UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MICRO LABS LIMITED AND MICRO LABS USA INC.,
Petitioner,

v.

SANTEN PHARMACEUTICAL CO., LTD. AND
ASAHI GLASS CO., LTD.,
Patent Owner.

Case IPR2017-01434
U.S. Patent No. 5,886,035

DECLARATION OF TIMOTHY L. MACDONALD, PH.D.

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I, Timothy L. Macdonald, Ph.D., declare and state as follows:

I. INTRODUCTION

1. I am Professor of Chemistry, and former Chair of Chemistry, at the University of Virginia ("UVA"). I also hold a secondary appointment as Professor of Pharmacology at UVA.

2. I have been retained on behalf of Patent Owners Santen Pharmaceutical Co., Ltd. and Asahi Glass Co., Ltd. (together, "Patent Owner") as an independent expert consultant in the above-referenced *inter partes* review ("IPR") proceeding, to provide information and opinions on the teachings of the prior art and the state of the art, as relevant to the issued claims of U.S. Patent No. 5,886,035 ("the '035 Patent"). Ex. 1001.

3. I am being compensated for my time spent in connection with this matter at my usual rate of $550 per hour. My compensation is in no way contingent on the outcome of this case.

II. QUALIFICATIONS

4. My full *curriculum vitae* is attached as Exhibit A to this Declaration, but I have summarized below some of the relevant aspects in relation to the issues in this proceeding.

5. I have approximately 40 years of academic and professional experience in the field of medicinal chemistry, and over 20 years of overlapping

experience in the field of molecular pharmacology. I received a Bachelor of Science degree with Honors in 1971 from the University of California, Los Angeles. In 1975, I received a Ph.D. in synthetic organic chemistry from Columbia University, followed by a postdoctoral fellowship at Stanford University from 1975 to 1977 (also in synthetic organic chemistry). I held the position of Assistant Professor of Chemistry at Vanderbilt University from 1977 to 1982. Beginning with my appointment at Vanderbilt, my research was further specialized in medicinal chemistry. From 1982-1988, I held the position of a tenured Associate Professor of Chemistry at UVA, and I have been a full Professor of Chemistry from 1988 to the present time (with a secondary appointment as Professor of Pharmacology from 2003 to the present time). During my tenure as Professor at UVA, I have mentored 63 Ph.D. students and approximately 35 postdoctoral fellows, and I served as Chair of Chemistry from 1997 to 2003.

6. I have authored or co-authored more than 200 scientific publications. I am also a named inventor on over 50 issued US patents (and several pending applications), and I am a founder of 6 biotechnology spin-out companies based on my research at UVA. I have served as a medicinal chemistry consultant to many pharmaceutical companies, including Allergan, Biogen Idec, Abbott, Wyeth and SmithKline French, as well as several biotechnology companies.

7. A major focus of my research has been the characterization of lipid signaling systems that include lipid mediators and their receptors. My research has involved synthesis of analogs of naturally-occurring lipid compounds (including agonists and antagonists), and the investigation of structure-activity relationships ("SAR") and molecular pharmacology with respect to such compounds.

8. My expertise is generally applicable to lipid signaling systems, including prostaglandins and prostaglandin receptors. In that regard, for nearly 30 years (approximately 1988-2015), I served as a technical consultant to Allergan (a leader in the eye care field), and in that capacity, I provided my expertise in medicinal chemistry and molecular pharmacology in connection with the discovery and evaluation of novel compounds, including prostaglandin analogs for the treatment of glaucoma and ocular hypertension. Notably, my work with Allergan often involved reviewing and evaluating intraocular pressure ("IOP")-lowering and side effect data from animal studies involving IOP-lowering agents, including prostaglandin analogs. I have also testified on behalf of Allergan in several patent litigations involving Lumigan® (bimatoprost) as an expert in medicinal chemistry and molecular pharmacology.

III. SUMMARY OF OPINIONS

9. My opinions in this Declaration are based on documents I have reviewed in connection with this proceeding, and are further informed by my

knowledge and experience, including my decades of experience in medicinal chemistry and molecular pharmacology. A list of the documents and materials that I considered in connection with the development of my opinions set forth in this declaration is attached hereto as Exhibit B.

