanded view of the spectrum which could further delay the turnaround time."

Do you see that?

A. Yes.

Q. Could you explain what you mean by that?

A. On occasion when integrating spectra, Ms. Hong may have selected a peak to relate the other integration towards.

So one peak would be given one proton and it may be that we wanted a different peak -- I wanted a different peak to be used as the -- to be equivalent to one proton as though other peaks would relate to that.

An expanded view of the spectrum would be when I was interested in a specific portion of the spectra to look in more detail, and it means to -- to zoom into a section of the spectra.

Q. How did you make these requests of Ms. Hong to re-integrate a spectrum?

A. I believe it was to the best of my recollection verbally either at Idenix when she collected or returned samples or over the
Stewart

Q. Approximately how long after receiving her first spectrum would it take you to make a request such as this to re-integrate a spectrum?

A. Maybe within one to two days.

Q. And how long would it take Ms. Hong to re-integrate a spectrum?

MR. KAFKA: Objection. Calls for speculation.

A. I don't know. Variable. It could be anything from the next day to two weeks, depending on her workload.

Q. Now, while I'm -- I'm not really asking how long it took her to get back to you. I'm just asking how long would it actually take to re-integrate a spectrum?

MR. KAFKA: Objection to the extent it calls for an expert opinion or it's asking -- speculating on what another person thought or did.

A. Could you repeat the question?

Q. Well, let me ask you another question.
Stewart—

Based on your experience in NMR spectra, how long would it take to actually re-integrate a spectrum once you had been asked to do so?

A. It could be within one to two days.

Q. And what takes one to two days to re-integrate a spectrum?

A. The ability -- I'm not an expert on NMR by any means, but you would need to convert the file from the spectrometer into a form that you could then manipulate to obtain the desired integration and then integrate that spectra to allow you to generate the integral of choice.

Q. And what do you mean in your declaration by "providing an expanded view of the spectrum"?

A. If you were specifically -- if you were interested in an area of the spectra between, for example, 1 to 2 ppm, a specific range, you would basically zoom into that region to give you a larger picture of that section.

Q. And how long does the actual work take to expand a view of the spectrum?

MR. KAFKA: Objection. Speculation.
Stewart——

And objection in that it calls for an expert opinion.

A. I'm not an expert in NMR. I believe it could be done in one day.

Q. I'm going to show you exhibit Idenix 1360, which was an attachment, an exhibit referenced in your declaration.

   My first question, Doctor Stewart, is have you seen this before?

   A. Yes.

   Q. And I'm just trying to get some basic understanding of what this is and how to read it. So if you could help me as we walk through it. Is this a collection of NMR spectra that was provided to you by Custom NMR Services?

   A. Yes.

   Q. And the first page is a proton NMR, correct?

   A. Yes.

   Q. And the second is a carbon NMR?

   A. Yes.

   Q. And the third is a 2D NMR, COSY NMR?

   A. Yes.

   Q. And these NMR spectra were provided
Stewart —

to you by fax, correct?

A. The third spectra has a fax -- I believe has a fax tacked on the side of it. It says January 18, 1900. The first two I can't answer.

Q. Okay. Let's look at the third page, the one -- so January 18, 1900, we know is not the correct date?

A. Yes.

Q. Can you tell from this document when it was actually faxed?

A. I believe it would be January 18th, but I don't know which year.

Q. Okay. So you think the date is actually right, it's just the year that's incorrect?

A. I can't say the date is correct. I don't know whether the fax machine corresponds to the specific date and the year it incorrect.

Q. And do you know who acquired the spectra that's in Exhibit 1360?

A. I submitted it to Custom NMR Services.

Q. Okay. But who acquired each of the
spectra?

A. I don't know. I would imagine Jin Hong.

Q. Now, I just want to look at -- and hopefully you can read on the top of the first Exhibit 1360, first page, there is a reference to an AS081024.

Do you see that?

A. Yes.

Q. Do you understand that that refers to Page 24 of your lab notebook 81?

A. Yes.

Q. And what does FR -- or is that TR? I think it's FR-818-16.

Do you see that?

A. It corresponds to fractions 8 to 16.

Q. And what does that mean?

A. It's fractions obtained from column chromatography purification.

Q. And the solvent used in this NMR analysis was DMSO, correct?

A. Yes.

Q. Is the date on the second line the date the NMR was obtained?
Stewart

A. I don't know.

Q. Is that your understanding?

A. My understanding it would be the 13th of December 2004...

Q. And is it your understanding that the date reflected on the NMR is the date that the NMR spectra was acquired?

A. Yes.

Q. So in this case, the NMR spectra was acquired on December 13th --

A. Yes.

Q. -- 2004, correct?

A. Yes.

Q. Just in general would each of the NMR spectra that Custom NMR Services acquired for you include the same type of information in the top left corner?

A. I believe so. I think it was dependent on the spectrometer that was used for the analysis, but I believe that's the case.

Q. On the first page there is a handwritten structure. Do you see that?

A. Yes.

Q. Is that your handwriting?
Stewart

A. Yes.

Q. Would you have drawn the structure before or after you analyzed the spectrum?

A. After.

Q. Do you know why the third page has a fax header but the other pages don't?

A. No.

Q. Does that indicate they weren't sent together?

A. I don't know.

Q. Now, I just want to -- if you look at -- I'm going to hand you Idenix Exhibit 1329, which is a copy of the lab notebook that's provided with your declaration.

First, if you could just confirm that this is a copy of pages from your laboratory notebook, notebook number 081.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. Yes.

Q. Just before we get into the specifics of it, was it your general practice to include in your lab notebook a copy of every NMR spectrum that you obtained for a sample?
A. No.

Q. What would cause you to put it in or not include it in your lab notebook?

A. On occasions where the spectra was not helpful to assign the stereochem — to assign the compound, it may not have been included. Or if I had additional spectra and I had them in a binder.

Q. So if there were spectra that were not included in your lab notebook, these would be in that binder that you referred to earlier that went to Iron Mountain?

A. Yes.

Q. In preparing your declaration and submitting your pages from your laboratory notebook, did you become aware that there are spectra that were performed on any of the samples described in the experiments in your lab notebook that you’re relying on that were not contained in your lab notebook?

A. Do you mean in terms of additional spectra that weren’t in the lab notebook —

Q. Yes.

A. -- for the specific experiment?
Stewart

I don't recall. There may -- I was only looking for the specific spectra in my lab notebook.

Q. When you asked Ms. Hong to re-integrate a given spectrum, would you include both the original and the re-integrated spectrum in your notebook?

A. No.

Q. What would you include?

A. The re-integrated spectra I imagine.

Q. So would this original spectra that was not put into your notebook, would that have been part of this binder collection?

A. It may well be.

Q. If you did, would you have kept copies of both the original and re-integrated spectra somewhere other than your lab notebook?

A. In a binder.

Q. Now, when you asked Ms. Hong to expand certain portions of a given spectra, would you include the original and each of the expanded portions in your lab notebook?

A. I don't recall. I may not have put it into my notebook.
Stewart

Q. Do you recall what you did put in your notebook?

A. Dependent. If there was a specific reason to include an expanded version, I would have included it, for example, with NOE experiments.

Q. Okay. And, again, would you have kept copies of both the original and each of the expanded portions of the spectrums somewhere other than in your lab notebook?

A. In a binder, I believe.

Q. If you could turn to Page 138 of your lab notebook.

A. (Whereupon the witness complies.)

THE WITNESS: Can I request a break?

MR. KLINE: Sure.

(Proceedings recessed at 11:47 a.m., and reconvened at 11:58 a.m.)

BY MR. KLINE:

Q. Doctor Stewart, just to follow up on a question from earlier this morning. The work -- the time you spent between May 2004 up through November 2004 and working to synthesize the 2'-C-methyl-2'-fluoro nucleoside compounds,
Stewart

the work you did on that project that you're relying on to show what you were doing is reflected in your declaration and the exhibits, right?

A. Yes.

Q. And there is nothing else outside of that you're relying on; true?

A. Yes.

Q. Now, I want to turn to -- if you need to orient yourself -- in Paragraph 18 of your declaration, which is Page 1241, there is a Scheme B.

A. Yes.

Q. And I guess the top portion has sub-Roman numeral (i), little (ii), and little (iii), right?

A. Yes.

Q. First, this Scheme B here, is this something you are aware of from the literature at the time as being described somewhere?

A. I believe maybe compounds (i) and (ii) -- little (i) and little (ii) and little (iv) were known in the literature.

Q. And just so for the record, those are
Stewart.

lactones, correct?

A. Yes.

Q. Other than little (i), little (ii) and little (iv), is it your understanding that none of the other compounds on Scheme B were described in the literature?

A. To the best of my knowledge, that's correct.

Q. And certainly it would be fair to say the entire Scheme B was not described anywhere in the literature to your knowledge, right?

A. To the best of my knowledge, that's correct.

Q. Now, if you look at compound, the bottom right compound in Scheme B which you've labeled capital roman numeral (I), right?

A. Yes.

Q. Okay. The compounds described on the top portion, (i), (ii), (iii), those would not lead you directly to that compound, correct?

MR. KAFKA: Objection. Calls for an expert opinion.

A. It may be possible to convert compound (ii) to big numeral (I).

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Stewart

Q. Your little roman (ii) has the opposite stereochemistry as roman sub (iv) that leads to compound (I), correct?

A. Yes.

Q. So at least with your compound roman sub (ii), it would not as depicted in this scheme result in number (ii), correct?

MR. KAFKA: Objection. Calls for expert opinion.

Q. Let me rephrase that.

Your Roman sub (ii) because it has the opposite stereochemistry of the lactone of roman sub (iv), would not lead to compound, the nucleoside described in Scheme B, correct?

MR. KAFKA: Same objection.

A. One could insert a number of steps between compound (ii) and compound (i) to obtain compound big numeral (I).

Q. But that's not described in your Scheme B, correct?

A. Correct.

Q. And why -- starting with your compound Roman -- sub Roman numeral (ii), to your knowledge did anyone ever complete the synthesis
Stewart

of the nucleoside depicted in Scheme B from your lactone roman sub (ii)?

A. I don't know.

Q. You did not, correct?

A. Correct.

Q. And you worked on this, part of the synthesis from November 30, 2004, through December 16, 2004?

A. Can I consult my declaration?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. Sorry. Can you repeat the question? The date range.

Q. Sure.

From November 30th through December 16, 2004.

A. I believe so, yes.

Q. All of the work you performed on this Scheme B involved trying to convert roman (i) to roman (ii), correct?

A. Just to clarify, all the work shown in Scheme B?

Q. Yes.
Stewart

A. I also tried to form compound (iii).  

Q. You say you tried. Did you succeed?  

A. I believe so. I need to consult my declaration.

Yes.

Q. And how do you know you succeeded?

A. I formed an experiment between December the 7th through December the 13th to obtain that compound.

Q. And did anyone ever -- what did you do at the compound (iii), roman numeral (iii), after you characterized them?

MR. KAFKA: Objection. Beyond the scope.

A. I don't recall. I analyzed the compound. I don't recall if I used it for a subsequent reaction.

Q. If you had used it for a subsequent reaction, would it have been in your lab notebook?

A. Yes.

Q. And do you recall seeing any description of that compound being used for any further synthesis?
Stewart

A. Can I consult my notebook?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. No. I don't believe so.

Q. And do you recall ever giving the compound Roman (iii) to anyone else at Idenix for further work?

A. I don't remember.

Q. Now, in Scheme B, the bottom portion has a box around it, right?

A. Yes.

Q. And you put that box around it in your declaration?

A. The scheme was provided to me by Jones Day.

Q. Why did you box it in your declaration?

A. To distinguish between the scheme -- to distinguish between the sequence shown by the compounds Roman numerals (i), (ii), and (iii).

Q. And to distinguish between -- in the top one, (i), (ii), and (iii), you're distinguishing that work that you actually
Stewart performed from a scheme that would lead to a compound nucleoside big (I), right? On the bottom.

A. Yes.

Q. Now, looking at the scheme in the box that will actually lead to the 2'-C-methyl-2'-fluoro nucleoside compound, the three steps described there, did you actually do any work attempting those reactions?

A. Yes. I attempted to convert (iv) to (v).

Q. And you never went any further than that, correct?

A. I did not.

Q. Do you know if anyone else attempted to do so with your compounds?

A. I know that people worked with compound (v). Ben Mayes worked with (v).

Q. When was that?

A. I believe it was -- I don't recall the exact date. I believe it was subsequent to April 2005, but I don't know the date. It was -- no, sorry. Subsequent to May 2005. It may have been late 2005, early 2006. I don't remember the
Stewart

date.

Q. To your knowledge with your compound sub (iii) that you made in December of 2004, to your knowledge did anyone ever complete the synthesis of the compound, the nucleoside Roman numeral (i) in Scheme B starting with that material?

A. I'm not aware of anybody having done so.

Q. Now, if you could turn to your lab notebook, 1239, on Page 8 I guess. This is the first experiment you performed on this project? Is that true?

A. Yes.

Q. I just want to ask you, at the top there is a project number. It says NB66. Do you see that?

A. Yes.

Q. What does "NB" stand for?

A. I believe it stands for Novirio Boston.

Q. So would that indicate it's a -- well, what does that indicate?

A. I believe at the time "NM" indicated
Stewart

compounds which were being made in Montpellier, and "NB" were compounds being made in Boston, Idenix Cambridge.

Q. And at what stage of the process would a number be assigned to a compound?

MR. KAFKA: Objection. Beyond the scope.

A. I believe it varied. Sometimes from the very beginning. Sometimes midway through.

Q. Okay. Well, for this project, when was the number NB66 assigned?

MR. KAFKA: Same objection.

A. I don't know.

Q. Did you know that number when you started this project?

MR. KAFKA: Same objection.

A. I was provided with that number by I believe Doctor Adel Moussa or Dick Storer.

Q. And what was your understanding of what NB66 was specifically?

MR. KAFKA: Same objection.

A. I believe NB66 corresponded to the 2'-C-methyl-2'-fluoro cytosine nucleoside shown in Scheme B as Roman numeral (ii).
Stewart

Q. So that would be where X equals NH2?
A. Correct.

Q. And in this first experiment could you just read what you wrote as the purpose?
A. "To prepare the dibenzoyl protected lactone to use for investigation of fluorination at a tertiary position."

Q. And why did you need to investigate fluorination in a tertiary position in November of 2004?
A. To understand how fluorination would proceed, as I had not performed that fluorination before on a tertiary center.

Q. Well, did that make it more complicated being a tertiary position?
MR. KAFKA: Objection. Calls for expert opinion.

Q. In your opinion.
A. In my opinion, no.

Q. Why not?
A. It would be, the purpose of the experiment is to see whether the ribo stereochemistry as shown in (i), (ii), proceeds with inversion of stereochemistry under the
Stewart

correct conditions to give you the fluorine and
an arabino configuration with fluorine up.

Q. Had you seen this reported in the
literature before at the time you began this
experiment?

A. What exactly?

Q. Fluorination of a tertiary -- at the
tertiary position of this lactone.

A. Of this lactone, no.

Q. Now, if you look at Page 18 of your
lab notebook, you wrote, "The purpose for this
experiment was to study whether it is possible to
introduce fluorine at the tertiary position of a
five-ring lactone," right?

A. Yes.

Q. Why were you wondering whether it was
even possible to do so?

A. I don't believe the lactone as shown
had been reported in the literature. It was not
-- this specific lactone had not been shown to
undergo fluorination reactions to the best of my
knowledge.

Q. And because it was not reported, it
was unknown whether it would occur, right?
Stewart

MR. KAFKA: Objection. Calls for expert opinion.

A. I am not aware of it having been reported.

Q. Right. And because it was not reported, you were unaware of whether this reaction would actually work to fluorinate this lactone, right?

A. We could predict that it would work. We would need to do the experiment to prove and confirm that.

Q. And you were conducting this experiment just to see whether it was even possible, right?

A: Conducting the experiment to see twofold: If it was possible, and if it proceeded with inversion of stereochemistry as predicted.

Q. I'm going to show you what is an exhibit to your declaration. It's Exhibit 1343. And could you just review that and, first, just identify what Exhibit 1343 is.

A. It's an e-mail from myself to Sarah Barker - now Sarah Jenkinson -
Stewart

Oxford University on January the 11th, 2005.

Q. If you could look at the third paragraph. And take whatever time you need to read, to familiarize yourself with your e-mail.

In the first full sentence of the third paragraph there is a portion of the first sentence says, "But I managed to make a tertiary fluoride (3) from the C-2 OH epimer (2) of your compound."

Do you see that?

A. Yes.

Q. Is that a reference to the work we were looking at on Page 18 of your lab notebook?

A. I need the exhibit that it's referring to to confirm the structures. I think it's called SFJ lactone.

Q. Well, do you see it attached to this? To your declaration?

A. Yes, and I believe it's Exhibit 1345.

Q. Okay.

(Whereupon Attorney Kline provides Idenix Exhibit 1345 to the witness.)

A. So what was the question? I'm sorry.

Q. My question is: Is this referring to
Stewart

the work we were talking earlier about Scheme B
going from (ii) to (iii)?

A. Yes.

Q. And that was the work we were looking
at on Page 18 of your lab notebook?

A. Yes.

Q. And you describe this as a huge step
in your e-mail to Sarah Barker, correct?

A. Yes.

Q. And you say, "Even on the wrong
stereoisomer as there is nothing in the
literature," right?

A. Yes.

Q. So you would agree that this
conversion of (ii) to (iii) was not based on
anything that was reported in the literature,
right?

A. A conversion of (ii) to (iii)?

Q. Yes.

A. For that specific lactone had not
been reported in the literature, yes.

Q. And why did you believe this was a
huge step?

A. It's a key step in the synthesis.
Stewart

Q. And after making this huge step, what did you do with the compound to carry out the synthesis?

A. I halted work on that compound after confirming the stereochemistry of (iii) and switched to the opposite stereochemistry at the C2 position shown in compound (iv) in Scheme B.

Q. And this would be -- just to keep going in your declaration, paragraph -- or Page 8. It says "Scheme C." Is that what you were referring to?

A. Yes.

Q. And you're saying that in Scheme C Roman (i) is analogous to what?

Well, I guess, Roman (ii), is that analogous to (iv)?

A. Yes. (iv) in the Scheme B.

Q. Now, why didn't you begin with Scheme C in your synthesis?

A. The availability of compound (i) shown in Scheme C. Compound (i) was not readily commercially available I believe. Whereas we had a commercial source for the ribonolactone, (i) shown in Scheme B.
Q. Now, your work on Scheme C began on December 8, 2004, and you worked on this up until December 16, 2004, correct?

A. Yes.

Can I just check my lab notebook just to confirm that answer?

Q. Sure.

A. Refresh my memory.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. I believe that is the case, yes.

Q. Now, your work -- well, this Scheme C, prior to your beginning to work on Scheme C in of December 2004, had you ever seen this entire scheme described anywhere in the literature?

A. To my knowledge, no.

Q. And that you testified you did extensive literature searches before starting your work here?

A. Yes.

Q. Now, the work you did on -- did you -- let me back up.

Before you started working on this
Stewart

Scheme C in your declaration, was it written down anywhere at Idenix the entire scheme?

MR. KAFKA: Objection. Calls for speculation.

A. I don't know.

Q. To your recollection, you never saw it written down, correct?

A. I'm not aware. I don't believe I saw it.

Q. Your work on Scheme C involved trying to get to, I guess, compound Roman numeral (iii), correct?

A. Yes, (iii).

Q. Right. You didn't do any further work under this scheme, right?

A. No.

Q. So your work involved trying to prepare the fluorinated lactone, right?

A. Yes.

Q. To your knowledge did anyone at Idenix ever complete the synthesis of the nucleoside using the lactone you prepared in this Scheme C?

A. I did not prepare lactone (iii) in
Stewart

Scheme C. I did not synthesize lactone (iii) in Scheme C.

Q. Who did? Did anyone?

A. Using this scheme, I don't believe -- I don't believe anyone did.

Q. And why is that?

A. I was not able to get the conversion of (ii) to (iii) to proceed with the conditions in the experiments that I performed.

Q. Okay. Then maybe I should --

starting with -- did anyone ever take your -- were you successful in preparing sub (ii), Roman (ii)?

A. Yes.

Q. Did anyone ever take that compound and successfully follow this scheme to completion to obtain the nucleoside described in Scheme C?

