

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MICRO LABS LIMITED and
MICRO LABS USA INC.,¹
Petitioner,

v.

SANTEN PHARMCEUTICAL CO., LTD. and
ASAHI GLASS CO., LTD.,
Patent Owner.

Case IPR2017-01434
Patent 5,886,035

Before JO-ANNE M. KOKOSKI, CHRISTOPHER G. PAULRAJ, and
DEBRA L. DENNETT, *Administrative Patent Judges*.

KOKOSKI, *Administrative Patent Judge*.

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

¹ The Board terminated Petitioner's involvement without terminating the proceeding under 35 U.S.C. § 317(a). Paper 52.

I. INTRODUCTION

We have jurisdiction to conduct this *inter partes* review under 35 U.S.C. § 6, and this Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons that follow, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–14 of U.S. Patent No. 5,886,035 (“the ’035 patent,” Ex. 1001) are unpatentable.

A. *Procedural History*

Micro Labs Limited and Micro Labs USA Inc. (collectively, “Petitioner”) filed a Petition (“Pet.,” Paper 1) to institute an *inter partes* review of claims 1–14 (“the challenged claims”) of the ’035 patent. Santen Pharmaceutical Co., Ltd. and Asahi Glass Co., Ltd. (collectively, “Patent Owner”) filed a Preliminary Response (“Prelim. Resp.,” Paper 10). Pursuant to 35 U.S.C. § 314(a), we instituted an *inter partes* review based on the following grounds: (1) whether claims 1–14 are unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Klimko,² Kishi,³ and Ueno;⁴ and (2) whether claims 1–14 are unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Klimko, Kishi, Bezuglov

² EP 0 639 563 A2, published Feb. 22, 1995 (Ex. 1003).

³ U.S. 5,292,754, issued March 8, 1994 (Ex. 1005).

⁴ Japanese Unexamined Patent App. Pub. No. H7-70054, published Mar. 14, 1995 (Ex. 1006). We refer to “Ueno” as the English translation of the original reference.

1982⁵ and/or Bezuglov 1986,⁶ and Ueno. Paper 11 (“Dec. on Inst.” or “Institution Decision”), 20.

After institution of trial, Patent Owner filed a Patent Owner Response (“PO Resp.,” Paper 22) and Petitioner filed a Reply (“Reply,” Paper 24). Petitioner relies on the Declaration and Supplemental Declaration of Mitchell A. deLong, Ph.D. (“deLong Declaration,” Ex. 1027; “Supplemental deLong Declaration,” Ex. 1031), and the Declaration and Supplemental Declaration of Aron D. Rose, M.D. (“Rose Declaration,” Ex. 1028; “Supplemental Rose Declaration,” Ex. 1032). Patent Owner relies on the Declaration and Supplemental Declaration of Timothy L. Macdonald, Ph.D. (“Macdonald Declaration,” Ex. 2001; “Supplemental Macdonald Declaration,” Ex. 2028), and the Declaration and Supplemental Declaration of Robert D. Fechtner, M.D. (“Fechtner Declaration,” Ex. 2002; “Supplemental Fechtner Declaration,” Ex. 2029). Patent Owner filed observations regarding the cross-examination of Dr. deLong (Paper 34) and Dr. Rose (Paper 35), and Petitioner filed responses (Papers 39, 40).

Petitioner filed a Motion to Exclude Exhibits 2023, 2027, 2034, 2038–2041, 2044, and 2047, and paragraphs 8–26 of the Supplemental Macdonald Declaration (Ex. 2028). Paper 30. Patent Owner filed an Opposition (Paper 37), and Petitioner filed a Reply (Paper 44). Patent Owner filed a Motion to Exclude Exhibits 1033–1035, 1037, 1038, 1040–1043, and 1045–

⁵ *Fluoroprostaglandins: A New Class of Bioactive Analogs of Natural Prostaglandins*, LIPIDS OF BIOLOGICAL MEMBRANES 88–91 (L. D. Bergelson, ed., 1982) (Ex. 1007). We refer to “Bezuglov 1982” as the English translation of the original reference.

⁶ *Fluorodeoxy Prostaglandins, Synthesis and Perspectives*, PROSTAGLANDINS AND CARDIOVASCULAR DISEASES 191–200 (Takayuki Ozawa et. al. eds., 1986)

1060, certain paragraphs of the Supplemental deLong and Rose Declarations, and the testimony at lines 117:23–118:23 of the deposition of Dr. Rose (Ex. 2026). Paper 32. Petitioner filed an Opposition (Paper 41), and Patent Owner filed a Reply (Paper 45).

An oral hearing was held on September 6, 2018, and a transcript is included in the record. Paper 49 (“Tr.”).

On November 27, 2018, with Board authorization, the parties filed a joint motion to terminate the instant proceeding. Papers 50, 51; Ex. 2066. In light of the advanced stage of the instant proceeding, the Board *granted-in-part* the motion to terminate. Paper 52. Consequently, the proceeding has been terminated with respect to Petitioner, but is not terminated with respect to Patent Owner. *Id.*

B. Related Proceedings

The parties indicate that the ’035 patent is asserted in *Santen Pharmaceutical Co., Ltd. v. Micro Labs Limited*, Case No. 16-cv-00353 (D. Del. 2016) and *Santen Pharmaceutical Co., Ltd. v. Sandoz Inc.*, Case No. 16-cv-00354 (D. Del. 2016). Pet. 4; Paper 3, 1.

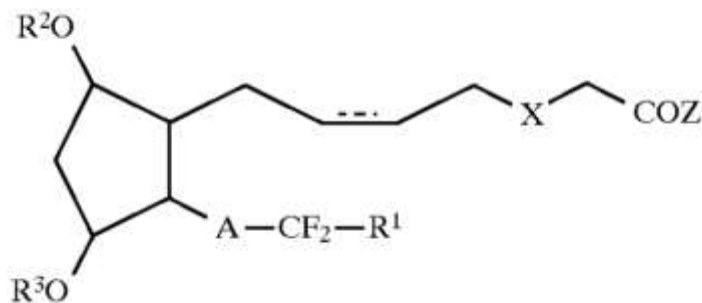
C. The ’035 Patent

The ’035 patent, titled “Difluoroprostaglandin Derivatives and Their Use,” is directed to “fluorine-containing prostaglandin derivatives having two fluorine atoms at the 15-position (or their salts) and medicines containing the compounds as an active ingredient, particularly, preventative or therapeutic medicines for eye diseases.” Ex. 1001, 1:4–8. These compounds are derivatives of a class of prostaglandins referred to as “prostaglandin Fs” or “PGFs.” *Id.* at 1:11–21, 61–63. The ’035 patent states that, although naturally-occurring prostaglandin Fs “are known to lower

intraocular pressure when topically applied to the eye,” they are also “irritant to the eye and have a problem of their inflammatory side effects such as congestion and damage to the cornea” (*id.* at 1:12–19), and “extensive research has been conducted both at home and abroad for development of long-lasting PGF derivatives having much the same biological activities as the naturally occurring one and few side effects” (*id.* at 1:44–47).

In that regard, the '035 patent discloses that “15,15-difluoro-15-deoxy-PGF_{2α} and its derivatives are superior to the known natural PGF_{2α} in the effect of lowering intraocular pressure[,] are scarcely irritant to the eye, scarcely affect the ocular tissues such as the cornea, the iris, and the conjunctive, and have long-lasting efficacy.” *Id.* at 2:7–12. The disclosed fluorine-containing prostaglandin derivatives also “are unlikely to decompose through metabolic processes such as hydrolysis and oxidation and [are] stable in the body,” and “hardly stimulate melanogenesis.” *Id.* at 19:21–28. As a result, “the medicine of the present invention is effective as a therapeutic agent, particularly for glaucoma or ocular hypertension.” *Id.* at 29–31.

