

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
BRECKENRIDGE PHARMACEUTICAL, INC., AND
ROXANE LABORATORIES, INC.,
Petitioners,

v.

NOVARTIS AG,
Patent Owner.

Case IPR2016-00084¹
Patent 5,665,772

Before LORA M. GREEN, CHRISTOPHER L. CRUMBLEY, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

CRUMBLEY, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318 and 37 C.F.R. § 42.73

¹ Breckenridge Pharmaceutical, Inc. was joined as a party to this proceeding via a Motion for Joinder in IPR2016-01023; Roxane Laboratories, Inc. was joined as a party via a Motion for Joinder in IPR2016-01102.

I. INTRODUCTION

In this *inter partes* review trial, instituted pursuant to 35 U.S.C. § 314, Petitioners Par Pharmaceutical, Inc., Breckenridge Pharmaceutical, Inc., and Roxane Laboratories, Inc. (collectively, “Par”) challenge the patentability of claims 1–3 and 8–10 of U.S. Patent No. 5,665,772 (“the ’772 patent,” Ex. 1001), owned by Novartis AG.

We have jurisdiction under 35 U.S.C. § 6(b). This Final Written Decision, issued pursuant to 35 U.S.C. § 318(a), addresses issues and arguments raised during trial. For the reasons discussed below, we determine that Par has not proven, by a preponderance of the evidence, that claims 1–3 and 8–10 of the ’772 patent are unpatentable.

A. Procedural History

On October 26, 2015, Par requested an *inter partes* review of claims 1–3 and 8–10 of the ’772 patent. Paper 2, “Pet.” Novartis filed a Patent Owner Preliminary Response. Paper 7. In a Decision on Institution of *Inter Partes* Review (Paper 8, “Dec. on Inst.”), we instituted trial as to claims 1–3 and 8–10 on the following grounds of unpatentability:

1. Whether claims 1–3 and 10 are unpatentable under 35 U.S.C. § 103(a) as having been obvious over Morris,² Van Duyne,³ Rossmann,⁴ Yalkowski,⁵ and Lemke⁶; and
2. Whether claims 8 and 9 are unpatentable under 35 U.S.C. § 103(a) as having been obvious over Morris, Van Duyne, Rossmann, Yalkowski, Lemke, and Hughes.⁷

Dec. on Inst. 18.

Novartis filed a Request for Rehearing of our decision to institute trial (Paper 10), which we denied (Paper 21).

Breckenridge filed a Petition and Motion for Joinder in IPR2016-01023, and Roxane filed a Petition and Motion for Joinder in IPR2016-01102. We granted Breckenridge's Motion and granted-in-part Roxane's Motion, and joined Breckenridge and Roxane as parties to this proceeding. Paper 37. We denied-in-part Roxane's Motion to the extent it sought to add

² Randall Ellis Morris, *Rapamycins: Antifungal, Antitumor, Antiproliferative, and Immunosuppressive Macrolides*, 6 TRANSPLANTATION REVIEWS 39-87 (1992) (Ex. 1005).

³ Gregory D. Van Duyne et al., *Atomic Structure of the Rapamycin Human Immunophilin FKBP-12 Complex*, 113 J. AM. CHEM. SOC'Y 7433–35 (1991) (Ex. 1006).

⁴ Michael G. Rossmann et al., *Three-Dimensional Coordinates from Stereodiagrams of Molecular Structures*, B36 ACTA CRYST. 819–823 (1980) (Ex. 1024).

⁵ Samuel H. Yalkowsky, *Estimation of Entropies of Fusion of Organic Compounds*, 18 INDUS. ENG'G CHEM. FUNDAM. 108–11 (1979) (Ex. 1007).

⁶ Thomas L. Lemke, *Chapter 16: Predicting Water Solubility*, REVIEW OF ORGANIC FUNCTIONAL GROUPS 113–21 (2d ed. 1988) (Ex. 1008).

⁷ U.S. Patent No. 5,233,036 to Hughes (Aug. 3, 1993) (Ex. 1009).

claim 7 of the '772 patent to the instituted trial, and also denied Par's Motion for Joinder in IPR2016-01059 and Breckenridge's Motion for Joinder in IPR2016-01103, both of which sought joinder of claim 7. *Id.* Par, Breckenridge, and Roxane filed requests for rehearing of these denials. IPR2016-01059, Paper 20; IPR2016-01102, Paper 19; IPR2016-01103, Paper 19. As set forth in a Decision entered today in the related cases, these requests for rehearing are moot in view of our determination herein that claim 1 has not been proven unpatentable.

Novartis filed a Patent Owner Response (Paper 27, "PO Resp."), and Par filed a Reply (Paper 46, "Pet. Reply").

Par supported its Petition with the Declaration of William L. Jorgensen, Ph.D. Ex. 1003. Novartis took cross-examination testimony of Dr. Jorgensen via deposition and submitted the transcript of that deposition. Ex. 2091.

With its Response, Novartis submitted three declarations: the Declaration of Alexander M. Klibanov (Ex. 2092); the Declaration of William R. Roush, Ph.D. (Ex. 2093); and the Declaration of Howard A. Burris, III, M.D. (Ex. 2095). Par cross-examined Novartis's experts via deposition, and submitted the transcripts. Exs. 1114 (Klibanov), 1115 (Roush), 1035 (Burris).

With its Reply, Par submitted a Supplemental Declaration of Dr. Jorgensen (Ex. 1118), and submitted the declaration testimony of a second witness, Mark J. Ratain, M.D. (Ex. 1119). Novartis took cross-examination testimony via deposition of Drs. Jorgensen and Ratain, and

submitted the transcripts to the Board. Exs. 2222 (Jorgensen), 2223 (Ratain).

Novartis filed separate Observations on the Cross-Examination of Drs. Jorgensen and Ratain (Papers 55, 57), and Par filed Responses to the Observations (Papers 58, 59).⁸ As authorized by the Board, Novartis also filed an Identification of Portions of Petitioner's Reply that allegedly exceed the proper scope of reply (Paper 63), and Par filed a Response to that list (Paper 65).

Novartis filed a Motion to Exclude various exhibits and papers submitted by Par (Paper 54, "Mot."), to which Par filed an Opposition (Paper 60) and Novartis filed a Reply (Paper 62).

Oral hearing was requested by both parties (Papers 51, 52), and argument before the Board was held February 2, 2017. A transcript of the oral hearing is included in the record. Paper 71, "Tr."⁹ Both parties filed

⁸ In its responses to Novartis' Observations, Par contends that by filing two, 15-page observations, Novartis has exceeded the Board's page limits. Paper 60, 2–3. We agree that our Scheduling Order only authorized a single filing of observations; thus, Novartis exceeded the page limit by 15 pages. Furthermore, as Par argues, Novartis' Observations are impermissibly argumentative because they characterize the witnesses' testimony rather than simply setting forth the testimony itself. Per our Trial Practice Guide, excessively long or argumentative observations may be refused entry. See 77 Fed. Reg. 48,756, 48,768. In view of Novartis' failure to comply with our rules, we have not considered the Observations in reaching our conclusions in this Decision.

