United States Court of Appeals for the Federal Circuit

RICHARD STORER, GILLES GOSSELIN, JEAN-PIERRE SOMMADOSSI, PAOLA LACOLLA,
Appellants

v.

JEREMY CLARK,
Appellee

UNITED STATES,
Intervenor

2015-1802

Appeal from the United States Patent and Trademark Office, Patent Trial and Appeal Board in No. 105,981.

Decided: June 21, 2017

GREGORY A. CASTANIAS, Jones Day, Washington, DC, argued for appellants. Also represented by JENNIFER LORAINE SWIZE; ANTHONY M. INSOGNA, JOHN DAVID KINTON, San Diego, CA; THOMAS EUGENE FRIEBEL, New York, NY; CALVIN GRIFFITH, Cleveland, OH.

FRANK SCHERKENBACH, Fish & Richardson PC, Boston, MA argued for appellee. Also represented by

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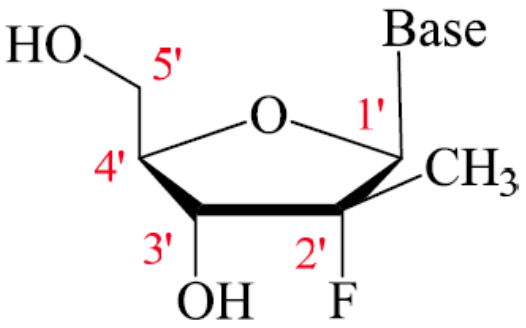
JOSEPH FORREST BUSA, Appellate Staff, Civil Division, United States Department of Justice, Washington, DC, argued for intervenor. Also represented BY MARK R. FREEMAN, BENJAMIN C. MIZER; THOMAS W. KRAUSE, Office of the Solicitor, United States Patent and Trademark Office, Alexandria, VA.

Before PROST, *Chief Judge,* NEWMAN, and DYK, *Circuit Judges.*

NEWMAN, *Circuit Judge.*

This patent interference contest involves methods of treating hepatitis C by administering compounds having a specific chemical and stereochemical structure, based on the following foundation formula of a five-membered ring having the fluorine substituent in the 2´(down) position:



Storer Br. at 8. The priority decision was based on enablement of this product. The interference was declared between an issued patent (Storer et al.) and a pending application (Clark), both of which were filed before the effective date of the America Invents Act, the statute that abolished the first-to-invent interference rule in favor of a

first-to-file rule. By the terms of the Act, § 3(n)(2), the prior, first-to-invent, law applies to this interference.

To establish priority, Storer relied on the disclosure in the provisional specification from which priority was claimed for conception and constructive reduction to practice. In its joint decision on Clark's motion to deny Storer the benefit of the provisional application and on Clark's motion to invalidate Storer's claims on the grounds of lack of enablement and written description,[1] the Patent Trial and Appeal Board (PTAB or "Board") held that Storer's provisional application was not enabling for the count of the interference, and on that ground the PTAB entered judgment granting priority to Clark.[2] Storer appeals that judgment and the underlying decision on Clark's motions.

We take note that Storer initially filed in the District of Delaware, seeking review of the Board's decision under 35 U.S.C. § 146. The district court dismissed the case, *Idenix Pharmaceuticals. LLC v. Gilead Pharmasset LLC*, 2016 WL 6804915, at *1 (D. Del. Nov. 16, 2016), based on this court's ruling in *Biogen MA, Inc. v. Japanese Foundation for Cancer Research*, 785 F.3d 648 (Fed. Cir. 2015), that the America Invents Act eliminated the option of district court review under Section 146 for interferences declared after September 15, 2012. Although Storer says that *Biogen* was incorrectly decided, that decision is binding on this panel. Storer's appeal of the district court's dismissal has been stayed pending the outcome of

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[1] Decision on Motions – Bd.R. 125, *Clark v. Storer*, Interference No. 105,981, (P.T.A.B. Jan. 16, 2015), Doc No. 687 ("Bd. Op.").

[2] *Clark v. Storer*, Interference No. 105,981, 2015 WL 1325503 (P.T.A.B. Mar. 23, 2015).

this appeal. Order, *Idenix Pharm. LLC v. Gilead Pharmasset LLC*, No. 17-1369 (Fed. Cir. Feb. 16, 2017).

