United States Court of Appeals for the Federal Circuit

IDENIX PHARMACEUTICALS LLC, UNIVERSITA DEGLI STUDI DI CAGLIARI,
Plaintiffs-Appellants

v.

GILEAD SCIENCES INC.,
Defendant-Appellee

2018-1691

Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-00846-LPS, Chief Judge Leonard P. Stark.

Decided: October 30, 2019

GREGORY A. CASTANIAS, Jones Day, Washington, DC, argued for plaintiffs-appellants. Also represented by JENNIFER LORAINE SWIZE; LISA LYNN FURBY, Chicago, IL; CALVIN GRIFFITH, RYAN BOYD MCCRUM, Cleveland, OH; ANTHONY INSOGNA, San Diego, CA; JEFFREY A. LAMKEN, SARAH JUSTINE NEWMAN, MICHAEL GREGORY PATTILLO, JR., MoloLamken LLP, Washington, DC.

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

Opinion for the court filed by *Chief Judge* PROST.

Dissenting opinion filed by *Circuit Judge* NEWMAN.

PROST, *Chief Judge*.

Idenix Pharmaceuticals LLC and Universita Degli Studi Di Cagliari (collectively, "Idenix") appeal from the decision of the U.S. District Court for the District of Delaware granting judgment as a matter of law ("JMOL") against Idenix and finding that U.S. Patent No. 7,608,597 is invalid for lack of enablement. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2018 WL 922125, at *25 (D. Del. Feb. 16, 2018) ("JMOL Opinion"). Gilead Sciences Inc., ("Gilead") argues that the patent is also invalid for failure to meet the written description requirement, and that the district court erred by failing to grant JMOL on that ground as well. We affirm as to non-enablement and hold that the patent is also invalid for lack of written description.

I

This appeal stems from Idenix's December 2013 patent infringement suit against Gilead, originally filed in the U.S. District Court for the District of Massachusetts and later transferred to the District of Delaware. J.A. 259–69. At the time of the suit, both Idenix and Gilead were researching and developing drugs for treatment of the hepatitis C virus ("HCV"). HCV is a leading cause of chronic liver disease, infecting hundreds of millions of people worldwide, and accounting for tens of thousands of

deaths per year in the United States alone. Idenix alleged that the imminent Food and Drug Administration approval, and launch, of Gilead's HCV treatment drug sofosbuvir would infringe Idenix's U.S. Pat. No. 7,608,597 (the "'597 patent").

Following years of litigation, Chief Judge Stark held a two-week jury trial in December 2016. Gilead stipulated to infringement under the district court's claim construction but argued that the '597 patent was invalid for failure to meet the written description and enablement requirements. The jury found for Idenix, upholding the validity of the patent and awarding damages. After trial, Gilead filed a renewed motion for JMOL with respect to written description and enablement. The district court denied the motion with respect to written description but granted JMOL on enablement, holding the '597 patent invalid.

Idenix timely appealed. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

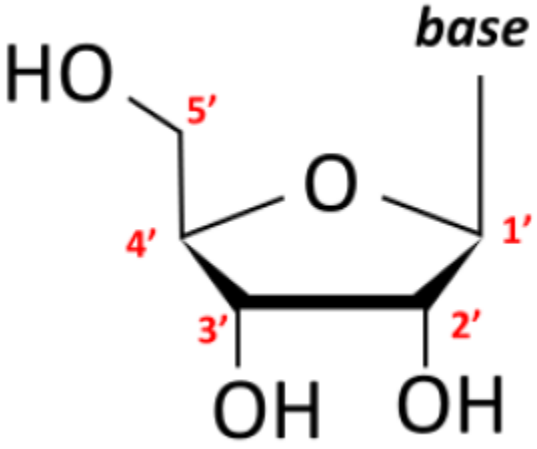
II

We review the denial or grant of a motion for JMOL under regional circuit law. *See Tr. of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1361 (Fed. Cir. 2018). Applying Third Circuit law, we "exercise plenary review over a district court's rulings on motions for JMOL, applying the same standard as the district court." *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1341–42 (Fed. Cir. 2008) (citing *Gagliardo v. Connaught Labs., Inc.*, 311 F.3d 565, 568 (3d Cir. 2002)). A grant of JMOL is appropriate "where a party has been fully heard on an issue during a jury trial and the court finds that a reasonable jury would not have had a legally sufficient evidentiary basis to find for the party on that issue." *Id.* at 1342; *see* Fed. R. Civ. P. 50(a).

Enablement requires that "the specification teach those in the art to make and use the invention without undue experimentation." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). A claim is not enabled when, "at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Whether a claim satisfies the enablement requirement is a question of law that we review de novo. *Tr. of Boston Univ.*, 896 F.3d at 1361. However, "in the context of a jury trial, we review the factual underpinnings of enablement for substantial evidence." *Id.*

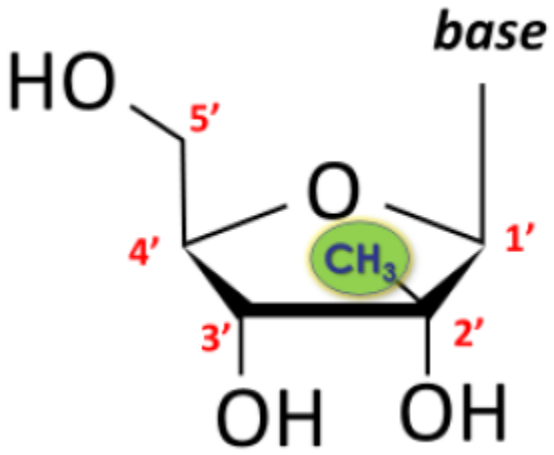
III

The '597 patent claims a method of treating HCV by administering nucleoside compounds having a specific chemical and stereochemical structure. The nucleosides claimed in the '597 patent contain a sugar ring having five carbon atoms, numbered 1' (one prime) to 5' (five prime), as well as a base. At each carbon, substituent atoms or groups of atoms can be added in either the "up" or "down" position. This structure is illustrated below, with a hydroxyl group (OH) shown attached at the 2'-down and 3'-down positions:



Appellant's Br. 8. The parties' arguments focus on the presence of various possible substituents at the 2'-up and 2'-down positions.

Idenix argues that the key to its invention, and to treatment of HCV, is the use of 2'-methyl-up nucleosides: nucleosides "having a methyl substitution ('CH3') at the 2' 'up' position of the molecule's sugar ring," illustrated below.



Appellant's Br. 7–8.

Gilead argues that this characterization is overly broad, as the '597 patent provides no guidance in determining which of the billions of potential 2'-methyl-up nucleosides are effective in treating HCV. *See* Appellee's Br. 8. According to Gilead, the '597 patent primarily describes 2'-methyl-up nucleosides that have a hydroxyl group (OH) at the 2'-down position. But Gilead's accused product has fluorine (F), not OH, at the 2'-down position. *Id.* According to Gilead, the '597 patent cannot enable the full scope of effective 2'-methyl-up nucleosides at least because its accused embodiment, 2'-methyl-up 2'-fluoro-

down, is not disclosed in or enabled by the specification.[1]

The only independent claim of the '597 patent recites:

> 1. A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine ß-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.