The fluorine-containing prostaglandin derivatives disclosed in the '035 patent have the following generic formula:

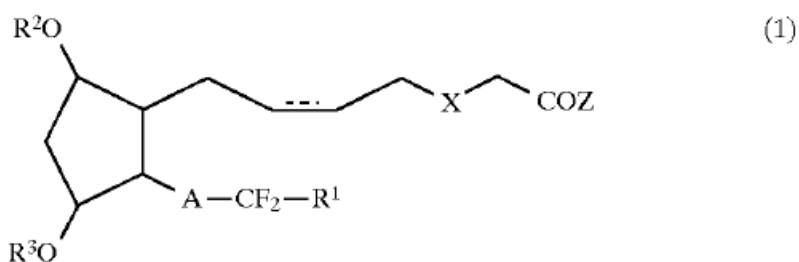


Ex. 1001, 2:20–29. These fluorine-containing derivatives “may be the same as the naturally occurring type except for the two fluorine atoms at the 15-

position”, i.e., “compounds wherein A is a vinylene group, R¹ is a n-pentyl group, both R² and R³ are hydrogen atoms, X is –CH₂–, Z is –OH, and the dual line is a cis-double bond.” *Id.* at 2:53–58. The ’035 patent further teaches that fluorine-containing prostaglandin derivatives “having an ω-chain which is not of the naturally[-]occurring type (namely, wherein A is a vinylene group, and R¹ is a n-pentyl group) are preferred.” *Id.* at 2:59–62; *see also id.* at 4:11–7:53 (setting forth compounds for A, X, R¹–R⁷, and Z that “are preferred from the standpoint of biological activities and physical properties”).

Claims 1 and 12 are the challenged independent claims, and are reproduced below.

1. A fluorine-containing prostaglandin derivative of the following formula (1) or a salt thereof:



wherein A is an ethylene group, a vinylene group, an ethylene group, –OCH₂– or –SCH₂–,

R¹ is a substituted or unsubstituted aryloxyalkyl group,

each of R² and R³ which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is –CH₂–, –O– or –S–,

Z is –OR⁴, –NHCOR⁵, –NHCO₂R⁶ or –SR⁷, or forms a single bond together with R² or R³,

each of R⁴, R⁵, R⁶ and R⁷ which are independent of one another, is a hydrogen atom, an alkyl group, an alkenyl

group, an alkynyl group, a cycloalkyl group, an aryl group or an aralkyl group,

and a dual line consisting of solid and broken lines is a single bond, a cis-double bond or a trans-double bond.

Ex. 1001, 31:2–26

12. A medicine containing 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-(3-chlorophenoxy)-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, 16-phenoxy-15-deoxy-15,15-difluoro-13,14-dihydro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ or an alkyl ester or salt thereof as an active agent.

Id. at 32:22–27.

The compound 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ (also referred to as tafluprost), which is specifically recited in dependent claim 3 and independent claim 12 and encompassed by the other challenged claims, is the focus of the parties' obviousness arguments and our analysis in this proceeding.

II. ANALYSIS

A. *Level of Ordinary Skill in the Art*

Petitioner contends that a person having ordinary skill in the art ("POSA") at the time of the '035 patent would have had "a Ph.D. in medicinal and/or organic chemistry" with "at least several years of experience researching and developing preventative or therapeutic medicines for treatment of eye diseases," and "familiarity designing, formulating and evaluating ophthalmic compositions for treatment of eye conditions that include glaucoma or ocular hypertension." Pet. 23–24. According to Petitioner, the POSA "would also have sufficient familiarity interpreting or evaluating studies that use animal models to test for [intraocular pressure]

reducing activity and side-effects of compounds having the potential to treat glaucoma or ocular hypertension,” and “would also draw upon the specialized experiences and skills of others on his team with these skills since it would be reasonable that the POSA would be working as part of a multi-disciplinary team with respect to the subject research.” *Id.* at 24 (citing Ex. 1027 ¶ 28; Ex. 1028 ¶ 22).

Patent Owner contends that a POSA “would have been an individual or team” having “a Ph.D. degree in medicinal or organic chemistry, 3 years of work experience in medicinal chemistry, and sufficient familiarity with interpreting or evaluating studies that use animal models to test for [intraocular pressure] reducing activity and side effects of compounds having the potential to treat glaucoma or ocular hypertension.” PO Resp. 23–24 (citing Ex. 2001 ¶ 51). Patent Owner disputes Petitioner’s contention that a POSA would be a chemist with experience researching therapies for eye diseases and familiarity interpreting and evaluating studies using animal models because “[c]hemists working on such projects often do not have specific prior experience with eye diseases or animal studies,” and, instead, would work as part of a multi-disciplinary team with respect to the subject research. *Id.* at 24 (citing Ex. 2001 ¶ 52; Ex. 2025, 247:17–23, 249:6–251:16). Patent Owner also disputes Petitioner’s contention that a POSA would have been familiar with designing, formulating, and evaluating ophthalmic compositions. *Id.* at 24–25. According to Patent Owner, the claims of the ’035 patent that “are generally directed to medicines containing at least one of the novel compounds as an active ingredient . . . do not recite any particular formulation details.” *Id.* at 26(citing Ex. 2001 ¶ 53).

Patent Owner’s assessment appears consistent with the level of ordinary skill in the art at the time of the invention as reflected in the prior art in this proceeding. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163–64 (Fed. Cir. 1985))). Accordingly, when evaluating the parties’ contentions regarding the scope and content of the art, and the differences between the prior art and the challenged claims, we take into consideration Patent Owner’s assertions regarding the level of ordinary skill. Nonetheless, we also note that our analysis and conclusions herein would not change even under Petitioner’s proposed skill level for a POSA.

B. Claim Interpretation

We interpret claims of an unexpired patent using the “broadest reasonable construction in light of the specification of the patent in which [the claims] appear[.]” 37 C.F.R. § 42.100(b) (May 2, 2016); *see Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016).⁷ Consistent with the broadest reasonable construction, claim terms are presumed to have their ordinary and customary meaning as understood by a person of ordinary

⁷ The revised claim construction standard for interpreting claims in *inter partes* review proceedings as set forth in the final rule published October 11, 2018 does not apply to this proceeding, because the new “rule is effective on November 13, 2018 and applies to all IPR, PGR and CBM petitions filed on or after the effective date.” Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board, 83 Fed. Reg. 51340 (Nov. 13, 2018) (to be codified at 37 C.F.R. pt. 42).

skill in the art in the context of the entire patent disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Only those terms in controversy need to be construed, and only to the extent necessary to resolve the controversy. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (“we need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

For purposes of the Institution Decision, we determined that, based on the record at that time, no claim term required express construction (Dec. on Inst. 7), and we see no reason to modify that determination in light of the record developed at trial.

C. *Principles of Law*

To prevail on its challenges to the patentability of the claims, a petitioner must establish facts supporting its challenge by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). “In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378–79 (Fed. Cir. 2015) (discussing the burdens of persuasion and production in *inter partes* review).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

A determination of whether a new chemical compound would have been obvious over the prior art typically follows a two-part inquiry that first considers “whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts,” and second, analyzes whether there was a reason to modify a lead compound to make the claimed compound with a reasonable expectation of success. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291–93 (Fed. Cir. 2012).