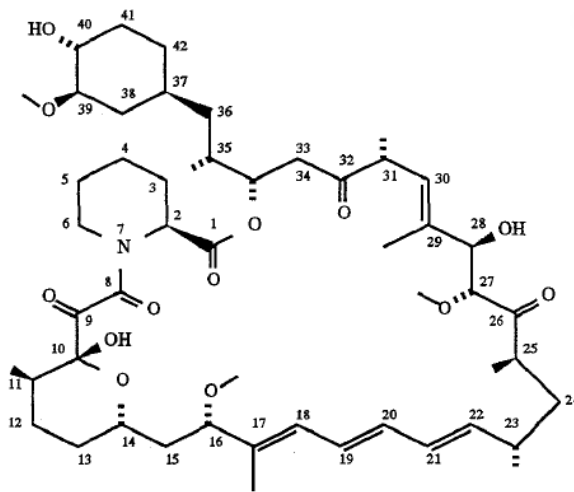
⁹ With the authorization of the Board, Novartis filed an Unopposed Notice of Transcription Error (Paper 72) regarding an alleged error on page 48 of the transcript.

with the Board demonstrative exhibits that were used during the oral hearing (Papers 68, 70), but in view of the parties' numerous objections to the exhibits (Papers 67, 69) and the fact that demonstratives are not evidence, the Board will expunge the demonstrative exhibits from the record.

B. The '772 Patent

The '772 patent, titled "O-alkylated Rapamycin Derivatives and Their Use, Particularly as Immunosuppressants," issued September 9, 1997, from U.S. Patent Application No. 08/416,673, filed on September 24, 1993. Ex. 1001, (54), (45), (21), (22). The patent is directed to derivatives of rapamycin, which are said to have pharmaceutical utility, particularly as immunosuppressants. Ex. 1001, Abstract.

Rapamycin is a known immunosuppressant having the following chemical structure:



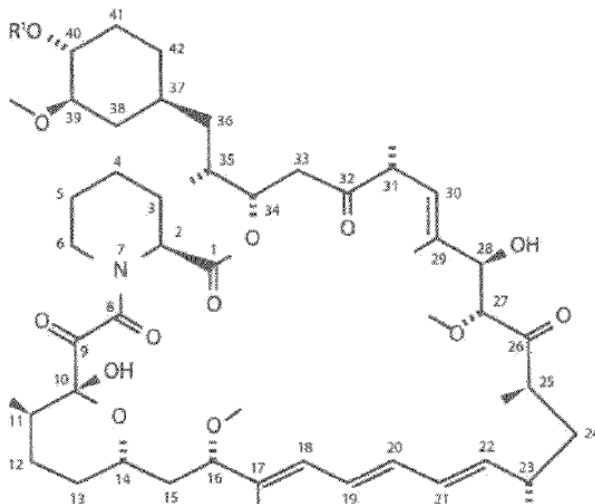
Id. at 1:15. The '772 patent discloses various derivatives of rapamycin, in particular alkylated derivatives having substitutions at the 9, 26, 28, 39, or 40 carbon. *Id.* at 1:50–2:19 (Formula I). Of these derivatives, the “preferred novel compounds” are the 40-O-substituted rapamycins. *Id.* at 2:55–56.

According to the '772 patent, the disclosed rapamycin derivatives are particularly useful for treatment and prevention of a range of conditions, including: organ or tissue transplant rejection; autoimmune disease and inflammatory conditions; asthma; multi-drug resistance; tumors; fungal infections; inflammation; infection; and overdoses of other immunosuppressants. *Id.* at 3:22–4:10. The preferred 40-O-substituted derivatives are said to be highly immunosuppressive and are particularly useful in treating transplant rejection or autoimmune disease. *Id.* at 4:21–25.

C. Illustrative Claim

Of the challenged claims, claim 1 is independent, and is reproduced below:

1. A compound of the formula:



wherein R¹ is hydroxy(C₁₋₆)alkyl or
hydroxy(C₁₋₃)alkoxy(C₁₋₃)alkyl.

Ex. 1001, 21:13–22:2.¹⁰

Claim 10 depends from claim 1 and is directed to a particular derivative of rapamycin, 40-O-(3-hydroxyethyl)-rapamycin, commonly called everolimus.

II. ANALYSIS

A. Claim Construction

For purposes of our Decision on Institution, we noted that neither party asked that we construe any term used in the challenged claims, and we agreed that no terms required an express construction. Dec. on Inst. 7. During the instituted trial, neither party disagreed with this assessment, and we again see no need to provide an express construction for any of the terms in the challenged claims.

B. Par's Theory of the Case

Par contends that claims 1–3 and 10 are unpatentable under 35 U.S.C. § 103(a), as their subject matter would have been obvious over the combined disclosures of Morris, Van Duyne, Rossmann, Yalkowski, and Lemke. Pet. 40–48. Par explains how the combined references teach the subject matter of each challenged claim and asserts that a person of ordinary skill in the art would have had reason to combine or modify the references. *Id.* Par also relies upon the Declaration of Dr. William Jorgensen (Ex. 1003) to support its positions.

¹⁰ The chemical formula of claim 1 was corrected in a Certificate of Correction dated February 9, 2016.

In our Decision on Institution, we summarized the cited prior art and then Par's theory of the case, which is based on a lead compound analysis. For completeness, we repeat those summaries below.

1. Summary of the Prior Art

Morris is a review of the research into rapamycin, "written relatively early in the research life of [rapamycin]." Ex. 1005, 41. Rapamycin is said to be "particularly intriguing because it inhibits the activation of immune cells by unique, relatively selective, and extremely potent and highly effective mechanisms." *Id.* at 39. Morris reports that while water soluble prodrugs of rapamycin have been synthesized, rapamycin itself is only minimally soluble in water, at 20 µg/mL. *Id.* at 46. Furthermore, Morris states that the toxicity of rapamycin is "not known," but that mice and rats appear to be very resistant to acute toxic effects of the drug. *Id.* at 49. Large animals were found to be more susceptible to toxic effects. *Id.* at 50–51. Nevertheless, Morris concludes that rapamycin and other new immunosuppressants "enable combination immunosuppressive therapy to reach new levels of sophistication" and "offer the hope that rejection can be prevented and treated more effectively and safely than ever before." *Id.* at 82.

Van Duyne is a study of the atomic structure of the complex of rapamycin and FKBP-12, the immunophilin to which rapamycin binds. Ex. 1006, 7433. Van Duyne contains a stereodiagram of the alpha-carbon structure of the rapamycin/FKBP-12 complex, and discloses that rapamycin binds in a cavity in the FKBP-12 protein. *Id.* at 7433–34. The interface is said to involve atoms from rapamycin's pyranose ring through the C28

hydroxyl, but also involves two additional hydrogen bonds, one being at the C40 hydroxyl. *Id.* at 7434. Van Duyne states that coordinates of the bound rapamycin complex are available from its authors, and will be deposited in the Brookhaven Protein Databank. *Id.*

Rossmann discloses a method of deriving three-dimensional coordinates from stereodiagrams of molecular architecture. Ex. 1024, 819. Rossmann notes that many publications provide stereodiagrams of proteins and nucleic acids, but do not provide coordinates for the structure which would permit quantitative use of the published structural data. *Id.*

Yalkowski discusses the estimation of the entropy of fusion for drugs and molecules of intermediate size. Ex. 1007, 108. Longer chains are said to contribute to internal entropy by $2.5(n - 5)$ eu, where n is the number of atoms in the chain. *Id.* at 111. Dr. Jorgensen testifies that this means that “each added rotatable bond is worth approximately 2.5 eu (cal/mol-K), which translates to a favorable contribution of $(298 \times 2.5 \times 0.001) = 0.745$ kcal/mol to the free energy of fusion. Based on fundamental thermodynamics of equilibrium ($\Delta G = -2.3RT \log K$), each 1.3 kcal/mol provides a factor of 10 change in an equilibrium process such as solubility.” Ex. 1003 ¶ 79.