'597 patent claim 1. The district court construed the structural limitation "ß-D-2'-methyl-ribofuranosyl nucleoside" to require "a methyl group in the 2' up position and non-hydrogen substituents at the 2' down and 3' down positions." *Idenix Pharm., Inc. v. Gilead Scis., Inc.*, 2015 WL 9048010, at *6 (D. Del. Dec. 16, 2015) ("Claim Construction Order"). Thus, while the claim requires methyl at the 2'-up position, it allows nearly any imaginable substituent at the 2'-down position.[2]

At Idenix's urging, the district court also construed the preamble, "[a] method for the treatment of a hepatitis C virus infection," as a narrowing functional limitation. *Idenix Pharm. LLC v. Gilead Scis., Inc.*, 2016 WL 6802481, at *5 (D. Del. Nov. 16, 2016). In combination with the requirement to administer an "effective amount," this claim language "limit[s] the scope of the claims to the use of some set of compounds that are effective for treatment of HCV." *Id.* at *6.

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[1] We have previously held that an Idenix patent on similar technology failed to enable 2'-methyl-up 2'-fluoro-down nucleosides, albeit in a different procedural posture. *See Storer v. Clark*, 860 F.3d 1340 (Fed. Cir. 2017).

[2] Neither party contends that the sole limitation on 2'-down, which excludes hydrogen substituents, is significant in this appeal.

Neither party challenges the district court's claim constructions in this appeal. Claim 1, therefore, encompasses any β-D nucleoside meeting both the structural limitations (including a methyl group at 2'-up) and the functional limitations (efficacy in treating HCV). It is undisputed, however, that there are billions of potential 2'-methyl-up nucleosides. The key enablement question is whether a person of ordinary skill in the art would know, without undue experimentation, which 2'-methyl-up nucleosides would be effective for treating HCV. We conclude that they would not.[3] Taking into account

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[3] The dissent, making an argument not advanced by Idenix at trial or before us, reaches the opposite conclusion only by disregarding the district court's binding claim construction, ignoring the resulting stipulation of infringement, and analyzing a case that is not the one presented to us.

Before the district court, Gilead proposed a narrow claim construction that required "hydroxyl groups at the 2' down and 3' down positions." Claim Construction Order at *6. Because Gilead's accused product has fluorine at 2'-down, rather than a hydroxyl group, this would have resulted in non-infringement. However, the district court expressly rejected that proposal, instead adopting a broader construction that allowed for any "non-hydrogen substituents," including fluorine. *Id.* On the basis of that broad construction, Gilead stipulated to infringement, and the parties held a trial solely on invalidity. J.A. 6. Neither side challenged the claim construction on appeal, and the issue is not before us.

The question before us is whether the '597 patent enables the full scope of its claims under the district court's broad construction. The dissent declines to answer that question, and instead applies its own "narrow" claim construction, under which only hydroxyl groups are permitted at the 2'-down position. Dissent at 3; *id.* at 7 (limiting

the evidence presented at trial, a reasonable jury would not have had a legally sufficient basis to find otherwise.

In analyzing undue experimentation, we consider the factors first enumerated in *In re Wands*. The uncontested jury instructions in this case formulate the *Wands* factors as follows:

> (1) the quantity of experimentation necessary;
>
> (2) how routine any necessary experimentation is in the relevant field;
>
> (3) whether the patent discloses specific working examples of the claimed invention;
>
> (4) the amount of guidance presented in the patent;
>
> (5) the nature and predictability of the field;
>
> (6) the level of ordinary skill; and

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claim to where "R^7 is OH"); *id.* at 12 ("narrow formula of three OH groups and a CH_3 group as pictured"). In essence, the dissent adopts Gilead's rejected claim construction. Indeed, the dissent admits that under its new claim construction, Gilead's accused product "is not within the scope of the claims." Dissent at 15.

We agree with the dissent that, under a narrower construction, the claims of the '597 patent might well be enabled, and the accused product would not infringe. But that is not the case before us. We are tasked with deciding whether the claims, *as construed*, are enabled. The dissent appears to agree with us that they are not. Dissent at 12 ("the '597 specification did not describe and enable products other than . . . the narrow formulas of three OH groups"). But rather than answer that question, the dissent has applied its newly invented claim construction to find a hypothetical narrower claim valid but not infringed. Respectfully, that is no way to conduct an appeal.

(7) the scope of the claimed invention.

J.A. 179; *see Wands*, 848 F.3d at 737. The parties agree that the level of ordinary skill in the art is high, but dispute the impact of the remaining factors. We discuss each in turn.

A

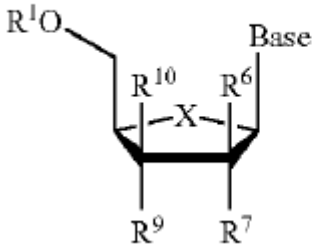
We agree with the district court that the quantity of experimentation required to determine which 2'-methyl-up nucleosides meet claim 1 is very high, which favors a finding of non-enablement. The evidence presented to the jury could not support any other finding. At trial, Gilead presented expert testimony that because the claim allows for nearly any substituent to be attached at any position (other than 2'-up), a person of ordinary skill in the art would understand that "billions and billions" of compounds literally meet the structural limitations of the claim. J.A. 37545.

Idenix did not dispute that math, but argued to the jury that this approach was merely "theoretical," because a person of ordinary skill in the art ("POSA") would not attach substituents at random. *See* J.A. 37734. Instead, Idenix argued, a POSA would know to "take into account the patent as a whole" to focus on a "significantly smaller" set of candidate compounds. *Id.* The district court accepted this argument, but concluded that even taking into account the knowledge and approach of a POSA, the candidate compounds number "likely[] millions or at least many, many thousands." JMOL Opinion, at *12.

On the evidence presented, a reasonable jury could only have concluded that at least "many, many thousands" of candidate compounds exist. Idenix's evidence, which supports at best an unspecified number "significantly smaller" than "billions," could not lead a reasonable jury to any other conclusion. As Gilead points out, even hundreds of millions is a "significantly smaller" number when the

starting point is "billions and billions." Appellee's Br. 35–36. Idenix's counsel conceded that in its "best case," considering the knowledge of a POSA, the structural limitations still encompass "some number of thousands" of compounds. J.A. 40013.

This conclusion is supported by the '597 patent itself, which discloses enormous quantities of 2'-methyl-up nucleosides that would need to be tested for efficacy against HCV. The specification contains 18 Formulas, each of which is represented by a diagram with variables at multiple positions. For example, Formula XVII, described as the "eleventh principal embodiment," provides:

> a compound of Formula XVII, or a pharmaceutically acceptable salt or prodrug thereof:
>
> (XVII)
>
> 
>
>
> wherein:
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> Base is a purine or pyrimidine base as defined herein;
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> R^1 and R^2 are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a

> cholesterol; or other pharmaceutically acceptable leaving group which when administered in vivo is capable of providing a compound wherein R^1 or R^2 is independently H or phosphate;
>
> R^6 is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, —C(O)O(alkyl), —C(O)O(lower alkyl), —O(acyl), —O(lower acyl), —O(alkyl), —O(lower alkyl), —O(alkenyl), chloro, bromo, fluoro, iodo, NO_2, NH_2, —NH(lower alkyl), —NH(acyl), —N(lower alkyl)$_2$, —N(acyl)$_2$;
>
> R^7 and R^9 are independently hydrogen, OR^2, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, —C(O)O(alkyl), —C(O)O(lower alkyl), —O(acyl), —O(lower acyl), —O(alkyl), —O(lower alkyl), —O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, —NH(lower alkyl), —NH(acyl), —N(lower alkyl)$_2$, —N(acyl)$_2$;
>
> R^{10} is H, alkyl (including lower alkyl), chlorine, bromine or iodine;
>
> alternatively, R^7 and R^9, or R7 and R^{10} can come together to form a pi bond; and
>
> X is O, S, SO_2 or CH_2.