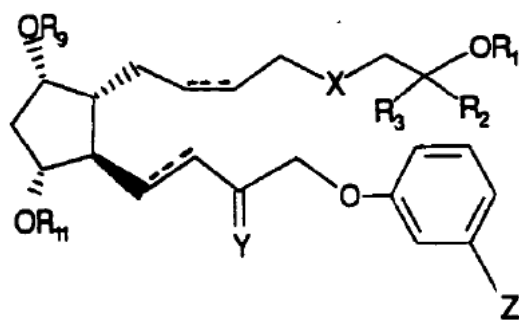
D. Overview of the Prior Art

1. Klimko

Klimko “relates to the use of cloprostenol, fluprostenol, their analogues and their pharmaceutically acceptable salts and esters to treat glaucoma and ocular hypertension.” Ex. 1003, 2:3–5. Cloprostenol and fluprostenol “are synthetic analogues of PGF_{2α}, a naturally-occurring F-series prostaglandin (PG).” *Id.* at 2:6–7. Klimko states that “[n]aturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after

topical ocular instillation, but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema,” and that “[m]any synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects.” *Id.* at 2:50–54. Klimko teaches that “the addition of a chlorine atom or a trifluoromethyl group to the meta position on the phenoxy ring at the end of the omega chain provides a compound having excellent IOP reduction without the significant side effects found with other, closely related compounds.” *Id.* at 3:50–53.

The compounds described in Klimko have the following general formula:



wherein R_1 is H, C_1 – C_{12} straight-chain or branched alkyl, C_1 – C_{12} straight-chain or branched acyl, C_3 – C_8 cycloalkyl, a cationic salt moiety, or a pharmaceutically acceptable amine moiety; R_2 and R_3 is H or C_1 – C_5 straight-chain or branched alkyl, or R_2 and R_3 taken together may be O; X is O, S, or CH_2 ; R_9 is H, C_1 – C_{10} straight-chain or branched alkyl, or C_1 – C_{10} straight-chain or branched acyl; R_{11} is H, C_1 – C_{10} straight-chain or branched alkyl, or C_1 – C_{10} straight-chain or branched acyl; Y is O, or H and OR_{15} , wherein R_{15} is H, C_1 – C_{10} straight-chain or branched alkyl, or C_1 – C_{10} straight-chain or branched acyl; and Z is Cl or CF_3 . *Id.* at 4:14–37. Klimko teaches that the

preferred compounds include cloprostenol isopropyl ester, fluprostenol isopropyl ester, the 3-oxa form of cloprostenol isopropyl ester, 13,14-dihydrofloprostenol isopropyl ester, cloprostenol-1-ol, and 13,14-dihydrocloprostenol-1-ol pivaloate. Ex. 1003, 4:55–58.

Klimko reports studies comparing the IOP-lowering activity and side effects of five compounds: A) cloprostenol isopropyl ester; B) fluprostenol isopropyl ester; C) 16-phenoxy-17,18,19,20-tetranor PGF_{2α}, isopropyl ester; D) 17-phenyl-18,19,20-trinor PGF_{2α}, isopropyl ester; and E) 13,14-dihydro-17-phenyl-18,19,20-trinor PGF_{2α}, isopropyl ester (known as latanoprost). *Id.* at 14:47–50; *see also id.* at 15, Tbl. 2 (showing the structures of compounds A–E). Tests of compounds A–E for hyperemia in guinea pigs show that compound C “produces significant hyperemia at low doses,” compound D “produces less hyperemia than compound C, but significantly more than compound E . . . , which produces only mild hyperemia,” and the hyperemia produced by compound A and compound B “appear to be intermediate between that of compound D and compound E, but this degree of hyperemia is also mild, and cannot be distinguished from that produced by compound E.” *Id.* at 17:56–18:6. Compounds A–E were also tested for IOP-lowering effects in cynomolgus monkey eyes. *Id.* at 18:10–25. Based on these tests, Klimko reports “that compounds A, B, C, and D produce similar degrees of IOP reduction with 0.3 μg doses,” but that “compound E is essentially inactive at this dose.” *Id.* at 19:29–30. Klimko further reports “that the IOP reduction with 1 μg of compound A is greater than that produced by 0.3 μg of compound A, and the response to either of these doses of compound A is greater than the maximum reduction produced by either dose of compound E.” *Id.* at 19:31–33. According to Klimko, these tests indicate compound A

“is both more potent and produces a greater maximum response for IOP reduction than compound E.” *Id.* at 19:33–35.

2. *Kishi*

Kishi “relates to the use of 15-deoxy-prostaglandin derivatives for the treatment of hypertension or glaucoma in the eyes.” Ex. 1005, 1:15–17. Kishi states that “[t]he inventors of the invention have found new useful compounds by screening a large amount of prostaglandin derivatives which are stable and capable of being chemically synthesized,” and also “found that derivatives of conventional prostaglandins which are derived from said conventional prostaglandins by deleting the hydroxy group at 15-position are more stable, particularly in the liquid phase, than the conventional prostaglandins, and that they show the intraocular pressure-reducing activity.” *Id.* at 1:62–2:3. According to Kishi, the described 15-deoxyprostaglandins “have a significant intraocular pressure-reducing activity, while they do not produce any side effects such as hyperemia of conjunctiva, and initial increase in intraocular pressure which are often observed in known prostaglandins.” *Id.* at 2:5–9.

3. *Ueno*

Ueno “relates to a new application for a 15-dehydroxy-prostaglandin compound, and to a specific new compound.” Ex. 1006 ¶ 1. Ueno recognizes that “[i]t is known that a group of 15-dehydroxy-PG compounds that do not have a hydroxyl group at position 15 of a so-called natural PG has intraocular pressure reducing action,” and that “15-dehydroxy-16-oxo PG compounds that do not have a hydroxyl group at position 15 and that have an oxo group at position 16 are effective for allergies, inflammation, and the like.” *Id.* ¶ 7. Ueno then states that “the present inventors

discovered that” the 15-dehydroxy-prostaglandin compounds that do not have a hydroxyl group or an oxo group at position 15 or position 16 “have superior antagonistic effect toward histamines, and therefore are useful for treating patients with allergies and inflammatory diseases.” *Id.* ¶ 8.

Based on testing in guinea pigs, Ueno reports that 13,14-dihydro-15-dehydroxy-17,17-difluoro-PGE 1 methyl ester “has an antagonistic action against histamine, which is an inducer of allergic diseases and inflammatory diseases,” and “is useful as an agent for treating allergic diseases, inflammatory diseases, and as a tracheal dilator.” *Id.* ¶¶ 87–88. Ueno includes conjunctivitis, iritis, uveitis, and central retinitis as examples of inflammatory diseases. *Id.* ¶ 12.

4. *Bezuglov 1982*

Bezuglov 1982 describes the synthesis and biological testing of 15-fluorine-15-deoxyfluoroprostaglandins. Ex. 1007, 88. Bezuglov 1982 teaches that “the replacement of the 15-hydroxyl group with fluorine protects the prostaglandin from the effects of 15-oxyprostaglandin dehydrogenase, which is a key enzyme in the metabolism of prostaglandins in the body.” *Id.* Bezuglov 1982 reports the results of biological tests that show that the synthesized 15-fluoroprostaglandins A₂, E_{2α}, F₂, and I₂ “did not lose the activity characteristic of prostaglandins” and “have prolonged activity compared to natural prostaglandins.” *Id.* at 90. According to Bezuglov 1982, replacing the 15-hydroxyl group with fluorine can lead “to the appearance of new properties in the analogs that were essentially absent in the corresponding natural prostaglandins.” *Id.* at 91.