BACKGROUND

Inventors Richard Storer et al. were issued U.S. Patent No. 7,608,600 ("the '600 Patent"), on a final application filed on June 27, 2003. The patent is assigned to Idenix Pharmaceuticals. In the interference proceeding, Storer was initially declared the senior party based on the June 28, 2002 filing date of provisional application No. 60/392,350 (called "the S1 application" by the Board). Clark's Application No. 11/854,218, assigned to Gilead Pharmasset, was filed September 12, 2007, with priority claimed to a provisional application filed on May 30, 2003.

Clark moved to deny Storer the priority date of the S1 application and to invalidate Storer's claims, arguing that the S1 application did not enable compounds having the 2´F(down) substituent. Storer argued that these compounds were generically disclosed in the S1 application, and were readily obtained based on the disclosure in the S1 provisional and the prior art. The Board did not agree, and by withdrawing entitlement to the provisional's filing date, the Board awarded priority to Clark. Storer now appeals that decision.

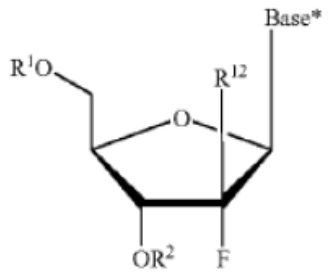
DISCUSSION

The Interfering Claims

Storer and Clark were investigating the treatment of hepatitis C using modified nucleoside compounds, including certain heterocyclic compounds having a fluorine substituent in the 2´ position. The PTAB identified the interfering subject matter, and selected claims for purposes of determining priority. From the Storer patent, the Board selected claim 1:

> 1. A method for the treatment of a host infected with a hepatitis C virus, comprising administer-

ing to the host infected with a hepatitis C virus an effective amount of a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 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 R^1 is H or phosphate;

R^2 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 R^2 is H;

Base* is selected from the group consisting of adenine, N^6-alkylpurine, N^6-acylpurine, N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkylpurine, N^6-alkylamino-purine, N^6-thioalkyl purine, N^2-alkylpurine, N^2-alkyl-6-thiopurine, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, 6-azacytosine, 2- and/or 4-mercaptopyrimidine, uracil, 5-halouracil, 5-fluorouracil, C^5-alkylpyrimidine, C^5-benzylpyrimidine, C^5-halopyrimidine, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl

pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-iodopyrimidine, C^6-iodo-pyrimidine, C^5-Br-vinyl pyrimidine, C^6-Br-vinylpyrimidine, C^5-nitropyrimidine, C^6-amino-pyrimidine, N^2-alkylpurine, N^2-alkyl-6-thiopurine, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, pyrazolopyrimidinyl, guanine, hypoxanthine, 2,6-diaminopurine, and 6-choropurine;

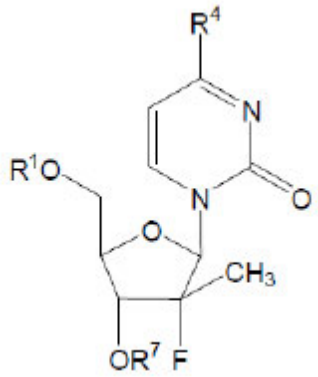
R^{12} is $C(Y^3)_3$; and

Y^3 is independently H or F.

From the Clark application, the Board selected claim 164:

164. A method for the treatment of hepatitis C infection, which comprises:

administering to a mammal in need thereof an antivirally effective amount of a (2′R)-2′-deoxy-2′-fluoro-2′-C-methyl nucleoside (β-D or β-L) or its pharmaceutically acceptable salt of the structure:



wherein R^1 and R^7 are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, an alkyl, an alkyl sulfonyl, or an arylalkyl sulfonyl; and R^4 is NH_2 or OH.

The parties agree that the only question focuses on whether the Storer S1 provisional together with the prior art enabled compounds having a 2´F(down) substituent.

Enablement

Enablement is relevant for validity and to the issue of whether the provisional application is a constructive reduction to practice. "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 a count." 37 C.F.R. § 41.201. "When a party to an interference seeks the benefit of an earlier-filed United States patent application, the earlier application must meet the requirements of 35 U.S.C. § 120 and 35 U.S.C. § 112 ¶ 1 for the subject matter of the count." *Hyatt v. Boone*, 146 F.3d 1348, 1352 (Fed. Cir. 1998) (footnotes omitted). Section 112 ¶ 1 requires:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112, para. 1.[3] Therefore, when the issue is priority based on the content of the specification, "[t]he earlier application must contain a written description of the subject matter of the interference count, and must meet the enablement requirement." *Hyatt*, 146 F.3d at 1352.