'597 patent col. 12 ll. 20–67. The 2'-up position in this formula, represented as R^6, includes a methyl group as one of two dozen possible substituents.[4] Even limiting this formula only to its 2'-methyl-up variations, however, the formula provides more than a dozen options at the R^1 position, more than a dozen independent options at the 2'-down position, more than a dozen independent options at the 3'-

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[4] The term "alkyl" is defined in the '597 patent to include methyl. '597 patent col. 37 ll. 9–25.

down position, and multiple independent options for the base.

As the district court meticulously calculated, this formula alone discloses more than 7,000 unique configurations of 2'-methyl-up nucleosides. JMOL Opinion, at *12.[5] Other formulas in the specification provide equally large numbers of compounds. Idenix argues that a POSA would have focused on only a narrow subset of billions of possible candidates, but the jury was not free to adopt a number lower than the many, many thousands of configurations identified as "principal embodiment[s]" in the patent itself. *See, e.g.*, '597 patent col. 12 ll. 20–22. Testing the compounds in the specification alone for efficacy against HCV requires enough experimentation for this factor to weigh in favor of non-enablement.

Idenix relatedly argues that a POSA would understand the "focus" of the claim to be "the inhibition of the NS5B polymerase" to effectively cure HCV. Appellant's Br. 16.

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[5] This figure is conservative, as the district court noted. JMOL Opinion, at *12 (noting that "Formula XVII on its own constitutes *at least* a minimum of approximately 7,000 unique configurations" (emphasis added)). The number of candidates disclosed by this formula is likely orders of magnitude higher. For example, the district court's calculation considered "alkyl" to be one possible option at each position. But the specification defines "alkyl" to include at least twenty distinct options that could be substituted. '597 patent col. 37 ll. 9–26. The terms "purine or pyrimidine base" and "acyl" are similarly each defined to include at least twenty independent options. *See id.* at col. 37 l. 59–col. 38 l. 29; JMOL Opinion, at *12 n.11 ("The number of possible configurations increases considerably (by an order of magnitude) when all the compounds the patent defines as a purine or pyrimidine base are taken into account.").

Therefore, Idenix argues, a POSA would know which candidates were likely to inhibit NS5B, and would test only those, resulting in a "predictable and manageable" group of candidate compounds. *Id.* This argument improperly attempts to narrow the claim to only those nucleosides that would inhibit the NS5B polymerase. But the district court's claim construction, not challenged in this appeal, made clear that "as a matter of law, NS5B activity is ***not*** a claim limitation." JMOL Opinion, at *26 (emphasis in original).

Moreover, it would be improper to rely on a POSA's knowledge of NS5B to fill the gaps in the specification. "It 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, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). Idenix's attempt to treat NS5B as a claim limitation, based on the knowledge of a POSA, would be an impermissible end-run around the requirement to enable the full scope of the claim.[6]

At oral argument here on appeal, Idenix presented an additional theory for why little or no experimentation was required. According to Idenix, "the jury could have concluded that ***all*** 2'-methyl-up ribonucleosides were active against the hepatitis C virus, so that the numbers don't matter. Screening [of each candidate for efficacy against HCV] was irrelevant." Oral Arg. at 6:07–6:18, No. 2018-1691, http://www.cafc.uscourts.gov/oral-argument-

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[6] Idenix does not argue that the full scope of the claim includes only compounds that inhibit the NS5B polymerase. Nor could it, as the '597 patent describes treating HCV in other ways. *See* '597 patent col. 139 ll. 30–32 ("Compounds can exhibit anti-hepatitis C activity by inhibiting HCV polymerase, or by inhibiting other enzymes needed in the replication cycle, or by other pathways.").

recordings. We do not agree that the evidence presented could have supported this conclusion. Indeed, Idenix's own evidence contradicts it.

At trial, Idenix's expert agreed that the field of modifying nucleosides for anti-HCV activity was "in its infancy" and "unpredictable." J.A. 37736. Another of Idenix's experts testified that screening was performed to "actually cut down on the number of compounds, by removing all inactive ones to a few interesting ones." J.A. 37747. A third Idenix expert testified that "you don't know whether or not a nucleoside will have activity against HCV until you make it and test it." J.A. 37411. And at oral argument on the post-trial motions, Idenix's counsel agreed that "not all 2' methyl up ribonucleosides will be effective to treat HCV," and therefore screening was necessary. J.A. 40007; *see also id.* ("But would one have to do some screening? Certainly.") In light of this evidence, and this concession, no reasonable jury could have concluded that all 2'-methyl-up nucleosides were effective against HCV or that no screening was needed.

Because the claims of the '597 patent encompass at least many, many thousands of 2'-methyl-up nucleosides which need to be screened for HCV efficacy, the quantity of experimentation needed is large and weighs in favor of non-enablement.

B

The district court concluded that a reasonable jury could only find that many candidate nucleosides would need to be synthesized before they could be screened, as not all candidate nucleosides were available for purchase. We agree.

Idenix argues that "a significant number of nucleosides were available off-the-shelf in libraries." Appellant's Br. 40. However, in light of the billions of possible 2'-methyl-up nucleosides, or even the many, many thousands of

nucleosides that meet the formulas provided in the patent, no reasonable jury could conclude that "a significant number" of available nucleosides removes the need for synthesis. Moreover, Idenix's expert testified that synthesis was often required even when starting with a compound purchased from a library or database. *See* J.A. 37735 ("the general approach is starting from an intact nucleoside that you can buy . . . and then you start doing chemistry on this intact nucleoside and modify the nucleoside structure in the sugar part or even the base part"). In light of this evidence, a reasonable jury could only have found that synthesis was necessary.[7]

We do agree with Idenix, however, that a jury could have found that the synthesis of an individual compound was largely routine. Gilead argued that synthesis was difficult, presenting the jury with evidence of an Idenix scientist who repeatedly tried and failed to synthesize 2'-methyl-up 2'-fluoro-down, which is the nucleoside at issue in Gilead's accused product. *See* JMOL Opinion, at *16. Idenix countered this with evidence of a scientist at a Gilead subsidiary who produced a 2'-methyl-up 2'-fluoro-down compound "in relatively short order." *See id.* As a reviewing court, "we are mindful that we 'may not weigh the evidence, determine the credibility of witnesses, or substitute [our] version of facts for the jury's version.'" *Agrizap*, 520 F.3d at 1342 (quoting *Lightning Lube, Inc. v. Witco Corp.*, 4 F.3d 1153, 1166 (3d Cir. 1993)). In light of this conflicting testimony, a reasonable jury was entitled to conclude that a POSA could synthesize this particular compound in relativity short order.

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[7] Our analysis does not rely on the contested statement in the district court's opinion as to whether or not Idenix's expert expressly testified that "not all compounds of interest were commercially available." JMOL Opinion, at *15.