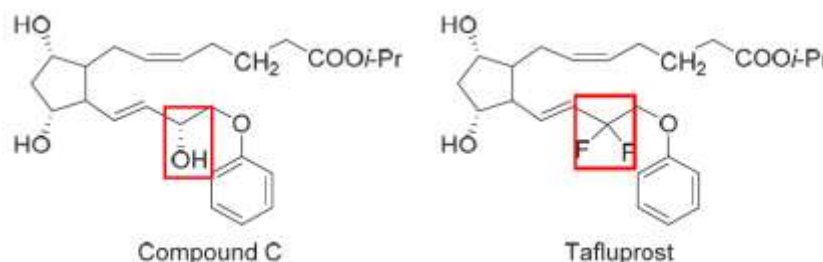
5. *Bezuglov 1986*

Bezuglov 1986 describes investigations of the synthesis and biological activity of fluorodeoxy prostaglandins. Ex. 1008, 191. In particular, Bezuglov 1986 focuses on the “substitution of the 15-hydroxyl group” because “biological deactivation of prostaglandins was induced by the action of 15-prostaglandin dehydrogenase.” *Id.* at 199. Bezuglov 1986 reports that the substitution of fluorine for the hydroxyl group in prostaglandins at C15 “changed also the character of their pharmacological action” and, in some cases, increase selectivity. *Id.* at 194. Bezuglov 1986 also reports that “[a]s expected, fluorination of prostaglandins in position 15 rendered them stable towards 15-prostaglandin dehydrogenase leading to prolonged activity of 15-fluorodeoxy prostaglandins upon intravenous injection in narcotized animals.” *Id.*

E. *Obviousness over Klimko, Kishi, and Ueno*

Petitioner contends that claims 1–14 are unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Klimko, Kishi, and Ueno. Pet. 41–62; Reply 2–18. In particular, Petitioner argues that it would have been obvious for one of ordinary skill in the art to (1) identify Klimko’s compound C (16-phenoxy-17,18,19,20-tetranor PGF_{2α}) as a lead compound for drug development; (2) recognize that the hydroxyl group at the C-15 position of Klimko’s compound C causes the negative side effect of hyperemia, and that removal of that hydroxyl would eliminate hyperemia but could result in loss of IOP-reducing activity; and (3) address these concerns by replacing the hydroxyl at the C-15 position with 2 fluorine atoms. Pet. 41–62. According to Petitioner, replacing the hydroxyl group at the C-15 position of Klimko’s compound C with two fluorine (F) atoms results in

tafluprost (16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$), a compound that is specifically identified in dependent claim 3 and independent claim 12, and which falls within the scope of the generic formula of independent claim 1, of the '035 patent. *Id.* at 10–11, 42–44. The chemical structures of Klimko's compound C and tafluprost are shown side-by-side below.



Id. at 11. As shown in the illustration, the only structural difference between Klimko's compound C on the left and tafluprost on the right is at the C-15 position (indicated by a red box), where Klimko's compound C has a hydroxyl group and tafluprost has two fluorine atoms.

1. *Obviousness of Tafluprost*

Petitioner contends that one of ordinary skill in the art would have selected Klimko's compound C ("compound C") as a lead compound in the development of $PGF_{2\alpha}$ analogues "due to its apparent long-lasting efficacy relative to the other compounds" disclosed in Klimko. Pet. 48 (citing Ex. 1028 ¶ 59). Having selected compound C as a lead, Petitioner contends that, based on the disclosures in Kishi, a POSA would have removed the hydroxyl group at the C-15 position to eliminate the side effect of hyperemia, and replaced it with a substituent other than hydrogen to ameliorate any loss of IOP-reducing activity. *Id.* at 50–51. Petitioner further contends that Ueno "teaches a POSA to replace the hydroxyl group

at the C-15 position of compound C disclosed in Klimko with two fluorine atoms in order to (1) eliminate the hyperemia associated with compound C, and (2) restore the IOP-reducing efficacy of compound C lost when the hydroxyl group is removed,” thereby yielding tafluprost, which is within the scope of the challenged claims. *Id.* at 52–53 (citing Ex. 1027 ¶ 115).

As explained by the Federal Circuit, “[t]o establish obviousness in cases involving new chemical compounds, [the proponent of the compounds’ obviousness] must identify some reason that would have led a chemist to modify a known compound.” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014). “Generally, an obviousness inquiry concerning such ‘known compounds’ focuses on the identity of a ‘lead compound.’” *Id.* (quoting *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2009)). “A lead compound is a compound in the prior art that would be ‘a natural choice for further development efforts.’” *Id.* (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). “The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art.” *Id.* Consistent with the flexible principles enunciated in *KSR*, to demonstrate that a claimed compound would have been obvious, “a showing that the prior art would have suggested making *the specific molecular modifications* necessary to achieve the claimed invention [i]s also required.” *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (internal quotations omitted, emphasis added).

Patent Owner argues that a POSA would not have considered compound C of Klimko to be a suitable lead compound. PO Resp. 28–51.

Patent Owner also argues that a POSA would not have found it obvious to modify compound C to arrive at the claimed compound. *Id.* at 51–65.

Based on our review of the full record in the present case, even assuming *arguendo* that an ordinary artisan would have selected Klimko’s compound C as a lead compound for further development, Petitioner does not persuade us that the prior art of record would have suggested making the specific modifications to compound C to yield tafluprost.

Petitioner argues that a POSA would have been motivated to remove the hydroxyl group at the C-15 position of compound C because (1) Kishi teaches prostaglandin analogues used to treat glaucoma or ocular hypertension wherein “the presence of a hydroxyl at the C-15 position is an underlying cause of the undesired hyperemia,” and removing it “results in compounds that ‘do not produce any side effects such as hyperemia’” (Pet. 50 (quoting Ex. 1005, 1:65–2:11)); and (2) Kishi teaches that removing the C-15 position hydroxyl group “also imparts stability to the compound, because naturally occurring PGF_{2α} that contain a hydroxyl group at C-15 are chemically and biological[ly] labile and easily subject to metabolic degradation” (*id.* (citing Ex. 1027 ¶ 74)). According to Petitioner, a POSA would have been motivated

to combine the teachings of Klimko and Kishi and would have had a reasonable expectation of success that removing the hydroxyl group at the C-15 position would improve the stability of compound C, would eliminate side-effects such as hyperemia caused by the hydroxyl group, and could potentially extend or prolong the IOP-reducing effect of a PGF_{2α} analogue.

Id. (citing Ex. 1027 ¶¶ 111–113; Ex. 1028 ¶¶ 68–70).