Lemke provides a summary of the solubilizing potential of various functional groups in Table 16–1. Ex. 1008, 115–16. For example, in a polyfunctional molecule, an alcohol group is said to have the potential to solubilize 3–4 carbons, while an amine group may solubilize 3 carbons. *Id.*

2. *Par's Lead Compound Analysis*

To support its contention of obviousness, Par sets forth a “lead compound analysis” explaining how a person of ordinary skill in the art would have modified rapamycin to arrive at everolimus, the compound recited in claim 10 of the ’772 patent. Pet. 40. A lead compound analysis follows a two-part inquiry. First, we “determine[] whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). A compound may be considered a candidate “lead compound” if it is “most promising to modify in order to improve upon its . . . activity,” or “a natural choice for further development efforts.” *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007); *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). The question of whether a person of ordinary skill in the art would have selected a compound as a lead compound is “guided by evidence of the compound’s pertinent properties.” *Otsuka*, 678 F.3d at 1292.

Once it is determined that a person of ordinary skill in the art would have selected a particular lead compound, the second part of the analysis asks whether the artisan would have had reason to modify the lead compound to make the claimed compound, with a reasonable expectation of success. *Id.*

Par’s proposed lead compound analysis may be summarized as follows. First, Par contends that a person of ordinary skill in the art would have selected rapamycin as a lead compound for developing improved

immunosuppressants. Pet. 26. As support, Par cites Morris' disclosure of rapamycin's "potent immunosuppressant activities," as well as its description of rapamycin as "particularly intriguing." *Id.* (citing Ex. 1005, 39–42). Dr. Jorgensen testifies in support of this contention, also citing Van Duyne's disclosure of the structure of rapamycin bound to FKBP-12, opining that this would have given the person of ordinary skill in the art further reason to select rapamycin as lead compound. Ex. 1003 ¶¶ 132–137.

Par notes, however, that rapamycin was known to have low solubility, and that this would have been understood to limit the bioavailability of the drug. Pet. 41 (citing Ex. 1005, 46; Ex. 1003 ¶¶ 138–140). Par contends that a person of ordinary skill in the art would have had reason to modify rapamycin's solubility to increase its bioavailability. *Id.* at 41–42.

Having selected rapamycin as a lead compound that might benefit from modification, Par alleges a person of ordinary skill in the art would have turned to Van Duyne's disclosure of the structure of rapamycin bound to the FKBP-12 protein, to understand the interaction of the drug with its known biological targets. *Id.* at 42. Dr. Jorgensen testifies that the skilled artisan would have first looked to rapamycin's hydroxyl groups located at C10, C28, and C40 as potential sites for substitution. Ex. 1003 ¶ 142. Van Duyne allegedly discloses that rapamycin's C40 carbon is located on the periphery of the binding with FKBP-12, whereas C10 and C28 are part of the binding domain. *Id.* ¶¶ 143–144; Ex. 1006, 7434.

Par contends the skilled artisan would have used the method of Rossmann to convert Van Duyne's stereograms into the alpha-carbon structural coordinates of the rapamycin/FKBP-12 complex, which would

have further confirmed the potential of C40 as a site for substitution. Pet. 43–44. Dr. Jorgensen goes further, stating that the coordinates of the full structure of the rapamycin/FKBP-12 complex could have been obtained by contacting the authors of Van Duyne, and a person of ordinary skill in the art could have constructed a full three-dimensional model of the complex using known computer models. Ex. 1003 ¶¶ 113–14. From these models, Dr. Jorgensen concludes, the skilled artisan would have confirmed the suitability of C40 as a potential site for substitution. *Id.* ¶¶ 115–20.

Finally, Par argues that a person of ordinary skill in the art would have looked to Yalkowski and Lemke to determine which substitutions to make at C40, and would have ultimately decided to attempt introduction of a flexible side chain containing an alcohol, amine, or carboxylic acid group. Pet. 44–47. Dr. Jorgensen testifies that small substituents would have been attempted first, therefore, the skilled artisan would have selected three initial candidates: the 2-hydroxyethoxy group (OCH₂CH₂OH), the 2-aminoethoxy group (OCH₂CH₂NH₂), and the carboxymethoxy group (OCH₂COOH). Ex. 1003 ¶¶ 150–53. Par notes that rapamycin modified to include a 2-hydroxyethoxy group at C40 is the particular derivative claimed in claim 10, 40-O-(2-hydroxyethyl)-rapamycin (everolimus). Pet. 48. Because this compound falls within the scope of claims 1–3 as well, Par asserts that this lead compound analysis demonstrates the obviousness of claims 1–3 and 10. *Id.*

3. *The Level of Ordinary Skill in the Art*

Par contends, supported by the testimony of Dr. Jorgensen, that a person of ordinary skill in the art at the time of the invention would

generally have a Ph.D. in organic chemistry or medicinal chemistry or physical chemistry or a related field, or a Masters or Bachelor degree in chemistry or a related field and at least three years' experience in drug discovery and design. Pet. 16 (citing Ex. 1003 ¶ 45). Novartis' experts, with insubstantial exceptions, agree with Dr. Jorgensen's recitation. Ex. 2092 ¶ 22 (Klibanov); Ex. 2093 ¶¶ 47–48 (Roush). We adopt the level of skill recited by the parties for purposes of our analysis herein.

C. The Parties' Factual Disputes

During the instituted trial, the parties disputed facts relevant to almost every stage of Par's proposed lead compound analysis. We resolve these factual disputes below, before turning to the question of obviousness.

1. Selection of Rapamycin as Lead Compound

Novartis first challenges Par's contention that a person of ordinary skill in the art would have selected rapamycin as a lead compound for developing improved immunosuppressants. PO Resp. 47–50. Novartis argues that, as evidenced by the totality of the prior art, as of October 1992 there were a number of known, promising immunosuppressants. *Id.* at 48 (citing Ex. 2001, 61 (cyclosporin A), Ex. 1012, 283 (tacrolimus), Ex. 2023, 517–18 (mycophenolate mofetil)). Some of these other compounds were reported to have effectiveness without major adverse effects, whereas rapamycin was known to be toxic. *Id.* Novartis argues that Par failed to provide any advantageous properties of rapamycin that would have led to its selection over these other compounds, other than its hindsight-based similarity to the claimed compound everolimus. *Id.* at 49–50.

Par responds that the law does not require it to identify the single most promising lead compound. Pet. Reply 3 (citing *Daiichi Sankyo v. Matrix Labs.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010)). Rather, rapamycin would have been among the group of lead compounds that a person of ordinary skill would have targeted for investigation, Par argues, because of rapamycin's known potency. *Id.* at 4. As evidence supporting this selection, Par notes that rapamycin's potency was known to be "greater than FK506 [tacrolimus] and much greater than CsA [cyclosporin A]." *Id.* (quoting Ex. 1005, 55). Citing the testimony of Novartis' expert Dr. Roush, Par also observes that researchers in the field were actually studying modifications to rapamycin during the relevant timeframe, further evidencing its potential as a lead compound. *Id.* (citing Ex. 2092 ¶¶ 63–83).