10. In my opinion, the claims of the '035 Patent are generally directed to a genus (and particular species) of 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ analogs, in which the omega chain is terminated by an aryloxyalkyl group, as well as medicines containing one of the claimed compounds as an active ingredient (including medicines for preventing or treating glaucoma or ocular hypertension). Therefore, in my opinion, a person of ordinary skill in the art ("POSITA") would have been an individual or a team with a Ph.D. degree in medicinal or organic chemistry, 3 years of work experience in medicinal chemistry, and sufficient familiarity interpreting or evaluating studies that use animal models to test for IOP reducing activity and side effects of compounds having the potential to treat glaucoma or ocular hypertension.

11. In my opinion, claims 1-14 of the '035 Patent do not contain any terms that require construction by the Board.

12. In my opinion, claims 1-14 of the '035 Patent would not have been obvious as of December 26, 1996 over Klimko (Ex. 1003) in view of Kishi (Ex. 1005) and Ueno Japan (Ex. 1006).

13. In my opinion, claims 1-14 of the '035 Patent would not have been obvious as of December 26, 1996 over Klimko (Ex. 1003) in view of Kishi (Ex. 1005), Ueno Japan (Ex. 1006) and Bezuglov 1982 (Ex. 1007) and/or Bezuglov 1986 (Ex. 1008).

14. In my opinion, without the benefit of improper hindsight, a POSITA as of December 26, 1996 would not have considered Compound C of Klimko to be a suitable lead compound. Klimko expressly teaches away from selection of Compound C as a lead compound. Accordingly, I disagree with both grounds of Petitioner's obviousness argument, each of which requires the selection of Compound C as a lead compound and its modification to obtain the claimed tafluprost compound.

15. In my opinion, even if Compound C had been considered a suitable lead compound as of December 26, 1996 (which it was not), it would not have been obvious to follow the elaborate and unpredictable development path proposed by Petitioner.

16. In my opinion, even if a POSITA had decided to pursue Petitioner's proposed development path toward a fluorinated Compound C, a POSITA would not have been motivated with a reasonable expectation of success to include **two** fluorines at the C15 position of Compound C.

17. In my opinion, Klimko '671 is not representative of the state of the art as of December 26, 1996 (as it was not yet published), but its explicit exclusion of C15 difluorination from its scope **does** establish that it would not have been obvious to C15 difluorinate Compound C of Klimko.

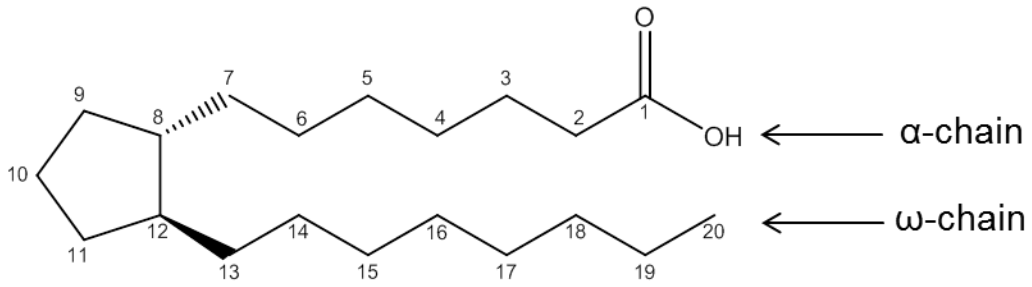
IV. STATE OF THE ART AS OF THE PRIORITY DATE OF THE '035 PATENT, DECEMBER 26, 1996

18. Since at least as early as 1977, researchers had been investigating the potential use of a class of compounds, called prostaglandins (described below), to reduce IOP for the treatment of glaucoma and ocular hypertension. Camras *et al*., "Reduction of intraocular pressure by prostaglandins applied topically to the eyes of conscious rabbits," *Invest. Ophthalmol. Vis. Sci.* 16:1125-1134 (1977) ("Camras 1977") (Ex. 2003). However, as of December 26, 1996 (nearly two decades later), only two prostaglandin analogs had made it to market. Xalatan® (latanoprost), developed by Pharmacia & Upjohn, was approved earlier in 1996 in the US, but only as second-line treatment. "Pharmacia Cleared To Market Xalatan, Drug for Glaucoma," *Wall St. J.* B7 (June 7, 1996) ("Xalatan 1996") (Ex. 2004). A second drug, isopropyl unoprostone (eventually marketed as Rescula®),[1] developed by R-

[1] In recent years, it has been determined that isopropyl unoprostone is not even a prostaglandin analog; it is now considered to be a "docosanoid" (a derivative of docosahexaenoic acid) that exhibits virtually no binding to prostaglandin receptor.