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[3] This section is now § 112(a).

Enablement is a matter of law, and is reviewed without deference; however, the factual underpinnings of enablement are reviewed for support by substantial evidence on the entirety of the PTO record. *Microsoft Corp. v. Proxyconn, Inc.,* 789 F.3d 1292, 1297 (Fed. Cir. 2015). To establish enablement of a claim whereby new chemical compounds are provided for use to treat disease, the application must enable production or synthesis of the new compounds. *See In re Brebner*, 455 F.2d 1402, 1404 (C.C.P.A. 1972) ("A method of making starting materials not known in the art must be set forth in order to comply with the enablement requirement.").

The Board held that the S1 provisional, taken together with the prior art, did not enable the specific compounds having the identified structure. Storer argued, and repeats on appeal, that a person of ordinary skill would have been able to make this class of compounds, having the requisite stereochemistry, based on information in the S1 provisional application and the prior art. "The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Research & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (quoting *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010)).

"Whether undue experimentation is required 'is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.'" *Id.* As summarized in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), relevant factors may "include (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."

The Board determined that the claimed compounds having a 2′F(down) substituent were not enabled in Storer's S1 provisional application, in that undue experimentation would be required to produce this structure. The Board analyzed the disclosure in terms of the evidentiary factors set forth in *Wands*.

Storer does not dispute the Board's findings as to the third, fourth, fifth, sixth, and eighth *Wands* factors, but argues that these factors are not dispositive of enablement. For the third *Wands* factor—the presence or absence of working examples—Storer does not dispute that the S1 provisional contains no specific examples of synthesis of compounds having the fluoro substituent in the 2′(down) position. Bd. Op. at 24.

For the fourth *Wands* factor—the nature of the invention—the Board found that:

> 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 HCV). 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.

Id. at 25 (footnote omitted). Storer does not dispute this finding.

For the fifth *Wands* factor—the state of the prior art—the Board found that:

> although DAST [N,N-diethylamino-sulfur trifluoride] 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.

Id. at 29. Storer does not dispute this finding.

With respect to the sixth *Wands* factor, the Board particularly relied on *Wands* factors 1, 2, 3, 4, and 7 and found that "the parties largely agree that the level of skill in the art is very high" and that

> a person possessing the ordinary level of skill in this art, as of the time of the 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.

Id. at 29–30. The Board also found that neither party argued the eighth *Wands* factor regarding the breadth of the claims. *Id.* at 34 n.64. These findings are not disputed.

The Board summarized the evidence and findings on which it concluded that undue experimentation would be needed to produce the designated molecule:

> (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′ "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.

Id. at 34–35.

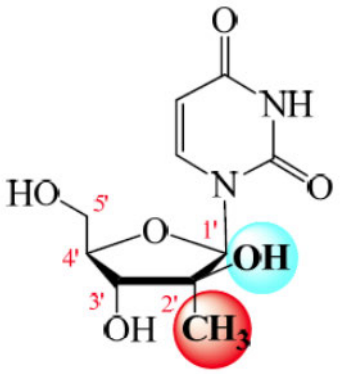
Based on these findings, the Board concluded that the interference subject matter was not enabled by Storer's S1 provisional application.

Argument on Appeal

Storer argues that the S1 provisional application "performed the substantial step of disclosing the precise chemical structure of the target compound." Storer Br. at 47. Storer does not, however, identify any specific structure having the 2´F(down) substituent. The pages of the S1 provisional cited by Storer include generic structures, and Clark does not dispute that the "target compounds," as the Board calls the 2´F(down) compounds, are generically included in the S1 provisional application's generic formulas.

Storer states that the prior art contains "a well-known precursor compound that is only one step away from the target compound." *Id.* at 8. Storer states that this precursor is "Matsuda Compound 17," citing Akira Matsuda et al., *Alkyl Addition Reaction of Pyrimidine 2´-Ketonucleosides: Synthesis of 2´-Branched-Chain Sugar Pyrimidine Nucleosides (Nucleosides and Nucleotides LXXXI)*, 36 CHEMICAL & PHARMACEUTICAL BULL., no. 3, Mar. 1988, at 945.