Petitioner further argues that “a POSA would also be aware from Kishi that removal of the hydroxyl at the C-15 position of a PGF_{2α} isopropyl

ester analogue like Compound C could result in some loss of IOP-reducing activity.” Pet. 51 (citing Ex. 1005, 41:59–43:36). Therefore, Petitioner argues, “a POSA would be further motivated to replace the C-15 hydroxyl group in compound C with a substituent other than hydrogen that could ameliorate any loss of IOP-reducing activity, with the reasonable expectation that the substitution would ameliorate or restore loss of IOP-reducing activity.” *Id.*

Petitioner then argues that a POSA would also consider the teachings of Ueno, because Ueno specifically references Kishi, and “would have been known to one operating in the field at the time.” Pet. 51 (citing Ex. 1006 ¶ 7). Petitioner contends that Ueno “discloses the incorporation of a difluoro moiety along the omega side-chain of prostaglandins, and particularly exemplifies substitution of the C-15 hydroxyl group for the difluoro substitution.” *Id.* at 52 (citing Ex. 1006 ¶¶ 87–90). According to Petitioner, the combination of Kishi and Ueno “teaches a POSA to replace the hydroxyl group at the C-15 position of compound C disclosed in Klimko with two fluorine atoms in order to (1) eliminate the hyperemia associated with compound C, and (2) restore the IOP-reducing efficacy of compound C lost when the hydroxyl group is removed.” *Id.* (citing Ex. 1027 ¶ 115).

Petitioner further argues that

other practical considerations motivating a POSA to make a direct difluorination substitution at the C-15 position include the understanding that a compound without a stereogenic center is easier to manufacture and analyze, and would result in reduced overall economic efficiency and corresponding regulatory efficiency in manufacturing and commercializing the compound as a drug.

Id. at 52–53 (citing Ex. 1027 ¶ 118).

Patent Owner responds that the field of medicinal chemistry viewed modifications of the C-15 hydroxyl group with skepticism because of the concern that it would diminish IOP-lowering activity. PO Resp. 52 (citing Ex. 2001 ¶ 98). Patent Owner contends that “Kishi only discloses replacing the C15 hydroxyl with hydrogen” in “prostaglandin derivatives in which the omega chain is a 6–12 carbon chain,” and “does not disclose any embodiment with a 16-phenoxy present on the omega chain” as in compound C. *Id.* (citing Ex. 2001 ¶ 98; Ex. 2025, 212:18–24, 219:23–220:7; Ex. 1005, Abstract). Patent Owner also contends that, because “the unpredictability of chemical modifications of prostaglandins was known in the art, it would have been impossible for a [POSA] to predict with any reasonable level of certainty that the reported results (for Kishi’s different omega chain) would carry over to the removal of the C15 hydroxyl” of compound C. *Id.* (citing Ex. 2001 ¶ 98).

Patent Owner further contends that “the prevailing view in the art was that the C15 hydroxyl group was important for binding receptors for lowering IOP,” and a POSA “would have expected that C15 fluorination would significantly change the properties of a prostaglandin analog.” PO Resp. 53 (citing Ex. 2028 ¶ 16). In that regard, Patent Owner contends that “[t]he different properties of C15 hydroxyl and C15 fluorine are numerous, including capacity for being a hydrogen bond donor and/or acceptor, Van der Waals radius, length of bond to the carbon, electronegativity, lipophilicity and effect on rotational conformation stability.” *Id.* at 54–55 (citing Ex. 2028 ¶ 17).

Patent Owner also contends that Ueno “discloses a broad and non-specific genus of prostaglandins lacking hydroxyl or oxo groups at positions

15 and 16,” and “is not directed to IOP-lowering.” PO Resp. 57–58 (citing Ex. 2001 ¶¶ 69–105; Ex. 1006, 48). With respect to the disclosed genus, Patent Owner contends that Ueno “includes a laundry list of possible derivatives, with fluorination (mono- or difluorination) at any of a number of positions on the omega chain,” and that the examples in Ueno “involve 15-dehydroxy PGE (not PGF_{2α}, as in tafluprost) derivatives difluorinated at C15, C16 or C17, with all but one example featuring C16 or C17 difluorination.” *Id.* at 58–59 (citing Ex. 1006, 54–57, 59–65; Ex. 2025, 165:16–23, 166:21–167:13, 171:8–179:10). Patent Owner also contends that Ueno does not provide an “assessment (nor any other disclosure) of ocular side effects with respect to the disclosed compounds,” and does not provide any “insights as to the side effect profile of a C15 difluorinated Compound C.” *Id.* at 60–61 (citing Ex. 2008 ¶ 108). Therefore, Patent Owner contends, a POSA “would not have associated the disclosed fluorination with improving or restoring C15-specific biological activity.” *Id.* at 59 (citing Ex. 2001 ¶ 106).

Having considered the rationale and supporting evidence advanced by Petitioner alongside Patent Owner’s arguments and supporting evidence, we determine that Petitioner has not shown sufficiently that the prior art of record would have suggested making the specified modifications to compound C required to yield tafluprost.

Petitioner relies on the testimony of Dr. deLong to support its contention that a POSA would have been motivated to remove the C-15 hydroxyl group in compound C, and would have had a reasonable expectation of success in doing so. *See* Pet. 50–51. In that regard, Dr. deLong testifies that, because “Kishi teaches a POSA that removing the

hydroxyl group at the C-15 position of naturally-occurring prostaglandins by replacing it with hydrogen eliminates the hyperemic effect,” a POSA would have been “motivated to explore making structural modifications to compound C in view of Kishi’s teaching in order to take advantage of the superior benefits of compound C, which include its long-lasting efficacy.”

Ex. 1027 ¶ 110. Dr. deLong goes on to testify:

Moreover, a POSA would understand that removing the hydroxyl group could also potentially extend or prolong the IOP-reducing effect of a $\text{PGF}_{2\alpha}$ analogue because Kishi discloses that naturally occurring $\text{PGF}_{2\alpha}$ “are chemically and biologically labile, and are easily subject to metabolic degradation because they contain in the chemical structure . . . a hydroxyl group at 15 position in the chain.” It is my opinion that a POSA would thus understand that removing the hydroxyl group could potentially extend or prolong the IOP-reducing effect of a $\text{PGF}_{2\alpha}$ analogue because deleting the hydroxyl group at C-15 leads to analogues that are also more stable chemically and biologically.

Id. ¶ 111.

Patent Owner, however, provides evidence that as of the priority date of the ’035 patent, medicinal chemistry was an unpredictable art, particularly with respect to prostaglandins. For example, Dr. Macdonald testifies that:

[S]tructural differences among prostaglandins – and the resulting preferential binding to different receptors – manifest in a wide-range of biological activities (*e.g.*, constriction or dilation of smooth muscle of circulatory, respiratory and gastrointestinal systems, aggregation or disaggregation of platelets, uterine contraction, regulation of hormones, regulation of inflammation, regulation of gastric acid, bicarbonate and mucus secretion, and regulation of mucosal integrity).

Ex. 2001 ¶ 22 (citing Ex. 2008, 5–11; Ex. 2007, 2). Dr. Macdonald further testifies that “the biological activities of the various prostaglandins were

known to overlap to varying degrees,” and “prostaglandins were known to be promiscuous molecules that can bind to multiple receptors to varying degrees – causing side effects – likely because of certain structural similarities among the prostaglandins (*i.e.*, the prostanoid acid skeleton, C15 hydroxyl, C13-C14 *trans* double bond, and some shared functional groups on the cyclopentane ring).” *Id.* ¶ 23 (citing Ex. 2009, 2; Ex. 2010, 1) (emphasis omitted).