Because a jury could only have found that synthesis of many 2'-methyl-up nucleosides was necessary, but could have concluded that synthesis of an individual nucleoside was largely routine, this factor weighs against a finding of non-enablement.

C

We analyze the presence of working examples and the amount of guidance presented in the specification together. Idenix argues that these factors weigh against non-enablement because the specification "identifies the 'key' modification (2'-methyl-up)" and contains "working examples of active 2'-methyl-up ribonucleosides that were tested." Appellant's Br. 44. We disagree.

Idenix contends that the '597 patent provides meaningful guidance as to which nucleosides meet the functional limitations of the claim because it identifies the "key" modification of 2'-methyl-up. Appellant's Br. 44. That is insufficient. An enabling disclosure must "be commensurate in scope with the claim." *In re Hyatt*, 708 F.2d 712, 714 (Fed. Cir. 1983). Claim 1 requires more than just an identification of 2'-methyl-up: it requires identification of which 2'-methyl-up nucleosides will effectively treat HCV. Without specific guidance on that point, the specification provides "only a starting point, a direction for further research." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010). That guidance is absent from the '597 specification.

Idenix argues that the '597 patent provides this guidance because a POSA would understand NS5B to be the "target" enzyme or would understand that the modified nucleoside must have "either the natural -OH (hydroxyl) or a mimicking substitute at 2'-down." Appellant's Br. 38, 44. But reliance on a POSA is insufficient to meet the enablement requirement. A patent owner is "required to provide an enabling disclosure in the specification; it cannot simply rely on the knowledge of a person of ordinary skill to serve

as a substitute for the missing information in the specification." *ALZA*, 603 F.3d at 941. Even if we credit Idenix's position that a POSA would look for compounds that would "target" NS5B, the specification fails to provide an enabling disclosure. It is not enough to identify a "target" to be the subject of future testing. A specification that requires a POSA to "engage in an iterative, trial-and-error process to practice the claimed invention" does not provide an enabling disclosure. *Id.*

It is true that the specification contains some data showing working examples of 2'-methyl-up nucleosides with efficacy against HCV. *See* '597 patent col. 139 l. 61–col. 142 l. 57. As discussed, however, the specification alone encompasses tens if not hundreds of thousands of "preferred" 2'-methyl-up nucleosides that would need to be tested for efficacy against HCV. In the face of that broad disclosure, four examples on a single sugar are insufficient to support enablement. Where, as here, working examples are present but are "very narrow, despite the wide breadth of the claims at issue," this factor weighs against enablement. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999); s*ee Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1348 (Fed. Cir. 2019) (working example that was "insufficient to enable the breadth of the claims here, especially in light of the unpredictability of the art" did not support enablement).

Because the '597 patent fails to provide meaningful guidance as to which 2'-methyl-up nucleosides are or are not effective against HCV, and because the only working examples provided are exceedingly narrow relative to the claim scope, these two factors weigh in favor of non-enablement.

D

Based on the testimony presented at trial, a reasonable jury could only have concluded that the use of modified nucleosides to treat HCV was an unpredictable art. Gilead's

experts testified at trial that the art was "highly unpredictable" because "in the nucleoside area . . . the smallest change can have a dramatic effect not only on the activity of that compound but on the toxicity of the compound. So nothing is predictable." J.A. 37547.

Idenix's experts also testified at trial that the field was new and unpredictable. On cross-examination, Idenix's expert admitted that at the time the '597 patent was invented, the field of "modified nucleosides activity for HCV" was "in its infancy." J.A. 37736. He also admitted that, even as late as 2012, it was "unpredictable to make a compound and determine whether or not it is active" against HCV. J.A. 37736–37. Another of Idenix's witnesses confirmed that "you don't know whether or not a nucleoside will have activity against HCV until you make it and test it." J.A. 37441.

In light of both parties' testimony that the art was unpredictable, this factor could only weigh in favor of non-enablement. *See In re Fisher*, 427 F.2d 833, 839 (CCPA 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.").

E

For largely the same reasons discussed with respect to the quantity of experimentation factor, we conclude that the scope of the claims could only support a finding of non-enablement. On appeal, Idenix makes two arguments specifically directed to this factor. Neither is persuasive.

First, Idenix argues that "[w]hen required to take all of the claim limitations into account, Gilead's witnesses described the claims as embracing only a 'small' number of compounds." Appellant's Br. 46. This analysis is backwards. Gilead's expert testified that, in order for the '597 patent to teach which 2'-methyl-up nucleosides effectively

treat HCV, the patent would need to detail "how to get from a large number [of candidate compounds] to a relatively speaking small number [of effective compounds]." J.A. 37546–47. In other words, the '597 patent leaves a POSA searching for a needle in a haystack to determine which of the "large number" of 2'-methyl-up nucleosides falls into the "small" group of candidates that effectively treats HCV. The size disparity between those two groups requires significant experimentation, which weighs against enablement, not for it.[8]

Second, Idenix argues that the claim is not broad because "evidence showed that the POSA, with common sense, the claims, and the specification as guidance, would focus on a narrow set of candidates." Appellant's Br. 46. This factor, however, considers the scope of the claim as written, not just the subset of the claim that a POSA might practice. Idenix does not, and cannot, argue that the scope of the claim is actually limited to this narrow set of candidates. "[A]s a matter of law, NS5B activity is ***not*** a claim limitation." JMOL Opinion, at *26 (emphasis in original). We therefore conclude that the breadth of the claims weighs in favor of non-enablement.

F

Weighing each of these factors, we conclude as a matter of law that the '597 patent is invalid for lack of enablement. As described above, a reasonable jury could only have found that at least many, many thousands of 2'-methyl-up nucleosides meet the structural limitations of claim 1, not all of which are effective to treat HCV. Due to the

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[8] Although not necessary to our decision, we also note that this "small number" argument is inconsistent with Idenix's claim at oral argument that the jury implicitly found that *all* 2'-methyl-up nucleosides are effective to treat HCV. Oral Arg. at 6:07–18.

unpredictability of the art, and as admitted by Idenix, each of these compounds would need to be screened in order to know whether or not they are effective against HCV. Moreover, a significant number of candidate 2'-methyl-up nucleosides would need to be synthesized before they could be screened, which increases at least the quantity of experimentation required, even if the synthesis was routine. Although the level of skill in the art is high, the '597 patent does not provide enough meaningful guidance or working examples, across the full scope of the claim, to allow a POSA to determine which 2'-methyl-up nucleosides would or would not be effective against HCV without extensive screening. The immense breadth of screening required to determine which 2'-methyl-up nucleosides are effective against HCV can only be described as undue experimentation.

Our decision in *Wyeth and Cordis Corp. v. Abbott Laboratories* compels this conclusion, and as the district court correctly acknowledged, the similarities between that case and this one are striking. In *Wyeth*, as here, we considered a claim that encompassed "millions of compounds made by varying the substituent groups," while only a "significantly smaller" subset of those compounds would have the claimed "functional effects." 720 F.3d at 1384. We then credited the patent owner's argument that, based on the knowledge of a POSA, the number of candidate compounds to be tested could be as little as "tens of thousands." *Id.* at 1384–85. In both cases, scientific testimony confirmed that practicing the full scope of the claims would require synthesizing and screening tens of thousands of candidate compounds for the claimed efficacy. *Compare id.* at 1385 (Wyeth scientist testifying "until you test [compounds], you can't really tell whether they work or not"), *with* J.A. 37441 (Idenix scientist testifying "you don't know whether or not a nucleoside will have activity against HCV until you make it and test it").