A. To the best of my knowledge, no, no one did.

Q. And your understanding is that -- and let me make sure I understand.

In your declaration in paragraph, I guess, 28 and 29 you say you worked on the synthesis of compound (iii), correct?
Stewart

A. Yes.

Q. But you're saying it never was successful?

A. Paragraph 28 Scheme C.

Q. Right. Oh, I'm sorry, yes.

Paragraph 28 Scheme C.

It was never successful, correct?

A. To the best of my knowledge, no.

Q. And how would I know that from reading this paragraph?

A. How would you know if it had been successfully completed?

Q. Yes.

A. You would not.

Q. Okay. How did you know it was not successfully completed?

A. From the lab notebook pages and my recollection of the experiment, I know that it was not successful.

Q. And what was the problem with the reaction?

A. I believe the major product that was forming was an eliminated species whereby the desired product was not obtained.
Q. So despite being successful in Scheme B in making the lactone with the opposite stereochemistry of Roman numeral (iii) in Scheme C, you were not successful in actually using or trying to prepare the fluorinated lactone with the chemistry -- stereochemistry needed to get to the actual nucleoside here, right?

A. Using the conditions that I attempted in the experiments, that's correct.

Q. And this was an important project at the time, right?

A. Yes.

Q. So you would put your best effort into it, right?

A. Yes.

Q. And despite your best effort, you didn't succeed in Scheme C going from (ii) to (iii), right?

A. Yes.

Q. And there was nothing in the literature that told you how to do this, right?

A. Yes. For this specific compound, that's correct.
Stewart

MR. KLINE: Going on to 1235. Do you want a break or keep going?

MR. KAFKA: Do you want to break for lunch?

THE WITNESS: I'm okay to keep going.

Oh, you said lunch. Let's have lunch.

MR. KLINE: Okay.

(Proceedings recessed at 12:35 p.m., for lunch.)
Stewart

AFTERNOON SESSION

(Whereupon the deposition reconvened at 1:20 p.m.; appearances same as noted.)

BY MR. KLINE:

Q. Doctor Stewart, I wanted to turn back to your declaration in Paragraph 19. I just want to make sure -- I'm not certain, it might be a typo. So I just want to...

If you could read Paragraph 19.

A. "I understood at the time that the conversion of compound (ii) to compound (iii) in Scheme B is important towards understanding the conversion of compound (iv) to compound (v) of Scheme B, and that a successful synthesis of compound (iii) of Scheme B would indicate that a similar strategy could be used to synthesize compound" -- it should be (v). Yes, you're correct. That's correct.

Q. Okay. That makes sense to me. I understand.

So you're saying that it should read "that a successful synthesis of compound (iii) of Scheme B would indicate that a similar strategy could be used to synthesize compound (v) of..."
Scheme B, correct?

A. Yes, compound (iv), correct.

Q. Because both of those are fluorinated compounds, right?

A. Correct. That's correct.

Q. Okay. And Scheme C, was your attempt to use a similar strategy as Scheme B to obtain compound (v) of Scheme B?

A. Yes, that's correct.

Q. And as you testified before the break, the similar strategy at Scheme B to fluorinate the lactone (iii) of Scheme C did not allow the synthesis of the compound in C, right?

A. Yes, the conversion of compound (ii) to compound (iii) in Scheme C was not successful in my hands.

Q. So although you believe based on your work in Scheme B subpart (iii) that a similar strategy could be used to synthesize compound (v) of Scheme B, in your hands it did not, correct?

A. That's correct.

Q. Would that indicate that the fluorination of the lactone described in Scheme B with the fluorine in the down position was
unpredictable?

MR. KAFKA: Objection. Calls for expert opinion.

A. Not -- I wouldn't say unpredictable. I would say it would potentially need fine-tuning with a protecting group strategy or the conditions of the reaction.

Q. You would agree that the strategy employed to fluorinate the lactone with the fluorine in the up position does not work necessarily for obtaining a similarly protected lactone to obtain a fluorine in the down position, correct?

MR. KAFKA: Objection. Calls for expert opinion.

A. In my hands, it was not successful.

Q. Now, I want to turn to Scheme D which is on Page 10.

The scheme depicted as Scheme D in your declaration, was that a scheme that was available in the literature as of December 2004 to your knowledge?

A. The entire scheme, no. I believe intermediate (i) to intermediate (ii) was known.
—Stewart

Sorry, (i) to (ii) was known, but the entire scheme was not to the best of my knowledge.

Q. To the best of your knowledge other than (i) to (ii), were any of the other steps known in the art at the time?

A. I'm not certain if (ii) to (iii) was known. That's the only one I believe that may have been in the literature.

Q. Okay. And the work you describe in your declaration only involves going from step (i) to step (iii), correct?

A. Can I consult my declaration?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. Can I consult my notebook?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. Sorry, could you just repeat the question?

Q. Let me rephrase it. The work that you attempted on this Scheme D that you put into your declaration, you
Stewart did not attempt to go beyond step (iii), correct?
A. That's correct. Yes.
Q. And were you successful in preparing step (iii)?
A. No.
Q. And what's your recollection of why that was unsuccessful?
A. According to Page 43 of my notebook, it states that it's believed that the compound (iii) may have been unstable.
Q. And because you were unsuccessful in converting to compound (iii) of Scheme D, it's fair to say you never obtain compound (iv), correct?
A. Yes.
Q. And because you were never able to successfully synthesize compound (iv) of Scheme D, you were never able to reach a conclusion as to whether a similar strategy could be used to synthesize compound (vi) of Scheme D?
A. Yes.
Q. And understanding whether that successful strategy could be used to synthesize compound (vi) of Scheme D was necessary in your
view as to whether that compound (vi) could then
be converted to the 2'-fluoro-2'-methyl
nucleoside, correct?
  A. Yes.
  Q. And that's information you did not
ever obtain while working on this project, right?
  A. Yes.
  Q. What were your priorities in December
of 2004 in working on this project?
  A. To investigate -- to obtain a
  synthesis of 2'-C-methyl-2'-fluoro cytidine.
  Q. And is it fair to say your initial
strategy was to begin with a lactone precursor?
  A. Yes.
  Q. And why was that?
  A. I had experience of lactone chemistry
in my Ph.D. work. Idenix has experience of
  2'-C-methyl-2'-hydroxyl lactones.
  Q. Now, with Scheme D that you were
working on, you would agree that the lactones you
were working on do not have the stereochemistry
required for obtaining the nucleoside with the F
in the down position, correct?
  A. Sorry. Could you say that again?
Q. Sure.

Scheme D that you were working on, you would agree that the lactones or the lactone that you were working on did not have the stereochemistry required for obtaining the nucleoside with the F in the down position, correct?

A. I don't know if it's possible to convert compound (iii) to (iv) or (vi), as I was not able to synthesize (iii).

Q. Well, at least as you understood the Scheme D at the time, you did not contemplate that (iii) would be converted to the nucleoside with the F in the down position, correct?

A. It was possible. I would have predicted inversion to give (iv).

Q. And when you say "(iv)," that's (iv) at the top, right?

A. Yes, that's correct.

Q. Okay. And (iv) at the top would not result in the compound depicted in the box, the nucleoside with the F in the down position, correct?

A. Not directly.
Q. Okay. And when you contemplated this scheme at the time, did you anticipate that you would convert (iv) to the nucleoside?
A. No.
Q. Just let me clarify that. You did not contemplate that (iv), compound (iv), could be converted to the nucleoside depicted in Scheme D, correct?
A. The nucleoside big (I) and big (II), that's correct.
Q. I want to turn to Scheme E which I believe the discussion begins at the bottom of Page 10, but the scheme itself is on Page 11.
A. Yes.
Q. Now, why did you -- first of all, you started working on this in December 14, 2004, up through January 31, 2005; is that right?
A. Can I consult my declaration?
Q. Yes. Sorry.
(Whereupon the witness peruses Idenix Exhibit 1241.)
A. Yes, that's correct.
Q. And you worked on the first two steps going from (i) to (ii) to (iii), right?
Stewart—

A. Yes.

Q. You did not attempt step 4, (iv)?

A. To convert (iii) to (iv), no.

Q. Nor did you attempt to convert (iv) to (v), correct?

A. That's correct.

Q. Nor did you obtain either of the nucleosides depicted in Scheme E as capital (I) or capital (II)?

A. Not using Scheme E, no.

Q. And were you successful in synthesizing compound (iii)?

A. No.

Q. And what is your understanding as to why that work did not succeed?

A. Can I consult my lab notebook?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. The conversion of compound (i) to compound (iii) using DAST was not successful in my hands.

I wrote in my notebook that I believed the protecting group fell off and the
conversion of the triflate was abandoned to
that's compound (i) to compound (iii).

Q. Just for the record, could you just
identify what page you're reading from in your
notebook?

A. Sure. It's Page 37 and Page 38 for
the conversion of (i) to (iii).

Q. Okay.

A. And Page 73 and Page 74 for the
conversion of (i) to (iii).

Q. Now, the Scheme E conversion of (i)
to (iii) is using a six-ring lactone, correct?

A. Yes.

Q. And we looked at previously your work
involved a five-ring lactone, correct?

A. Yes.

Q. Why did you switch or start
experimenting with a six-ring lactone in December
of 2004?

A. The reactivity and orientation of the
groups on five-and six-ring lactones are very
different.

Q. So you were taking a different
approach?
Stewart —

A. Yes.

Q. And whose suggestion was it to take a different approach?

A. It was a -- to the best of my knowledge, it arose from meeting with Professor Fleet in May 2004.

Q. So you had this meeting in May of 2004 but you didn't attempt it until December of 2004; is that correct?

A. Yes.

Q. Why?

A. I was looking at other reactions prior to that time.

Q. And why were you looking at other reactions prior to that time?

A. I could not do all the reactions at the same time.

Q. And why did you prioritize the five-member lactone approach first?

A. As the five -- I mention the commercial availability of the five-ring ribonolactone was such that it was readily available.

This lactone was obtained from
Professor Fleet's laboratory.

Q. And when did you obtain the six-member lactone used in your Scheme E from Doctor Fleet?

A. It was from Sarah Jenkinson. I believe it is -- the best of my memory it was early January 2005. Maybe the 2nd or 3rd of January.

Sorry, can I correct that?

Q. Yes.

A. I just found on Page 37 I've used it on the 14th of December.

Q. Right. But you don't know when you would have received it?

A. No, I don't. It may have been mentioned in an e-mail that I received it from Sarah Jenkinson.

Q. In any event, the attempts to use the Sarah Jenkinson six-membered lactone to obtain (iii) were not successful in your hands?

A. In my hands, that's correct.

Q. Now, if you could turn to the next scheme, Scheme F, is this a scheme you had seen described in the literature at the time you
started attempting to carry out parts of the scheme?

Q. That's not my question. My question is: Is this a scheme that you had seen in the literature at the time you started attempting to carry out parts of the scheme?

A. No.

Q. So as far as you're aware, this Scheme F was not described anywhere in the literature as of December of 2004?

A. To the best of my knowledge, yes.

Q. And you were certainly scouring the literature on this project, right?

A. Yes.

Q. Now, this is a different approach than what you had been trying to obtain, the compounds, right?

A. Yes.

Q. This started with a nucleoside, right?

A. Yes.
Stewart

Q. How did it come about that you started an approach starting with a nucleoside in December 2004?

A. I believe I requested compound, I think it's compound (i) or (ii) from Doctor Griffon having reviewed a 2002/2004 report from him.

Q. The 2002/2004 report you're referring to is not attached to your declaration?

A. Yes, that's correct.

Q. It is not?

A. Is not attached.

Q. It's not in the record?

A. Yes, it is not in the record.

Q. Now, your work on Scheme F consisted of trying to make up through compound (iii)?

A. Yes.

Q. And did you succeed in making compound (iii)?

A. No.

Q. And what's your understanding -- and when you talk about -- well. Did you make compound (iii)?

A. Yes.
Q. How would you describe that reaction, going from (i) to (iii)?

A. It's protection of the 5' and 3' hydroxyl groups with benzoyl protecting groups.

Q. So you were successful in the benzoyl protection of the 3 and 5 positions, correct?

A. Yes.

Q. And then going from step two -- or (ii) to (iii), that was the fluorination reaction, correct?

A. Yes.

Q. Okay. And you're saying that did not succeed, correct?

A. My colleague Jingyang Wang was able to show the evidence of a compound with a molecular weight of (iii) on the mass spec, but I did not.

Q. You did not?

A. No.

Q. And where is that reflected in your lab notebook?

A. I don't believe it is.

Q. But your recollection is that you were unable to obtain (iii)?
Stewart

A. Yes, that's correct.

Q. And what's your understanding as to why in your hands the fluorination from (ii) to (iii) was unsuccessful?

A. I believe the scale of the reaction I performed did not allow me to identify that compound.

Q. And because you were unsuccessful in making (iii), is it fair to say you did not complete the remaining steps of Scheme F?

A. Yes.

Q. Would you turn to Page 74 of your lab notebook which is Exhibit 1329.

A. Yes.

Q. Can you just read into the record what it says on this page?

A. "Reaction abandoned owing to change of priorities."

Q. And which reaction was abandoned?

A. It was the reaction of a triflate depicted in Scheme B, (ii), in an attempt to form (iii) in Scheme E.

Q. And what was the change in priorities in -- what was the date of this? January 20,
2005; is that correct?

A. Yes.

Q. Okay. What was the change of
priorities that occurred on this project on
January 20, 2005?

A. I don't recall. I don't remember.

Q. You don't remember a change in the
priorities on this project?

A. I believe -- looking at my notebook,
I believe this is where I became aware of a
patent application.

Q. What patent application did you
become aware of in January of 2005?

A. A Clark, Jeremy Clark patent
application.

Q. And how did you become aware of a
Jeremy Clark patent application in January of
2005?

A. I don't recall if I found it via
SciFinder or if I was given it by Doctor Adel
Moussa or Jingyang Wang.

Q. And how did the discovery of the
Jeremy Clark patent application in January 2005
change your priorities on this project?
Stewart

A. We were working on the uracil analog of the nucleoside as depicted in Scheme G, and we switched to working on the cytosine-containing nucleoside.

That is actually Scheme F. My mistake.

Q. So why did you switch from the uracil analog to the cytosine?

A. I was instructed to by Doctor Moussa.

Q. And did he explain why?

A. I don't recall.

Q. No recollection of why you switched your priorities?

A. No. I don't remember.

Q. Just to make sure I understand. So before you saw the Clark patent application, were you contemplating making the 2'-fluoro-2'-methyl ribocytosine compound?

A. Yes.

Q. So how did it change your priorities?

A. We had the uracil analog available from Doctor Griffon, and we were looking at that transformation on the uracil analog at that time.

Q. Now, at the time you had changed your
priorities in January 20, 2005, after obtaining
the Clark patent application, you had not
actually made one of these -- synthesized a
2'-fluoro-2'-methyl ribonucleoside with either
uracil or cytosine; true?
A. Yes.

Q. And after receiving -- well, did you
receive a copy of the Clark application?
A. I don't recall. I think -- I can't
remember if I found it or I was provided it by
Doctor Moussa or Jingyang Wang. But I certainly
saw a copy of it.

Q. You certainly saw it and you read it?
A. Yes.

Q. Okay. And did you use any of the
procedures in there to obtain the compound?
A. Yes.

Q. Did you follow them as written?
A. Yes.

Q. Okay. And following them as written,
were you able to make compounds that led to the
actual successful synthesis of
2'-fluoro-2'-methyl ribo compounds?
A. We adapted some of the conditions in
Stewart

terms of the purification of the compounds. And yes.

Q. And let me just clarify. When I talk about following the Clark procedures to obtain -- to synthesize the 2' -fluoro-2'-methyl ribonucleosides, I'm referring to the F in the down position, correct?

A. Yes.

Q. And it's only after receiving that patent application that Idenix was successful, right?

A. To the best of my knowledge, yes.

Q. And that was the first time you had seen a description in the literature of a synthesis process for obtaining 2' -fluoro-2'-methyl ribonucleosides with the F in the down position?

A. To the best of my knowledge, yes.

Q. Let me show you what is Clark Exhibit 2008, and I just want you to let me know is this a copy of the Clark patent application, publication, that you were referring to as having received in January of 2005 that enabled you and Idenix to successfully synthesize the nucleoside
Stewart

with the F in the down position?

MR. KAFKA: Objection. Assumes

facts.

A. This is the patent application that I
saw and that I used. I'm not certain as to the
rest of Idenix. I can only talk for myself.

Q. Okay. At least for yourself, this is
the patent application you used in your attempts
to synthesize the 2'-methyl-2'-fluoro
ribonucleosides with the F in the down position,
correct?

A. Yes.

Q. And based on reading this, you were
able to succeed in synthesizing that compound,
right?

A. Yes.

Q. Now, if you look at Scheme H in your
declaration, which is on Page 17, is this scheme
based on the Clark patent application?

A. Yes.

Q. And that's the first-time you had
ever seen it published anywhere?

A. Yes.

Q. You prepared some of the -- you
Stewart performed some of these steps, right?

A. Yes.

Q. And did you also perform some of these steps and give the product to Jingyang?

A. Jingyang Wang, yes.

Q. Jingyang Wang, okay.

Yes?

A. Yes.

Q. And do you know if she was able, based on what you had produced following this scheme depicted in the Clark application, to successfully complete the scheme?

A. Yes.

Q. And do you know when that was?

A. I don't recall.

Q. Let me switch gears for just a second.

I wanted to go back to your discussions with Doctor Fleet in May of 2004.

Let me get 1330.

Let me show you 1330, Idenix Exhibit 1330. And, first, could you just identify what this is?

A. It's a list of schemes that arose
from a meeting with Professor Fleet at Idenix in May 2004.

Q. And this was a meeting you were present at?
A. Yes.

Q. Who else was present?
A. I believe Ben Mayes, Adel Moussa were present. And I'm not certain if Jingyang Wang was present. I cannot recall.

Q. In this Exhibit 1330, is there any discussion of a 2'-fluoro-2'-methyl riboC or riboU nucleoside?
A. No.

Q. So it would also be correct there is no depiction of a chemical structure of a 2'-fluoro-2'-methyl ribo uracil or a cytosine nucleoside, correct?
A. Correct.

Q. And it's your understanding that prior to this meeting in May of 2004, no one at Idenix had made a 2'-fluoro-2'-methyl ribonucleoside, right?
A. To the best of my knowledge, that is correct.
Stewart

Q. Now, the various -- just looking at

G1, for example, these lactones.

These could be used to make a variety

of different types of nucleosides, right?

A. They could.

Q. Right. It's not limited just to the

synthesis of a 2'-fluoro-2'-methyl nucleoside,

right?

A. Correct.

Q. Now, going back to your declaration,

Paragraph 49 describes a Scheme I.

A. Yes.

Q. And just explain what this is.

A. It depicts the deprotection of an

anhydro uracil containing nucleoside with a

2'-C-methyl substituent.

Q. And why were you performing this

work?

A. I was trying to prepare an anhydro

nucleoside to study if it could be opened to give

the desired 2'-C-methyl-2'-fluoro down compound.

Q. And were you able to ever do that?

A. Yes.

Q. And when?
Stewart

A. I believe it was 2006.
Q. So it was after your work reflected in your lab notebook?
A. Yes.
Q. And it took how long?
A. I don't recall. We outsourced the work to a company called Manchester Organics.
Q. So you didn't actually do the work?
A. We outsourced the work.
Q. All right. So --
A. Owing to the nature of the reagents being used.
Q. So in your hands you were never able to use Scheme I to synthesize the 2-fluoro-2'-methyl ribonucleosides?
A. Correct.

THE WITNESS: May I request a break?
MR. KLINE: Sure.
Off the record.
(Proceedings recessed at 2:07 p.m., and reconvened at 2:23 p.m.)

BY MR. KLINE:
Q. Doctor Stewart, I put in front of you what is Exhibit 1352 to your declaration.
Stewart

Can you just identify for the record what this is?

A. I believe it is a scheme that I sent to—can I consult my declaration?

Q. Certainly.

Let me hand you also 1351 which may be part of it.

A. I think it's Doctor Jenkinson, an e-mail.

Q. Does that help?

A. Yes, it does. Thank you.

Q. Okay. Now, with Idenix Exhibit 1351 and Idenix Exhibit 1352, can you just describe for the record what Idenix Exhibit 1352 is?