We credit Dr. Macdonald’s opinions over Dr. deLong’s opinions in this regard, as we find Dr. Macdonald’s opinions to be better supported by other evidence of record. Collins⁸ teaches “[t]he side effects observed with [prostaglandins] are due to their multiple pharmacological and physiological activities all of which may be manifested when the body is exposed to them systemically,” and that, “[i]n general, modification strategies employed by medicinal chemists have been directed at one or more of these problems.” Ex. 2010, 1–2. According to Collins, “[s]uccess in finding acceptable drug candidates has been difficult and has also been compounded by poor clinical efficacy in many therapeutic areas.” *Id.* at 2. Stjernschantz and Alm⁹ teach that “[t]here are at least eight different prostanoid receptors,” some of which “furthermore exist in several splice variants,” and that “[n]aturally occurring prostaglandins tend to spill over on many different prostanoid receptors resulting in a mixed pharmacological effect.” Ex. 2009, 1–2. Stjernschantz and Alm further teach that “the ocular irritating effect of PGF_{2α} is probably

⁸ *Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs*, Graefe’s Arch. Clin. Exp. Ophthalmol. 222:139–141 (1985) (Ex. 2010).

⁹ *Latanoprost as a new horizon in the medical management of glaucoma*, Curr. Opin. Ophthalmol. 7(2):11–17 (1996) (Ex. 2009).

at least partly due to the fact that this prostaglandin is a relatively effective agonist also on several of the EP receptors.” *Id.* at 2. Konturek and Pawlik¹⁰ similarly teach that the biological actions of prostaglandins “comprise a wide spectrum of effects,” and that “[s]ome have directly opposing actions in many systems, and prostanoid-mediated control of cellular, tissue, or organ functions reflects the interactions between different” prostaglandins, thromboxanes, and leukotrienes. Ex. 2008, 5; *see also id.* at 5–11 (describing the physiological functions and pharmacological functions of various prostaglandins, including PGF_{2α}, with respect to various systems such as kidney and urinary formation, smooth muscle, and reproductive and endocrine systems).

Additionally, as Patent Owner notes (PO Resp. 52–53), Klimko recognizes that the “seemingly slight structural differences” between tested compounds A through E “produce greatly different IOP-lowering effects and levels of hyperemia.” Ex. 1003, 15:54–56. For example, Klimko shows that the percent IOP reduction demonstrated by compound E (which differs from compound C in that it does not have a C13-C14 *trans* double bond, and includes a 17-phenyl instead of a 16-phenoxy group) is approximately 20% less than the IOP reduction produced by compound C. *Id.* at 18, Table 4. Klimko also shows that compound D (which differs from compound C only in that it has a 17-phenyl instead of a 16-phenoxy group) displays significantly less hyperemia than compound C. *Id.* at 17–18, Table 3. Taken as a whole, therefore, we find that the evidence of record indicates that modifying a prostaglandin such as compound C to achieve a particular

¹⁰ *Physiology and Pharmacology of Prostaglandins*, Dig. Dis. Sci. 31(2 Suppl.):6S–19S (1986) (Ex. 2008).

result at the time of the '035 patent was an unpredictable endeavor, and would not be as straightforward as Petitioner and Dr. deLong appear to contend.

We are also not persuaded that the disclosures in Kishi would have provided a reasonable expectation of success that removing the C-15 hydroxyl from compound C would improve the stability of compound C, eliminate hyperemia, and “could potentially extend or prolong the IOP-reducing effect of a $\text{PGF}_{2\alpha}$ analogue” as Petitioner maintains. Pet. 50 (citing Ex. 1027 ¶¶ 111–113; Ex. 1028 ¶¶ 68–70).

Kishi is directed to 15-deoxyprostaglandin derivatives wherein the omega chain is a 6–12 carbon chain, which does not encompass compound C. *See, e.g.*, Ex. 1005, 2:16–50 (describing 15-deoxyprostaglandin derivatives where the omega chain “ R^2 is $\text{C}_6\text{--C}_{12}$ alkyl, $\text{C}_6\text{--C}_{12}$ alkenyl or $\text{C}_6\text{--C}_{12}$ alkadienyl or a pharmaceutically acceptable salt thereof”). Although Kishi teaches that deleting the hydroxyl group at C-15 results in prostaglandin derivatives that “are more stable, particularly in the liquid phase, than the conventional prostaglandins, and that they show” IOP-reducing activity without producing side effects such as hyperemia, it is not evident from Kishi whether those same results would occur in a prostaglandin derivative that has a different omega chain, such as compound C. *Id.* at 1:65–2:9. As Dr. Macdonald notes, “Kishi does not disclose any embodiment with the 16-phenoxy group that is present on the omega chain” of compound C, which “is a significant structural difference.” Ex. 2001 ¶ 98; *see also* Ex. 2025, 218:18–24, 219:23–220:7 (Dr. deLong agreeing that Kishi does not provide data that removing the C-15 hydroxyl group from a prostaglandin analogue with a phenoxy group on the omega chain can

eliminate hyperemia, or is easily subject to metabolic degradation); Ex. 1003, 15:54–56 (“As is apparent in Table 2, the five compounds differ only slightly in structure; however, as Examples 5 and 6 will show, such seemingly slight structural differences produce greatly different IOP-lowering effects and levels of hyperemia.”). In light of the unpredictability involved in modifying prostaglandins, neither Petitioner nor Dr. deLong provide sufficient evidence demonstrating that a POSA would have reasonably expected that removing the C-15 hydroxyl group from compound C would produce the same results as those produced by the 15-deoxyprostaglandin derivatives in Kishi.

Likewise, there is insufficient evidence that the proposed modification of the C-15 hydroxyl of compound C would have been reasonably expected to prolong or extend IOP-reducing effect. Kishi does teach that “natural prostaglandins are chemically and biologically labile, and are easily subject to metabolic degradation because they contain in the chemical structure a labile allyl alcohol moiety comprising a double bond between 13 and 14 positions and a hydroxy group at 15 position in the ω chain,” and that prostaglandin derivatives with the 15-position hydroxyl group deleted “are more stable, particularly in liquid phase, than the conventional prostaglandins, and that they show the intraocular pressure-reducing activity.” Ex. 1005, 1:50–56, 1:65–2:3. Dr. deLong testifies that, from these disclosures in Kishi, a POSA would “understand that removing the hydroxyl group could potentially extend or prolong the IOP-reducing effect of $\text{PGF}_{2\alpha}$ analogue.” Ex. 1027 ¶ 111. Dr. deLong, however, does not provide adequate explanation as to why a POSA would understand Kishi’s disclosure that the 15-deoxyprostanglandin derivatives “are more stable,

particularly in the liquid phase” to mean that such derivatives have extended or prolonged IOP-reducing effect as compared to conventional prostaglandins, particularly in light of Kishi’s disclosure that conventional PGF_{2α} (isopropyl ester) displays better IOP-reducing activity than the 15-deoxyprostaglandin derivative. *See id.* ¶ 113 (citing Ex. 1005, col. 43, Table 1). Dr. deLong’s opinions in this regard also fail to address the structural differences between Kishi’s 15-deoxyprostaglandin derivatives and compound C, and how or why a POSA would have expected compound C to display the same properties as the Kishi’s compounds. *See* Ex. 2001 ¶ 98 (Dr. Macdonald testifying that the “significant structural differences” between Kishi’s prostaglandin derivatives and compound C make “it impossible to predict with any reasonable level of certainty that the reported results would carry over to the removal of the C15 hydroxyl of” compound C).

Moreover, even if Kishi would have motivated a POSA to remove the C-15 hydroxyl group from compound C, we are not persuaded that a POSA would also have been motivated to then difluorinate the C-15 position and have had a reasonable expectation of success of restoring the IOP-reducing activity that was lost upon the removal of the C-15 hydroxyl group.