Notwithstanding the fact that screening an individual compound for effectiveness was considered "routine," we concluded as a matter of law in *Wyeth* that the claim was not enabled because there were "at least tens of thousands of candidate compounds" and "it would be necessary to first synthesize and then screen *each* candidate compound." *Id.* at 1385–86. As we explicitly stated: "The remaining question is whether having to synthesize and screen each of at least tens of thousands of candidate compounds constitutes undue experimentation. We hold that it does." *Id.* at 1385. That principle controls here. A reasonable jury could only have concluded that there were at least many, many thousands of candidate compounds, many of which would require synthesis and each of which would require screening. That constitutes undue experimentation.

We are not persuaded by Idenix's attempts to distinguish *Wyeth* based on the state of the arts of screening and synthesis in 1992, when the *Wyeth* patent application was filed, as compared to 2000, when Idenix's first application was filed. Our decision in *Wyeth*, and our decision here, rests on the "limits on permissible experimentation," not on the relative time that the experimentation would take. *Id.* at 1386. We found the patent in *Wyeth* not enabled even while "putting the challenges of synthesis aside," and accepting as true that screening was "routine[]." *Id.* at 1384, 1386. Where, as here, "practicing the full scope of the claims would have required excessive experimentation, even if routine," the patent is invalid for lack of enablement. *Id.* at 1384.

IV

We separately address the district court's denial of JMOL on the issue of written description. The Patent Act contains a written description requirement distinct from the enablement requirement. 35 U.S.C. § 112; *see Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1340 (Fed. Cir. 2010) (en banc). To fulfill the written description

requirement, a patent owner "must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (citation omitted) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed. Cir. 1991)). That test "requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad*, 598 F.3d at 1351.

The question in this case is whether the '597 patent demonstrates that the inventor was in possession of those 2'-methyl-up nucleosides that fall within the boundaries of the claim (i.e., are effective against HCV), but are not encompassed by the explicit formulas or examples provided in the specification. The parties focus in particular on whether the specification demonstrates possession of the 2'-methyl-up 2'-fluoro-down nucleosides that are the basis for Gilead's accused product.

There is no dispute that neither the '597 patent nor any of its predecessor applications discloses a 2'-methyl-up 2'-fluoro-down nucleoside, including in any formulas or examples. *See* J.A. 37102–03 (admission of Idenix's inventor). Nor is there any dispute as to why. Idenix "only came up with the methyl up fluoro down embodiment a year or so after the application was filed." *See* J.A. 25562 (admission of Idenix's counsel). Idenix argues instead that its claims are directed to the entire genus of 2'-methyl-up compounds for treating HCV, and are enabled by the disclosure of a number of examples, without needing to disclose each species of nucleoside. *See* Reply Br. 31–32.

Idenix is correct that generally a genus can be sufficiently disclosed by "either a representative number of species falling within the scope of the genus or structural features common to the members of the genus so that one

of skill in the art can visualize or recognize the members of the genus." *Ariad*, 598 F.3d at 1350 (internal quotation marks omitted). We have alternatively described this inquiry as "looking for blaze marks which single out particular trees" in a forest, rather than simply "pointing to trees." *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1570 (Fed. Cir. 1996) (quoting *In re Ruschig*, 379 F.2d 990, 994–95 (CCPA 1967)).

In this case, we hold that the '597 patent is invalid for lack of written description, as it fails to provide sufficient blaze marks to direct a POSA to the specific subset of 2'-methyl-up nucleosides that are effective in treating HCV. The patent provides eighteen position-by-position formulas describing "principal embodiments" of compounds that may treat HCV. *See generally* '597 patent col. 5 l. 29–col. 13 l. 42. However, other than generic language regarding "pharmaceutically acceptable salts and prodrugs thereof" (a category not at issue here), the specification provides no indication that any nucleosides outside of those disclosed in its formulas could be effective to treat HCV—much less any indication as to *which* of those undisclosed nucleosides would be effective. *See id.* at col. 15 l. 51–col. 16 l. 10. "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name' of the claimed subject matter sufficient to distinguish it from other materials." *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1363 (Fed. Cir. 2011) (quoting *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). The '597 patent provides adequate written description for the compounds within its formulas. The specification, however, provides no method of distinguishing effective from ineffective compounds for the compounds reaching beyond the formulas disclosed in the '597 patent.

Idenix argues that it provides "abundant traditional blazemarks for the claims—working examples, formulas,

data, synthesis routes, and the target." Reply Br. 32. Each of these suffer from the same flaw. They provide lists or examples of supposedly effective nucleosides, but do not explain what makes them effective, or why. As a result, a POSA is deprived of any meaningful guidance into what compounds beyond the examples and formulas, if any, would provide the same result. In the absence of that guidance, the listed examples and formulas cannot provide adequate written description support for undisclosed nucleosides that also happens to treat HCV. The written description requirement specifically defends against such attempts to "cover any compound later actually invented and determined to fall within the claim's functional boundaries." *See Ariad*, 598 F.3d at 1353.

We are mindful of *Ariad*'s caution that written description does not require "a nucleotide-by-nucleotide recitation of the entire genus." *Id.* at 1352. The purpose of that rule is to allow relatively few representative examples or formulas to support a claim on a structurally similar genus. *See id.* It does not extend to this case, where the specification lists tens or hundreds of thousands of possible nucleosides, substituent-by-substituent, with dozens of distinct stereochemical structures, and yet the compound in question is conspicuously absent.

The absence of 2'-fluoro-down is indeed conspicuous. Seven of the provided formulas permit 2'-methyl-up. *See, e.g.*, '597 patent col. 6 ll. 5–20 (Formula II), col. 8 ll. 5–20 (Formula V), col. 10 ll. 5–47 (Formulas X and XI), col. 11 l. 42–col. 12 l. 17 (Formula XVI), col. 12 ll. 23–54 (Formula XVII), col. 13 ll. 5–41 (Formula XVIII). All seven formulas explicitly list fluorine as a possibility at other positions, including 2'-up. *See, e.g.*, *id.* at col. 10 ll. 42–47 (listing "fluoro" at 2'-up). Yet not one of them includes fluorine at 2'-down, despite each listing more than a dozen possible substituents at that position. This is true even though the formulas include every other recited halogen at both positions. *Compare* '597 patent col. 8 ll. 48–54 (listing "chloro,

bromo, fluoro, iodo" at 2'-up), *with* col. 8 ll. 55–61 (listing "chlorine, bromine, iodine," but not fluorine, at 2'-down).

Further, to the extent Idenix argues that, although not disclosed, a POSA would have known to include fluorine at 2'-down based on its similarities to other halogens, that is insufficient for written description. "[A] description that merely renders the invention obvious does not satisfy" the written description requirement. *Ariad*, 598 F.3d at 1352.

We therefore disagree with Idenix's characterization that "the specification plainly embraces the use of the [2'-fluoro-down] embodiment." Reply Br. 34. In light of the conspicuous absence of that compound, a POSA would not "visualize or recognize the members of the genus" as including 2'-fluoro-down, and the specification could not demonstrate to a POSA that the inventor had possession of that embodiment at the time of filing. *Ariad*, 598 F.3d at 1350.