Upon review of the record, we find that the evidence supports Par's contention that a person of ordinary skill in the art would have recognized the potency of rapamycin and its potential for development of new immunosuppressant. Indeed, this known potency is recognized in the '772 patent's discussion of the prior art, stating that the "known macrolide antibiotic" rapamycin "is an extremely potent immunosuppressant." Ex. 1001, 1:10–35. We also find it relevant that others in the field were working to modify rapamycin, as Novartis' expert acknowledged. Ex. 2029 ¶¶ 63–83; *see also* Ex. 1005 (describing rapamycin as "particularly intriguing"). The fact that other immunosuppressants have other beneficial characteristics such as lower toxicity does not convince us that a person of ordinary skill in the art would only investigate those compounds, ruling out rapamycin entirely.

That said, it is relevant to the lead compound analysis that rapamycin was only one of several known immunosuppressants, each of which had relative strengths and weaknesses. We find that a skilled researcher would have investigated rapamycin as a lead compound, but not to the exclusion of these other immunosuppressants.

2. Rationale to Modify Rapamycin to Increase Solubility

Having selected rapamycin as a lead compound, Par next contends that a person of ordinary skill in the art would have had reason to modify rapamycin in order to increase its solubility, and thus its bioavailability as a drug. Pet. 41–42. As support for this contention, Par observes that Morris reported rapamycin as being “only minimally soluble in water.” Ex. 1005, 46. Dr. Jorgensen, Par’s expert, testifies that because “[a]queous solubility of a molecule influences its absorption in animals,” a skilled artisan would have recognized that improving the solubility of a poorly soluble drug would increase its bioavailability. Ex. 1003 ¶ 140. In turn, Dr. Jorgensen testifies, this increased bioavailability would allow lower doses of the drug to be administered, and allow the drug to be administered via oral administration. *Id.*

Novartis contends that a person of ordinary skill in the art in 1992 would not have had reason to attempt to increase rapamycin’s solubility. PO Resp. 51–52. According to Novartis, the prior art does not reflect any belief that rapamycin’s water solubility was problematically low, or that its bioavailability needed to be increased. *Id.* Novartis also cites the trial testimony of Dr. Partridge, Par’s expert in a copending District Court

action¹¹ involving the '772 patent, who agreed that as of October 1992 rapamycin was “water soluble enough” to be used as an immunosuppressant and that it was not necessary to modify rapamycin for its immunosuppressant activity “to be realized.” Ex. 2107, 228:24–229:11.

Alternatively, even if there existed a reason to increase the solubility of rapamycin in October 1992, Novartis argues, a person of ordinary skill in the art had other known ways of increasing solubility other than modifying the molecule itself. PO Resp. 53–55. For example, known techniques for improving water solubility at the time included formulation approaches such as reduced particle size or surfactants, the creation of prodrugs, and water-soluble salts. *Id.* (citing Ex. 2092 ¶¶ 157–159 (formulation), ¶¶ 161–170 (prodrugs), ¶¶ 171–173 (water-soluble salts)). Novartis argues that each of these techniques would have been preferred over synthesizing a new derivative of rapamycin, because they would have had a better chance at maintaining the drug’s activity and would have been seen as “safer” than the “risky and uncertain” derivatives approach. *Id.* (quoting *Janssen Pharm. N.V. v. Mylan Pharms., Inc.*, 456 F. Supp. 2d 644, 666–67 (D.N.J. 2006)).

Par responds to Novartis’ first argument by noting that the insolubility of rapamycin was a recognized problem in the art (Pet. Reply 6 (citing Ex. 1034, 116), and that even if it were not explicitly recognized, a person of ordinary skill in the art would have understood the benefits of increased

¹¹ *Novartis Pharm. Corp. et al. v. Par Pharm., Inc.*, No. 14-1289-RGA (D. Del.). Trial was consolidated with *Novartis Pharm. Corp. et al. v. Breckenridge Pharm., Inc.*, No. 14-1043-RGA (D. Del.) and *Novartis Pharm. Corp. et al. v. Roxane Labs., Inc.*, No. 14-1196-RGA (D. Del.), and held on August 29–September 1, 2016.

bioavailability that could be achieved through increased solubility. *Id.* at 5 (citing Ex. 1118 ¶¶ 25–26). Furthermore, Par contends, the fact that rapamycin was “soluble enough” to be used as an immunosuppressant does not mean that a person of ordinary skill in the art would not have tried to increase that solubility. *Id.*

To Novartis’ second argument, Par responds that other approaches to increasing solubility, “while legitimate avenues for research, [] pose particular challenges of their own.” *Id.* at 7. For example, Par notes that formulation approaches carried risks such as increased toxicity (*id.* at 6 (citing Ex. 1034, 116)), while prodrugs require metabolic conversion and create the potential for inter- and intra-subject variability (*id.* at 7).

We agree with Par on both counts. The record supports the conclusion that a person of ordinary skill in the art would have had reason to increase the solubility of the “minimally soluble” rapamycin, and one possible strategy to do so would be to create a derivative of the compound. For example, the Stella¹² patent recognized that “there is a need in the art for a rapamycin derivative or prodrug which is relatively soluble in water so as to form a safe and injectable solution and which is as effective as rapamycin in the treatment of tumors.” Ex. 1010, 1:25–30. Par is correct in noting that a method selected to address a known problem need not be “the *best* option, only . . . a *suitable* option from which the prior art did not teach away.” *Par Pharm. v. TWi Pharm.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014). The fact that a derivative approach is “risky and uncertain,” and had known

¹² U.S. Patent No. 4,650,803 to Stella et al. (Mar. 17, 1987) (Ex. 1010).

disadvantages such as potential reduction in immunosuppressant activity, is not sufficient to convince us that the art taught away from such approaches. Rather, the record supports the conclusion that *all* experimental approaches had potential benefits and drawbacks; indeed, this is inherent in the pursuit of scientific study. Alternative approaches, such as prodrugs or water-soluble salts, were not so clearly better than derivative synthesis that a person of ordinary skill in the art would have ruled out the latter.¹³ By the same token, however, we note that the derivatives approach was not clearly better than the alternatives Novartis raises; it was merely one of many possible approaches. This is certainly relevant to the obviousness analysis, which will be discussed below.

3. Reasonable Expectation of Success in Making the Modification

Next, Novartis contends that even if a person of ordinary skill in the art in October 1992 would have had reason to modify rapamycin, there would have been no reasonable expectation of success in doing so. “The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). Novartis argues that there must also be a “reasonable expectation of success in achieving *the actual combination of properties that the claimed compound possesses.*” PO. Resp. 56 (emphasis

¹³ At oral argument, Novartis’ counsel conceded that, “certainly[,] one of ordinary skill would consider making derivatives as one particular option.” Tr. 64:1–3.

in original). Because the record does not support the conclusion that a person of ordinary skill in the art would have expected “everolimus’ unique combination of properties, including immunosuppressant and antitumor activity,” Novartis contends the obviousness ground must fail. *Id.* at 56–60.