Matsuda Compound 17 is presented in Storer's brief as

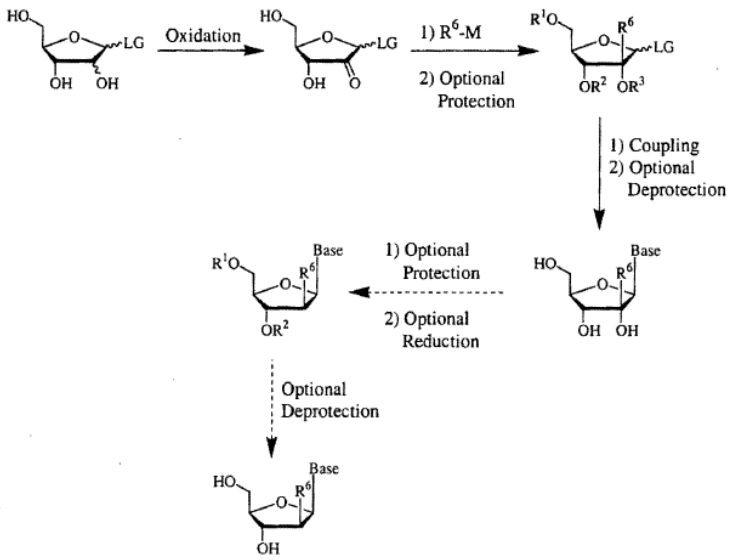


Matsuda Compound 17

Storer Br. at 12. Matsuda Compound 17 contains a methyl group in the 2′(down) position, and Storer states that Matsuda Compound 17 is readily converted into the target compound by known methods to produce the desired stereochemistry. Matsuda Compound 17 is not mentioned in the S1 provisional, but Storer argues that the precursor to Matsuda Compound 17 is in the S1 provisional, "as is that precursor's conversion to the Matsuda compound," *Id.* at 48 n.16. Storer states that the precursor "is only two steps away from the desired 2′-methyl 'up', 2′-fluoro 'down' configuration," and "each scheme discloses how to modify the 2′-keto precursor to obtain" Matsuda Compound 17. *Id.* at 9.

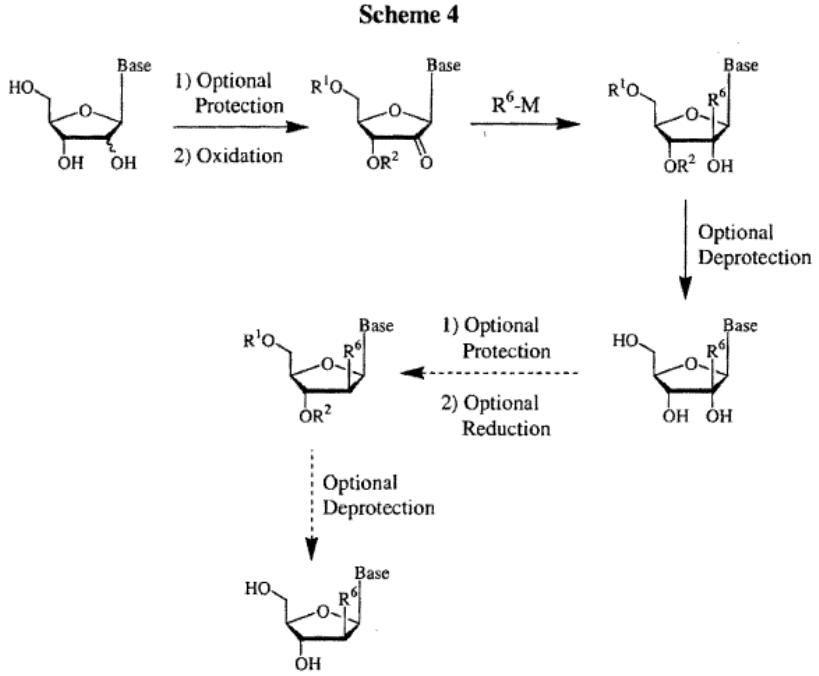
Thus Storer argues that the Matsuda reference, together with the information in the S1 provisional, enable synthesis of 2′F(down) compounds. Storer states that Schemes 3, 4 and 8 in the S1 provisional each describes a "2′-keto precursor, *i.e.*, a compound with '=O' at the 2′ position," and that this is the path to the 2′F(down) molecule. *Id.* at 9. The three schemes from the S1 provisional are:

Scheme 3



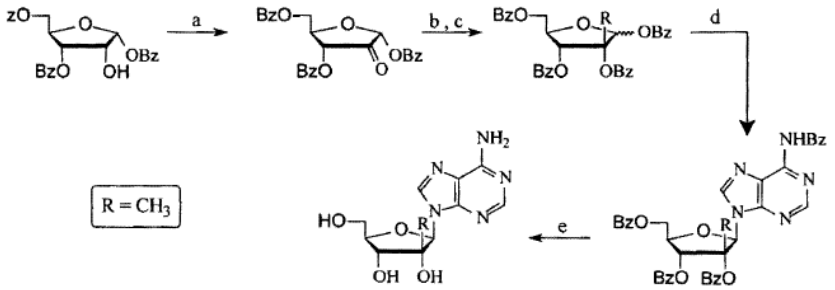
Storer Prov. Appl. at 119.

Scheme 4



Id. at 120.

Scheme 8



(a) Dess-Martin periodinane; (b) MeMgBr / $TiCl_4$; (c) BzCl, DMAP, Et_3N; (d) bis(trimethylsilyl)acetamide, N^6-benzoyl adenine, TMSOTf; (e) NH_3 / MeOH

Id. at 1948.

These three schemes indeed show a compound with =O at the 2′ position, but none shows conversion to Matsuda Compound 17 or further conversion to the 2′F(down) analog. Clark points out that each scheme produces compounds with the opposite spatial arrangement from Matsuda Compound 17, for in Matsuda Compound 17 the 2′-OH is "up," whereas in Scheme 4 the 2′-OH is "down." Clark Br. at 5.

Storer does not dispute the chemical facts, but argues that the difference between Matsuda 17 and the provisional synthesis schemes does not negate enablement because

> if the alkylation reagent is methyl lithium (MeLi) or methyl Grignard (MeMgBr) for methylation as taught by the specification, one of ordinary skill in the art will obtain products with the orientation (*i.e.*, "stereochemistry") of the OH and methyl groups needed to synthesize the target compound using DAST or Deoxo-Fluor. Furthermore, the prior art teaches how to control the stereochemistry of these groups.

Storer Br. at 9-10 n.5. Although the S1 provisional schemes show products with the opposite stereochemistry, Storer argues that a person of ordinary skill could make Matsuda Compound 17 employing these schemes. Storer argues that "a skilled artisan would have recognized that Matsuda Compound 17 was a viable precursor," *id.* at 48, and that: "With knowledge of those structures, the hypothetical person would have known to use a common, one-step synthesis to modify the well-known precursor to obtain the target compound." *Id.* Storer states that "simply by looking at the chemical structure of the target compound disclosed by Idenix, a person of ordinary skill would know to use a fluorination reagent," *id.*, and "DAST and Deoxo-Fluor were the most well-known fluorinating reagents at the time for one-step fluorination reactions." *Id.* at 49. Storer argues that Matsuda provides any necessary information not in the S1 provisional.

Clark responds that these are overstatements, for neither Matsuda Compound 17 nor any compound with the 2´F(down) structure is mentioned in the Storer S1 provisional. Clark points out that none of the several synthetic schemes in Storer's provisional application shows conversion of any precursor into Matsuda Compound 17. Clark states that Storer's synthetic schemes only disclose compounds with the "wrong stereochemistry." Clark Br. at 37.

The Board agreed with Clark's position, and held that the S1 provisional's description of the 2´-keto precursor, in combination with the Matsuda reference, was insufficient to enable and thereby to establish possession of the 2´F(down) methyl(up) compound of claim 1 before Clark's priority date. The Board stated, correctly, that for new chemical compounds the specification must provide sufficient guidance that undue experimentation is not required to obtain the new compounds.

ANALYSIS

The boundary between a teaching sufficient to enable a person of ordinary skill in the field, and the need for undue experimentation, varies with the complexity of the science. Knowledge of the prior art is presumed, as well as skill in the field of the invention. The specification need not recite textbook science, but it must be more than an invitation for further research. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

In *Genentech* the patentee argued that the prior art taught a method that could be used to produce a claimed human growth hormone product, compensating for lack of detail in the specification. The patentee argued that it did not need to include information in the prior art. This court agreed, but stressed the need to assure enablement of the novel aspects of the invention:

> It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986). However, ... [i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech, 108 F.3d at 1366.