V

For the foregoing reasons, we affirm the district court's grant of judgment as a matter of law that the '597 patent is invalid for lack of enablement. We reverse the district court's denial of judgment as a matter of law for failure to meet the written description requirement and hold that the '597 patent is invalid for lack of written description as well.

AFFIRMED-IN-PART AND REVERSED-IN-PART

COSTS

Costs to appellee.

United States Court of Appeals for the Federal Circuit

IDENIX PHARMACEUTICALS LLC, UNIVERSITA DEGLI STUDI DI CAGLIARI,
Plaintiffs-Appellants

v.

GILEAD SCIENCES INC.,
Defendant-Appellee

2018-1691

Appeal from the United States District Court for the District of Delaware in No. 1:14-cv-00846-LPS, Chief Judge Leonard P. Stark.

NEWMAN, *Circuit Judge*, dissenting.

I respectfully dissent. The court errs in holding that the specific narrow claims of the '597 patent are invalid. The large number of unclaimed chemical variants in the specification are not described, not synthesized, and not tested for antiviral activity. It is incorrect to include these variants in the claims and then to invalidate the claims because these variants are not described and not enabled.

The panel majority, overturning the jury verdict, finds the '597 claims invalid on the grounds of non-enablement and inadequate description. The majority finds that there are "billions and billions" of possible nucleosides in the omnibus specification. On this reasoning, the majority finds

invalid the narrow claims of the '597 patent. However, a reasonable jury could have understood the claims as directed to the nucleosides that are specifically described and that are shown to have the claimed antiviral activity. A reasonable jury could have credited the evidence that the '597 claims are for these specific compounds, not the "billions and billions" of unsynthesized and unevaluated variants in the specification. It is not disputed that the specific claimed compounds meet the requirements of 35 U.S.C. § 112. The jury verdict of validity must be viewed in light of the evidence and argument before the jury.

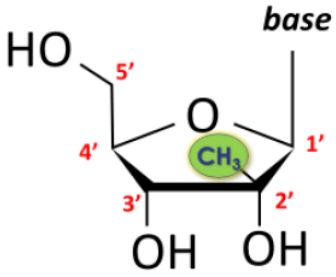
The majority's holding that validity under section 112 is determined based on whether unclaimed subject matter is described and enabled, provides a new path of uncertainty and unreliability of the patent grant. I respectfully dissent.

I

I write in concern for the majority's flawed theory of section 112, whereby the court requires description and enablement of the unclaimed and unsupported subject matter, in order to sustain validity of claims to the supported subject matter. A reasonable jury could have applied the jury instructions, in light of the patent document and the testimony of witnesses, to understand that the claims are for the subject matter that is produced and described and evaluated for antiviral activity. On the correct claim construction, a reasonable jury could have found the claimed subject matter to be described and enabled.

A reasonable jury could have understood that subject matter that is unclaimed is irrelevant to validity under section 112. With all respect to my colleagues, they err in holding that because "billions and billions" of nucleosides are within the specification but not characterized and not evaluated, the claims to the products that are synthesized and shown to have antiviral activity are invalid as "indefinite."

The jury could have found, as witnesses testified, that the claims are directed to the nucleosides that are synthesized as shown in the '597 specification, and shown to have antiviral efficacy. This is a narrow class of nucleosides, pictured as set forth in the briefs and in the majority's opinion:



Idenix Br. 8; Gilead Br. 8; Maj. Op. at 5.

The '597 specification is an omnibus disclosure of eighteen broad "Formulas" of nucleosides—variants that are untested, uncharacterized, and unclaimed. In contrast, only the above molecule is included in the patent Figures that report antiviral data. The specification describes Figures 2 and 3 as follows:

> FIG. **2** is a line graph of the pharmacokinetics (plasma concentrations) of ß-D-2'-CH_3-riboG administered to six Cynomolgus Monkeys over time after administration.
>
> FIGS. **3***a* and **3***b* are line graphs of the pharmacokinetics (plasma concentrations) of ß-D-2'-CH_3-riboG administered to Cynomolgus Monkeys either intravenously (**3***a*) or orally (**3***b*) over time after administration.

'597 patent, col. 15, ll. 31–38. Figure 1, captioned "Chemical Structure of Illustrative Nucleosides," presents the structures of eight nucleosides and two comparative compounds. '597 patent, col. 15, ll. 27–30 ("FIAU and Ribavirin, which are used as comparative examples"). All eight

nucleosides have the three OH groups in the positions and stereochemistry pictured above, and six of the eight structures in Figure 1 also have a methyl group in the 2'-up position as required by all the claims.

The jury was told by Dr. Meier, an expert witness for Idenix, that for all of the 2'-methyl-up nucleosides in Figure 1, "all of the compounds have hydroxide at the 2' down position." J.A. 37673 at 1859:25–1860:2. Dr. Secrist, an expert witness for Gilead, testified that the first four compounds in Figure 1 are ß-D-2'-methyl-ribofuranosyl nucleosides, stating "[a]ll of them have a 2' up methyl and a 2' down hydroxyl, yes, and they are ribonucleoside." J.A. 37638 at 1721:8–11.

My colleagues err in ruling that the claims cover "billions" of variants. The '597 specification recites a very large number of substituents for nucleosides that are not synthesized, not characterized, not evaluated, and not included in the claims. Some of these variants have been claimed in other patents and applications.[1] However, they are not claimed in the '597 patent. My colleagues err in holding that because other substituents and modifications

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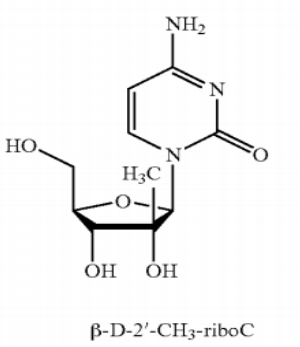
[1] At least nine additional patents and applications are reported to claim priority from this Provisional Application No. 60/206,585, *viz.* Patent No. 6,914,054 (claiming Formulas V, X, XI, XVI, XVII, and XVIII); Patent No. 7,169,766 (claiming Formula XVII); Application No. 10/602,142 (claiming Formulas X, XI, and XVII); Patent No. 7,157,441 (claiming Formulas II, X, XI, XVII); Patent No. 8,299,038 (claiming Formulas II and V); Application No. 13/623,674 (claiming Formulas X, XI, XVI, XVII, and XVIII); Patent No. 10,363,265 (claiming Formulas V and X); Application No. 13/953,687 (claiming Formula XI); Application No. 16/440,659. *See* USPTO's PAIR database at http://portal.uspto.gov/pair/PublicPair, tab "Continuity Data."

are mentioned in the specification, claims that do not include such variants are invalid on grounds of indefiniteness and lack of written description.

The broadest claim of the '597 patent is claim 1:

> 1. A method for the treatment of a hepatitis C virus infection, comprising administering an effective amount of a purine or pyrimidine ß-D-2'-methyl-ribofuranosyl nucleoside or a phosphate thereof, or a pharmaceutically acceptable salt or ester thereof.