A. It's a summary of results that I performed which was involving DAST reactions sent to Sarah Barker — Sarah Jenkinson — Oxford University.

I'm sorry. Can I say Sarah Barker even though her name changed?

Q. You can say whatever you want—

A. Okay.

Q. Just for the record, Sarah Barker is Sarah Jenkinson?
A. Correct. Sarah Jenkinson.

Q. Okay. Under "Uracil Nucleosides" at the bottom, it says, "Same result with patent conditions: Toluene, minus 20 degrees C, and no ET3N."

Do you see that?

A. Yes.

Q. What does that mean?

A. Can I consult my lab notebook?

Q. Sure.

A. Okay. This is why I was attempting to use the results listed in the -- the conditions listed in the Clark application on compound (iv), and I obtained compound (v) as I believe the major product.

Q. So when you refer to the patent conditions in Idenix Exhibit 1352, you are referring to the patent condition or the conditions described in the Clark patent application, correct?

A. Yes.

Q. And you followed those to achieve going from the compound (iv) depicted on Exhibit 1352 to compound (v)?
Stewart

A. Yes.

Q. What was your practice as far as signing your lab notebook?

A. I would sign or initial at the end of experiments where sections needed to be completed. If there was a blank space, I would draw a line through and initial and date those sections.

And after reviewing what I had written, I would then sign the notebook and have a coworker countersign.

Q. If you look at your -- I'm just trying to figure out in your lab notebook -- example -- let's just start at the beginning.

Page 8.

There is a part at the bottom that says, "Invented By," and that's your signature, right?

A. Yes.

Q. And then there is a date?

A. Yes.

Q. When would you typically sign your lab notebook?

A. After I had reviewed what I had
Stewart

written and inserted all the data that was
required for the experiment.

Q. Did you have a regular practice as to
how often you would do that?
A. After every experiment.

Q. Once the experiment is completed you
mean?
A. After having reviewed the data and
the experiment performed.

Q. "And what about the "Witnessed" and
"Understood By" portion? When would that
typically be done?
A. It could vary from the next day to a
few months after the experiment had taken place.

Q. If you look on Page 8, do you see the
project number at the top?
A. Yes.

Q. Okay. And it has something stricken
through. Do you know what it says under that?
A. Yes.

Q. What was that?
A. LDDA.

Q. What is LDDA?
A. It stand for L-dideoxyadenosine.
Stewart

Q. What is LDDA?
A. A nucleoside, an L-nucleoside containing adenine as the base.

Q. Could the scheme depicted on Page 8 be used to make LDDA?
A. No.

Q. Were you working on a project for LDDA?
MR. KAFKA: Objection. Beyond the scope.
A. I don't recall prior to this project. It's possible.

Q. All right. But you did write at one time LDDA on there, right?
A. Yes.

Q. Do you know when the number NB66 was assigned to this project?
A. No.

Q. Did you make photocopies of your lab notebook at any time?
A. I believe I may have done of specific experiments.

Q. And do you know why you did that?
A. I may have shared them with
Doctor Jenkinson, and I would need to check my declaration. Can I do that?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. It's not listed in my declaration.

Q. I'm going to show you what is in your declaration. Maybe this will refresh your recollection. But it's Idenix Exhibit 1357 and Idenix Exhibit 1358.

Can you identify what this is for the record?

A. Yes. It's an experimental procedure from my notebook depicting the synthesis of a triflate from ribonolactone starting material. Protected.

Q. And just can you confirm that Idenix Exhibit 1358 was an attachment to this e-mail?

A. Yes. I believe it is triflateprocedure.zip in Exhibit 1357.

Q. And Exhibit 1358, the first two pages, are from your lab notebook, correct?

A. Yes.

Q. And do you know whose lab notebook
Stewart

the last page is from?

A. Yes.

Q. Whose?

A. Jingyang Wang.

Q. And how did you obtain these lab 
notebook pages that are attached?

A. I photocopied them — I photocopied 
the pages from my lab notebook. I cannot recall 
if Jingyang gave me this page or if I photocopied 
it from her notebook.

Q. And when did you photocopy the pages 
from your notebook?

A. I imagine it was February the 10th, 
around February the 10th, prior to the e-mail to 
Sarah Barker. But I cannot recall exactly.

Q. Can you turn in your lab notebook to 
Page 1329 Page 34.

A. (Whereupon the witness complies.)

Q. And if you can compare that to the 
first page of Idenix Exhibit 1358.

A. (Whereupon the witness complies.)

Q. Are these the same lab notebook 
pages?

A. No.
Q. How are they different?
A. They're not -- this one is not signed.

Q. Right. But according to your lab notebook, you signed it in December of 2004?
A. Yes.

Q. Yet when you sent it to Ms. Jenkinson in February of 2005, there is no signature on the page, is there?
A. That's correct.

Q. Nor is there a project number at the top?
A. No.

Q. How do you explain that?
A. I don't know.

Q. You have no explanation as to how that happened?
A. I think it's possible that I sent it and then -- no. I don't know.

Q. Could you turn to the second page of Idenix Exhibit 1358.
Is this Page 35 from your lab notebook?
A. Yes.
Stewart

Q. Again, there is no signature at the bottom?

A. Correct.

Q. No project number at the top?

A. Correct.

Q. When did you put the project number at the top of your Page 35?

A. I don't recall.

Q. Okay. And when did you actually sign lab page 35?

A. I don't recall.

Q. Sitting here today, do you have any explanation as to why the e-mail attachment of Pages 34 and 35 were unsigned --

A. No.

Q. -- at the time you sent them in February of 2005?

A. It's possible that the witness noticed it wasn't signed. But I don't know.

Q. Okay. Any explanation as to why your signature does not appear on Idenix Exhibit 1358?

A. No.

MR. KLINE: Do you want to go off the record?
Stewart

MR. KAFKA: Sure.

(Proceedings recessed at 2:39 p.m.,
and reconvened at 2:47 p.m.)

BY MR. KLINE:

Q. Doctor Stewart, at the time you were
working on this project in 2004/2005,
approximately how many years of experience did
you have in synthesizing nucleosides?

A. Approximately -- I started my Ph.D. I
believe in '99. So approximately -- sorry, what
was the end date? When we started --

Q. When you were doing your work.

A. Okay. Probably four to five years.

Q. If you could turn back in your
declaration on Page 25, there is a Scheme J.

A. (Whereupon the witness complies.)

Yes.

Q. And this is work you performed
beginning in March 29, 2005; is that right?

A. Yes.

Q. And in this Scheme J, your work
involved going up through step (iii); is that
right?

A. Can I consult my declaration?
Stewart

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. Yes. That's correct.

Q. And were you successful in synthesizing the product of step (iii)?

A. Can I consult my notebook?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. Your question was was I successful in synthesizing (iii)?

Q. Right.

A. No.

Q. Okay. I just want to look at Page 146 and 147. That's one attempt to make (iii), correct?

A. Yes.

Q. And you wrote in the conclusion, if I'm reading this correctly -- well, maybe I'll have you read the conclusion on Page 147 of your lab notebook.

A. Sure.

"Reaction was abandoned owing to
Stewart.

other priorities and it seems as though formamide
group is unstable towards aqueous workup."

Q. Do you recall what the other
priorities were at the time you were performing
this experiment around March 30, 2005?

A. No.

Q. And if you look at Page 158 of your
lab notebook, is this another attempt to make
(iii) of Scheme J?

A. Yes.

Q. And is your conclusion basically the
same as what you observed for the previous
experiment to make (iii)?

A. Yes.

Q. And so neither of these attempts were
successful in making (iii), correct?

A. Yes.

Q. Needless to say, given your lack of
success in getting to step (iii), is it fair to
say you were never able to complete Scheme J to
make the 2'-fluoro-2'-methyl ribonucleosides with
the F in the down position, correct?

A. Yes.

Q. And to your knowledge did anyone at
Stewart.

Idenix ever succeed in following the scheme to make the nucleoside?

A. I don't know in terms of other people at Idenix. To my knowledge, no.

Q. Now I want to turn to Scheme K which is on Page 26.

And does this reflect a scheme that you worked on parts of while working on this project?

A. Yes.

Q. And you worked on trying to get from step (i) to step (ii); is that correct?

A. Can I consult my declaration?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1241.)

A. Yes, that's correct.

Q. And were you successful in making the compound of step (ii)?

A. Can I consult my notebook?

Q. Sure.

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. I don't know. I believe I may have
Stewart made it, but it appears I wrote in my notebook on Page 149 "Contaminated by methanol."

Q. Is it fair to say you never proceeded to complete Scheme L, correct?
A. Scheme L?
Q. I'm sorry. Scheme K.
A. Scheme K. That's correct.
Q. And as far as you're aware, did anyone at Idenix ever complete Scheme K to obtain a nucleoside with the F in the down position?
A. To the best of my knowledge, no.
Q. Do you recall why you were working on this scheme at this time?
A. To study whether I could obtain intermediate (iii) by shorter sequence.
Q. But you never got to step (iii)?
A. Correct.
Q. Okay. And Scheme L on Page 29.
A. Yes.
Q. This is another scheme you worked on, correct?
A. Yes.
Q. And your work consisted of trying to convert step (i) to compound in step two, (ii)?
Stewart

A. Yes.

Q. And you did not attempt to go beyond that step, correct?

A. Can I consult my --

Q. Sure.

A. -- notebook?

(Whereupon the witness peruses Idenix Exhibit 1329.)

A. So was the question did I get beyond compound (ii)?

Q. Correct.

A. That's correct. No, I did not.

Q. And were you successful in obtaining compound (ii)?

A. Yes.

Q. Why did you not proceed further with this step? Or this scheme? Scheme L.

A. I don't remember.

Q. To your knowledge did anyone else at Idenix work on Scheme L and successfully synthesize the nucleoside depicted as (i) or (ii) at the bottom?

A. I believe Jingyang Wang worked on the scheme. I'm not aware as to whether she was able
Stewart

to successfully generate big (I), big (II),
depicted in Scheme L.

Q. Do you recall when she worked on the scheme?
A. No.

Q. And the next scheme in your declaration, Scheme M, is this a scheme you worked on?
A. Yes.

Q. And your work involved trying to go from step (i) to step (ii)?
A. Correct.

Q. And was that work successful?
A. No. Not in my hands.

Q. So it's fair to say you did not complete Scheme M to obtain the nucleoside depicted as Roman (II) or (I), correct?
A. Correct.

Q. And to your knowledge did anyone at Idenix follow Scheme M to obtain the nucleoside depicted in Scheme M with the fluorine in the down position?
A. Again, I believe Jingyang Wang worked on Scheme M. I'm not aware if she was able to
Stewart

take it to nucleoside big Roman numeral (I), big
Roman numeral (II) in Scheme M.

Q. Now, if you look at Paragraph 120 of
your declaration, you refer to having worked
towards the synthesis from at least December 20,
2004, to at least May 1, 2005.

Do you see that?

A. Yes.

Q. Is it fair to say you stopped working
on the project around May 1, 2005?

A. No.

Q. You continued working on it?

A. Continued working on routes towards
that compound, correct.

Q. But you're just not relying on that
work for purposes of your declaration; is that --

A. Yes.

Q. Of the schemes B through M in your
declaration, to your knowledge as of May 1, 2005,
which of those schemes had Idenix been able to
successfully use to synthesize
2'-fluoro-2'-methyl ribonucleosides with the F in
the down position?

A. Scheme H.
Stewart

Q. And is that the only one?
A. And the time period of the question?
Q. In May 2005.
A. Yes, exactly. As of May 2005.
Q. And that was the scheme you found in
the Clark patent application?
A. Yes.

MR. KLINE: We have no further
questions.

Thank you very much.

(Proceedings recessed at 3:02 p.m.,
and reconvened at 3:07 p.m.)

EXAMINATION BY

MR. KAFKA:

Q. Doctor Stewart, do you have
Exhibit 2008, the Clark patent application in
front of you?
A. Yes.

Q. Do you recall Mr. Kline asking
questions about your use of this application in
synthesis of the compound?
A. Yes.

Q. What steps, if any, towards the
synthesis of a 2'-fluoro-2'-methyl ribonucleoside
Stewart

did you have in mind prior to seeing the Clark
application?

A. My recollection is that we were
working towards the synthesis of the
2'-fluoro-2'-methyl nucleosides using a very
similar, well, identical scheme for the uracil
analog up to intermediate 4-4 shown in the patent
application on page -- I believe it's Page 29.
The 5' benzoyl 5' -- 3'-benzoyl-arabino-uracil
nucleoside which was made by Jean-Francois
Griffon.

And the steps prior to that showing
the silyl protection of cytidine, oxidation to
the ketone, introduction of a methyl group at
deprotection, and re-protection with a benzoyl
protecting group had been performed by my
colleague Jean-Francois Griffon in Montpellier.

And just to add to that,

Jean-Francois Griffon and myself attempted the
DAST reaction, as did Jingyang Wang, on the
uracil analog as shown in 4-4 shown on Page 29 of
the Clark application.

Q. And was that before or after you saw
the Clark application?
Stewart

A. That was before.

Q. Do you recall when you first saw the Clark application?

A. I believe it was early January 2005.

Q. Do you see the cover of Clark Exhibit 2008? Do you see a publication date on that application?


Q. Does that at all help you remember when you first saw the Clark application?

A. I believe it was very close to that date. Subsequent to the publication date.

Q. You said in your earlier testimony that Scheme H of your declaration shows a route which you used that's related to the chemistry shown in the Clark application?

MR. KLINE: Objection to form.

A. Yes.

Q. Did the steps that you used to come up with that scheme differ or were they the same as the Clark procedure in any way?

A. We -- I -- I believe I used -- no, I exchanged methyllithium for I believe methyl -- trimethylaluminum to try to introduce the methyl
Stewart

group and attempted to remove column
chromatography from the procedure.

Q. Did you recall anything else that you
did that was different from the procedure shown
in Clark with respect to your work shown in
Scheme H?

MR. KLINE: Objection to the form.

A. The -- I believe the DMSO quantity
that was used in the patent was incorrect, and I
had to change that when performing this step from
(iii) to (iv).

MR. KAFKA: No further questions.

MR. KLINE: Just let me follow up a

EXAMINATION BY

MR. KLINE:

Q. Your use of the methyllithium you
were talking about. What step is that in?

A. I believe it's step (iv). Compound
(iv) to (v). I might have misspoken. I think I
said (iii) to (iv).

Q. And the use of the DMSO, what step
were you talking about?

A. That's the oxidation from (iii) to
Stewart

(iv) shown in Scheme H.

Q. But you did use DMSO just like the
Clark application, right?

A. Correct.

Q. And from going from Step 1 to Step 2
in the Clark application, you use the same
reagents, right?

A. Can I check my notebook?

Q. Sure.

(Whereupon the witness peruses Idenix
Exhibit 1329.)

A. I believe I switched from DMF listed
in the patent application to dioxane.

Q. Well, why don't you look at your
first experiment you performed on Page 75 and 76.
Is that the first attempt you made to
do Step 1?

A. Yes.

Q. And did you use the identical
reagents you used in Clark?

A. Publication, yes.

Q. Yes.

A. Yes.

Q. And when you repeated the experiment
on January 25/26, 2005 on Pages 79 to 80 of your lab notebook on Exhibit 1329, did you again use the identical reagents of Step 1 of the Clark patent application?

A. Yes.

Q. So you would agree that you did copy the Clark application Step 1 in your laboratory notebook, right?

MR. KAFKA: Objection; assumes facts.

Objection; lack of foundation.

A. I employed the procedure used as displayed in the patent application.

Q. Right. Using the same reagents; same conditions?

A. For the initial experiments, yes.

Q. Right.

And that succeeded, right?

A. Yes.

Q. Now, let's go to Step 2. Step 2 to 3, did you use the same conditions as the Clark patent application in converting compound (ii) to compound (iii) in your Scheme H?

A. Yes.
Stewart

Q. You used the same reagents, right?
A. Yes.

Q. And the same conditions, right?
A. Yes.

Q. Let's look at your conversion of step (iii) to step (iv). This is where you were dissolving the protected cytidine in THF, right?
A. Compound (iii) to compound (iv) did you say?

Q. Yes.
A. Yeah, okay.

Q. If you look at, for example, Pages 96 to 98 of your lab notebook, is that your attempt to go from --
A. Yes.

Q. -- (iii) to (iv)?
A. Yes, it is.

Q. And did you use the same conditions that are described in the Clark patent application, including the same reagents?
A. Yes.

Q. So, again, you copied the Clark patent procedure to convert from (iii) to (iv)?
For the first attempt to do that, right?
Stewart

A. Yes.

Q. Now, let's talk about your conversion from compound (iv) to (v).

I believe this is the one you told me there were some differences, right?

A. It's in the previous step of (iii) to (iv) of the initial experiment where I used the conditions displayed in the patent as described. I altered the quantity of DMSO as it was incorrect in the patent.

Q. If you look at Page 115 of your lab notebook.

A. Yes.

Q. Does this describe the conditions in the Clark application to go from compound (iv) to (v)?

A. Yes.

Q. Okay. And you struck that and gave that to Jingyang, right?

A. Yes.

Q. Okay. So as much as you know, she did that step, right?

A. Correct. As far as I am aware.

Q. And why did you give her that step?
Stewart

A. I was looking into methyllumination and
to see if it was a sauer alternative to
methyllithium. Trimethylaluminum.

Q. Did you direct her to run this
reaction?

A. I did direct her.

Q. Did you ask her to run the reaction?

A. Not to the best of my knowledge.

Q. What do you mean by "gave to
Jingyang"?

A. The -- I don't know. I don't know if
I supplied her with the starting material
perhaps. The ketone (iv).

Q. Okay. But, again, your notebook
reflects you were copying the procedure of the
Clark patent example to go from -- to convert
(iv) to (v), right?

MR. KAFKA: Objection. Assumes
facts.

A. It looks as though I was starting to
do it but didn't complete -- didn't start the
reaction. I was planning -- I should say I was
planning to perform.

Q. Now, your conversion from (v) to (vi)
Stewart

in carrying out that step, did you copy the reagents and conditions of the Clark patent publication?

A. Yes.

Q. Anything you note as different?

A. To the best of my knowledge, no.

Q. And in going from step (vii) -- or step (vi) to step (vii) in your scheme, did you, again, use the Clark patent publication procedures including the reagents and conditions to obtain that compound?

A. Yes.

Q. Okay. And the next step, the conversion of (vii) to (viii) of Scheme H in performing that step of Scheme H, did you employ the conditions and reagents used in the Clark publication?

A. Yes.

Q. And in going from compound (viii) to the final product, Roman (II), the removal of benzoyl groups with methanolic ammonia, is that how you performed the reaction?

A. Yes.

Q. And is that how it's done in the
Stewart

Clark publication?

A. Sorry. Could you repeat that?

Q. Sure.

A. Methanolic ammonia?

Q. Right.

Let me just ask it a different way.

Did you use the Clark publication, conditions, and reagents to obtain the final product, the nucleoside depicted in Scheme H?

A. Yes.

Q. Same conditions; same reagents?

A. Yes.

Q. Now, earlier on redirect you had referred to work by Jean-Francois Griffon.

A. Yes.

Q. Work he did.

A. Yes.

Q. Do you remember telling me earlier on the day you had no idea what he was working on?

A. No. I said I received a report 2002 to 2004.

Q. You weren't even working there in 2002. So when did you receive this report?

A. I believe it was at the start of when
I worked on the project in May 2004.

Q. As far as you're aware, was anyone ever able to successfully synthesize the compound of Scheme H prior to April of 2005 at Idenix?

A. Compound (II) big Roman numerals, no.

Q. Okay. And was anyone ever able to successfully synthesize the compound -- well, look at Scheme G with the OH.

A. The uracil.

Q. Yes, the uracil nucleoside.

A. To the best of my knowledge, no.

Q. And that includes Jean Griffon, correct?

A. Yes.

MR. KLINE: Okay. Nothing further.
MR. KAFKA: I don't have any questions.

(Time: 3:27 p.m.)

DR. ALISTAIR STEWART

Subscribed and sworn to before me this day of 2013.
## INDEX

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## EXHIBITS

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(No exhibits marked.)
CERTIFICATE OF OFFICER

I hereby certify that:

(1) The witness was duly sworn by me before commencement of testimony by the witness;

(2) The attached transcript is a true record of the testimony given by the witness;

(3) I personally recorded the testimony;

(4) The following opponents were present:

(a) on behalf of Party Clark:
   Steven C. Kline, Esq.
   Erica L. Norey, Esq.