The Storer provisional specification does not describe synthesis of the 2´F(down) target compounds. The question devolves to the adequacy of the disclosure in the provisional of general schemes for synthesizing these general classes of modified nucleosides, taken with the knowledge of the art. The S1 provisional discloses two general approaches. Provisional schemes 3 and 8 modify the sugar portion of the target compound and then add the base portion, as the provisional application calls the

"Glycosylation of the nucleobase with an appropriately modified sugar." Storer Prov. Appl. at 117.

Provisional scheme 4 shows modifying a compound with the base already attached, to achieve the desired structure. The provisional calls this "Modification of a pre-formed nucleoside." *Id.* at 119. The Board observed that none of the approaches in the provisional proceeds through a compound like Matsuda Compound 17, or suggests how Matsuda 17 may be converted into the target 2´F(down) compounds. The Board found that the Storer provisional does not exemplify such a reaction, or lead a person of ordinary skill to perform it. The Board also observed that the S1 provisional schemes produce compounds with opposite spatial arrangement from Matsuda Compound 17.

On review, we conclude that substantial evidence supports the Board's findings that the synthetic schemes in Storer's provisional application do not teach or suggest conversion of any precursor into the 2´F(down) structure, and that the Matsuda synthesis of a corresponding 2´-methyl (down), 2´-hydroxyl (up) structure does not enable a person of ordinary skill to produce the target compounds without undue experimentation.

Wands factor 7, the predictability or unpredictability of the art, appears to be particularly relevant. Although Storer states that this is predictable chemistry, and therefore that detailed specific examples are not necessary, the Board's findings are in accord with the record. The Board found:

> 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 synthesize its high-priority target nucleoside, and as further

> evinced by the statements of Dr. Coe and Dr. Storer.

Bd. Op. at 33–34. Regarding Dr. Coe's and Dr. Storer's statements, the Board stated:

> 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. at 31 (quoting from the record). The Board also referred to evidence presented on behalf of Clark that "attempted fluorination reactions (including those involving DAST) could fail, resulting in unfluorinated elimination and/or rearrangement products, or products with incorrect stereochemistry." *Id.* at 30.

Even on Storer's position that a person skilled in this science would have started with Matsuda Compound 17, Storer has not shown that the critical stereochemical result would predictably ensue, although the reaction had never been performed. The Board received evidence of side reactions and the skepticism of experts. The Board received evidence that Storer and his team had difficulty and failures in synthesizing the target compound, as well as evidence that Clark and his team were more readily successful using apparently the same method. The Board's finding that the chemistry was unpredictable is in accord with the evidence.

The first *Wands* factor is concerned with "undue" experimentation, and recognizes that what is "undue" of itself depends on the subject matter and skill. The Board discussed the amount of experimentation needed to produce the claimed compounds, and found 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 the fields and additional formal training.

Id. at 19. The Board discussed the evidence showing Storer's continuing research after the S1 provisional was filed, including the following findings:

- "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." *Id.* at 14.
- "Idenix scientists also corresponded with consultants Dr. George Fleet and Dr. Paul Coe in an attempt to effect a synthesis of the desired compound." *Id.* at 14.
- "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." *Id.* at 15.
- "Dr. Jean-François Griffon, 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." *Id.* at 15.
- "[A]ttempts by the Montpellier team to use DAST in the synthesis of a 2′-fluoro-2′-methyl nucleoside produced similar failures." *Id.* at 16.

- "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. 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.* at 17 (citations to the record omitted).

Storer argues that the Board failed to address the fact that Clark readily synthesized a target compound in a single step from Matsuda Compound 17. The Board acknowledged Storer's argument that it was "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.* at 13. Storer states that "Clark's experiments directly contradict the Board's reliance on the allegedly failed attempts of Griffon." Storer Br. at 55. There was evidence that Clark used a method similar to that attempted by Griffon on the Storer team, and that Clark succeeded where Griffon apparently failed. Storer stated to the Board that Griffon actually produced the target compound, but was not able to purify it from the reaction mixture.

The Board found, on consideration of the entire record, that a person of ordinary skill, with the disclosure in the provisional application and knowledge of the prior art, would not have been led to make the target compound, and could not do so without undue experimentation. The Board received evidence that successful fluorination reactions of the desired stereochemistry had not been reported for structurally similar compounds.

We conclude that substantial evidence supports the Board's finding that "a high amount of experimentation is necessary to synthesize" the target compound. The record before the Board showed sufficient variability and unpredictability to support the Board's conclusion that Storer's provisional application did not enable the interference subject matter. The Board's decision is affirmed.

AFFIRMED