'597 patent, col. 142, ll. 63–67. This nucleoside with pyrimidine base is pictured and labeled in the specification as follows:



β-D-2′-CH_3-riboC

'597 patent, col. 142, ll. 43–55. The specification provides pharmacologic data for the ß-D-2'-methyl-ribofuranosyl nucleosides of the claimed structure. The narrow scope exemplified in the specification cannot be reconciled with the majority's count of "billions and billions," Maj. Op. at 9; or "hundreds of millions," *id.*; or even "many, many thousands," *id.* at 12, of nucleosides covered by the claims.

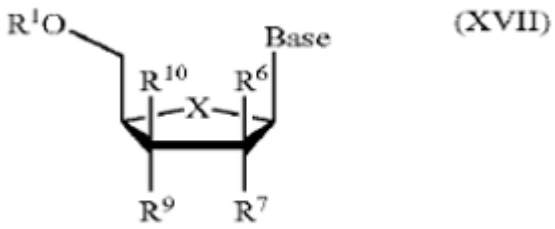
The jury was instructed that the claims define a patent's scope:

> The claims are important because it is the words of the claims that define what a patent covers. The claims are intended to define, in words, the

> boundaries of the invention that constitute the patent owner's property rights. The figures and text in the rest of the patent provide a description and/or examples of the invention and provide a context for the claims, but it is the claims that define the breadth of the patent's coverage. Each of the asserted claims must be considered individually.

J.A. 169; J.A. 37800 at 2068:17–25 (instructing the jury).

The panel majority discards this instruction, and reproduces in the majority opinion portions of the specification that relate to the other "Formulas" that are pictured in the specification and directed to other nucleosides, some of which are the subject of continuation patents and applications. *See* n.1, *ante*. For example, the majority presents the specification structure designated Formula XVII, which depicts, with "R" and "X" designations, a large number of substituents of the molecule:



(XVII)

Maj. Op. at 10–11 (citing '597 patent, col. 12, ll. 20–67). The majority states that the variants for Formula XVII are "more than 7,000." *Id.* at 12. However, a reasonable jury could have understood, as witnesses for both sides testified, that the only variants synthesized and evaluated in the '597 patent have the structure where R^1 is H, R^9 is OH, R^{10} is H, R^7 is OH, R^6 is CH_3, and X is oxygen.

The '597 patent was the subject of expert testimony throughout the two-week jury trial. The patent was given to the jury; *see* J.A. 170 ("[R]efer to the copy of the '597 patent that you have been given."). Following is a sampling of the expert testimony:

- Q. Is the difference between DNA and RNA at 2' down, so OH in RNA, the H in DNA, is that important to a nucleoside chemist in 2000-2001? A. Oh, yes. It is a critical distinction, of course. J.A. 37543 at 1568:9–12.
- Q. Now, you have depicted the treatment with an OH down at 2'. Is that correct? A. Yes. Q. Why did you do that? A. Well, it's – number one, you would expect, when you're making something – this is in the 2001 time frame, you would expect modified nucleotides to have that OH down because you want to be accepted by the machinery that makes that RNA virus. So you want to have that 2- down. J.A. 37544 at 1571:1–10.
- Q. [Discussing a 1998 publication concerning the enzymes] If you look at the end of the paragraph, it concludes with the statement that "These results indicate that the HCV enzyme has a strict specificity for ribonucleoside 5' triphosphates and requires the 2' and 3'-OH groups." . . . What does that mean with respect to this 2' position you and I have just been talking about? A. Well, as I have always maintained, the entire molecule, when you are making a drug, is absolutely critical. However, in the case of doing something for RNA, then having this 2' prime, for the reasons I talked about earlier, that's what the enzymes use, is really important. J.A. 37545 at 1574:16–1575:2.

- Q. In the patent, did you see, after reading it, any data on any other nucleoside that had something different at 2' down than the OH known as hydroxyl? A. No. J.A. 37548 at 1588:18–21.
- Q. What did these examples teach a skilled person to put at the 2' down position in a nucleoside? A. Well, if you are thinking about effective treatment of HCV, at best they teach that you would put an OH down at the 2' along with a methyl up at the 2 prime. J.A. 37548 at 1588:22–1589:1.
- Q. And is that teaching, OH down at 2', is that consistent or inconsistent with the conventional wisdom of nucleoside chemists at the time? A. Well, speaking as a nucleoside chemist at the time, I would have expected and certainly not been surprised by compounds identified that had 2' down hydroxyls. J.A. 37548 at 1589:4–9.
- Q. We talked about this, but . . . is there any antiviral data to guide the person of skill amongst the possibilities covered by that 2'-Beta-D-methyl-ribofuranosyl nucleoside? A. No. We heard about it before but there is no antiviral data in this patent application. J.A. 37549–50 at 1593:20–1594:1.
- Q. And even considering that other data, does that cover a lot of compounds or only a few? A. Well, it only covers the four compounds and they all have the 2' down OH only at this critical spot, 2' down. J.A. 37550 at 1594:2–5.
- Q. Let's turn to the making of the compound. What kind of guidance does the patent provide and what kind of compounds are actually – or

the patent teaches you can actually make? A. Well, it gives, I'll say, standard literature ways to make nucleosides that have 2' up methyl and a 2' or maybe even a 2' up alkyl and a 2' down OH. J.A. 37550 at 1594:6–12.

- Q. [Displaying the '597 patent] What are we looking at here, Dr. Secrist, at DDX-721, which excerpts the patent at column 48, lines 30 to page [sic] 49, line 5? A. This is one of two general schemes that are in the patent, and I won't go through it other than to note that you take a starting material, that you go through a whole series of steps, and you end up with a nucleoside with a down OH. J.A. 37550 at 1594:13–21.
- Q. And a 2'-methyl up? A. A 2'-methyl, or as you can sigh [sic] in ours, it could be another group up. J.A. 37550 at 1595:16–18.
- Q. What compound does the patent show being made in relation to the 2' position? A. Okay. It shows only compounds that have a 2' down hydroxyl group. J.A. 37550 at 1595:12–15.
- Q. Are there any other synthetic schemes, any other schemes in the patent that show something different at 2' down? A. No, just OH. J.A. 37550 at 1595:19–22.
- Q. Does the patent show any of these compounds being made at R7 other than 2' OH down? A. No. J.A. 37551 at 1598:10–12.
- Q. So Dr. De Francesco, we were just talking about your 2003 paper. We were talking about the phrase . . . Beta-D 2' methyl ribofuranosyl guanosine, and I think where we left off was that you were confirming that that phrasing describes the structure . . . that's a methyl up

> at the 2' position, OH or hydroxy down at the 2' and 3' position? A. Right. Correct. J.A. 37755 at 2001:19–2002:3.

There's much more, as the jury was informed concerning the chemical structure, the specification, and the claims. The verdict form was explicit as to the asserted claims and the burden of proof:

> [1] Has Gilead proven by clear and convincing evidence that each of the asserted claims of the '597 patent is invalid because the specification of the '597 patent does not enable the asserted claims?
>
> [2] Has Gilead proven by clear and convincing evidence that each of the asserted claims of the '597 patent is invalid because the specification of the '597 patent does not contain an adequate written description of the asserted claims?

J.A. 143. The jury answered "No" to both questions. *Id.*

The panel majority now discards the jury verdict, stating "the jury was not free to adopt a number lower than the many, many thousands of configurations identified as 'principal embodiment[s]' in the patent itself." Maj. Op. at 12 (alteration in original). However, the jury was not free to adopt an incorrect view of the patent, for almost all of the embodiments that the specification calls "principal embodiments" are for Formulas for which no synthesis and no evaluation data are provided in the '597 specification.