(B) on behalf of party Sommadossi:
   Mark Kafka, Esq.
   Thomas Friebel, Esq.

(5) The deposition was taken at the following place: Jones Day, 100 Summer Street, Boston, Massachusetts 02110

   The deposition began at the following date and time: June 19, 2013, at 9:58 a.m.
   The deposition ended at the following date and time: June 19, 2013, at 3:27 p.m.

(6) I am an officer authorized by law to take depositions and to be used in the Courts of the U.S. or of the State where I reside;

(7) I have no disqualifying interest, personal or financial in a party.

SIGNATURE OF OFFICER DATE: 6/20/13

MARYJO O'CONNOR, RPR/CSR
NAME OF OFFICER
DECLARATION OF DEPONENT

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of Sommadossi's U.S. application 12/131,868 or any patent issuing thereon.

[Signature]

25th JULY 2013

DR. ALISTAIR STEWART

DATE
INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made. After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.

It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.
ERRATA

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ERRATA

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I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of Sommadossi's U.S. application 12/131,868 or any patent issuing thereon.

[Signature]

DR. ALISTAIR STEWART 26th JULY 2013 DATE

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UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT TRIAL AND APPEAL BOARD

Patent Interference 105,871
Technology Center 1600

JEAN-PIERRE SOMMA DOSSI, PAOLO LACOLLA, RICHARD STORER, and
GILLES GOSS ELIN,

Application 12/131,868,
Junior Party

v.

JEREMY CLARK,

Patent 7,429,572,
Senior Party

Decision - Priority
Bd. R. 125(a)

Before SALLY G. LANE, RAE LYNN P. GUEST, and DEBORAH KATZ,
Administrative Patent Judges.

KATZ, Administrative Patent Judge.
I. Statement of the Case

Following the Decision on Motions in this Interference (Paper 426, see also Decision on Rehearing, Paper 434), both parties move for judgment on priority. (See Sommadossi Substitute Substantive Motion 9, Paper 454, and Clark Substantive Motion 9, Paper 448.)

We determine that Sommadossi did not conceive of the subject matter before Clark’s accorded benefit date and, even if it had been the first to conceive, it was not diligent in reducing the invention to practice.

A. The Count

The interfering subject matter is an antiviral drug, specifically, a synthetic compound with similarities to naturally occurring nucleotides for treating infection by the Hepatitis C Virus. (See Substitute Declaration of Victor E. Marquez, Ph.D. (“Marquez Decl.”), Exh. 2001, ¶¶ 22 and 23; see also Declaration of Masad J. Dahma, Ph.D. (“Dahma Decl.”), Exh. 1101, ¶¶ 21-22.) The Count, which defines this subject matter and sets the scope of the admissible proofs for priority, is:

A compound of the formula:

\[ R^1O - X - CH_3 \]

or a pharmaceutically acceptable salt thereof, wherein:

- \( X = O; \)
- \( R^1 \) is H, a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl;

1 Sommadossi Substitute Substantive Motion 9 is incorrectly numbered as Motion 8. (Paper 454; see also “Sommadossi Substantive Motion 8,” Paper 437) We refer to Sommadossi’s motion for judgment on priority as “Sommadossi Motion 9.”
$R^7$ is H, a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and
Base is a pyrimidine represented by the following formula:

\[
\begin{array}{c}
\text{R}^4 \\
\text{R}^3 \\
\text{N} \\
\text{N} \\
\text{R}^2 \\
\text{R}^1 \\
\end{array}
\]

wherein,
$R^3$ is H; and
$R^4$ is NH₂ or OH.

(Declaration, Paper 1, at 8.)

B. Junior Party Sommadossi

Junior Party Sommadossi is involved based on its U.S. patent application 12/131,868. (Declaration, Paper 1.) The real party-in-interest of Sommadossi is Idenix Pharmaceuticals, Inc. (Paper 5.)

The involved Sommadossi application was filed 2 June 2008. (Declaration, Paper 1, at 7.) Though Sommadossi was originally accorded the benefit of U.S. patent application 10/608,907, filed 27 June 2003 (Declaration, Paper 1 at 10), during the motions phase of this Interference Sommadossi was denied benefit of that application. (Decision on Motions, Paper 426, at 18-25.) Thus, Sommadossi has not been accorded the benefit of priority of any application earlier than its involved application. (Redeclaration, Paper 427, at 4.)

Sommadossi asserts that its inventors conceived of an embodiment within the scope of the Count as of 18 December 2001, again on 23 July 2002, (Sommadossi Motion 9, Paper 454, at 3:1-5:17), and reduced it to practice as of 25 March 2005 (id. at 11:13-15:11).
Sommadossi relies on the testimony of Masad J. Dahma, Ph.D. Dr. Dahma who testifies that he is the James McGill Professor of Chemistry at McGill University and has held academic positions in chemistry since 1987. (Dahma Decl., Exh. 1281 at ¶2.) He testifies that he has published approximately 140 papers and book chapters in peer-reviewed journals, many relating to nucleoside analog synthesis. (Id. at ¶7.) Dr. Dahma testifies further that he has been the president or on the board of directors of the Oligonucleotides Therapeutics Society and the International Society of Nucleosides, Nucleotides & Nucleic Acids, has consulted for pharmaceutical companies on the synthesis and applications of nucleosides, oligonucleotides, and their analogs, and has received numerous medals and honors for his research work. (Id. at ¶¶ 4, 5, and 9.)

The activities, publications, and awards about which Dr. Dahma testifies indicate that he is qualified to provide opinions about the subject matter of this Interference.

C. Senior Party Clark

Senior party Clark is involved based on its U.S. patent 7,429,572. (Declaration, Paper 1.) The real party-in-interest of Clark is Gilead Pharmasset LLC. (Paper 8.)

The application that became the involved Clark patent, U.S. application 10/828,753, was filed on 21 April 2004. (Declaration, Paper 1, at 6.) During the motions phase of this Interference, Clark was accorded the benefit of its provisional application 60/474,368, filed 30 May 2003. (Decision on Motions, Paper 426, at 15-18; see Redeclaration, Paper 427, at 4.)

Clark asserts that its inventors conceived of an embodiment within the scope of the Count by at least 31 January 2003 and, at the latest, by 23 May 2003. (Clark Motion 9, Paper 448, at 4:14-21:4.)
Clark relies on the testimony of Dr. Victor E. Marquez. Dr. Marquez testifies that he is a Scientist Emeritus at the Chemical Biology Laboratory of the Center for Cancer Research at the National Cancer Institute in the National Institutes of Health. (Substitute Declaration of Victor E. Marquez, Ph.D. ("Marquez Decl."), Exh. 2001, at ¶ 9.) Dr. Marquez testifies that he has been employed as an academic chemist since 1970 and that he has published more than 375 papers and book chapters, including over 225 relating to nucleosides, dinucleotides, or oligonucleotides and more than 25 relating to fluorinated nucleosides. (Id. at ¶¶ 12 and 15.) Dr. Marquez testifies that he has often lectured on the topic of nucleosides. (Id. at ¶ 16.) Dr. Marquez testifies further that he has received numerous medals and honors for his research work. (Id. at ¶ 14.)

The activities, publications, and awards about which Dr. Marquez testifies indicate that he is qualified to provide opinions about the subject matter of this Interference.

II. Priority

Under 35 U.S.C. § 102(g), (enforced on claims with an effective filing date before the Leahy-Smith America Invents Act, 16 March 2013), a party is not entitled to a patent if "during the course of an interference . . . another inventor involved therein establishes . . . that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed . . . " To prevail under §102(g), junior a party may show, by presenting persuasive, admissible evidence, that it was the first to reduce an embodiment of the invention to practice. A junior party also may prevail by showing that it conceived of the invention first and that it was diligent in reducing it to practice from the time just before the invention was conceived by the other party. See Cooper v. Goldfarb, 154 F.3d 1321, 1327 (Fed. Cir. 1998) ("[P]riority of invention goes to the first party to reduce an invention to practice unless the other party can
show that it was the first to conceive of the invention and that it exercised reasonable diligence in later reducing that invention to practice.”

Sommadossi asserts that it reduced an embodiment of the Count to practice by 25 March 2005. (Sommadossi Motion 9, Paper 454, at 11:8-21.) This date is after the filing date, 30 May 2003, of Clark’s accorded benefit application and, thus, after the date that Clark constructively reduced the invention to practice. To prevail, Sommadossi must show that it conceived of an embodiment of the Count before Clark and must also show that it was diligent in reducing it to practice from at least just before Clark conceived of it.

Sommadossi must provide clear and convincing evidence that it was either the first to reduce an embodiment of the Count to practice or the first to conceive of it and was diligent in reducing it to practice. Even if Sommadossi were held to the lower standard of a preponderance of the evidence, though, it would not prevail.

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2 Clark argues that Sommadossi is estopped from arguing an actual reduction to practice in 2005 because its priority statement did not assert one (see Sommadossi Priority Statement, Paper 24) and Sommadossi never sought to amend the priority statement. (Clark Opps. 9, Paper 460, at 19:4-16.) Because we determine there was a lack of diligence even before the actual reduction to practice asserted by Sommadossi, we need not reach this issue. We note, though, that Sommadossi might have avoided any possible estoppel by requesting to file an amended Priority Statement after the Decision on Motions and Redeclaration.

3 Sommadossi is held to this heightened standard because it did not constructively reduce its invention to practice until 2 June 2008, with the filing of application 12/131,868. This date is after the date, 13 January 2005, when the application that became Clark’s involved patent was published. See 37 C.F.R. § 207(a)(2) (“Priority may be proved by a preponderance of the evidence except a party must prove priority by clear and convincing evidence if the date of its earliest constructive reduction to practice is after the issue date of an involved patent or the publication date under 35 U.S.C. 122(b) of an involved application or patent.”).
A. Sommadossi Argument for Priority

i. Conception

Sommadossi argues that as of either 18 December 2001 or 23 July 2002, the structure of a compound within the scope of the Count was conceived by the named inventors (Sommadossi Motion 9, Paper 454, at 3:6-8) and that this conception was complete because “an operative method for making the compound with conventional techniques was a matter of common knowledge and routine experimentation to a person of skill in the art as of December 18, 2001” (id. at 5:21-23).

Conception requires (1) the idea of the structure of the chemical compound, and (2) possession of an operative method of making it. . . . When, as is often the case, a method of making a compound with conventional techniques is a matter of routine knowledge among those skilled in the art, a compound has been deemed to have been conceived when it was described, and the question of whether the conceiver was in possession of a method of making it is simply not raised.

Oka v. Youssefeyeh, 849 F.2d 581, 583 (Fed. Cir. 1988). Clark opposes Sommadossi’s argument, countering that making 2’-F-Me-RiboC was not a matter of common knowledge and required more than routine experimentation at the time Sommadossi asserts it was conceived. (Clark Opp. 9, Paper 460, at 5:22-6:5.)

Our previous decision that Sommadossi’s S4 application is not enabling for an embodiment of the Count (Decision, Paper 426, at 25) does not preclude us from considering the evidence Sommadossi now presents regarding conception of an embodiment of the Count. Contrary to Clark’s argument (Clark Opp. 9, Paper 460, at 5:10-20), a decision regarding whether named inventors had conceived of an invention is not necessarily the same as a decision regarding whether a
particular disclosure is enabling, even if both questions involve a determination of the level of skill in the art.

**Findings of Fact**

The following findings of fact, as well as others in this opinion, are supported by substantial evidence in the record.

1. Sommadossi inventor Richard Storer testifies that he prepared and distributed a 2001 Meeting Agenda to Sommadossi inventors Jean-Pierre Sommadossi, Paolo LaColla, and Gilles Gosselin, among others, at a chemistry meeting convened by Novirio in Maui, HI on 18 December 2001. (Substitute Declaration of Richard Storer, D.Phil. ("Storer Decl."), Exh. 1429, at ¶ 8-11 and 13.)

2. Exhibit 1250 is entitled "Novirio Chemistry Discussion Meeting" and is the document Sommadossi asserts is the 2001 Meeting Agenda. Exhibit 1250 includes the chemical structure reproduced below.

   ![Chemical Structure](image)

   (Novirio Chemistry Discussion Meeting ("2001 Meeting Agenda"), Exh. 1250 at 9.)

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4 Dr. Storer testifies that Novirio Pharmaceuticals, Ltd. is the former name of Idenix, Inc. the real party-in-interest of Sommadossi. (Storer Decl., Exh. 1429, ¶ 6.)
3. The structure depicts a 2'-F-2'-Me-ribo molecule wherein the 2'-methyl group ("2'-Me") is represented as "H₂C" in the "up" position, and the X can be fluorine and is in the "down" position. (See Sommadossi Motion 9, Paper 454, at 3:6-12; Storer Decl., Exh. 1429, ¶ 8.)

4. The 2001 Meeting Agenda states: "We know that C and G appear to be the best for activity from the selection tried so far." (2001 Meeting Agenda, Exh. 1250 at 5.)

5. Dr. Storer calculates that the structure depicted above, with the base as either C or G, and X as a flourine, would include 16 different molecules, each with 2'-Me in the "up" position. (Storer Decl., Exh. 1429, at ¶ 8.)


\[ \text{New synthetic priority for Jean-François Griffon:} \]

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{OH} & \quad F \\
\end{align*}
\]

The structure depicts a 2'-F-2'-Me-ribo molecule with fluorine. (Summary Montpellier Meeting, Exh. 1251, at 2.)

7. Dr. Dahma, Sommadossi's witness, testifies that 2'-F-2'-Me-RiboC is a nucleoside cytidine that contains two "simple" structural modifications of the naturally occurring cytidine nucleoside: (1) the hydrogen ("H") of cytidine is replaced with an Me group in the "up" position and (2) the alcohol ("OH") of cytidine is replaced with an F in the "down" position. The following structures compare cytidine and 2'-F-2'Me-riboC.
8. Dr. Dahma testifies that a reaction depicted below converting arabinonucleoside to 2'-F-Ribonucleoside using the reagent DAST had been reported in the literature, specifically by Van Aerschot in 1989 (Exh. 1214) and by Hayakawa in 1990 (Exh. 1215). (Dahma Decl., Exh. 1281, ¶ 26.)

9. Dr. Dahma testifies that the reaction depicted in Finding of Fact ("FF") 8 above includes (i) the replacement of the 2'-OH of arabinouridine with F and (ii) the simultaneous inversion of the stereochemistry of the 2'-carbon of arabinouridine, wherein the OH group in the "up" position of the arabinouridine is replaced with an F group in the "down" position in the 2'-F-Ribouridine. (Dahma Decl., Exh. 1281, at ¶ 26.)

10. Dr. Dahma testifies that the 2'-F-ribouridine depicted above in FF 8 is an "adjacent homolog" of 2'-F-2'-Me-RiboU, a compound within the scope of Count 1 because 2'-F-ribouridine has an H group in the 2' "up" position and 2'-F-
2′-Me-RiboU of Count 1 has a methyl group (CH₃) in the same 2′ “up” position. Dr. Dahma testifies that the stereochemistry of the fluorine atom of 2′-F-ribouridine is identical to that of 2′-F-2′-Me-RiboU of Count 1, because both fluorines are in the “down” position at the 2′ location. Dr. Dahma provides the following comparative structures of 2′-F-2′-Me-RiboU and 2′-F-ribouridine.

![Structures](image)

(Dahma Decl., Exh. 1281, at ¶¶ 27 and 28.)

11. Dr. Dahma testifies that because the stereochemistry of the 2′-F-ribouridine depicted in FF10 above shows the same “spatial identity” to that of 2′-F-2′-Me-RiboU of Count 1, one of skill in the art would have known that the DAST methods of Van Aerschot (Exh. 1214) and Hayakawa (Exh. 1215) would be applicable to the synthesis of 2′-F-2′-Me-RiboU. (Dahma Decl., Exh. 1281, at ¶ 28.)

12. Dr. Dahma testifies that the reaction depicted below

![Reaction](image)

in which 2′-F-ribothymidine is prepared in a single step by reacting arabinothymidine with DAST, wherein (i) the 2′-OH of arabinothymidine is
replaced with F and (ii) the stereochemistry of the 2'-carbon on arabinothymidine is simultaneously inverted, was reported by Dr. Marquez, Clark's witness, in 1998 (Exh. 1212) and by Herdewjin et al. in 1989 (Exh. 1213). (Dahma Decl., Exh. 1281, at ¶ 29.)

13. Dr. Dahma testifies that because the stereochemistry of the fluorine atom at the 2' position of 2'-F-Ribothymidine is identical to that of 2'-F-2'-Me-RiboU, as shown in FF 11 above, one of skill in the art would have known that the DAST methods of Marquez (Exh. 1212) and Herdewjin (Exh. 1213) would have been applicable to the synthesis of 2'-F-2'-Me-RiboU. (Dahma Decl., Exh. 1281, at ¶ 30.)

14. The reactions discussed in FFs 8 and 11 above involve the transformation of a “secondary” OH to F because the OH group is attached to a carbon that is itself attached to two other carbons.

15. Dr. Dahma testifies that in 1999 Wachtmeister (Exh. 1120), reported the reaction depicted below

![Diagram](image-url)

in which a “tertiary” OH, one attached to a carbon that is itself attached to three other carbons, is transformed to a tertiary F in single step with DAST or Deoxofluor using a protecting group. Dr. Dahma testifies that in the reaction, (i) the tertiary OH is replaced with F and (ii) the stereochemistry is simultaneously inverted at the tertiary carbon. (Dahma Decl., Exh. 1281, ¶ 32, citing Wachtmeister, Exh. 1120, p. 10763, II. 14-17, Scheme 2.)

16. The reactions recited in FF 15 depict transformation of a tertiary alcohol at the 4' position of the nucleoside.
17. Dr. Dahma testifies that as of 18 December 2001, many F-nucleosides had been reported in the literature, including in Heredewijn (Exh. 1248, at 165), which states that DAST "has been successfully applied for the replacement of a hydroxyl group by a fluorine atom and for the replacement of an anomic hydroxyl group in the preparation of glycosyl fluorides. It also reacts easily with tertiary alcohol . . . DAST has been extensively used for the introduction of fluorine into carbohydrates." (Dahma Decl., Exh. 1281, ¶ 36.)

18. Dr. Dahma testifies that from the literature available on 18 December 2001, a person skilled in the art would have concluded that DAST was a suitable fluorinating reagent for converting an arabinonucleoside to a 2'-F-ribonucleoside regardless of whether the 2'-OH of the arabinonucleoside was secondary or tertiary because the DAST reaction had predictably and reliably proceeded with inversion of the stereochemistry. (Dahma Decl., Exh. 1281, ¶ 34.)

19. Dr. Dahma proposes that Scheme A for the synthesis of 2'-F-2'Me-RiboU would have been within the skill of one in the art in 2001, wherein 2'-Me-arbinouracil taught by Matsuda (Exh. 1144) is used as the starting material and DAST is used to convert the 2'-OH to F with a simultaneous inversion of stereochemistry at the 2' carbon as depicted below.

Scheme A

(Dahma Decl., Exh. 1281, at ¶ 37-39.)

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5 This page number reflects the page of the exhibit, not the underlying document.
20. Scheme A, depicted in FF 19, requires the conversion of a tertiary alcohol (OH) to a fluorine (F) and inversion of the stereochemistry at the 2’ carbon.

21. Dr. Dahma testifies that DAST and other similar reagents, such as Deoxofluor, were commercially available as of December 2001. (Dahma Decl., Exh. 1281, ¶ 40.)

22. Dr. Dahma testifies that “the most obvious route” for synthesis of a 2’F-2’-Me-ribonucleoside of Count 1 would have been by the route depicted in Scheme A of FF 19 and that a person skilled in the art would have predicted that the fluorination reaction of an arabinonucleotide with DAST would lead to the inversion of stereochemistry at the 2’-carbon to form a 2’-F-ribonucleoside. (Marquez Decl., Exh. 1281, ¶¶ 53-55.)

23. Dr. Marquez, Clark’s expert, testifies that the use of DAST to make a 2’-flouro-2’methyl-nucleoside was not reported in the literature until the publication of the application that became the involved Clark patent. (Fourth Marquez Decl., Exh. 2152, ¶ 29.)