Alternatively, even if our analysis is more narrowly focused on the solubility of the compound, Novartis argues there would have been no reasonable expectation of success. *Id.* at 29–30. According to Novartis, Par does not identify the degree of improved solubility or bioavailability that would have been considered a “success.” *Id.* at 30–31

Par responds first by asserting that the law does not require that a person of skill in the art anticipate all properties of the claimed compound to have a reasonable expectation of success. Pet. Reply 17. Novartis’ argument, Par contends, confuses the reasonable expectation of success with the secondary consideration of unexpected results. *Id.* at 17–18 (citing *Bristol-Myers Squibb v. Teva Pharm. USA*, 752 F.3d 967, 976 (Fed. Cir. 2014)).

Par is correct; the law does not require that a person of ordinary skill have a reasonable expectation of success in achieving a compound with *all* the properties of the claimed compound. Rather, as the Federal Circuit noted, it is the *limitations of the claims* themselves that define the reasonable expectation of success. See *Intelligent Bio-Sys.*, 821 F.3d at 1367 (referring to the “likelihood of success in combining references *to meet the limitations of the claimed invention*” (emphasis added)). Put differently, “one must have a motivation to combine accompanied by a reasonable expectation of *achieving what is claimed in the patent-at-issue.*” *Id.*

The cases cited by Novartis do not compel a contrary result. *In re Rosuvastatin*, 703 F.3d 511 (Fed. Cir. 2012), noted that at trial, the plaintiffs had “argued that the prior art provided no suggestion of rosuvastatin’s unexpectedly superior properties,” but the Federal Circuit did not rely on this argument as a basis for affirming the trial court’s conclusion of nonobviousness. *Id.* at 517–518. The Federal Circuit in *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000) defined success as “finding a compound that had high activity, few side effects, and lacked toxicity.” *Id.* at 1345. But this conclusion was guided by the particular facts of the case, which evidenced that during the relevant timeframe, “drug manufacturers searched for H₂ antagonists with improved pharmacological properties, including low toxicity, high activity, and lack of side effects.” *Id.* at 1341. In the present case, the motivation to modify rapamycin asserted by Par is increasing solubility, not to achieving previously-unknown properties such as antitumor activity, as Novartis alleges. As noted in *Bristol-Myers Squibb*, “additional unexpected properties [of the claimed compound] did not upset an already established motivation to modify a prior art compound based on the expected properties. . . . Rather, as secondary considerations of nonobviousness, they come into play in determining ‘the ultimate question of patentability.’” 752 F.3d at 976.

The relevant question on reasonable expectation of success is defined by the reason to modify or combine the prior art advanced by Par, which is to improve the bioavailability of rapamycin by increasing solubility. We must determine whether a person of ordinary skill in the art would have had

a reasonable expectation of success in increasing the solubility of rapamycin. We find that the record supports such a conclusion. Par was not required to specify a particular degree of solubility improvement that would be considered a “success.” We credit Dr. Jorgensen’s testimony that solubility improvements are context-dependent (Ex. 2091, 167:2–23), that “moderate increases in rapamycin’s solubility would significantly improve its utility as a pharmaceutical” (Ex. 1003 ¶ 76), and that a person of skill in the art would be able to determine through experimentation the degree of solubility that would improve usage in assays or oral dosage (Ex. 2091, 187:2–188:15). The reasonable expectation of success is not absolute, and does not require a guarantee of success. *See Pfizer v. Apotex*, 480 F.3d 1348, 1364 (Fed. Cir. 2007).

4. Selection of C40 as the Substitution Site

Par contends that, having selected rapamycin as a lead compound that might benefit from modification, the skilled artisan would have determined that the C40 carbon of rapamycin held the most potential as a substitution site. Pet. 42–44. Dr. Jorgensen testifies that hydroxyl groups have high potential for substitution because their reactions are “fundamental and elementary,” and notes that rapamycin has hydroxyl groups located at its C10, C28, and C40 positions. Ex. 1003 ¶ 142.

Because the activity of rapamycin was known to derive from its binding to the FKBP-12 protein (Ex. 1006, 7433), Par asserts that a person of ordinary skill would have attempted to avoid substitutions that would interfere with the binding region to FKBP-12. Pet. 42; Ex. 1003 ¶ 141. Relying on Van Duyne, Dr. Jorgensen notes that the C10 and C28 hydroxyl

groups are in the binding domain, whereas C40 is peripheral to the binding interactions, and therefore the C40 carbon would therefore be the “optimal position for modification of rapamycin.” Ex. 1003 ¶ 112.

Novartis disputes that a person of ordinary skill in the art would have had reason to single out the C40 carbon for substitution, observing that the large rapamycin molecule has a number of potential substitution sites and there was no reason to choose C40 over the other positions. PO Resp. 55–56. According to Novartis, the prior art as of October 1992 contained multiple references that showed substitutions at the C9, C26, C27, C28, and C32 carbons. *Id.* Novartis relies on the testimony of Dr. Roush, who testifies that Dr. Jorgensen’s focus on only hydroxyl groups is inconsistent with the prior art as a whole. Ex. 2093 ¶ 197. In addition, Dr. Roush disputes Dr. Jorgensen’s testimony that the C40 carbon is outside the binding domain of FKBP-12, and that if a person of ordinary skill in the art would have avoided the C10 and C28 hydroxyl groups, they would have also avoided the C40 hydroxyl. *Id.* ¶ 202–203. Finally, Dr. Roush surveys the prior art, and discusses a number of contemporaneous patents that reported modifications to rapamycin at locations other than C40, but still retained immunosuppressant activity. *Id.* ¶¶ 206–216.

In reply, Par maintains that the C40 hydroxyl group would have been the preferred position for modification of rapamycin, relying on Dr. Jorgensen’s testimony. Pet. Reply 8–9. While Par concedes that modifications at other positions were possible, it argues that the person of ordinary skill in the art would not have started at those positions because they would not have been understood to be more likely to result in an active

rapamycin derivative. *Id.* Par also notes that Dr. Roush's survey demonstrates that rapamycin modified at C40 retains more immunosuppressant activity than modifications at other positions. *Id.* Dr. Jorgensen responds that, although rapamycin's C40 may be in the binding region with FKBP-12, it is on the periphery and therefore less likely to interfere with activity than C10 or C28. Ex. 1118 ¶ 55.

Based on our review of the entirety of the record, we cannot conclude, as Par contends, that the C40 hydroxyl group would be the obvious, optimal, or preferred location for substitutions to rapamycin. Dr. Jorgensen's testimony to that effect is premised on his assertion that a person of ordinary skill in the art would have first narrowed the group of possible substitution positions to the C10, C28, or C40, because those are the hydroxyl groups of rapamycin. Ex. 1003 ¶ 142 ("person of ordinary skill in the art would have focused on hydroxyl groups on rapamycin as initial targets for modification."). This statement, however, is based only on Dr. Jorgensen's statement that the reactions of hydroxyl groups are "among the most fundamental and elementary reactions taught in beginning organic chemistry courses." *Id.* Dr. Jorgensen provides no objective, documentary evidence that would indicate that starting with hydroxyl groups was an accepted rule followed by medicinal chemists in the field.