Tech Ueno, had been marketed in Japan since 1994, but there was limited experience with the drug outside the Japanese market. Linden and Alm, "Prostaglandin Analogues in the Treatment of Glaucoma," *Drug Aging*, 14(5):387-398 (1999) ("Linden 1999") (Ex. 2006) at 2.

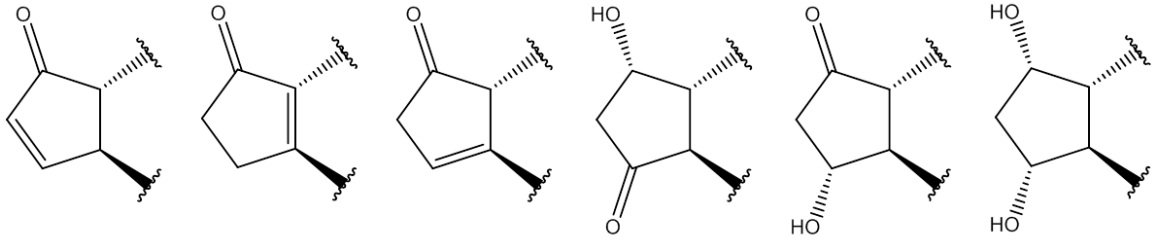
19. Prostaglandins are lipid compounds with the 20-carbon skeleton of prostanoic acid, which includes an alpha chain (α-chain), a cyclopentane ring, and an omega chain (ω-chain):



Nelson, "Prostaglandin Nomenclature," *J. Med. Chem.* 17(9):911-918 (1974) ("Nelson 1974") (Ex. 1026) at 1. As illustrated above, it was known that each carbon of the skeleton was numbered sequentially, C1 through C20. *Id*.

Fung and Whitson, "An evidence-based review of unoprostone isopropyl ophthalmic solution 0.15% for glaucoma: place in therapy," *Clin. Ophthalmol.* 8:543-554 (2014) (Ex. 2005) at 2.

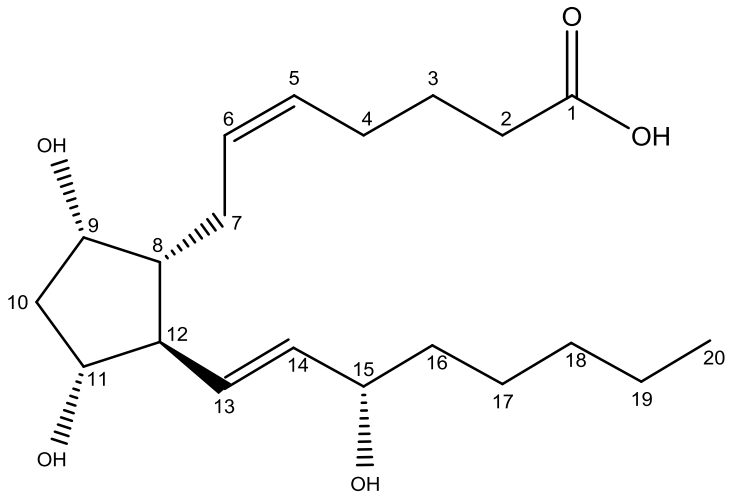
20. As of December 26, 1996, prostaglandins had been broken down into subclasses, A through J, based on the functional groups of the cyclopentane ring, *e.g.*:



Id. at 1-2. (In the case of PGF, the stereochemistry of the hydroxyl (-OH) group at the C9 position was indicated by an α or β designation. *Id*.) It was known in the art at that time that the small structural differences above lead to preferential binding to different classes of receptors. For example, PGD, PGE, PGF and PGI were known to preferentially bind DP, EP, FP and IP receptors, respectively. Coleman *et al.*, "VIII. International Union of Pharmacology Classification of Prostanoid Receptors: Properties, Distribution, and Structure of the Receptors and Their Subtypes," *Pharmacol. Rev.* 46(2):205-229 (1994) ("Coleman 1994") (Ex. 2007) at 3.