24. Dr. Marquez testifies that “[t]he fact that a compound is reported to have been made using such ‘known’ reagents and techniques does not mean its synthesis was straightforward. An extensive amount of experimentation, including numerous unreported failures, may have been required to arrive at the ultimately successful synthetic route.” (Second Marquez Decl., Exh. 2066, ¶ 211.)

25. Dr. Marquez testifies that Dr. Dahma oversimplifies the understanding in the art of using DAST to fluorinate all substrates with tertiary alcohols because Dr. Dahma does not consider the complexities and uncertainties associated with using DAST with a substrate having different structural features from the substrates previously reported. (Fourth Marquez Decl., Exh. 2152, ¶ 33.)
26. Dr. Marquez testifies that the documents Sommadossi relies on to support diligence show that using DAST could fail to produce the desired fluorinated product because reacting nucleosides having a 2’hydroxyl group in the “up” position can produce elimination and anhydro products. (Fourth Marquez Decl., Exh. 2152, ¶ 29, citing Sommadossi Exhs. 1468, 1352, and 1355.)

27. Sommadossi Exhibit 1468 is a copy of an e-mail and attachments from Alistair Stewart and Adel Moussa, Idenix personnel (see Substitute Declaration of Adel Moussa, Exh. 1428, at ¶ 3, 5; et seq.; see Substitute Declaration of Alistair Stewart, Exh. 1241, at ¶ 3 et seq.), dated 7 January 2005. The attachments depict fluorination reactions, including, on page 3 of the exhibit, “DAST reaction on nucleoside 1464-JFN,” and the comment: “Elimination confirmed by loss of methyl group in $^1$H NMR and mass spec. Originally fluorine was found in $^19$F NMR but then disappeared on changing from CD$_3$CN to DMSO” (Exhibit 1468.)

28. Dr. Marquez testifies that that Dr. Coe, the expert consulted by Sommadossi inventor Storer (see Storer Decl., Exh. 1429, at ¶ 29-34) expressed concerns about using DAST because of the possibility of elimination, participation of blocking groups, and migration. (Fourth Marquez Decl., Exh. 2152, at ¶ 30.)

29. Exhibit 1418 is a letter from Dr. Coe, which is undated, but which Sommadossi dates as 9 April 2003 (see Sommadossi Diligence Timeline, Paper 454, App’x 4, ¶ 125), and states:

in our experience and indeed in that of manner [sic] other particularly the de Clerc group the most viable routes to fluoro nucleosides are by sugar/base condensation methods the anomer problem notwithstanding, for the very reasons you have discovered, in that the leaving groups generated in site e.g. in DAST reactions are readily attacked by the pyrimidine ring nucleophiles or elimination and/or participation of blocking groups. Further migrations of groups can readily occur see our papers in JFC 1993 62 145 and 1993 60 239[.]
Having said this some of the route [sic] you have tried are OK except that I think you are using the wrong reagents, leaving groups and reaction conditions.

(Exh. 1418, pp. 1-2.)

30. Dr. Coe was described by inventor Storer as an “expert in organofluorine chemistry.” (Deposition of Richard Storer (“Storer Deposition”), 14 June 2013, Exh. 1644, at 74:21-24.)

31. Dr. Marquez testifies that e-mail correspondence, dated 11 November 2004 (Exh. 1336), between Sommadossi inventor Storer, Dr. Alistair Stewart, and Dr. Adel Moussa, other members of the Idexx team, demonstrates the differences between synthesizing secondary and tertiary fluorine compounds. (Fourth Marquez Decl., Exh. 2152, ¶ 34.)

32. Exhibit 1336 is a copy of an e-mail from Dr. Storer to Drs. Stewart and Moussa, which expresses Dr. Storer’s understanding in November 2004 that “[a] lot of things which look simple on paper in related systems have been tried and don’t work in this series. Having to make the tertiary fluoride in very different to having to make secondary.” (E-mail from Dr. Storer to Drs. Stewart and Moussa, 11 November 2004, Exh. 1336.)

33. The e-mail correspondence between Drs. Storer, Stewart, and Moussa (Exhibit 1336), includes Mr. Stewart’s reply:

We had problems in the past where an azide had been successful when trying to introduce fluoride (see scheme), but could be very different at the now tertiary position. It’d be very handy if he’s got any of the useful intermediates (2, 3 or 10) available, if we end up doing it rather than them. Looks like the best approach so far. I was surprised that any formation of a tertiary fluoride from a tertiary alcohol had been reported until we found it yesterday, but I haven’t looked through literature that was ordered yet (in any case, no relevant sugar or nucleosides was reported).
(E-mail from Dr. Storer to Adel Moussa and Alistair Stewart, 11 November 2004, Exh. 1336.)

34. Dr. Marquez testifies that none of the reports of using DAST cited by Dr. Dahma show fluorination of tertiary alcohols at the 2' position of a nucleoside. (Fourth Marquez Decl., Exh. 2152, ¶ 32.)

35. Dr. Marquez testifies that neither Herdewijn (Exh. 1248), which was relied upon by Dr. Dahma to show that DAST was known at the time to fluorinate tertiary OH groups, nor any of the references cited within Herdewijn (see Exhs. 1118, 2153, and 2154), describe fluorination of a tertiary OH on the sugar of a nucleoside by DAST. (Fourth Marquez Decl., Exh. 2152, ¶ 32.)

36. Dr. Marquez testifies that neither Herdewijn (Exh. 1248) nor any of the references cited in it would have informed an artisan about the use of DAST to prepare a compound from a nucleoside precursor having a tertiary alcohol. (Fourth Marquez Decl., Exh. 2152, ¶ 32.)

Analysis

Conception of a chemical compound requires that inventors possess the idea of the structure of the chemical compound and an operative method of making it. Coleman v. Dines, 754 F.2d 353, 359 (Fed. Cir. 1985); Fina Oil & Chem. Co. v. Ewen, 123 F.3d 1466, 1473 (Fed. Cir. 1997). That is, in addition to knowing the desired result, inventors must also know a means for effectively carrying out that result. For example, conception is complete only when the means for doing the invention are known. In Oka, when inventors were unable to make a chemical compound they had described, even after considerable effort, the court found that they had not fully conceived of the compound. See Oka, 849 F.2d at 583 (reversing the Board’s decision that appellee conceived of a compound with the
scope of the count where the Board had found that a skilled Ph.D. chemist had spent over six months and was not successful in preparing such a compound).

Sommadossi argues that the structure of the 2'-F-2'-Me-ribonucleoside in the 2001 Meeting Agenda and the summary of the Montpellier meeting demonstrate that a compound within the Count was conceived by Sommadossi⁶ by at least 23 July 2002 because, even though Sommadossi inventors did not actually make the compound until March 2005, skilled artisans could have easily made it by December 2001. According to Dr. Dahma, Sommadossi’s witness, the knowledge of using a DAST reaction to synthesize 2'-F-2'-Me-riboC was available to those of skill in the art as of December 2001 from the published reports of reactions using DAST to convert an OH group to a fluorine.

Specifically, Dr. Dahma testifies that the literature taught fluorinating the sugar at the 2’ position of a deoxy-arabinonucleoside or arabinonucleoside with the reagent DAST. (FFs 11-13). According to Dr. Dahma, because these reactions include replacing an OH group with a fluorine and inverting the stereochemistry so that the fluorine is in the “down” position, those in the art would have considered these reactions to be the same as the reactions needed to make 2'-F-2'Me-ribonucleoside within Count 1. Dr. Dahma also testifies that even though the nucleoside fluorinations with DAST reported in the literature as of December 2001

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⁶ Clark argues that Sommadossi fails to identify who conceived of the structure of the 2'-F-2'-MeRiboC included in the 2001 Meeting Agenda and so has failed to prove conception by any named applicant. (Clark Opp. 9, Paper 460, at 4:15-5:9; see Sommadossi admission of Clark Material Fact 99, Paper 464, at Appx. 3-1.) Sommadossi argues that there is a presumption that the inventors named on an application are the true inventors. (Sommadossi Reply 9, Paper 464, at 1:14-18.) Any presumption, however, does not negate Sommadossi’s burden to show conception by the named inventors. Because we determine that Sommadossi otherwise has not shown conception, we need not, and do not, reach the issue of whether conception is attributable to the named Sommadossi inventors.
were fluorinations of secondary alcohols, fluorinations of tertiary alcohols with DAST were also known. (FFs 15-17.)

Clark opposes Sommadossi's argument, relying on the opinion of its witness, Dr. Marquez. According to Dr. Marquez, the evidence presented by Dr. Dahma does not show that those in the art would have considered using DAST to synthesize a 2'-F-2'-Me-nucleoside because it would have been too unpredictable. Dr. Marquez testifies that those of skill in the art would have been aware of the risks of producing elimination and anhydro products when using DAST and would have understood that DAST had not been shown to produce a tertiary fluorine on the 2' carbon of the sugar of a nucleoside. (FFs 26.) In support, Dr. Marquez cites to correspondence between Idenix personnel and to the advice of consultants hired by Idenix, which were critical of the proposed schemes. (FFs 27-33.)

Clark also argues that Sommadossi's own diligence period attests to the lack of knowledge about how make a compound within the scope of Count 1 at the time of Sommadossi’s asserted conception. (Clark Opp. 9, Paper 460, at 3:17-4:4.) Clark argues that six Ph.D. level chemists at Idenix, as well as other researchers, with the help of two consultants (Dr. Fleet (see Storer Deposition, Exh. 1644, 73:22-24 (describing Dr. Fleet as a "world expert on carbohydrate chemistry")) and Dr. Coe (see id., 74:23-24 (describing Dr. Coe as an "expert in organofluorine chemistry")), worked for over three years to make a 2'-F-2'Me-ribonucleoside. (Clark Opp., Paper 460, at 9:5-9.) Clark also notes that at least one member of the Idenix team (Dr. Griffon and Claire Pierra, see Storer Decl., Exh. 1429, at ¶ 35) attended a four-day training course in fluorination chemistry to gain the necessary knowledge and, further, that Sommadossi was only able to actually reduce to practice an embodiment of the Count after the publication of a synthesis pathway in the application that became the Clark patent. (Clark Opp. 9, Paper 460, at 9:6-7 and 3:17-22.) According to Clark, this effort was not routine and demonstrates the
lack of skill of any artisan at the time, as well as an incomplete conception by the Sommadossi inventors by their asserted conception dates.

We are persuaded by Clark's argument. Though Dr. Dahma presents evidence to show that each step of the synthesis of a 2'-F-2'Me-ribonucleoside would have been known to those in the art, the skepticism shown by Dr. Coe, who was consulted for his expertise, and in the communications between Drs. Storer and Stewart support Dr. Marquez's opinion that those of skill in the art would not have had the necessary skill.

In addition, we are persuaded that the length of time Idenix personnel spent trying to synthesize a 2'-F-2'Me-ribonucleoside does not exemplify routine experimentation. Sommadossi argues that it is improper to look to the activities of specific people to show what was known by a skilled artisan at the time because such analysis "is premised on the false assumption that those efforts were made by the hypothetical person instead of real people with imperfect awareness of the relevant art." (Sommadossi Reply 9, Paper 464, at 3:20-23.) According to Sommadossi, if there is an operative method of making a compound in the art, it is irrelevant that the actual inventor tried and failed, even many times, to make it. (Sommadossi Reply 9, Paper 464, at 3:20-4:10.)

Sommadossi's argument does not persuade us to ignore the evidence of the Idenix personnel's extraordinary effort. To make a determination of what the hypothetical ordinarily skilled artisan would have been able to do, we look to evidence of not only what information was publically available, but also evidence of what actual artisans did with that knowledge.

Both Drs. Dahma and Marquez agree that a hypothetical person skilled in the art of synthesizing a compound of the count would have an advanced education (Ph.D. or master's degree) and additional experience in the chemical aspects of drug discovery (i.e., synthetic organic chemistry). (See Dahma Decl., Exh. 1281,
¶ 16; Marquez Decl., Exh. 2001, ¶ 70.) The members of the Idenix team were all employed as chemists and several had doctoral degrees. (See, e.g., Storer Decl., Exh. 1429, ¶ 2 (testifying that he has a D.Phil. degree in chemistry); Substitute Declaration of Jean-Francois Griffon, Exh. 1471, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Adel Moussa, Exh. 1428, ¶ 2 (testifying that he has a Ph.D. degree in organic chemistry); Substitute Declaration of Alistair Steward, Exh. 1241, ¶ 2-3 (testifying that he has a Ph.D. degree in organic chemistry.) Sommadossi does not argue that they were not at least ordinarily skilled artisans. On the record before us, we have no reason to exclude them as representative of ordinarily skilled artisans at the time. Thus, the evidence of the effort exerted by the Idenix team to eventually synthesize a 2'-F-2'Me-ribonucleoside is informative of what the hypothetical skilled artisan could do.

Furthermore, the evidence of the effort exerted by the Idenix team shows that it was not just one chemist who was unable to synthesize a compound within Count 1 with routine experimentation, but a team of chemists, even after they had consulted with others considered to be experts and had sought additional training. From this record it is reasonable to find that if after all of this effort, a compound within the scope of the count could not be synthesized easily, a hypothetical person of ordinary skill would not have known how to synthesis such a compound either.

Sommadossi argues that Dr. Marquez’s testimony regarding what was expected by those in the art about DAST fluorination is inconsistent. (Sommadossi Reply 9, Paper 464, at 5:15-20.) According to Sommadossi, Dr. Marquez characterized DAST as highly unpredictable in regard to enablement of Sommadossi application 10/608,907 (which Clark argued did not provide benefit of priority as to Count 1 during the first phase of this interference, see Clark Motion 2, Paper 33), but that he now testifies that DAST would be expected to
yield the desired product in regard to Clark's conception. Sommadossi points to Dr. Marquez's first declaration, Exhibit 2001, at paragraphs 221-222, and to statements in his deposition on 15 July 2013, which is provided in Exhibit 2148 (specifically at 64:13-88:11, 89:13-90:21, 122:3-16, 126:22-129:10)\(^7\).

We agree with Sommadossi that Dr. Marquez testified in his declaration that fluorination with DAST was unpredictable, even as late as July 2003 (see Marquez Decl., Exh. 2001, at ¶ 221: "In other words, the stereochemical outcome of a fluorination reaction such as one performed using DAST could not be known until one actually performed the reaction because the outcome could be affected by the unique characteristics of the specific compound being fluorinated."), but we do not agree that his testimony on cross-examination contradicts this direct testimony. Instead, Dr. Marquez testifies that in 2003, it was unknown by what mechanism DAST would work and that one of skill in the art would just "do the reaction and see what happens," determining later if it had worked. (Deposition of Victor E. Marquez, Ph.D., 15 July 2013, Exh. 2148, at 90:7-21.) This seems to confirm Dr. Marquez's original testimony that fluorination with DAST would have been unpredictable. We are not persuaded that Dr. Marquez's testimony is inconsistent or biased, as Sommadossi argues.

\(^7\) At oral argument, Sommadossi cited to portions of Dr. Marquez's deposition that were not cited in its briefs. (See Sommadossi Filing of Demonstrative Exhibits, Paper 1003, at 6-14.) New evidence cited in demonstrative exhibits at oral argument will not be considered. Even if Sommadossi had timely cited to this evidence, it is not persuasive that Dr. Marquez's testimony is inconsistent. For example, at pages 77 and 126-127 of Dr. Marquez's 15 July 2013 deposition (Exh. 2148), he is asked whether one of skill in the art could have conducted a certain reaction without extensive research, given the method, not whether making the resulting compound would have been predictable to a skilled artisan before being given the method.
ii. Diligence

Sommadossi argues that it exercised reasonable diligence from before Clark's alleged conception to a reduction to practice. (Sommadossi Motion 9, paper 454, at 23:9-32:11.) "The law regarding diligence is settled. The evidence must show that the alleged earlier inventor was diligent throughout the entire critical period. . . . However, there need not necessarily be evidence of activity on every single day if a satisfactory explanation is evidenced." Monsanto Co. v. Mycogen Plant Sci. Inc., 261 F.3d 1356, 1369 (Fed. Cir. 2001) (citations omitted). For example, in Rey-Bellet v. Englehardt, 493 F.2d 1380, 1389 (C.C.P.A. 1974), diligence was found even though there had been a delay in testing a compound for three months because specific testimony was presented to show that test monkeys were unavailable. Similarly, to persuade us that it was diligent, Sommadossi must present evidence that any delay or period of inactivity is explained by specific circumstances.

Sommadossi presents Appendix 4 to its motion for judgment on priority as a timeline of the activities from just before 6 December 2002, the earliest conception date alleged by Clark, to 25 March 2005, when Sommadossi asserts a compound within the scope of Count 1 was actually reduced to practice. (Sommadossi Motion 9, Paper 454, at 23:19-23.) As Clark notes, there are many gaps of significant length in the diligence chart. (Clark Opp. 9, Paper 460, at 16:6-9.) For example, there are no explanatory entries for over 50 of the workdays between from 1 September 2003 to 9 December 2003.8 (See Sommadossi Motion 9, paper 454, at Appendix 4-36 to 4-41.) Sommadossi argues that these gaps are excusable because Idenix was a small company with limited personnel and resources so that

---

8 Because these gaps occur after Clark's accorded benefit date of 30 May 2003, we need not and do not reach the issue of whether Clark established an even earlier conception.
“occasionally its scientists were required to maintain equipment, attend administrative meetings, draft reports, and other activities that required time away from their activities in the laboratory.” (Sommadossi Motion 9, Paper 454, at 24:16-25:2; see also Sommadossi Reply 9, paper 464, at 7:16-22.)

We are not persuaded by Sommadossi’s argument. In the absence of any specific explanation and evidence about the nature of the activities occupying the Idenix personnel for almost three months, we cannot assume these activities were necessary because Idenix was a small company. For example, although Jean-François Griffon testifies that he had other duties around the time period in question, including preparing reports, managing starting materials, maintenance of equipment, and training of Bachelor of Science students (see Sommadossi Motion 9, Paper 454, at 24:16-22 and Material Fact (“MF”) 60, citing Substitute Declaration of Jean-François Griffon (“Griffon Decl.”), Exh. 1471, at ¶¶ 8-9), none of these activities are provided as specific reason why he was not working towards reduction to practice for any particular day between 1 September 2003 and 9 December 2003. We have not been directed to evidence on the record before us with which we can evaluate whether Dr. Griffon was engaged in activities considered to be within the scope of reasonable diligence for those working in a small company.

Without citation to such specific evidence, any excuse for unexplained days between 1 September 2003 and 9 December 2003, as well as other gaps in the Sommadossi diligence timeline, are merely attorney argument. Meitzner v. Mindick, 549 F.2d 775, 782 (CCPA 1977) (“Argument of counsel cannot take the place of evidence lacking in the record.”).

Furthermore, several of the days between 1 September 2003 and 9 December 2003 that do have corresponding explanations, indicate only that Audrey Chappe-Dumas was on vacation or sick. (See, e.g., 1 September 2003, 24...
October 2003, 3 and 4 November 2003.) Sommadossi does not direct us to evidence explaining why when Audrey Chappe-Dumas was unavailable others could not have performed her duties towards synthesizing a compound. For example, Dr. Griffon testifies that Ms. Chappe-Dumas worked under his supervision (Griffon Decl., Exh. 1471, ¶ 9), but Sommadossi does not explain why he could not have assumed her duties when she was away.

In summary, even if Sommadossi had shown conception as of 18 December 2001 or 12 July 2002, it has failed to provide sufficient evidence of diligence from before Clark’s earliest constructive reduction to practice, 30 May 2003, to Sommadossi’s asserted reduction to practice in 2005. Accordingly, Sommadossi’s Motion 9 for priority is denied.

B. Clark Argument for Priority

Because Sommadossi has failed to persuade us that it conceived of or was diligent in reducing a compound within the scope of Count 1 before Clark’s accorded benefit date, 30 May 2003, we need not reach Clark’s argument for an earlier date of conception. Accordingly, Clark Motion 9 is dismissed as moot.

III. Miscellaneous Motions

Both parties filed Miscellaneous Motions to exclude evidence of the other. (Sommadossi Miscellaneous Motion 10, Paper 47; Clark Miscellaneous Motion 10, Paper 476.)

Clark Miscellaneous Motion 10 is moot because even if we consider the evidence Clark seeks to exclude, we deny Sommadossi Motion 9 for priority.