To the contrary, Dr. Roush testifies that Dr. Jorgensen's focus on rapamycin's hydroxyl groups is inconsistent with the prior art as a whole, and provides multiple citations to the documentary evidence in the record supporting his testimony. Ex. 2093 ¶¶ 197, 206–216 (citing prior art modifications at the C9, C26, C27, C28, and C32 positions). For example,

Ondeyka¹⁴ discloses demethylation of the methoxy group at rapamycin's C29 position, while Caulfield¹⁵ discloses oxime substitutions at C32.¹⁶ We have weighed the testimony of Drs. Jorgensen and Roush on this point, and find Dr. Roush's to be the more credible. While we agree with Par that a person of ordinary skill in the art would have considered rapamycin's C40 position as a candidate for substitution, that site must be evaluated as one potential substitution site among many that were being modified in the field at the time of the invention.

5. Group of Substituents to be Considered

Turning from the site of the substitution to the substituent itself, Par contends that a person of ordinary skill in the art would have begun with a narrow genus of three potential substituents: the 2-hydroxyethoxy group (OCH₂CH₂OH), the 2-aminoethoxy group (OCH₂CH₂NH₂), and the carboxymethoxy group (OCH₂COOH). Pet. 47 (citing Ex. 1003 ¶ 153). Dr. Jorgensen arrives at this contention by citing the disclosures of Yalkowski and Lemke, which we summarized above. In his initial Declaration, Dr. Jorgensen testifies that Yalkowski "teaches that adding

¹⁴ U.S. Patent No. 5,091,389 to Ondeyka et al. (Feb. 25, 1992) (Ex. 2041).

¹⁵ U.S. Patent No. 5,023,264 to Caulfield et al. (Jun. 11, 1991) (Ex. 2117).

¹⁶ Dr. Jorgensen attempts to distinguish these references showing substitution at other positions as "not rapamycin derivatives with added substituents but rather . . . simply functional group changes" that "do not indicate that these positions would be able to accommodate added substituents." Ex. 1118 ¶ 54. But Caulfield, for example, shows added substituents, including Example 2 which shows substitution with a relatively large benzyl group. Ex. 2117, 6:42–57.

rotatable bonds provides a free energy benefit that favors dissolution of a molecule,” so the skilled artisan would attempt to add rotatable bonds to increase solubility. *Id.* ¶ 147. In particular, Dr. Jorgensen cites a passage of Yalkowski which teaches that, in his words, “each added rotatable bond is worth approximately 2.5 eu (cal/mol-K), which translates to a favorable contribution of $(298 \times 2.5 \times 0.001) = 0.745$ kcal/mol to the free energy of fusion.” *Id.* ¶ 79.

Dr. Jorgensen cites Lemke—and, in particular, Table 16-1 of Lemke, reproduced below—as teaching the substituents with the most solubilizing potential being the “alcohol (hydroxyl), phenol, amines, carboxylic acid, ester and amide groups.” *Id.* ¶ 148.

Table 16-1.
Water-Solubilizing Potential of Organic Functional Groups
When Present in a Mono- or Polyfunctional Molecule.
Water Solubility Is Defined As >1% Solubility.

Functional Group	Monofunctional Molecule	Polyfunctional Molecule
Alcohol	5 to 6 carbons	3 to 4 carbons
Phenol	6 to 7 carbons	3 to 4 carbons
Ether	4 to 5 carbons	2 carbons
Aldehyde	4 to 5 carbons	2 carbons
Ketone	5 to 6 carbons	2 carbons
Amine	6 to 7 carbons	3 carbons
Carboxylic Acid	5 to 6 carbons	3 carbons
Ester	6 carbons	3 carbons
Amide	6 carbons	2 to 3 carbons
Urea, Carbonate, Carbamate		2 carbons

Table 16-1 of Lemke, as highlighted by Dr. Jorgensen to show the substituents with the highest solubilizing potential.

Eliminating the larger substituents that might interfere with rapamycin's biological activity, as well as substituents that would hydrolyze or form dimers, Dr. Jorgensen is left with alcohols, amines, and carboxylic acids. *Id.* ¶ 149. Finally, Dr. Jorgensen asserts that:

When making substitutions at the C40 position, a person of ordinary skill in the art would be highly motivated to use relatively small substituents, because they recognized that, as a general rule, it is preferable to start with the smallest, simplest substitutions possible and to progress to larger groups, if needed. As the size of a modification increases so do the risks of metabolic difficulties and other side effects. Further, a person of ordinary skill in the art would be aware that rapamycin is already unusually large for a pharmaceutical drug and, therefore, would have been additionally motivated to consider smaller substitutions so as to avoid further increases in molecular size.

Id. ¶ 150.

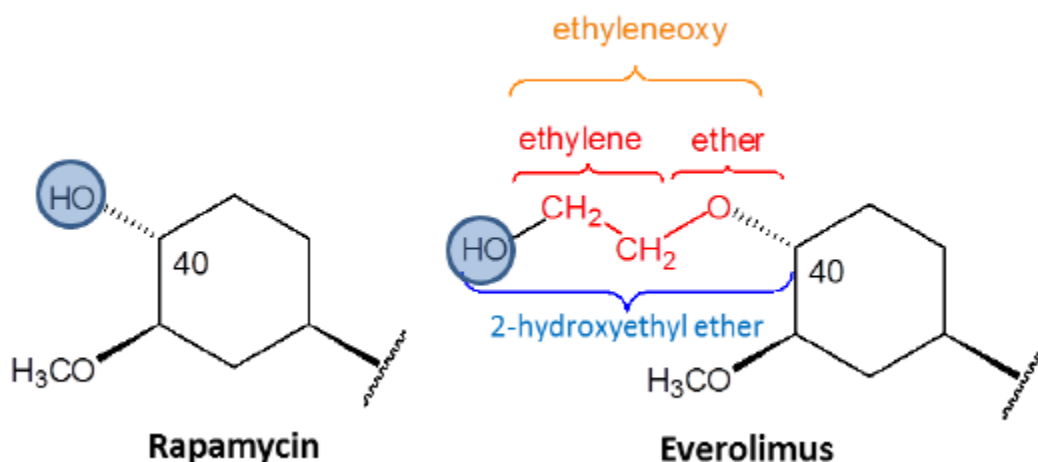
Combining the teachings of Yalkowski and Lemke, as well as this “general rule” of starting with the smallest possible substituents, Dr. Jorgensen derives a set of three potential substituents that have two alkyl carbons and an alcohol, amine, or carboxyl group. *Id.* ¶ 153.

Novartis focuses heavily on the disclosures of Yalkowski and Lemke, and raises a number of arguments in response. PO Resp. 7–31. We summarize several of the most persuasive. First, with respect to Yalkowski, Novartis observes that the reference does not state that “each added rotatable bond is worth approximately 2.5 eu,” as Dr. Jorgensen testifies, but rather that “[f]or longer chains we can estimate the contribution to internal entropy by adding $2.5(n - 5)$ eu, where n is the total number of chain atoms.” Ex. 1007, 111. According to Novartis, the side chain of everolimus at C40

is only four atoms long, therefore Yalkowski would predict no net change in internal entropy. PO Resp. 22–23.