21. As of December 26, 1996, naturally-occurring prostaglandins were known to contain a hydroxyl group at the C15 position, as well as a *trans* double bond between C13 and C14. Nelson 1974 (Ex. 1026) at 1-2. (PGG was the lone exception, as it was known to contain a C15 hydroperoxyl (-O-OH) group, rather

than a C15 hydroxyl; but it was believed to be quickly converted *in vivo* to PGH. *Id*.) Prostaglandins were further classified by the numbers 1 through 3, representing the number of double bonds, *e.g.*, PGE_1 (1 double bond) or $PGF_{2\alpha}$ (2 double bonds). *Id*. For example, $PGF_{2\alpha}$ was known to have the following structure, containing the requisite C15 hydroxyl and C13-C14 double bond, as well as a second *cis* double bond at the C5-C6 position:



22. It was known as of December 26, 1996 that such structural 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). Konturek and Pawlik, "Physiology

and pharmacology of prostaglandins," *Dig. Dis. Sci*. 31(2 Suppl):6S-19S (1986) (Ex. 2008) at 5-11; Coleman 1994 (Ex. 2007) at 2.

23. At the same time, the biological activities of the various prostaglandins were known to overlap to varying degrees. In that regard, prostaglandins were known to be promiscuous molecules that can bind multiple receptors to varying degrees - causing side effects - likely because of certain structural **similarities** among the prostaglandins (*i.e.*, the prostanoic acid skeleton, C15 hydroxyl, C13-C14 *trans* double bond, and some shared functional groups on the cyclopentane ring). Stjernschantz and Alm, "Latanoprost as a new horizon in the medical management of glaucoma," *Curr. Opin. Ophthalmol.* 7(2):11-17 (1996) ("Stjernschantz 1996") (Ex. 2009) at 2 ("Naturally occurring prostaglandins tend to spill over on many different prostanoid receptors resulting in a mixed pharmacological response. For instance the ocular irritating effect of $PGF_{2\alpha}$ is probably at least partly due to the fact that this prostaglandin is a relatively effective agonist also on several of the EP receptors."); *see also* Collins and Djuric, "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs," *Chem. Rev.* 93:1533-1564 (1993) ("Collins 1993") (Ex. 2010) at 1 ("The side effects observed with PGs are due to their multiple pharmacological and physiological activities all of which may be manifested when the body is exposed to them systemically."). Further complicating matters is the fact that another

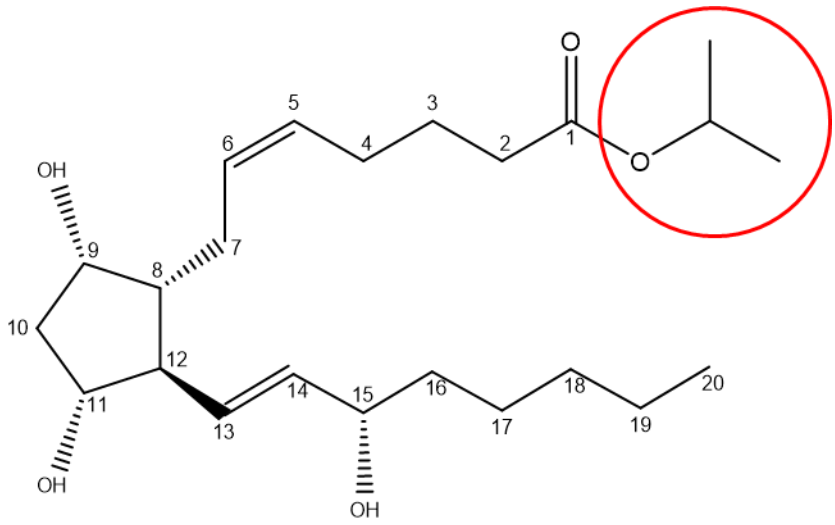
related group of compounds, thromboxanes, bind the prostaglandins' receptors, and vice-versa. Coleman 1994 (Ex. 2007) at 2.