Petitioner contends that, because Ueno “discloses incorporation of a difluoro moiety along the omega side-chain of prostaglandins, and particularly exemplifies substitution of the C-15 hydroxyl group for the difluoro substitution,” the combination of Kishi and Ueno “teaches a POSA to replace the hydroxyl group at the C-15 position of compound C” with two fluorine atoms to eliminate hyperemia and restore IOP-reducing activity. Pet. 52. To support this contention, Petitioner relies on Dr. deLong’s

testimony that Ueno “teaches that the hydroxyl group at position C-15 can be replaced by difluorination” and that a “POSA would have the reasonable expectation that difluorination would offset any potential reduction in IOP-lowering efficacy as taught by Kishi since there would no longer be a hydroxyl group at C-15.” Ex. 1027 ¶ 115. Dr. deLong’s testimony in this regard, however, is conclusory in nature, and thus we give it little weight. *Id.* ¶¶ 111–113; see 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985) (stating a lack of objective support for an expert opinion “may render the testimony of little probative value in [a patentability] determination”). In particular, Dr. deLong’s testimony does not provide objective support for his opinion that a POSA would have reasonably expected, based on Ueno, that difluorinating the C-15 position of compound C would offset the IOP-reducing effect of removing the hydroxyl group.

Ueno describes “a new 15-dehydroxy-PG compound and an allergic disease treating agent, inflammatory disease treating agent, antihistaminic agent, and bronchial dilating agent containing 15-dehydroxy-PG compound as an active ingredient,” and identifies conjunctivitis, iritis, uveitis, and central retinitis among a list of other inflammatory diseases. *Id.* ¶¶ 9, 12. Ueno also states that the 15-dehydroxy-PG compound “may be any PG derivative that does not have a hydroxy group or an oxo group at position 15 and 16, and these may be saturated substances, or may have a double bond between, for example, position 5 and 6, position 13 and 14, or position 18 and 19.” *Id.* ¶ 21. As Patent Owner notes, the examples in Ueno “involve

15-dehydroxy PGE (not PGF_{2α}, as in tafluprost) derivatives difluorinated at C15, C16, or C17, with all but one example featuring C16 or C17 difluorination.” PO Resp. 59 (citing Ex. 1006, 54–57; Ex. 2025, 166:21–167:13, 171:8–179:10). Patent Owner further notes that Ueno “does not attribute any specific role to the fluorines in the disclosed compounds.” *Id.* (citing Ex. 2001 ¶ 106). In that regard, Dr. Macdonald testifies that “[g]iven the nonspecific nature of the disclosed fluorination” in Ueno, a POSA “would not have associated the disclosed fluorination with C15-specific biological activity (or any specific biological activity.” Ex. 2001 ¶ 106. Dr. Macdonald also explains that Ueno

does not test any compound for IOP-lowering or any other traditional prostaglandin-associated activity. Rather, Ueno Japan tests only a single compound – 13,14-dihydro-15-dehydroxy-17,17-difluoro-PGE 1 methyl ester – which is difluorinated at C17. [Ex. 1006] at 64–65. And, Ueno Japan only tests the above compound for inhibition of histamine activity and for inhibition of acute liver injury. *Id.* Ueno Japan does not test for IOP-lowering, nor does it suggest any proposed mechanism of action for its disclosed compounds that could be applied to the IOP-lowering context.

Id. ¶ 107 (emphases omitted).

Ueno does recognize, citing Kishi, that “[i]t is known that a group of 15-dehydroxy-PG compounds that do not have a hydroxyl group at position 15 of a so-called natural PG has intraocular pressure reducing action.” Ex. 1006 ¶ 7. This, however, is the extent of Ueno’s teachings with regard to the IOP-reducing activity of any prostaglandin compounds, including the compounds of Ueno’s invention. It does not necessarily follow from Ueno’s general teaching that its compounds can be used to treat inflammatory eye diseases that difluorinating the C-15 position of a prostaglandin such as

compound C would offset the IOP-lowering effects of removing the C-15 hydroxyl group. We also agree with and credit Dr. Macdonald's testimony that Ueno "provides no assessment (nor any other disclosure) of ocular side effects with respect to the disclosed compounds," and, therefore, a POSA "would not have had any understanding from Ueno as to the side effect profile of a C15 difluorinated Compound C; this is especially critical here because of the unacceptable side effects," namely, hyperemia, of compound C. Ex. 2001 ¶ 108.

Bezuglov 1982 and Bezuglov 1986 further support Patent Owner's position that a POSA would not have been motivated to difluorinate compound C as proposed by Petitioner. Bezuglov 1982 reports that "[t]he introduction of fluorine in place of hydroxyl in the prostaglandin molecule changes its immunological properties," and that "replacement of the hydroxyl group with fluorine at position 15 leads to the appearance of new properties in the analogs that were essentially absent in the corresponding natural prostaglandins." Ex. 1007, 91. As an example, Bezuglov 1982 notes that "15-fluoro-15-deoxyprostaglandin $F_{2\alpha}$ is a platelet aggregation inducer at concentrations two orders of magnitude lower than that of natural prostaglandin $F_{2\alpha}$." *Id.* Similarly, Bezuglov 1986 concludes that "[s]ubstitution of hydroxyl for fluorine in prostaglandins leads to substantial changes in their physiological properties." Ex. 1008, 199; *see also id.* ("Introduction of fluorine into position 15 of $\text{PGF}_{2\alpha}$ caused a selective increase of the pressor effect with concomitant decrease of the muscle contractile activity on the gastrointestinal tract."). These disclosures in Bezuglov 1982 and Bezuglov 1986 are also consistent with the evidence, described above, that establishes that modifying a prostaglandin such as

compound C to achieve a particular result at the time of the '035 patent was an unpredictable endeavor.

Furthermore, we do not find Petitioner's argument that the '671 application¹¹ "represents the state of the art and the general thinking of those skilled in the art prior to the time of the '035 patent's earliest claimed priority date, which was to make PGF_{2α} analogues with fluorine substitutions at the C-15 position," to be persuasive. Pet. 22. As Petitioner recognizes, the '671 application is not statutory prior art. *Id.* at n. 4. The '671 application is directed to "15-fluoro prostaglandin analogs believed to have functional PGF_{2α} receptor agonist activity" and their use in the treatment of glaucoma and ocular hypertension. Ex. 1012, 3:29–4:1. The '671 application, however, explicitly states that "the mechanism of action by which PGF_{2α} type prostaglandins lower IOP is not well understood." *Id.* at 4:1–3. The '671 application further recognizes that "the mechanism of action of the compounds of the present invention is not fully understood," and the inventors only provide a theory as to that mechanism of action. *Id.* at 4:3–5. The '671 application also states that although "some prostaglandins with fluorine in the omega chain are known in the art," "the novel compounds of the present invention and their favorable therapeutic profiles in the treatment of glaucoma are neither disclosed nor suggested in that art." *Id.* at 3:18–23.

To the extent that the '671 application represents the state of the art as of its November 12, 1996 priority date, it establishes that (1) the relationship between PGF_{2α} receptor activation and IOP lowering effect was not well understood (Ex. 1012, 2:18–19); (2) many of the PGF_{2α}-type molecules

¹¹ PCT/US97/20671, published on May 22, 1998 (Ex. 1012).

known to lower IOP were also “associated with undesirable side effects” such as “an initial increase in IOP, breakdown of the blood aqueous barrier and conjunctival hyperemia” (*id.* at 3:2–5); and (3) monofluorinated PGF_{2α} prostaglandins with favorable therapeutic profiles for treating glaucoma were not known in the art (*id.* at 3:18–23). Moreover, the ’671 application describes its finding that 15-fluoro substituted PGF_{2α} analogs of the invention exhibit an improved therapeutic profile in the treatment of glaucoma and ocular hypertension as compared to natural prostaglandins as “unexpected.” *Id.* at 4:12–15. Thus, contrary to Petitioner’s contentions, the ’671 application demonstrates that the general thinking in the prior art at the time of the ’035 patent did not include making PGF_{2α} analogues with fluorine substitutions at the C-15 position.