Similarly, Sommadossi Motion 10 is moot because we do not consider any of the evidence Sommadossi argues is not admissible. Specifically, Sommadossi argues that evidence relied on by Clark to prove priority is inadmissible, but we do not reach Clark’s argument for priority. Although we do rely on Dr. Marquez’s Fourth Declaration (Exh. 2151), we do not rely on paragraph 17, which
Sommadossi argues is improper opinion testimony. (Sommadossi Motion 10, paper 473, at 10:23-11:14.) Accordingly, we need not consider whether this paragraph is admissible or not.

IV. Conclusion

Because Sommadossi does not provide sufficient evidence to persuade us that it was either diligent in reducing to practice or conceived of an embodiment of Count 1 before Clark's accorded constructive reduction to practice, the Sommadossi Motion for judgment on priority is DENIED.

Judgment will be entered separately.
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UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT TRIAL AND APPEAL BOARD

Patent Interference 105,871 (DK)
Technology Center 1600

JEAN-PIERRE SOMMADOSSI, PAOLO LACOLLA, RICHARD
STORER, and GILLES GOSSELIN,

Application 12/131,868,
Junior Party

v.

JEREMY CLARK,

Patent 7,429,572,
Senior Party,

4th DECLARATION OF VICTOR E. MARQUEZ, Ph.D.
(in support of Senior Party CLARK's opposition)

CLARK EXHIBIT 2152
Sommadossi v. Clark
Contested Case 105,871

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I, Victor E. Marquez, Ph.D., hereby declare:

I. Introduction

1. I am the same Victor E. Marquez who executed the “Substitute Declaration of Victor E. Marquez, Ph.D.” (Ex 2001), the “Substitute 2nd Declaration of Victor E. Marquez, Ph.D.” (Ex 2066) and the "3rd Declaration of Victor E. Marquez, Ph.D." (Ex 2133) on Clark’s behalf in the above-captioned interference.

2. I have been advised that the interference has one “count,” referred to as Count 1, which reads:

Count 1

A compound of the formula:

```
    R'O
    O
    R
    X
    R'O
```

or a pharmaceutically acceptable salt thereof, wherein:

X is O;

R¹ is H, a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an aryalkyl sulfonyl;

R² is H, a monophosphate, a diphosphate, a triphosphate, an alkyl, an alkyl sulfonyl, or an aryalkyl sulfonyl; and

Base is a pyrimidine represented by the following formula:
VICTOR E. MARQUEZ, Ph.D.

\[
\begin{array}{c}
\text{wherein,} \\
R^3 \text{ is } H; \text{ and} \\
R^4 \text{ is } \text{NH}_2 \text{ or } \text{OH.}
\end{array}
\]

3. Count 1 defines a group of nucleosides having, \textit{inter alia}, a specific substitution pattern on the sugar ring. In particular, Count 1 requires a methyl group (CH₃) as the 2' "up" substituent and a fluorine atom (F) as the 2' "down" substituent. Hereinafter, I shall refer to nucleosides having such a substitution pattern at the 2' position as "2'-fluoro-2'-methyl nucleosides."

II. Materials Reviewed

4. During preparation of this declaration (designated as Ex 2152), I reviewed the following materials:

Table 1: Materials Reviewed

<table>
<thead>
<tr>
<th>EXHIBIT</th>
<th>DESCRIPTION</th>
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<tr>
<td>1004</td>
<td>Clark, United States Patent 7,429,572, issued September 30, 2008 from United States application 10/828,753, filed April 21, 2004</td>
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<tr>
<td>1101</td>
<td>Declaration of Masad J. Damha, Ph.D., signed June 2, 2012</td>
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<tr>
<td>1248</td>
<td>Herdewijn et al., 1989, Nucleosides Nucleotides 8: 65-96</td>
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<td>1260</td>
<td>English translation of Notebook 4 of Audrey Chappe-Dumas</td>
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<td>1281</td>
<td>Declaration of Masad J. Damha, Ph.D., signed May 2, 2013</td>
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<td>1297</td>
<td>Copy of email from Jean-François Griffon to Dick Storer dated December 9, 2002</td>
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<td>1300</td>
<td>December 2002 progress report prepared by Jean-François Griffon</td>
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<tr>
<td>1302</td>
<td>Email from Jean-François Griffon to Dick Storer dated February 3, 2003 with attached January 2003 progress report</td>
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<tr>
<td>1303</td>
<td>Email from Jean-François Griffon to Dick Storer dated March 4, 2003 with attached February 2003 progress report</td>
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<td>1304</td>
<td>Report on fluorination Scientific Update Training Course</td>
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<td>1308</td>
<td>Email from Jean-François Griffon to Dick Storer dated June 3, 2003 with attached May 2003 progress report</td>
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<td>1310</td>
<td>Idenix memorandum for meeting held on July 31, 2003</td>
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<td>1311</td>
<td>Email from Jean-François Griffon to Dick Storer dated August 28, 2003 with attached July-August 2003 progress report</td>
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<tr>
<td>1318</td>
<td>Report of December 2, 2002 Idenix meeting in Montpellier, France</td>
</tr>
<tr>
<td>1319</td>
<td>Summary of May 10, 2004 Idenix meeting in Cambridge, MA</td>
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<td>1335</td>
<td>Prioritized Summary of Idenix Meeting with Professor Fleet on May 10, 2004</td>
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<tr>
<td>1336</td>
<td>Email from Dr. Stewart to Dr. Storer dated November 11, 2004</td>
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VICTOR E. MARQUEZ, Ph.D.

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<tr>
<td>1355</td>
<td>Email attachment of Ex 1354</td>
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<tr>
<td>1413</td>
<td>June 9, 2003 Email from Dick Storer to Adel Moussa, Narayan Chaudhuri, Steven Mathieu, Jingyang Wang</td>
</tr>
<tr>
<td>1418</td>
<td>Reply from Paul Coe to Dick Storer</td>
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<td>1468</td>
<td>January 7, 2005 email correspondence between Adel Moussa and Alistair Stewart</td>
</tr>
<tr>
<td>1627</td>
<td>English Translation of Internship Report of Elodie Pecheux</td>
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<tr>
<td>1653</td>
<td>Deposition Transcript of Masad Damha, Ph.D. dated July 10, 2013</td>
</tr>
<tr>
<td>2001</td>
<td>Substitute Declaration of Victor E. Marquez, Ph.D.</td>
</tr>
<tr>
<td>2066</td>
<td>Substitute 2nd Declaration of Victor E. Marquez, Ph.D.</td>
</tr>
<tr>
<td>2093</td>
<td>Transcript of Deposition of Victor E. Marquez, Ph.D., taken September 26, 2012</td>
</tr>
<tr>
<td>2148</td>
<td>Transcript of Deposition of Victor E. Marquez, Ph.D. taken July 15, 2013</td>
</tr>
</tbody>
</table>

III. Overview of Topics Discussed

5. The main topics that I will address in this declaration include:
VICTOR E. MARQUEZ, Ph.D.

(1) My opinion that an extraordinary amount of experimentation would have been required for a hypothetical person having ordinary skill in the art as of the time period from December 18, 2001 up to just before January 13, 2005 (i.e., January 12, 2005) to make a Count 1 compound based on knowledge of its chemical structure, alone;

(2) The manner in which I believe Sommadossi’s documents purportedly illustrating its attempts to make a 2’-fluoro-2’-methyl nucleoside support my opinion, addressed herein and in my prior declarations (Ex 2001, Ex 2066) and depositions (Ex 2065, Ex 2093, Ex 2148), and refute the opinion Dr. Damha has provided in Ex 1281; and

(3) The manner in which Dr. Damha’s opinion in Ex 1281 mischaracterizes my prior testimony in an attempt to make it appear as if he and I agree.

IV. Level of Ordinary Skill in the Art

6. I was asked to consider whether a hypothetical person having ordinary skill in the art as of the time period from December 18, 2001 up to just before January 13, 2005 (hereinafter the “artisan”) could have made a Count 1 compound by engaging in only routine experimentation, based solely on knowledge of the chemical structure of such a compound.

7. In my previous declarations, I provided a definition of a “person having ordinary skill in the art” to which Count 1 pertains throughout the June 28, 2002 through June 2, 2008 timeframe. (E.g., Ex 2001, ¶¶ 64-73.) It is my opinion that the same definition applies throughout the time period from December 18, 2001 up to just before January 13, 2005.
8. My understanding of the artisan’s qualifications is based on my education and work experience in this field, and my review of Count 1 and the materials mentioned in Table 1, above.

V. An Extraordinary Amount of Experimentation Would Have Been Required for an Artisan to Make a Count 1 Compound Based on Knowledge of Its Chemical Structure, Alone

9. I have been advised that Sommadossi contends a person skilled in the art as of December 18, 2001 could “simply look” at the structure of a compound Sommadossi calls “2’-F-2’-Me-RiboC”:

\[
\begin{align*}
\text{2’-F-2’-Me-RiboC}
\end{align*}
\]

and “devise a simple synthetic route” for making it according to the following Scheme 1:

```
Scheme 1
```

I have also been advised that Sommadossi relies on the opinion of Masad J. Damha, Ph.D., as expressed in Ex 1281, to support the foregoing contention.
VICTOR E. MARQUEZ, Ph.D.

10. Dr. Damha's declaration, Ex 1281, contains the following Scheme A, which illustrates a reaction similar to the first step of Scheme 1 depicted in the preceding paragraph:

Scheme A

(Ex 1281, ¶ 38.) Dr. Damha refers to Matsuda et al. (Ex 1144) when asserting that "2'-Me-AraU" was a compound that had been reported in the literature as of December 18, 2001. (Ex 1281, ¶ 37.)

11. To my knowledge, neither "Scheme 1," depicted in ¶ 9, nor "Scheme A" depicted in ¶ 10, above, was available in the literature as of the time period from December 18, 2001 up to just before January 13, 2005. Rather, to my knowledge, the first publication describing the synthesis of a 2'-fluoro-2'-methyl nucleoside (via any route) was the January 13, 2005 Clark Publication. (Ex 2008, cover page (Item (43)), ¶¶ [0293]-[0335].)

12. "Scheme 1" and "Scheme A" reproduced in ¶¶ 9 and 10, respectively, both depict the synthesis of a 2'-fluoro-2'-methyl nucleoside by treating a nucleoside substituted at the 2' position with a methyl group (CH₃) "down" and a hydroxyl group (OH) "up" with the fluorinating reagent (diethylamino)sulfur trifluoride ("DAST"). I note that the Clark Publication teaches such a step for making 2'-fluoro-2'-methyl nucleosides. (Ex 2008, ¶¶ [0310], [0325], [0332].) Dr. Damha's declaration also states that the fluorinating regent
Deoxofluor could have been used to perform the fluorination step depicted in "Scheme A" reproduced in ¶ 10. (Ex 1281, ¶ 40.) The Clark Publication also states that the fluorinating reagent Deoxofluor may be used as an alternative to DAST. (Ex 2008, ¶[0310].)

13. The Clark Publication sets forth the following Scheme 4 corresponding to "Example 2: Synthesis of (2'R)-2'-Deoxy-2'-Fluoro-2'-C-Methyl-cytidine Starting from Cytidine":

![Scheme 4](image)

(Ex 2008, ¶[0319].)

14. Scheme 4 reproduced in ¶ 13 (corresponding to Example 2 in the Clark Publication) illustrates the synthesis of a 2'-fluoro-2'-methyl nucleoside according to the following sequence of transformations:

(1) Protection of the 3' and 5' hydroxyl groups (OH) and the exocyclic amino group (NH₂) of cytidine to give Compound 4-1;
(2) Oxidation of the 2' hydroxyl group (OH) of Compound 4-1 to provide Compound 4-2 having a ketone functionality (=O) at the 2' position;

(3) Treatment of Compound 4-2 with the alkylating reagent methylithium ("MeLi") to generate a protected nucleoside intermediate with a 2' "down" methyl group (CH₃) and a 2' "up" hydroxyl group (OH), followed by removal of the 3' and 5' protecting group to give Compound 4-3;

(4) Benzoyl protection of the 3' and 5' hydroxyl groups of Compound 4-3 to provide Compound 4-4;

(5) Treatment of Compound 4-4 with DAST to provide a protected 2'-fluoro-2'-methyl nucleoside Compound 4-5; and

(6) Removal of the protecting groups to give the 2'-fluoro-2'-methyl nucleoside Compound 4-6.

(Ex 2008, ¶¶ [0319]-[0326].) Example 2 of the Clark Publication involves a nucleoside with a cytosine base, which is protected with a benzoyl (Bz) group until the final step of the synthesis. (Ex 2008, ¶¶ [0319]-[0326].) Example 3 of the Clark Publication describes a similar process for a nucleoside with a 6-chloropurine base. (Ex 2008, ¶¶ [0327]-[0333].)

15. In Ex 1281, Dr. Damha contends that a route similar to the aforementioned examples in the Clark Publication would have been "the most logical or obvious to try" to make a Count 1 compound. (Compare Ex 1281, ¶¶ 19, 36-44 with Ex 2008, ¶¶ [0319]-[0326].) Dr. Damha illustrates such a route involving a nucleoside with an unprotected uracil base, followed by conversion of the uracil base to a cytosine base. (Ex 1281, ¶¶ 37-44). In Section VI, below, I discuss complications that may arise from reacting DAST with a nucleoside having an unprotected uracil base as depicted in "Scheme 1" and
VICTOR E. MARQUEZ, Ph.D.

“Scheme A” reproduced in ¶¶ 9 and 10, above. Nonetheless, I wish to point out that the chemical transformation Dr. Damha relies on for installing the 2'-fluoro-2'-methyl substitution using DAST is the same step as taught by the Clark Publication. (Compare Ex 1281, ¶¶ 37-43 with Ex 2008, ¶¶ [0319]-[0333].) I noted this similarity during my July 15, 2013 deposition. (Ex 2148, p. 150:3-13.)

16. I have been advised that the application published on January 13, 2005 as the Clark Publication (Ex 2008) subsequently issued as the Clark Patent (Ex 1004; Ex 2009). (See Ex 1004, cover page, item (65); Ex 2009, cover page, item (65).) Dr. Damha states in his declaration, Ex 1281, that he reviewed the Clark Patent when forming the opinions expressed therein. (Ex 1281, ¶ 15, Appx. 2-1 (List of Exhibits).) I have also reviewed the transcript of Dr. Damha’s July 10, 2013 deposition and note that he stated he remembered and was “quite aware” of the content of the Clark Patent when preparing both his first (Ex 1101) and second (Ex 1281) declarations. (Ex 1653, pp. 32:4-33:3.)

17. I find it curious that Dr. Damha has proposed that a person skilled in the art as of December 18, 2001 would have selected a synthetic route to make a Count 1 compound that is so similar to a method Clark first published in 2005. (Compare Ex 1281, ¶¶ 37-43 with Ex 2008, ¶¶ [0319]-[0333]; see also Ex 2009, cols. 54:6-60:13.) I believe Dr. Damha's opinion has been influenced by the hindsight knowledge that Clark's route was reported to be successful. I also noted during my deposition on July 15, 2013 that I believe it is a hindsight-based approach to contend that an artisan would have known to make a 2'-fluoro-2'-methyl nucleoside by reacting DAST with a 2'-methyl "down"-2'-hydroxy "up"-substituted nucleoside from Matsuda et al. (See Ex 2148, pp. 141:10-145:13, 146:21-147:8.) To my knowledge, the literature available prior to January 13, 2005 did not suggest using any
nucleoside from Matsuda et al. to make a 2'-fluoro-2'-methyl nucleoside or suggest any particular fluorinating reagent for doing so. In other words, an artisan would not have had the hindsight benefit of Clark’s later-published teachings.

18. As I previously explained, it is my opinion that an artisan attempting to make a 2'-fluoro-2'-methyl nucleoside (prior to Clark’s 2005 publication) would have performed a retrosynthetic analysis and, in so doing, considered many possible routes to try, some or all of which might have failed. (See Ex 2066, ¶¶ 206-209.) Given the many possible approaches an artisan could have considered trying, I disagree with Dr. Damha’s opinions expressed in Ex 1101 and Ex 1281 that an artisan would have selected to make a 2'-fluoro-2'-methyl nucleoside according to each of the two general routes taught in the 2005 Clark Publication. (See Ex 2066, ¶¶ 181-202 (comparing the schemes in Dr. Damha’s declaration, Ex 1101, with Schemes 1 and 3 in the Clark Patent).)

19. Rather, it is my opinion that the synthetic routes taught in the Clark Publication are unlikely to have been the first ones that an artisan would have tried. For example, as I noted during my July 15, 2013 deposition, an artisan might have considered attempting the difficult fluorination step earlier in the synthesis. (Ex 2148, pp. 144:9-145:13, 151:14-152:3; see also id. at pp. 141:10-142:12.) This is a further reason that I believe an artisan would have been unlikely to arrive at the routes disclosed in the Clark Publication (and discussed in Dr. Damha’s declarations) without engaging in an extraordinary amount of experimentation.

20. Contrary to Dr. Damha, I believe that an extraordinary amount of experimentation would have been required for an artisan to make a 2'-fluoro-2'-methyl nucleoside falling within Count 1. In my previous declarations, I provided and explained my
opinion that an extraordinary amount of experimentation would have been required for a person having ordinary skill in the art to make a Count 1 compound as of the June 28, 2002 filing date of Sommadossi’s U.S. Provisional Appln. No. 60/392,350 or the June 27, 2003 filing date of Sommadossi’s U.S. Patent Appln. No. 10/608,907. (Ex 2001, ¶¶ 214-230; Ex 2066, ¶¶ 206-214.) I stand by my previously-rendered opinions, and I believe that the same holds true throughout the period from December 18, 2001 up to just before Clark’s January 13, 2005 publication. As described in more detail below, documents that I have been advised Sommadossi contends show its attempts to make a 2’-fluoro-2’-methyl nucleoside of Count 1 support my previously-rendered opinions and refute the opinions of Dr. Damha.

VI. **Documents on Which Sommadossi Relies to Show Attempts to Make a 2’-Fluoro-2’-Methyl Nucleoside Refute Dr. Damha’s Opinion and Illustrate the Type of Extraordinary Experimentation Required to Make a Count 1 Compound Prior to January 13, 2005**

21. As discussed below, I have considered several documents that I have been advised Sommadossi contends illustrate work-done by chemists and/or consultants employed by Idenix Pharmaceuticals, Inc. (“Idenix”) in an attempt to make a 2’-fluoro-2’-methyl nucleoside during the 2002-2005 timeframe. I have been asked to assume, in forming my opinion, that these documents accurately reflect the activities of Idenix’s chemists and/or consultants. As explained below, I believe these documents support my opinion while refuting Dr. Damha’s opinion as expressed in Ex 1281. In this regard, I note that Dr. Damha stated during his July 10, 2013 deposition that he did not consider any Idenix documents such as meeting minutes, research reports or e-mails, in forming the opinions expressed in his declaration, Ex 1281, nor did he rely on any Idenix lab notebooks for that purpose. (Ex 1653, pp. 37:8-39:5.)
22. Dr. Damha contends that 2'-fluoro-2'-methyl nucleosides he calls “2’-F-2’-Me-RiboU” and “2’-F-2’-Me-RiboC” have “only two simple structural differences” from the naturally-occurring nucleosides uridine and cytidine, respectively, as if to suggest that these structural differences mean making 2’-F-2’-Me-RiboU and 2’-F-2’-Me-RiboC would have been “simple” as of December 18, 2001. (Ex 1281, ¶¶ 20, 21, 53.) However, synthesizing a compound is not like building a LEGO® structure, where one can simply snap on and off discrete components with ease. Synthesizing a new nucleoside that differs from previously-reported compounds with respect to one or two substituents on the sugar ring may require the development of new routes very different from those used to make the previously-reported compounds.