24. As of December 26, 1996, medicinal chemistry was a highly unpredictable art, and it remains so to this day. This is especially true with respect to prostaglandins - a large class of compounds with very different, but overlapping, receptor profiles, which generate various distinct biological activities. Collins 1993 (Ex. 2010) at 1-2.

25. The complex relationship between chemical structure and biological activity (SAR) of the prostaglandins was reflected in slow progress toward a useful prostaglandin-based compound for the reduction of IOP in patients with glaucoma and ocular hypertension. As of 1977, researchers were already aware, based on animal studies, of the potential IOP-reducing activity of prostaglandins. Camras 1977 (Ex. 2003). And, by 1985, it had been demonstrated that $PGF_{2\alpha}$ could lower IOP in humans. Giuffrè, "The effects of prostaglandin $F_{2\alpha}$ in the human eye," *Graefe's Arch. Clin. Exp. Ophthalmol.* 222:139-141 (1985) (Ex. 2011). However, administration of $PGF_{2\alpha}$ also caused severe side effects, including conjuctival hyperemia (eye redness), eye irritation and pain, and headaches. *Id*. at 1, 3. Such side effects made prostaglandins an unattractive therapeutic option. There had also been concern regarding the initial **increase** in IOP after administration of prostaglandins, an unacceptable outcome for a drug intended to reduce IOP. *See*,

e.g., Camras 1977 (Ex. 2003) at 1 ("the well-known initial hypertensive phase"). This led to intensive research to develop a prostaglandin **analog** that could significantly reduce IOP while minimizing side effects.

26. Subsequent efforts unsuccessfully focused on esterification of $PGF_{2\alpha}$, a modification that had been previously shown to increase potency. For example, researchers investigated the following isopropyl ester (indicated in red) of $PGF_{2\alpha}$ ("$PGF_{2\alpha}$-IE"):



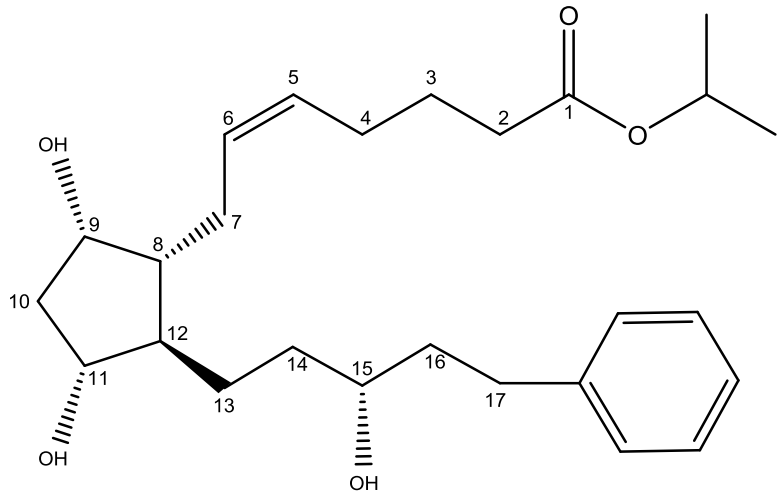
See, e.g., Bito and Baroody, "The ocular pharmacokinetics of eicosanoids and their derivatives: 1. Comparison of ocular eicosanoid penetration and distribution following the topical application of $PGF_{2\alpha}$, $PGF_{2\alpha}$ -1-methyl ester, and $PGF_{2\alpha}$ -1-isopropyl ester," *Exp. Eye Res.* 44:217-26 (1987) (Ex. 2012). It was found that the enhanced potency of $PGF_{2\alpha}$-IE was due to enhanced penetration of the compound into the eye. *Id*. at 7. It was also found that $PGF_{2\alpha}$-IE acted as a pro-drug, and was converted inside the eye to the active, free-acid form of $PGF_{2\alpha}$. *Id*. However,

while $PGF_{2\alpha}$-IE analog provided enhanced bioavailability and IOP-lowering activity, it did not eliminate the side effects that plagued the naturally-occurring $PGF_{2\alpha}$ compound: "The use of very low doses of $PGF_{2\alpha}$, made possible with the increased lipid solubility of the ester, did not cause a sufficiently efficient separation of effect and subjective side effects." Villumsen and Alm, "Prostaglandin $F_{2\alpha}$-isopropylester eye drops: effects in normal human eyes," *Br. J. Ophthalmol.* 73:419-26 (1989) (Ex. 2013) at 7.