In light of the disclosures in the prior art, as discussed above, neither Petitioner nor Dr. deLong explains sufficiently why a POSA would have difluorinated the C-15 position of compound C with the reasonable expectation that doing so would restore IOP-lowering activity and eliminate hyperemia. In an obviousness determination, we must avoid analyzing the prior art through the prism of hindsight. Instead, we must “cast the mind back to the time the invention was made” and “occupy the mind of one skilled in the art who is presented with only the references, and who is normally guided by then-accepted wisdom in the art.” *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1554 (Fed. Cir. 1983); *see also Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1368 (Fed. Cir. 2012) (quoting *Innogenetics, N.V. v. Abbott Labs.*, 521 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (“We must still be careful not to allow hindsight reconstruction of the references to reach the claimed invention without any

explanation as to how or why the references would be combined to produce the claimed invention.”)). Here, Petitioner attempts to imbue one of ordinary skill in the art with the knowledge of tafluprost and its properties, when no prior art reference, references of record, or other evidence conveys or suggests that knowledge. Petitioner’s proposed rationale relies upon general and conclusory statements from Dr. deLong regarding how a POSA would have understood Klimko, Kishi, and Ueno that are not sufficiently supported by objective evidence in the record. Instead, Dr. deLong’s testimony appears to be based on impermissible use of hindsight after review of the ’035 patent. *See KSR*, 550 U.S. at 421 (stating that the factfinder must be aware “of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning”). In order to establish a reason that would have led a chemist to modify compound C, Petitioner needed to explain sufficiently how the prior art would have suggested making the specific molecular modifications Petitioner contends are necessary to result in tafluprost. Petitioner failed to provide such explanation.

For the foregoing reasons, we are not persuaded that Petitioner has made a sufficient showing that a POSA would have modified compound C in the manner proposed. Accordingly, we find that Petitioner has not shown by a preponderance of the evidence that independent claim 1 of the ’035 patent, and claims 2–11 that depend, directly or indirectly, therefrom, would have been obvious over the combined teachings of Klimko, Kishi and Ueno.

Independent claim 12 is directed to a medicine containing tafluprost or other, specifically identified compounds that fall within the genus of compounds recited in claim 1. *See* Pet. 60–62. Therefore, for the same reasons, Petitioner has not established by a preponderance of the evidence

that claim 12, and claims 13 and 14 that depend, directly or indirectly, therefrom, would have been obvious over the combined teachings of Klimko, Kishi, and Ueno.

F. Obviousness over Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno

Petitioner contends that claims 1–14 are unpatentable under 35 U.S.C. § 103 as obvious over the combined teachings of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno. Pet. 62–66. Petitioner relies on the arguments it made with respect to the combination of Klimko, Kishi, and Ueno to support its contentions that (1) a POSA would have been motivated to select Klimko’s compound C as a lead compound, and would have been motivated to remove the C-15 hydroxyl group to eliminate the hyperemic side effect as taught by Kishi; and (2) a POSA would have been motivated to incorporate two fluorine atoms at the C-15 position based on the disclosures in Ueno. *See id.* at 62, 65–66. Petitioner further argues that a POSA would have been motivated “in view of Bezuglov 1982 and/or Bezuglov 1986 to replace the hydroxyl group at the C-15 position of compound C disclosed in Klimko with a fluorine atom, with the reasonable expectation that this substitution would enhance and prolong the IOP-reducing activity of” compound C, “or, at a minimum, restore the IOP-reducing activity resulting from the removal of the hydroxyl group.” *Id.* at 64. As set forth above with respect to Petitioner’s proposed combination of Klimko, Kishi, and Ueno, we are not persuaded that a POSA would have been motivated to modify compound C by removing the C-15 hydroxyl group based on the disclosures of Kishi, or to difluorinate the C-15 position based on the disclosures of Ueno. *See supra* Section II.E.1. Petitioner does not rely on Bezuglov 1982 and Bezuglov 1986 to remedy these deficiencies. Accordingly, for the same

reasons given above, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1–14 of the '035 patent would have been obvious over the combined teachings of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno.

G. Secondary Considerations of Non-obviousness

Patent Owner contends that secondary considerations of non-obviousness, including commercial success, unexpected results, long-felt need, and failure of others “further support the non-obviousness of tafluprost.” PO Resp. 65; *see id.* at 65–70. As discussed above, we find that Petitioner has not established that claims 1–14 of the '035 patent would have been obvious over the combined teachings of Klimko, Kishi, and Ueno, or the combined teachings of Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno. Thus, we need not address Patent Owner’s evidence regarding secondary considerations of non-obviousness.

III. PETITIONER’S MOTION TO EXCLUDE

Petitioner moves to exclude Exhibits 2023, 2027, 2034, 2038–2041, 2044, 2047, and 2056–2060, paragraphs 8–26 of the Supplemental Macdonald Declaration (Ex. 2028), and portions Exhibits 2061 and 2062 related to Exhibits 2056–2060. Paper 30. We do not reach the merits of Petitioner’s Motion to Exclude because our Decision does not rely on Exhibits 2023, 2027, 2034, 2038–2041, 2044, 2047, and 2056–2060, paragraphs 8–26 of the Supplemental Macdonald Declaration (Ex. 2028), or the portions of Exhibits 2061 and 2062 related to Exhibits 2056–2060. Accordingly, we dismiss Petitioner’s Motion to Exclude as moot.

IV. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner moves to exclude (1) paragraph 6–8, 10–71, and 75–98 of the Supplemental deLong Declaration (Ex. 1031); (2) paragraphs 20–33, 36–41, and 48–73 of the Supplemental Rose Declaration (Ex. 1032); (3) Exhibits 1033–1035, 1037, 1038, 1040–1043, and 1045–1060; (4) testimony in paragraphs 16, 39, 43, 49, 50, 55, 57, 59, 69, 81–83, 85, and 86 of the Supplemental deLong Declaration (Ex. 1031) relating to Exhibits 1040 and 1045–1060; (5) testimony in paragraphs 24, 26, 27, 41, 44, 47, 49, 56, 57, 59, and 60 of the Supplemental Rose Declaration (Ex. 1032) relating to Exhibits 1033–1035, 1037, and 1038; and (6) testimony at 117:23–118:23 of Ex. 2062. Paper 32. We do not reach the merits of Patent Owner's Motion to Exclude because our Decision does not rely on any of the evidence identified in Patent Owner's Motion. Accordingly, we dismiss Patent Owner's Motion to Exclude as moot.

V. CONCLUSION

After reviewing the record and weighing the evidence offered by both parties, we determine that Petitioner has not established, by a preponderance of the evidence, that claims 1–14 of the '035 patent are unpatentable as obvious over the combined teachings of Klimko, Kishi, and Ueno, or Klimko, Kishi, Bezuglov 1982 and/or Bezuglov 1986, and Ueno.

VI. ORDER

In consideration of the foregoing, it is hereby

ORDERED that Petitioner has not shown by a preponderance of the evidence that claims 1–14 of the '035 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude (Paper 33) is *dismissed*;

FURTHER ORDERED that Patent Owner's Motion to Exclude
(Paper 32) is *dismissed*; 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.

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