23. Dr. Damha also states that the experimentation required to make a Count 1 compound (e.g., 2’-F-2’-Me-RiboC or 2’-F-2’-Me-RiboU) would have been “routine” as of December 18, 2001. (Ex 1281, ¶¶ 19, 36, 39.) However, as I noted in ¶ 19, above, I do not believe the routes disclosed in the Clark Publication (and discussed in Dr. Damha’s declarations) would have been the first ones an artisan would have tried. Further, I have been advised that Sommadossi contends Idenix had multiple Ph.D. chemists (including both bench chemists and their supervisors), as well as at least two consultants, involved in attempting to make a 2’-fluoro-2’-methyl nucleoside according to various routes for more than three years. Further, I have been advised that Sommadossi’s witnesses have stated that Idenix first made a 2’-fluoro-2’-methyl nucleoside by considering the Clark Publication and following one of the examples therein. In my opinion, such efforts illustrate that an extraordinary amount of experimentation was required to make a 2’-fluoro-2’-methyl nucleoside prior to Clark’s 2005 publication. This also refutes Dr. Damha’s opinion that only “routine” experimentation would

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have been required and his statements during cross-examination that it would have taken a skilled person as of 2001 between one day and one month to make a 2'-fluoro-2'-methyl nucleoside given its chemical structure. (Ex 1653, pp. 47:6-48:5, 52:16-20.)

24. Dr. Damha also suggests that a single route for making a Count 1 compound would have been the "most logical or obvious path to try" as of December 18, 2001. (Ex 1281, ¶ 19; see also id. at ¶ 53.) However, with no guidance other than the chemical structure, an artisan might have considered any number of potential routes to try to make a 2'-fluoro-2'-methyl nucleoside of Count 1, some or all of which could have failed. I noted this during my July 15, 2013 deposition, where I stated that, given a particular 2'-fluoro-2'-methyl nucleoside as a target compound (prior to Clark's publication), 10 organic chemists likely would have come up with 10 different schemes proposing how to attempt to make such a compound. (Ex 2148, pp. 145:25-146:10.)

25. Based on my review of the materials listed in Table 1, above, and consistent with my current and prior testimony, chemists and/or consultants working for Idenix purportedly contemplated and/or unsuccessfully tried numerous routes during the 2002-2005 timeframe, including approaches I have outlined in Table 2, below:

14
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## Table 2: Examples of Synthetic Routes Allegedly Tried/Contemplated by Idenix

<table>
<thead>
<tr>
<th>ROUTE</th>
<th>EXHIBIT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routes involving various 2,2'-anhydro nucleosides</td>
<td>Ex 1297, p. 2 (numbered p. 1) (2002)</td>
</tr>
<tr>
<td></td>
<td>Ex 1468, p. 4 (numbered p. 3) (2005)</td>
</tr>
<tr>
<td></td>
<td>Ex 1468, p. 3 (numbered p. 2) (2005)</td>
</tr>
<tr>
<td>Routes involving 2'-methyl-2'-OSO₂(Imidazole) nucleosides</td>
<td>Ex 1308, p. 2 (numbered p. 11) (2003)</td>
</tr>
<tr>
<td>Routes involving fluorination at the 2-position of a dihydrofuranone (which would need to be followed by conversion to a dihydrofuranosyl sugar and condensation with a nucleobase)</td>
<td>Ex 1468, p. 2 (numbered p. 1) (2005)</td>
</tr>
<tr>
<td>Routes involving either electrophilic or nucleophilic fluorination at the 2-position of a pyranose sugar, followed by ring contraction to a 5-membered lactone (which would need to be followed by conversion of the lactone to a dihydrofuranosyl sugar and condensation with a nucleobase)</td>
<td>Ex 1318, p. 2 (2002)</td>
</tr>
<tr>
<td></td>
<td>Ex 1319, p. 1 (Scheme G1) (2004)</td>
</tr>
<tr>
<td></td>
<td>Ex 1335, p. 3 (2004)</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>ROUTE</th>
<th>EXHIBIT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routes involving making an acyclic fluorinated intermediate, followed by cyclization to make a sugar ring (which would need to be followed by condensation with a base)</td>
<td>Ex 1627, pp. 14, 24-27, 30 (2004) See also Ex 1335, p. 2 (2004)</td>
</tr>
</tbody>
</table>

(See also Ex 1310, p. 2 (2003, meeting summary stating “all procedures starting from a nucleoside were unsuccessful” and “[a] strategy starting from the corresponding fluorinated sugar might be the solution”); Ex 1418, p. 1 (undated letter suggesting “sugar/base condensation methods the anomer problem not withstanding”)).

26. I believe the number and variety of routes listed in Table 2, above, are consistent with my opinion that an artisan attempting to make a 2'-fluoro-2'-methyl nucleoside of Count 1 would have considered a number of possible ways to attempt to do so, some or all of which might have failed. According to the documents I reviewed, tellingly none of the routes mentioned in Table 2, above, were successfully carried out to make a Count 1 compound during the December 2002 up to March 2005 timeframe, when I have been advised Idenix scientists purportedly reproduced a route disclosed in the Clark Publication. The foregoing also refutes Dr. Damha’s opinion that the route he discusses in Ex 1281 would have been the “most logical or obvious path to try.”

27. Further, I note that most of the routes mentioned in Table 2, above, are not similar to the route that Dr. Damha describes in his declaration, Ex 1281, e.g., because they involve different fluorinating reagents and different intermediates. The routes depicted in Ex 1303 and Ex 1468, which may appear to bear some similarity, apparently failed to lead to either the formation and/or isolation of any fluorinated product. This illustrates how the
addition of a methyl group at the 2'-position, which may at first appear to be a "simple"
structural change, can dramatically affect the outcome of the reaction. Further, preventative
measures (e.g., protecting the base) were ignored in the routes depicted in Ex 1303 and Ex
1468.

28. Dr. Damba also suggests that it would have been obvious for a person
skilled in the art as of December 18, 2001 to select DAST (which is a nucleophilic fluorinating
reagent) to use to make a Count 1 compound. (See Ex 1281, ¶¶ 27-34.) However, based on
my review of the materials listed in Table 1, above, and again consistent with my prior
testimony, chemists and/or consultants working for Idenix purportedly tried and/or
contemplated trying a number of both nucleophilic and electrophilic fluorinating reagents
during the 2002-2005 timeframe, including those I have listed in Table 3, below:

Table 3: Examples of Fluorinating Reagents Allegedly Tried/Contemplated by Idenix

<table>
<thead>
<tr>
<th>FLUORINATING REAGENT</th>
<th>EXHIBIT(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF-pyridine</td>
<td>Ex 1297, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td></td>
<td>Ex 1300, pp. 1-2</td>
</tr>
<tr>
<td></td>
<td>Ex 1418, p. 10</td>
</tr>
<tr>
<td>HF-pyridine/AlF₃</td>
<td>Ex 1302, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td></td>
<td>Ex 1303, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td>KHF₂</td>
<td>Ex 1302, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td></td>
<td>Ex 1303, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td>KF</td>
<td>Ex 1303, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td>FLUORINATING REAGENT</td>
<td>EXHIBIT(S)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Deoxofluor</td>
<td>Ex 1303, p. 2 (numbered p. 1)</td>
</tr>
<tr>
<td></td>
<td>see also Ex 1468, p. 3 (numbered p. 2)</td>
</tr>
<tr>
<td>Diethylaminosulfur trifluoride (DAST)</td>
<td>Ex 1468, pp. 2, 3 (numbered pp. 1, 2)</td>
</tr>
<tr>
<td>Et3N·3HF</td>
<td>Ex 1308, p. 2 (numbered p. 11)</td>
</tr>
<tr>
<td></td>
<td>Ex 1418, pp. 7, 8 (figs. a, 2)</td>
</tr>
<tr>
<td>Bu4NHF2 / Fe(ACAc)3</td>
<td>Ex 1311, p. 2 (numbered p. 16)</td>
</tr>
<tr>
<td>Tetrabutylammonium fluoride (TBAF)</td>
<td>Ex 1319, p. 1 (Scheme G1)</td>
</tr>
<tr>
<td>Tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)</td>
<td>Ex 1319, p. 1 (Scheme G1)</td>
</tr>
<tr>
<td>Tetrabutylammonium dihydrogen trifluoride (Bu4NH2F3)</td>
<td>Ex 1418, pp. 3, 6</td>
</tr>
<tr>
<td>Perfluoro-1-butanesulfonyl fluoride (PBSF)</td>
<td>Ex 1468, p. 3 (numbered p. 2)</td>
</tr>
<tr>
<td>SelectFluor (an electrophilic fluorinating reagent)</td>
<td>Ex 1468, p. 4 (numbered p. 3)</td>
</tr>
<tr>
<td>Anhydrous HF</td>
<td>Ex 1468, p. 4 (numbered p. 2)</td>
</tr>
<tr>
<td>HF / Fe(ACAc)</td>
<td>Ex 1418, p. 9 (fig. 3)</td>
</tr>
<tr>
<td>Bu4NH2F / Fe(ACAc)3</td>
<td>Ex 1308, p. 2 (numbered p. 11)</td>
</tr>
<tr>
<td></td>
<td>Ex 1418, p. 9 (fig. 3)</td>
</tr>
</tbody>
</table>

(See also Ex 1318, p. 2 (referring to a “positive fluorine source” (i.e., an electrophilic fluorinating reagent)); Ex 1304, pp. 1-10 (referring to a large number of both electrophilic and...)
nucleophilic fluorinating reagents); Ex 1413, p. 1 (referring to “electrophilic and nucleophilic fluorine sources”). The foregoing is consistent with my opinion that an artisan would have considered trying a number of different fluorinating reagents to make a 2′-fluoro-2′-methyl nucleoside of Count 1 and refutes Dr. Damha’s contention that it would have been obvious to select DAST to make such a compound.

29. Dr. Damha also contends that the use of DAST to convert “an arabinonucleoside to a 2′-F-ribonucleoside” was predictable as of December 18, 2001. (See Ex 1281, ¶¶ 22-30, 54, 55). However, to my knowledge the use of DAST to make a 2′-fluoro-2′-methyl nucleoside was not reported in the literature until Clark’s January 13, 2005 publication. Further, Sommadossi’s documents illustrate that attempted fluorinations using DAST could fail to produce the desired fluorinated product, instead resulting in, e.g., elimination or anhydro products. For example, Ex 1468, 1352 and 1355 all depict reactions between nucleosides having a 2′ “up” hydroxyl group and DAST resulting in elimination products. (Ex 1468, p. 3 (numbered p. 2); Ex 1352, p. 1; Ex 1355, p. 1.) Ex 1355 also depicts such a reaction resulting in an anhydro product. (Ex 1355, p. 1.)

30. Further in this regard, I have been advised that Sommadossi asserts Ex 1418 is a letter from Idenix’s consultant, Paul Coe, received in approximately April 2003. In this letter, Dr. Coe apparently expressed concerns regarding the use of DAST, including the possibilities of elimination, participation of blocking groups and migration. (Ex 1418, pp. 1-2.) Dr. Coe also noted that leaving groups generated in situ from DAST are readily attacked by pyrimidine ring nucleophiles. None of the routes Dr. Coe proposed for making a 2′-fluoro-2′-methyl nucleoside in Ex 1418 involved the use of DAST as the fluorinating reagent. (Ex 1418, pp. 1-3, 5-10.)
31. I would also like to point out that Dr. Damha’s declaration and “Scheme 1” reproduced in ¶9, above, fail to account for one of the complexities of using DAST that Dr. Coe noted in Ex 1418, which is the possibility of pyrimidine ring nucleophiles attacking leaving groups generated in situ from the DAST reagent. (See Ex 1418, p. 1.) “Scheme 1” and “Scheme A” reproduced in ¶¶9 and 10, above, both depict the use of DAST with a nucleoside having an unprotected uracil base. Such an unprotected pyrimidine base may act as a nucleophile and attack an intermediate generated during the course of the reaction between an alcohol and the DAST reagent. Such nucleophilic attack by the pyrimidine base can lead to the formation of anhydro and elimination products. Nucleophilic attack by an unprotected pyrimidine base may also occur for an intermediate generated in situ from the reagent Deoxofluor. This could explain why an elimination product (rather than any fluorinated product) was apparently observed for a reaction between Deoxofluor and a nucleoside having an unprotected uracil base as depicted in Ex 1303. (Ex 1303, p. 2 (numbered p. 1) (reaction of Compound 5 with Deoxofluor to give Compound 6b and not Compound 6a).) Similarly, this could explain why elimination and anhydro products (rather than fluorinated products) were apparently observed for the reactions involving DAST and nucleosides having unprotected uracil bases depicted in Ex 1352 and 1355. (Ex 1352, p. 1; Ex 1355, p. 1.) Dr. Damha’s declaration and “Scheme 1” reproduced in ¶9, above, fail to appreciate the importance of protecting the pyrimidine base in order to avoid such nucleophilic attack.

32. Dr. Damha also suggests that the use of DAST to fluorinate tertiary alcohols with inversion of stereochemistry was “well developed and known.” (Ex 1281, ¶¶31-34.) However, I am not aware of literature precedent prior to January 13, 2005 for using DAST to fluorinate tertiary alcohols at the 2’ position of nucleosides. Nor does the article on
which Dr. Damha relies for his statement regarding the use of DAST with tertiary alcohols, Herdewijn et al. (Ex 1248), describe the reaction of a nucleoside having a tertiary alcohol on the sugar ring with DAST\textsubscript{w} (Ex 1248, pp. 65-96.) Further, the articles Herdewijn et al. cites regarding the use of DAST with tertiary alcohols also do not discuss the use of DAST to fluorinate tertiary alcohols on nucleoside sugar rings. (See Ex 1118, pp. 574-578 (listed as Ref. 126 in Ex 1248, p. 96); Ex 2153, pp. 2315-2316 (listed as Ref. 129 in Ex 1248, p. 96); Ex 2154, pp. 251-254 (listed as Ref. 130 in Ex 1248, p. 96.) Accordingly, these references would not have informed an artisan about the use of DAST to prepare a compound of Count 1 from a nucleoside precursor having a tertiary alcohol.

33. I believe it is an oversimplification to assert that, because DAST had been shown to fluorinate certain tertiary alcohols with inversion of stereochemistry, it was therefore “well developed and known” that it would react similarly with all substrates. Such an assertion fails to take into account the complexities and uncertainties associated with attempting to use DAST with a substrate having different structural features from those for which reactions with DAST had previously been reported. For example, as I mentioned in ¶¶ 30-31, above, complications may arise from the interaction of intermediates generated \textit{in situ} from DAST with the base of a pyrimidine nucleoside. I also noted the uncertainties associate with treating tertiary alcohols with DAST during my July 15, 2013 cross-examination. (Ex 2148, pp. 86:13-88:3.) Further in this regard, Sommadossi’s documents illustrate failures when attempting to fluorinate even certain secondary alcohols using DAST. (E.g., Ex 1260, pp. 38, 40.)

34. Sommadossi’s documents also comment on differences between the synthesis of compounds with secondary fluorides as compared to compounds with tertiary
fluorides, and they refer to a lack of precedent in the literature for fluorination reactions involving tertiary alcohols relevant to making 2'-fluoro-2'-methyl nucleosides. For example, I have been advised that Sommadossi contends Ex 1336 is an e-mail from November 2004 related to efforts to make a 2'-fluoro-2'-methyl nucleoside of Count 1. This document recites: “Having to make a tertiary fluoride is very different to having to make a secondary.” (Ex 1336, p. 1 (bottom half).) This document also recites: “I was surprised that any formation of a tertiary fluoride from a tertiary alcohol had been reported ... in any case, no relevant reaction on sugar or nucleoside was reported.” (Ex 1336, p. 1 (top half).) Thése documents refute Dr. Damha’s contention in Ex 1281 that the use of DAST to fluorinate tertiary alcohols with inversion of stereochemistry (in the context of making a 2'-fluoro-2'-methyl nucleoside of Count 1) was “well developed and known” as of December 18, 2001.

35. In summary, the documents discussed in the preceding paragraphs, purportedly showing Sommadossi’s efforts to make a 2'-fluoro-2'-methyl nucleoside from 2002 to 2005 support my opinion that an extraordinary amount of experimentation would have been required for an artisan to synthesize a Count 1 compound. The same documents refute Dr. Damha’s opinion that the synthesis of a Count 1 compound would have been “routine” and “obvious” as of December 18, 2001.

VII. Dr. Damha Mischaracterizes My Prior Testimony in an Attempt to Suggest He and I Agree

36. As I explain in the following paragraphs, Dr. Damha’s declaration, Ex 1281, mischaracterizes my prior testimony on several points in an attempt to suggest that I agree with his testimony.
VICTOR E. MARQUEZ, Ph.D.

37. In ¶ 45 of Ex 1281, Dr. Damha contends he and I agree “that a person skilled in the art could devise a synthetic route for a compound based on its structural information alone[,]” citing to my prior cross-examination testimony at Ex 2093, pp. 171:21-172:21. Dr. Damha then contends that a person skilled in the art could “simply look at the structure and immediately devise” a route to make a Count 1 compound, implying I agree with his opinion. (Ex 1281, ¶ 45.)

38. As is clear from the portion of my prior cross-examination testimony that Dr. Damha cited in ¶ 45 of Ex 1281, I testified that the structure of a compound provides information for thinking about synthetic routes and “guides me in terms of what problems I may encounter in the synthesis.” (Ex 2093, pp. 171:21-172:21.) I do not agree with Dr. Damha that, based on the structure of a Count 1 compound alone, a person skilled in the art as of December 18, 2001 would have immediately devised a working route for making it. As explained above, the fact that Idenix chemists purportedly worked for more than three years trying to figure out how to make a 2'-fluoro-2'-methyl nucleoside of Count 1, and finally resorted to copying an example in the Clark Publication, confirms that a working route for making a Count 1 compound was clearly not “immediately” apparent prior to Clark’s January 13, 2005 publication.

39. In ¶ 46 of Ex 1281, Dr. Damha contends he and I agree that “methods for making the compounds of Count 1 were readily available and ‘not the issue here’ as of June 28, 2002[,]” citing to my prior cross-examination testimony at Ex 2093, pp. 163:24-164:21. Dr. Damha also seems to imply in ¶¶ 47-50 of Ex 1281 that I agree with his conclusions regarding the synthesis of a Count 1 compound because certain starting materials and/or reagents had been reported in the literature as of June 28, 2002.
40. My prior testimony that Dr. Damha cited in ¶ 46 of Ex 1281 made clear that, in my opinion, it is not the existence of synthetic methods (i.e., discrete chemical transformations) that is "the issue" but rather "putting together the scheme in a logical way." (Ex 2093, p. 164:8-21.) As I explained, most compounds are made using methods and/or reagents that were previously reported in the literature, but devising the proper sequence of steps using appropriate reagents may nonetheless require inventive skill. (Id.; see also Ex 2148, pp. 143:9-144:12.) In my opinion, Idenix's failed attempts to make a 2'-fluoro-2'-methyl nucleoside for more than three years suggest that an extraordinary amount of experimentation (or, alternatively, inventive skill) would have been required to make a Count I compound prior to Clark's January 13, 2005 publication.

VIII. Conclusion

41. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

42. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of Clark's U.S. Patent No. 7,429,572 B2.
VICTOR E. MARQUEZ, Ph.D.

Dated: July 25, 2013

[Signature]

Victor E. Marquez, Ph.D.
VIRAL REPLICATION

Structural basis for RNA replication by the hepatitis C virus polymerase

Todd C. Appleby,* Jason K. Perry,† Eiisuke Murakami,‡ Ona Barauskas,§ Joy Feng,† Aestop Cho,§ David Fox III,§ Diana R. Wetmore,∥ Mary E. McGrath,¶ Adrian S. Ray,∥ Michael J. Sofia,∥ S. Swamjithan,‖ Thomas E. Edwards*†

Nucleotide analog inhibitors have shown clinical success in the treatment of hepatitis C virus (HCV) infection, despite an incomplete mechanistic understanding of NS5B, the viral RNA-dependent RNA polymerase. Here, we study the details of HCV RNA replication by determining the structure of stalled polymerase ternary complexes. Our analysis revealed that highly conserved active-site residues in NS5B position the primer for in-line attack on the incoming nucleotide. A β loop and a C-terminal membrane–anchoring linker occlude the active-site cavity in the apo state, retract in the primed initiation assembly to enforce replication of the HCV genome from the 3′ terminus, and vacate the active-site cavity during elongation. We investigated the incorporation of nucleotide analog inhibitors, including the clinically active metabolite formed by sofosbuvir, to elucidate key molecular interactions in the active site.

epatitis C virus (HCV) is a positive-sense, single-stranded RNA virus of the family Flaviviridae and genus Hepacivirus and is the cause of hepatitis C in humans (1). Long-term infection with HCV can lead to end-stage liver disease, including hepatocellular carcinoma and cirrhosis, making hepatitis C the leading cause of liver transplantation in the United States (2). Direct-acting antiviral drugs were approved in 2011, but they exhibited limited efficacy and had the potential for adverse side effects (3). The catalytic core of the viral replication complex, the NS5B RNA-dependent RNA polymerase (RdRp), supports a staggering rate of viral production, estimated to be 1.3 × 1020 virions produced per day in each infected patient (4). Because the NS5B polymerase with enzymes, RNA templates, RNA primers, incoming nucleotides, and catalytic metal ions during both primed initiation and elongation of RNA synthesis. Our analysis revealed that highly conserved active-site residues in NS5B position the primer for in-line attack on the incoming nucleotide. A β loop and a C-terminal membrane–anchoring linker occlude the active-site cavity in the apo state, retract in the primed initiation assembly to enforce replication of the HCV genome from the 3′ terminus, and vacate the active-site cavity during elongation. We investigated the incorporation of nucleotide analog inhibitors, including the clinically active metabolite formed by sofosbuvir, to elucidate key molecular interactions in the active site.