The panel majority makes no mention of the relation of the '597 claims to the Figures, the examples, and the data in the specification, holding only that the claims are invalid based on "billions and billions" of unclaimed nucleosides. Gilead's expert Dr. Secrist testified that the preferred subembodiments of Formula XVII "ends up with a total of five compounds":

> Q. To be fair, the patent does boil these formulas down a little bit down into something called preferred embodiments. Is that true? A. Absolutely, it does.
>
> Q. Can you explain, it is a term we haven't heard before, can you explain to the jury what your understanding of a preferred embodiment is? A. Well, you take—I will do my best. If you have this many compounds that you are starting with, a preferred embodiment would narrow it down by some means, usually by looking at data, to this many, in a more preferred embodiment similarly by some means, usually data would get down to this number of compounds. So you would go from here to here with preferred embodiments, usually based on seeing the data for compounds that are in these embodiments. . . .
>
> Q. If we go to [the '597 patent]. What are we looking at here, Dr. Secrist, from Column 32 of the patent, lines 42 to 59? A. On the right is the same structures, Roman Numeral XVII that we have already seen. Now we are looking at what's up and what's down at the 2' position. . . . I have suggested it is an important position. It is. What they show is a methyl up, you can see it, R6 is methyl in all cases and a hydroxyl down in all cases. This ends up with a total of five compounds.

J.A. 37554 at 1612:4–1613:7.

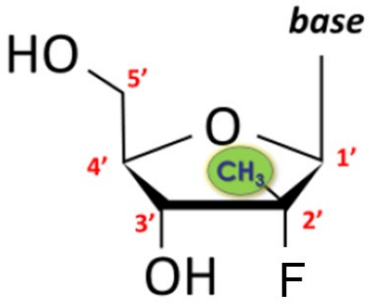
A patent specification must "contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112 para. 1. It was undisputed that the '597 specification did not describe and enable products other than those whose synthesis and antiviral properties were shown in the

specification, all of which had the narrow formula of three OH groups and a CH_3 group as pictured. A reasonable jury could have so viewed the claims. "Courts are not free to reweigh the evidence and set aside the jury verdict merely because the jury could have drawn different inferences or conclusions or because judges feel that other results are more reasonable." *Tennant v. Peoria & P.U. Ry. Co.*, 321 U.S. 29, 35 (1944).

Based on the evidence, a reasonable jury could have found that the claims are directed to the subject matter that was described and evaluated. "Our appellate role ends when there is shown to be substantial evidence, on the record as a whole, as could have been accepted by a reasonable jury as probative of the issue." *Nat'l Presto Indus., Inc. v. West Bend Co.*, 76 F.3d 1185, 1192 (Fed. Cir. 1996). My colleagues err in holding that the '597 claims are invalid unless the billons or millions or thousands of variants are synthesized and shown to have antiviral activity. The evidence could reasonably support a jury finding that the claims are of the scope that is described and enabled in conformity with section 112. From my colleagues' contrary ruling, I respectfully dissent.

II

The basis of this litigation is Idenix's complaint that the '597 patent is infringed by the Gilead product sofosbuvir, which has a fluorine substituent in the 2'-down position, as follows:



The issue in litigation was whether this product infringes the '597 claims. Gilead presented extensive testimony and argument on this question. For example, there was testimony that this product could not be made by the procedures in the '597 specification. There was testimony that an Idenix scientist had tried and failed to synthesize this fluorine-containing molecule. J.A. 37402–03 at 1178:2–1179:20. A witness testified that attaching fluorine to a nucleoside is "very tricky," for "it could lead to compounds that explode." J.A. 37279 at 836:12–837:1. There was testimony that it was known that 2'-F nucleosides were toxic. J.A. 37196 at 696:6–10, J.A. 37286 at 866:5–14, J.A. 37327 at 1030:7–22. There was testimony about stereochemical doubts that this molecule could be produced. J.A. 37314 at 976:22–977:13, J.A. 37319 at 998:6–999:23.

It is pointed out that fluorine is conspicuously omitted from the list of halogen substituents at 2'-down in several of the general "Formulas" in the '597 specification. Gilead Br. at 68–69 (citing '597 patent, col. 10, ll. 42–55, col. 12, ll. 5–12, col. 12, ll. 55–61). It is pointed out that Idenix lost an interference contest on this specific molecule. Gilead Br. at 1 (citing *Storer v. Clark*, 860 F.3d 1340 (Fed. Cir. 2017)).

The panel majority states that this aspect was "not advanced by Idenix at trial or before us." Maj. Op. at 7–8 n.3. However, Gilead did advance this aspect at trial, and argues it on this appeal. At the trial Gilead presented evidence with respect to the 2'-down fluorine substituent, as I have outlined, and on appeal Gilead devotes a substantial portion of its brief to the argument that its fluorinated compound is not within the scope of correctly construed claims. The issue was not waived, although the Supreme Court has recognized that even issues that were waived may be considered on appeal. The Court has explained:

> Nor did prudence oblige the Court of Appeals to treat the unasserted argument . . . as having been waived. . . . [A] court may consider an issue "antecedent to . . . and ultimately dispositive of" the dispute before it, even an issue the parties fail to identify and brief. . . . [A] court "need not render judgment on the basis of a rule of law . . . simply because the parties agree upon it."

U.S. Nat'l Bank of Or. v. Indep. Ins. Agents of Am., 508 U.S. 439, 447 (1993) (quoting *Arcadia v. Ohio Power Co.*, 498 U.S. 73, 77 (1990) and *United States v. Burke*, 504 U.S. 229, 246 (1992) (Scalia, J., concurring in judgment)).

The judicial responsibility and authority are to assure that the correct law is applied. Contrary to my colleagues' position, the Court admonishes that:

> Rules of practice and procedure are devised to promote the ends of justice, not to defeat them. A rigid and undeviating judicially declared practice under which courts of review would invariably and under all circumstances decline to consider all questions which had not previously been specifically urged would be out of harmony with this policy. Orderly rules of procedure do not require sacrifice of the rules of fundamental justice.

Hormel v. Helvering, 312 U.S. 552, 557 (1941); *see Singleton v. Wulff*, 428 U.S. 106, 121 (1976) ("The matter of what questions may be taken up and resolved for the first time on appeal is one left primarily to the discretion of the courts of appeals, to be exercised on the facts of individual cases. We announce no general rule.").

The Federal Circuit has so recognized. *See Wilson v. Principi*, 391 F.3d 1203, 1211 (Fed. Cir. 2004) ("The Court stated that such instances should be based on 'particular circumstances which will prompt a reviewing or appellate court, where injustice might otherwise result, to consider

questions of law which were neither pressed nor passed upon . . . below.' The matter is one left largely to the discretion of the court of appeals." (quoting *Hormel*, 312 U.S. at 557)). On appeal, our responsibility is to the law, and just conduct of the appeal.

There was substantial evidence that Gilead's fluorinated product is not within the scope of the claims as they reasonably could have been viewed by the jury. The jury verdict of validity under section 112 is in accordance with law and supported by substantial evidence. I would decide this appeal on the ground that the claims, correctly construed, are valid and not infringed. From my colleagues' contrary rulings, I respectfully dissent.