At deposition, Dr. Jorgensen retreated from his reliance on the portion of Yalkowski that provides the “2.5 eu” figure in his original Declaration, and instead focused on Figure 2 of Yalkowski. Ex. 2091, 44:25–45:5 (“my use of [Yalkowski] is to point out Figure 2 in this very elementary concept in chemistry of the increase in entropy when molecules that include chains, flexible chains, are put in solution or melted.”), 86:2–3 (“the 2.5 is taken with a grain of salt.”). But as Novartis points out, Yalkowski describes Figure 2 as depicting “the change from the uniform conformation of flexible molecules of the crystal to the random conformation of such molecules in the liquid,” which is “not applicable to rigid molecules and thus to most drugs. It does become important, however, for long-chain molecules.” Ex. 1007, 109. For this reason, we find that this disclosure of Yalkowski has limited applicability to the proposed modifications to rapamycin Par proposes.

Second, Novartis observes that Table 16-1 of Lemke estimates the solubilizing potential of a functional group when it is added to a molecule, and that Dr. Jorgensen relies on the solubilizing potential of an additional hydroxyl group (listed in the Table as an alcohol). PO Resp. 7–8. But, as Novartis notes, the difference between rapamycin and everolimus is not an additional hydroxyl group, as both have the same number of hydroxyl groups; rather, everolimus differs from rapamycin by an ethyleneoxy group, as depicted below:



Id. at 8. Reading Table 16-1 of Lemke, Novartis argues that such a modification would have been expected to have no net effect on solubility of the molecule. *Id.* at 9–10. Dr. Klibanov testifies that if a person of ordinary skill in the art were indeed focused on adding a hydroxyl group as Dr. Jorgensen contends, then molecules other than everolimus would have been the result. Ex. 2092 ¶¶ 39–40.

Again, at his deposition, Dr. Jorgensen modified his reliance on Lemke, no longer focusing on the quantitative disclosures of Table 16-1. Instead, Dr. Jorgensen stated that “Lemke is not something I . . . would turn to, to try to make some quantitative estimate,” but rather that “what Lemke is doing is simply restating this notion that to improve solubility, you want to add [nitrogen] and [oxygen].” Ex. 2091, 95:10–12, 23–25; *see also id.* at 99:14–19 (“Table 16.1 . . . would simply confirm the medicinal chemist’s fundamental knowledge that, as we’ve discussed, adding nitrogens and oxygen are a good thing if you’re trying to improve solubility.”). This testimony is far more generalized than Dr. Jorgensen’s original Declaration, which stated that Lemke teaches, for example, that “hydroxyl (alcohol)

groups have the potential to solubilize 3 to 4 carbons.” Ex. 1003 ¶ 82. Indeed, Dr. Jorgensen made his initial selection of potential substituents from Table 16-1 of Lemke based on the ones with the highest quantitative solubilizing potential. *Id.* ¶¶ 148–149.

Finally, Novartis contests Par’s reliance on Dr. Jorgensen’s “general rule” that a person of ordinary skill in the art would start with the “smallest, simplest substitutions possible.” PO Resp. 31–32 (citing Ex. 1003 ¶¶ 149–150). Novartis points out that Dr. Jorgensen provides no support for this general rule. *Id.* Furthermore, Dr. Roush disputes that any such general rule existed, and testifies that even if it did, the rule would not be applicable to modifications to rapamycin in view of the other, specific disclosures of the prior art. Ex. 2093 ¶ 63. To that end, Dr. Roush points to a number of contemporaneous references that teach modification of rapamycin at the C40 position through the addition of rather large substituents, some exceeding 10 atoms in length. *Id.* ¶¶ 64–78. Dr. Jorgensen responds that while some of these derivatives with large substitutions retained activity, a skilled artisan would have still chosen to make small modifications *first* because they carry less risk of interfering with activity. Ex. 1118 ¶ 11.¹⁷

¹⁷ At oral argument, Par’s counsel also attempted to distinguish the examples of large substituents cited by Dr. Roush as involving prodrugs, which because they are intended to be cleaved raise less concerns regarding the size of the substituent interfering with activity. Tr. 16:12–17:11. Dr. Jorgensen does not cite this distinction, and it does not appear to be supported in the record elsewhere. Therefore, it is unsupported attorney argument, and we consider it accordingly. In any event, the Hughes and Scheiser references, cited by Dr. Jorgensen as examples of “modifications to the C40 position [that] resulted in rapamycin derivatives” (Ex. 1003 ¶ 65),

After reviewing the record, and in particular Dr. Jorgensen's testimony regarding Yalkowski and Lemke, it is clear that Petitioner's arguments regarding these references shifted focus during trial. At the outset, Dr. Jorgensen's testimony was based on quantitative aspects of both references, which he used to narrow down the group of potential substituents to a very small set of three. See Ex. 1003 ¶ 153 ("the smallest flexible carbon linker a person of ordinary skill in the art would first consider using in order to add the alcohol and amine substituents taught by Lemke and the rotatable bonds taught by Yalkowsky would be two alkyl carbons (CH₂CH₂)"). In response to Novartis' arguments, however, Petitioner's arguments and Dr. Jorgensen's testimony changed to something less rigid and more holistic. See Pet. Reply 10 ("Lemke and Yalkowsky *together* taught that adding flexible side chains (to increase internal entropy) containing polar groups (to increase hydrophilicity) is likely to improve solubility." (emphasis in original)); Ex. 1118 ¶ 47 ("it is the *combination* of the teachings reflected in these references that would lead a POSA to modify rapamycin with flexible side chains containing polar groups (*i.e.*, groups that have oxygen or nitrogen atoms) in order to improve rapamycin's water solubility." (emphasis in original)). While these shifts do not rise to the level of a wholly new argument in reply that would merit exclusion, they do influence the weight that should be given Dr. Jorgensen's conclusions in his original Declaration.

disclose substitution at the C40 position of groups up to 10 carbon atoms long. Ex. 1009, 2:20–34; Ex. 1011, 2:1–9.

Furthermore, the necessary result of generalizing the teachings of Yalkowski and Lemke to “flexible side chains containing polar groups” is to expand the number of potential substituents that a person of ordinary skill in the art would have considered. At oral argument, counsel for Par recognized as much, conceding that the three substitutions identified by Dr. Jorgensen are not an exclusive list, but rather the first that would have been investigated. Tr. 36:7–22. But the basis for selecting Dr. Jorgensen’s three substituents first, according to counsel, was a “systematic approach” guided by Dr. Jorgensen’s “general rule” of starting with the smallest substituents first. *Id.* This “rule,” however, lacks support in the record beyond Dr. Jorgensen’s testimony.

In the portion of his initial Declaration discussing the “general rule” that smallest substituents are considered first, it is telling that Dr. Jorgensen cites no support for his statement. Ex. 1003 ¶ 150. In addition, when challenged on this rule by Dr. Roush, Dr. Jorgensen did not provide any additional support in his reply Declaration. Rather, he again stated that the skilled artisan would have chosen to make small modifications first because “smaller modifications would have a greater probability of not interfering with biological interactions that convey biological activity.” Ex. 1118 ¶ 11. Again, there is no citation for this assertion, nor does Par provide any prior art that discussed such a rule. To the contrary, Dr. Roush points out numerous examples of rapamycin derivatives having larger substituents that retained immunosuppressant activity. Ex. 2093 ¶¶ 63–79. As Dr. Roush notes:

Even if a person of ordinary skill in the art believed that “as a general rule,” the “smallest, simplest substitutions” should be

tried first, a person of ordinary skill in the art would have viewed that “general rule” in the context of what was known about rapamycin and rapamycin derivatives, that is, based on the prior art as a whole.