27. Similarly, because the C15 hydroxyl was believed to be essential for biological activity in prostaglandins, researchers attempted - again unsuccessfully - to esterify $PGF_{2\alpha}$ at the C15 hydroxyl. Villumsen and Alm, "Ocular effects of two different prostaglandin $F_{2\alpha}$ esters: a doublemasked cross-over study on normotensive eyes," *Acta Ophthalmol.* 68:341-343 (1990) (Ex. 2014). The hope had been that the prostaglandin analog would exhibit decreased activity until the compound had penetrated the eye, resulting in decreased side effects. *Id.* at 1. However, again, the researchers observed that the new compound did not "provide[] a better separation between effect [on IOP] and side effects than $PGF_{2\alpha}$-IE." *Id.* at 3. The researchers expressly noted that "[o]ur results indicate that more radical changes of the parent molecule may be necessary to achieve this goal." *Id.*

28. As explained above, as of December 26, 1996, the only two compounds that had advanced to the point of being approved for reduction of IOP

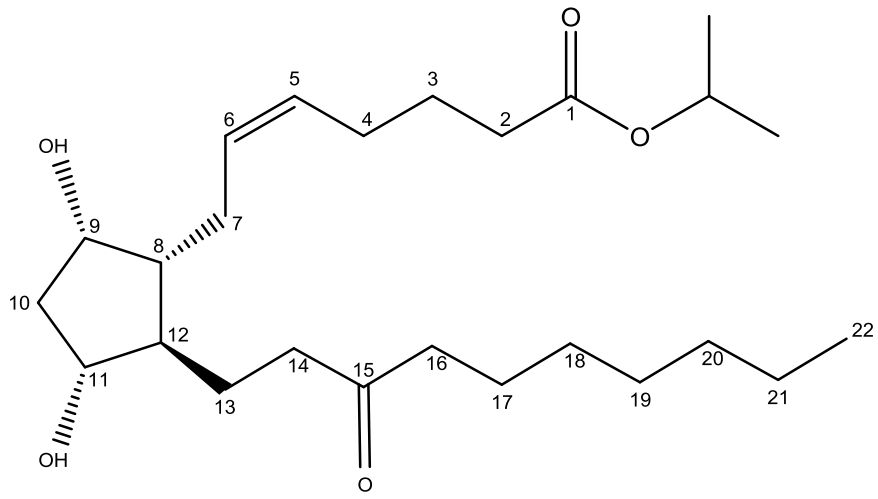
were Xalatan® (latanoprost) and isopropyl unoprostone. Latanoprost is 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (where the prefix "-nor" indicates the removal of carbon atoms from a parent compound; "trinor" indicates the removal of three carbon atoms, C18, C19 and C20):



Stjernschantz 1996 (Ex. 2009) at 2. Unlike $PGF_{2\alpha}$-IE, latanoprost replaced C18, C19 and C20 on the ω-chain with a phenyl group, and included a C13-C14 single bond (rather than a double bond). Latanoprost was heralded as an improvement over $PGF_{2\alpha}$ and $PGF_{2\alpha}$-IE, with less eye irritation and hyperemia, while maintaining significant IOP-lowering activity. Nevertheless, latanoprost was known to exhibit other significant side effects, *e.g.*, iridial pigmentation (discoloration of the iris of the eye). Xalatan 1996 (Ex. 2004).