To gain insight into the mechanism of HCV RNA replication and its inhibition by nucleotide analog inhibitors, we determined atomic-resolution ternary structures of NS5B in both primed initiation and elongation states. Because traditional approaches failed to yield ternary complexes (see the supplementary materials), we prepared multiple staked enzyme-RNA-nucleotide ternary complex structures containing several designed features. First, we used NS5B from the JFH1 genotype 2a isolate of HCV, which is extraordinarily efficient at RNA synthesis (23). Second, we exploited a conformational stabilization strategy that had been developed for structural analysis of G protein–coupled receptors (44). We hypothesized that a triple resistance NS5B mutant isolated under selective pressure of a guanosine analog inhibitor that exhibits 1.5 times the initiation activity of the wild type (35) might stabilize a specific conformational state along the initiation pathway. Indeed, this triple mutant exhibits a substantial structural rearrangement of the polymerase (35), which is consistent with the structural rearrangement observed in binary complexes of a β-loop deletion mutant bound to primer-template RNA (36). The triple mutant was able to incorporate native and nucleotide analog inhibitors with the RNA samples used in structure determination (fig. S1). The use of nucleotide diphosphate substrates rather than nucleotide triphosphates (fig. S2) generates staked polymerase complexes in a catalytically relevant conformation. Ternary complexes could be obtained only with Mn2+, which lowers the Michaelis constant (Km) of the initiating nucleotide (17) and increases the activity of NS5B 20-fold relative to Mg2+ (28), and only with a nucleotide/Mn2+ double-stranded RNA ratio of 1.0/0.6/0.2. These approaches designed to stabilize the incoming nucleotide allowed for soaking experiments targeting several distinct assemblages.

Hepatitis C Virus NS5B initiates RNA synthesis by a primer-independent mechanism. Two slow steps in the catalytic pathway have been identified, including the formation of an initial dimers

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12. Materials and methods are available as supplementary materials on Science Online.

ACKNOWLEDGMENTS
We thank M. A. Barlow and N. Stier for critical discussions and L. Amard-Zettler, M. G. Chapman, G. Leonard, and R. Williams for helpful reading of the manuscript. We also thank the anonymous reviewers for their constructive comments. This work was conducted within the Marine Debris Working Group at the National Center for Ecological Analysis and Synthesis, University of California, Santa Barbara, with support from the Ocean Conservancy. Our data and model can be found at http://jpmceachern.uga.edu/lookupplot/ and in the supplementary materials.

SUPPLEMENTARY MATERIALS
www.sciencemag.org/content/347/6223/768/suppl/DC1
Materials and Methods
Supplementary Text
Fig S1
Tables S1 to S6
References (23–35)
25 August 2014; accepted 16 January 2015
10.1126/science.1260352
Fig. 1. NSSB primed initiation assembly. (A) Overall structure of the stalled
NSSB ternary primed initiation complex. The protein is represented by ribbons and
colored by subdomain (pink, fingers; light blue, palm; pale green, thumb),
with the β-loop highlighted in yellow and the position of the last visible residue
44 of the C terminus labeled “C.” The RNA template (5'-UACC; cyan carbons),
15 nucleotide primers (magenta carbons), and incoming UDP nucleotide
n carbons) are represented by sticks and colored according to atom type
(red, oxygen; blue, nitrogen; orange, phosphate). The two catalytic Mn²⁺ ions
are shown as purple spheres. (B) e RdRp de novo initiation assembly, with the
priming nucleotide colored by atom type with brown carbons, the incoming
nucleotide colored by atom type with magenta carbons, and an active-site loop
shown in yellow. (C) Primed initiation assembly of HCV, which is one catalytic
step after the de novo initiation assembly. Thus, the dinucleotide primer is
colored as in (B) after catalysis, with the next incoming nucleotide colored by
atom type with green carbons. The 2Fobs - Fcalc electron density map is con-
toured at 1σ and superimposed on the refined ligand and β-loop atoms.

Fig. 2. Recognition of the incoming nucleotide. (A) Stereoscopic view of the
NSSB active site during primed initiation. Select protein atoms are represented by
sticks and are colored by atom type with gray carbons, except for the β-loop
residues, which are highlighted in yellow. RNA bases are labeled according to
standard polymerase numbering conventions. Protein-ligand hydrogen bonds are
shown as gray dashed lines, whereas base-pair hydrogen bonds are shown as red
dashed lines. The proposed path of in-line attack by the 3'-hydroxyl on the β
phosphate of the incoming nucleotide is illustrated by a green dashed line. (B)
Close-up view of the RNA template binding site. (C) Comparison of the 3' end
of RNA primers, metal ions, and incoming nucleotides from the Norwalk virus
polymerase ternary complex containing cytidine triphosphate (CTP) as the in-
coming nucleotide [PDB ID: 3BSO (23)] and the NSSB ternary complex containing
UDP as the incoming nucleotide. The Norwalk structure atoms are colored ac-
cording to atom type with yellow carbons and gold metal ions, whereas the NSSB
ternary complex atoms are colored by atom type with green carbons and purple met-
als. (D) Common chemical mechanism of polymerases (24). (E) Molecular
mechanism for recognizing ribonucleotide substrates. Protein atoms of the apo
enzyme are colored with gray carbons, whereas protein atoms of the substrate
complex are colored with yellow carbons. Dashed lines represent the hydrogen
bonding network formed upon binding to an incoming ribonucleotide.
(Fig. 1) or with a 5′-pCC RNA primer and an incoming UDP (2.15 Å) or guanosine diphosphate (GDP) (2.8 Å) (fig. S3 and tables S1 to S3). These results show that primed assemblies form via both purine and pyrimidine dinucleotide primers, with all possible natural ribonucleotides as incoming substrates.

The 5′-untranslated region of the HCV genome contains an internal ribosomal entry site, necessitating replication at the exact 3′ end of the viral genome before copyback of the (-) strand into a (+) strand. The NS5B thumb domain β-loop insertion has been proposed to position the 3′ terminus of the genomic template during initiation (22), yet the β loop and the C-terminal membrane-anchoring linker appear in a conformation too deep within the active site to be compatible with binding to the RNA template and incoming nucleotides (9–11). In the five primed initiation ternary assemblies presented here, the fingertips and thumb domains have undergone substantial rearrangements to accommodate the nucleic acid (fig. S4). Furthermore, the β loop retracted 5 Å relative to several apo HCV polymerase genotype 2a structures (23, 25), providing space for RNA replication initiation (Fig. 1A) (fig. S4). These structures reveal

Fig. 3. NS5B elongation assembly and 2′ modified nucleotide inhibitor recognition. (A) Overall structure of the stalled NS5B ternary elongation complex. The protein is represented by ribbons and is colored and labeled as in Fig. 1A. The sequence and position of the truncated β loop (tS) are highlighted in yellow. The self-complementary RNA is depicted with the template strand in cyan and the primer strand in magenta and numbered according to convention; residues lacking electron density are depicted in gray. The incoming UDP nucleotide is represented in green. The two catalytic Mn2+ ions are shown as purple spheres. (B) Close-up view of the active site. Substrates are colored as in (A), and select protein residues are represented by sticks, colored by beige carbons, and labeled accordingly. The hydrogen bonding network involved in 2′-hydroxyl recognition of the incoming nucleotide is indicated with dashed lines. (C to E) Close-up views comparing the active sites with (C) UDP (gray carbons); (D) 2′-OH/2′-CH2-UDP (yellow carbons), or (E) 2′-F/2′-CH2-UDP (diphosphate metabolite of sofosbuvir; brown carbons). The hydrogen bond networks involved in recognizing the 2′-hydroxyl of ribonucleotide substrates are shown by dashed lines. Binding of 2′-F/2′-CH2-UDP reveals a disruption in the normal hydrogen bonding pattern observed for natural nucleotide substrates and 2′-OH/2′-CH2-containing analogs.

Fig. 4. Model of HCV replication by NS5B. Schematic of representative steps during RNA synthesis by HCV NS5B RdRp. In the apo form, a portion of the RNA binding groove is occluded by both the C terminus (blue line) and the β loop (yellow). During de novo initiation, the RNA template and incoming and priming nucleotides enter the active site. Catalysis results in the formation of an initial dinucleotide primer (first slow step). The next nucleotide is incorporated into the dinucleotide primed initiation assembly. De novo initiation and primed initiation are often referred to collectively as “initiation,” although they are distinct states. Further conformational changes result in movement of the β loop and C terminus out of the RNA binding groove (second slow step), allowing the enzyme to transition into a processive elongation state.
molecular details of a platform for RNA synthesis in which the tip of the β loop now buttresses the end of the short RNA duplex. A similar global arrangement has been observed previously in the de novo initiation assembly of RNA bacteriophages (18, 19), which suggests the catalytic event preceding the primed initiation state of HCV (Fig. 1C). These β-loop interactions appear critical for setting the register to ensure that the polymerase initiates transcription at the 3′ end of the viral genome. In general, the β-loop residues exhibit increased temperature factors and contain weaker electron density compared with the apo enzyme, indicating that the β loop starts to become disposed during primed initiation (fig. S6). In addition to retraction of the β loop, the C terminus vacated the active-site cavity now occupied by nucleic acid and appeared disposed beyond residue T592 (22) in the primed assemblies. These movements generate space to accommodate only two Watson-Crick pairs upstream of the incoming nucleotide, suggesting that further conformational changes are required to accommodate additional phosphotransfer and translocation events. This in turn, at a minimum, an opening of the thumb in via reorientation of the β loop. Thus, structures demonstrate the polymerase assembly before the second slow step in RNA replication (19).

Mutational analysis of NS5B revealed R386 of the primer grip motif to be important for dinucleotide-initiated RNA synthesis (22), and the primed-state assemblies show that both R386 and R394 of the primer grip helix form salt bridges with the β-phosphate of the dinucleotide primer (Fig. 2A). The conserved catalytic residues D220, D231, and D319 coordinate the two catalytic Mg²⁺ ions, which in turn coordinate the α and β phosphates of the incoming nucleotide. Conserved basic residues R48 and R158 coordinate the α and β phosphates respectively, the metal ions. The incoming nucleotide forms a Watson-Crick interaction with the pairing residue of the template strand, which packs against conserved hydrophobic residues I160 and Y161 (Fig. 2B). The 3′-hydroxyl of the dinucleotide primer forms an inner-sphere coordination with a catalytic metal ion in an in-line conformation with the scissile of the incoming nucleotide, nearly identical to observed for the Norwalk virus RdRp (23) (Fig. 2C). Thus, the nucleotide dinophosphates exhibit enzymatically competent conformations consistent with the common polymerase mechanism (24) (Fig. 2D).

In HIV reverse transcriptase, Y115 provides specificity for deoxynucleotides triphosphates by serving as a steric gate to prevent the binding of ribonucleotide triphosphates (NTPs) (25), and it was predicted that the structurally homologous residue in HCV, conserved D225, would be involved in recognition of the 2′-hydroxyl of incoming NTPs (9-12). In the NS5B ternary complex, the conserved D225 (Fig. 2B) allows its side chain to swing out and hydrogen bond with the 2′-hydroxyl of the substrate and the carbonylic acid of D225, which moves away from the nucleotide substrate during binding (Fig. 2E). The 2′-hydroxyl of the incoming ribonucleotide also forms a direct hydrogen bond with the side chain amine of N291 on the opposite face of the ribose ring. This network of hydrogen bonds, together with the catalytic base pairing to the template, provides the structural basis for recognition of the correct ribonucleotide substrate.

Crystal structures of a β-loop deletion construct of the HCV NS5B polymerase were solved as apo (2.5 Å resolution) or via soaking (19) (see supplementary materials and methods) with a symmetrical RNA primer-template pair (36) and an incoming UDP (2.8 Å), GDP (2.7 Å), or GDP (2.9 Å) (Fig. 3, figs. S6 to S8, and tables S4 to S6). These ternary complex probably represent the highly processive elongation phase of viral genome replication after the transition from the primed state in the second slow step of polymerization (29). These high-resolution elongation stage structures were obtained via soaking into the same crystal form as the triple mutant structures with the intact β loop but could only be obtained with a construct containing both the triple mutant (35) and the β-loop deletion (16) (see supplementary materials and methods). Overall, there is excellent overlap between the catalytic residues, the 3′ end of the primer, and the incoming nucleotide when comparing the elongation complexes with the primed initiation assemblies, including the same in-line conformation of the 3′-hydroxyl of the primer with the template terminal base. The thumb domain moved away from the palm and fingers domains by an additional 1.5 Å for similar Cas atoms, demonstrating a slightly more relaxed state of the polymerase during elongation. In addition, the C-terminal residues downstream of A534 have vacated the RNA binding groove and become disposed, preventing overlap with the template strand. Thus, these structures provide further evidence for concerted movements of the β loop, the thumb domain, and the C terminus once RNA elongation begins. Moreover, they provide the structural basis for the hypothesis that these elements provide a "swinging gate" that allows the polymerase to initiate at the terminus of the RNA genome and then transition to a processive elongation state, thereby replicating the complete genome (22).

The crystal structures presented here lead us to propose a model of the structural events involved in HCV genome replication (Fig. 4). At the outset, the β loop and the C-terminal membrane-analyzing linker are buried within the encircled active-site cavity. In the first of two slow steps in HCV RNA replication (19), the 3′ end of the viral RNA template and the incoming nucleotides enter the active site, possibly with accompanying conformational changes, and the initial phosphoryl transfer step generates a dinucleotide primer. This de novo initiation step immediately precedes the primed initiation assembly captured here. At this early stage, the complex remains unstable, which may allow for the observed large quantity of two- to four-nucleotide-long abortive transcripts (26, 27). As the dinucleotide primer is extended by another one to three nucleotides, the build-up of tension displaces the β loop and the remaining C-terminal residues, further opening the cavity and allowing the RNA duplex to exit during the second slow step in replication (19).

With both the β-hairpin loop and the C terminus expelled from the active site, the polymerase transitions into the highly processive elongation mode also captured here. By using an extended hydrogen bond network to recognize the 2′-hydroxyl of the incoming nucleotide (Fig. 3C), HCV NS5B displays stringent selectivity for ribonucleotides. Consequently, 2′- deoxyribonucleotide chain terminators such as azidothymidine are ineffective against HCV, whereas 2′-modified nucleotides are effective for HCV antivirals (6).

The nucleotide analog inhibitor salsaludin is a 2′-F-2′-C-methylribonucleotide monophosphate drug (28-30) and is approved for the treatment of chronic HCV infection (7, 8). Efficacy of chain-terminating nucleotide analogs requires viral RdRp to recognize and successfully incorporate the inhibitors into the growing RNA strand. To gain insight into the molecular details of 2′-modified nucleotide analog recognition, we determined elongation-phase ternary complexes of both 2′OH-2′-CH₃-UDP and 2′ F-2′-CH₃-UDP at 2.6 and 2.2 Å resolution, respectively (table S7). The stalled ternary complex with 2′OH-2′-CH₃-UDP as the incoming nucleotide was essentially identical to the UDP-bound elongation assembly, with S282 undergoing the same conformational change to interact directly with the 2′-hydroxyl of the incoming nucleotide bond with D225 (Fig. 3D). Although the addition of the 2′-C-methyl group of the inhibitor places it within 3.1 Å of the S282 cysteine, previous biochemical studies using 2′-C-methyl nucleotides reveal that these analogs are readily incorporated into the growing chain with Km values approaching those of the natural ribonucleotide substrates (31). In contrast, the trapped elongation assembly containing 2′F-2′-CH₃-UDP (i.e., salsaludin) shows a significantly different conformation of the nucleotide and the enzyme. The loss of the hydrogen bonding network involving S282 results in a substantially higher Km for 2′F-2′-CH₃-modified nucleotides. Nevertheless, recognition of the 2′F by N291 and Watson-Crick pairing with the template allows salsaludin to form a more stable in-line conformation necessary for incorporation into the growing chain, thereby promoting non-obligate chain termination. Key contacts formed by S282 with the incoming nucleotide and the surrounding environment give insight into the in vitro selection of a threonine as a potential resistance mutation to some 2′-CH₃-modified nucleotides (32, 33), although S282-728 has been infrequently observed in the clinic (34). In particular, a steric clash between the T282 side chain and the 2′-CH₃ would be predicted based on the structure determined with 2′OH-2′-CH₃-UDP (29).

The results presented here establish the structural requirements for HCV genomic replication from primed initiation to elongation and demonstrate the structural basis for inhibitor recognition. The
TIGHT JUNCTIONS

Structural insight into tight junction disassembly by Clostridioides perfringens enterotoxin

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The C-terminal region of Clostridioides perfringens enterotoxin (CPE) can bind to specific Claudins, resulting in the disintegration of tight junctions (TJs) and an increase in the paracellular permeability across epithelial cell sheets. Here we present the structure of mammalian claudin-19 in complex with CPE at 3.7 Å resolution. The structure shows that CPE forms extensive hydrophobic and hydrophilic interactions with the two extracellular segments of claudin-19. The claudin-19/CPE complex shows no density of a short para cellular helix that is critical for claudin to assemble into TJ strands. The helix laceration may thus underlie CPE-mediated disassembly of TJs.

Infection with Clostridioides perfringens type A by eating contaminated food is a common cause of food poisoning in humans and animals. In the intestines, this bacterium produces Clostridioides perfringens enterotoxins (CPEs) that trigger foodborne illness (1). Upon binding to their receptor, the complexes aggregate on the intestinal cell surface and form a large oligomer that inserts into the membrane and forms an ion pathway. The resulting Ca²⁺ influx triggers cell death (2, 3). The receptors for CPE, initially named CPE-R and RVP-1 (4, 5), were later recognized as claudin-4 and -3, respectively (6), based on their sequence similarity with claudin-1 and -2, known constituents of cell-to-cell tight junctional complexes (7, 8). The carboxy-terminal half of CPE (CPE-C) mediates the interaction with specific Claudins (9, 10), which reversibly modulates the paracellular permeability of tight junctions (TJs), whereas its amino-terminal half is responsible for pore formation and thus for cellular cytotoxicity (11).

Claudins have a common structural topology consisting of four transmembrane (TM) segments; a large first extracellular segment (EC1), which contains the claudin consensuss motif; and a shorter second extracellular segment (EC2) (12–14). The adhesion and polymerization properties of Claudins enable them to form linear polymers, called TJ strands, which connect adjacent cells and form the structural backbone of TJs (15). TJs serve mainly as barriers that restrict the diffusion of solutes through intercellular spaces in epithelial and endothelial cell sheets (16), thus separating internal tissue compartments from external environments to maintain the homeostasis of our bodies (6).

To understand the structural basis for how CPE recognizes specific Claudins, we expressed all mouse claudin subtypes in Sf9 insect cells and assessed their capacity to bind CPE by using fluorescence-detection size-exclusion chromatography (FDECC) (7). Mouse claudin-19 showed considerable affinity for CPE (Fig. S3A) (17). When expressed in a mammalian epithelial-like cell line, mouse claudin-19 formed TJs in the plasma membranes of cell-to-cell contact regions (Fig. 1A). Although a previous study reported that a synthetic EC3 peptide of claudin-19 had no affinity for CPE (5), a 24-hour incubation with CPE resulted in a significant destabilization of the claudin-19 signal away from the junctional borders (Fig. 1A), suggesting that binding of CPE causes claudin-19 to dissociate from TJs. The disruption of TJs by incubating cells expressing

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