Id. ¶ 79. We agree.¹⁸ While the record supports Dr. Jorgensen’s testimony that a person of ordinary skill in the art may have tried the three substituents he identified, we cannot conclude that the group of candidates would have been limited to only those three, or that those would have been the first investigated.

D. Obviousness Analysis

Par analogizes its obviousness case to the one in *Bristol-Myers Squibb*, and argues that the lead compound analysis we should carry out “is exemplified” by the Federal Circuit’s decision. Tr. 8:12–14. But as we have set them forth above, the facts of this case differ significantly from the ones in *Bristol-Myers Squibb* that the Federal Circuit found supported a conclusion of obviousness.

Bristol-Myers Squibb concerned claims to entecavir, a modified version of the natural nucleoside deoxyguanosine. 752 F.3d at 969. As the

¹⁸ At oral argument, Par’s counsel also cited the *Bristol-Myers Squibb* case as support for the “start small” rule, arguing that the basis for the Federal Circuit’s decision was “a fundamental principle of medicinal chemistry, you start with small conservative changes and you go from there.” Tr. 37:17–21. We disagree that the Federal Circuit’s decision established any such rule. Rather, the Court noted that at trial, “*both experts . . . agreed* that a chemist in drug development would seek to make small, conservative changes.” 752 F.3d at 974 (emphasis added). To the extent the agreement of the experts in that case established anything, it is limited to the facts of that case.

Federal Circuit noted, entecavir is structurally identical to deoxyguanosine except for the presence of an exocyclic methylene group in place of deoxyguanosine's oxygen. *Id.* The court noted that "structurally similar compounds often have similar properties," and that this may support a reasonable expectation of success. *Id.* at 976. Par compares this to the instant case, arguing that "what we have is precisely what the law deems to be the expectation. The claimed 40-O-(2-hydroxyethyl) derivative of rapamycin represents a straightforward minor structural change, and that change results in a compound with similar properties to the prior art rapamycin compound." Tr. 9:7–12.

There are, however, any number of compounds that differ only slightly from rapamycin, among which everolimus is but one. By Par's reasoning, each of these derivatives would be obvious barring evidence of unexpected results. The law does not support such a conclusion. "Evidence of obviousness . . . is insufficient unless it indicates that the possible options skilled artisans would have encountered were 'finite,' 'small,' or 'easily traversed,' and that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) (quoting *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)).

Indeed, for the court in *Bristol-Myers Squibb*, the structural similarity of the claimed compound to the prior art was only one piece of the puzzle. At trial, the District Court found that carbocyclic analogs were "a promising area" for antiviral drug discovery, as compared to other analogs which were

a more crowded field. 752 F.3d at 974. Furthermore, both parties' experts agreed that a chemist would have made "small, conservative changes" to the lead compound. *Id.* And finally, the court found that "[u]nrefuted expert testimony also explained how the next obvious choice for modification would have been either the 2' or 5' position on the carbocyclic ring," and "[b]oth experts agreed that a skilled artisan would focus on the smallest elements on the top row of the periodic table." *Id.* at 975.

The facts of the case at hand provide a stark contrast. As we have found above, while the prior art recognized rapamycin as a promising immunosuppressant, it was only one among many possible lead compounds. Furthermore, the prior art shows that chemists were pursuing a number of avenues to increase solubility, including making derivatives but also other approaches such as formulation techniques or prodrugs. And most tellingly, in contrast to *Bristol-Myers Squibb* where the experts agreed on the type and location of the potential substituents, here the experts diverge significantly. As discussed above, we credit the testimony of Novartis' experts over Par's, and find that the options of substituent and substituent position would not have been as narrow as those proposed by Par.

In sum, we find that the person of ordinary skill in the art at the time the invention was made would have been faced with a large number of decision points along the lead compound analysis proposed by Par. The number of potential compounds encompassed by this decision tree is unclear, but would be far larger than the three compounds Dr. Jorgensen discusses. Only by making the "right" choice at each step would the skilled artisan arrive at everolimus, the compound of claim 10 and the basis of Par's

obviousness challenge. In light of these facts, we cannot conclude that the options faced would have been—in the words of the Federal Circuit—finite, small, or easily traversed. We, therefore, cannot conclude that the compound of claim 10, and by extension, the compounds of claims 1–3, would have been obvious to one of skill in the art as of October 1992.

With respect to the second ground of unpatentability, pertaining to the method of treatment claims 8 and 9, Par’s obviousness arguments are premised on the conclusion that everolimus would have been obvious. *See* Pet. 48–51 (“claims 8 and 9 would have been obvious to a person of ordinary skill in the art in view of the art that makes the 40-O-2-hydroxyethyl-rapamycin derivative obvious”). As we conclude that everolimus has not been shown to be obvious, we reach the same conclusion as to the methods of claims 8 and 9. The addition of Hughes to the ground of unpatentability does not provide any of the teachings we found lacking from the art asserted in the first ground of unpatentability.

As we have concluded that Par’s articulated lead compound analysis is insufficient to establish the obviousness of any of the challenged claims, we need not reach, and do not evaluate, the objective indicia of obviousness submitted by Novartis. PO Resp. 60–68.

E. Motion to Exclude and New Arguments

Novartis moves to exclude various exhibits filed by Par, namely Exhibits 1008, 1034, 1036–1038, 1041–1063, 1065-1113, 1117, 1120–1123, portions of Dr. Jorgensen’s testimony (Exs. 1003 and 1118), and portions of Dr. Ratain’s testimony (Ex. 1119). Mot. 1–2. The basis for the Motion is Novartis’s prior objections to these exhibits on grounds of relevance (FRE

702), incompleteness (FRE 106), or timeliness. Even having considered these objected-to exhibits, however, we have found in Novartis's favor on the merits of Par's patentability challenge. As such, the grant or denial of Novartis's Motion would have no effect on the outcome of the proceeding. We, therefore, dismiss the Motion to Exclude as moot.

Similarly, Novartis filed, with the Board's permission, a short paper identifying portions of Par's Reply that allegedly exceeded the proper scope of reply or raised new arguments. Paper 63. As we have found in Novartis' favor even considering these arguments, we consider moot the question of whether to strike them from the record (or disregard them).

III. CONCLUSION

For the foregoing reasons, based on a review of the complete record developed during trial, we conclude that Par has not proven, by a preponderance of the evidence, that claims 1–3 and 8–10 are unpatentable.

IV. ORDER

Accordingly, it is:

ORDERED that claims 1–3 and 8–10 of U.S. Patent No. 5,665,772 *have not been proven unpatentable*;

FURTHER ORDERED that, pursuant to 35 U.S.C. § 318(b), upon expiration of the time for appeal of this decision, or the termination of any such appeal, a certificate shall issue confirming the patentability of claims 1–3 and 8–10 of U.S. Patent No. 5,665,772;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 54) is *dismissed as moot*;

FURTHER ORDERED that the parties' demonstrative exhibits (Papers 68, 70), submitted for the purpose of oral argument, are expunged from record; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2016-00084
Patent 5,665,772

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