29. As of December 26, 1996, the only other commercially-available drug for IOP-reduction was isopropyl unoprostone, which was not widely available

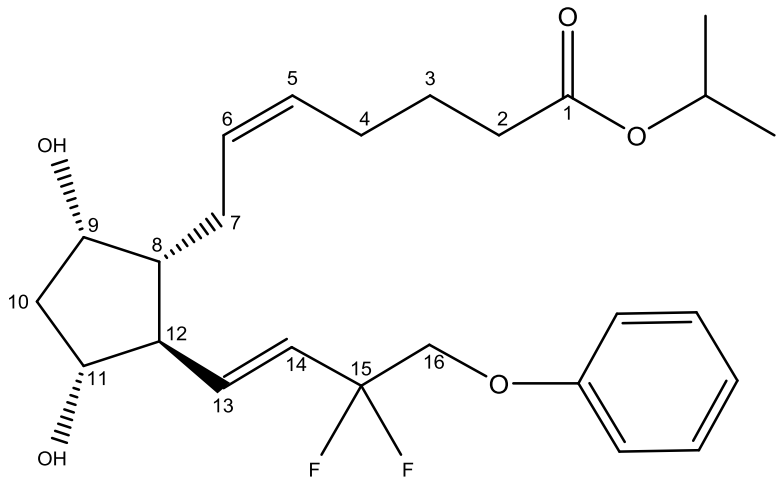
outside of Japan. Isopropyl unoprostone is 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$-IE:



Linden 1999 (Ex. 2006) at 4. Isopropyl unoprostone takes a very different approach, structurally, than latanoprost. There is no 17-phenyl group; instead the ω-chain is lengthened by 2 carbons. Moreover, the C15 hydroxyl is converted to a ketone. Indeed, it had been reported that isopropyl unoprostone targeted a different receptor than latanoprost; whereas latanoprost targeted the FP receptor, isopropyl unoprostone had very little affinity for that receptor. *Id.* at 5 ("Latanoprost is a more selective FP-receptor agonist than $PGF_{2\alpha}$. . ."), 8 ("In contrast to latanoprost, it has been reported that unoprostone only has a weak agonist activity for FP-receptors . . ."). Also, compared to latanoprost, isopropyl unoprostone was less effective and at least 20 times less potent. Camras and Alm, "Initial Clinical Studies with Prostaglandins and Their Analogues," *Surv.*

Ophthalmol. 41(Suppl. 2):S61-S68 (1997) (Ex. 2015) at 6 (citing Camras, "Prostaglandins," in *The Glaucomas* 69:1449-1461 (1996) (Ex. 2016)).

30. Notably, both commercially available prostaglandin analogs as of December 26, 1996 contained significant structural differences compared to Patent Owner's tafluprost compound (16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, isopropyl ester), the subject of this proceeding:



Neither of the commercially available prostaglandin analogs as of December 26, 1996 was fluorinated (let alone difluorinated, and at the C15 position specifically), neither contained a 16-phenoxy group, and neither contained a C13-C14 double bond.

V. SUMMARY OF THE '035 PATENT

31. The '035 Patent is generally directed to "15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its derivatives and their use as medicines, in particular, as medicines for eye diseases," and preferably for "glaucoma or ocular hypertension." Ex. 1001 at

2:16-18, 2:65-67; *see also id*. at 19:29-31 ("[T]he medicine of the present invention is effective as a therapeutic agent, particularly for glaucoma or ocular hypertension."). The inventive compounds include tafluprost (16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, isopropyl ester), which is within the scope of all of the claims of the '035 Patent, and is the sole subject of the Petitioner's obviousness arguments. *Id*. at 14:25-26, 22:36-23:15 (Example 9), 31:1-32:31 (claims). Unlike the commercially-available prostaglandin analogs of the time, tafluprost was C15 difluorinated, contained a 16-phenoxy group, and a C13-C14 double bond.

32. The specification explains that naturally-occurring PGF compounds are able to lower IOP, but "they are irrita[ting] to the eye and have a problem of their inflammatory side effects such as congestion and damage to the cornea." *Id*. at 1:11-18. Therefore, achieving a suitable side effect profile was a major goal of the research into prostaglandin derivatives for the treatment of glaucoma. *Id*. at 1:18-21. Although latanoprost had been licensed as of December 26, 1996 for the treatment of glaucoma and ocular hypertension, it still caused certain undesirable side effects, and there was room for improvement in the duration of efficacy. *Id*. at 1:31-43. With respect to side effects, latanoprost was known to induce melanin production, causing "iridial pigmentation," *i.e.*, discoloration of the iris of the eye. *Id*. at 1:40-43. "For this reason, 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.

33. The inventors of the '035 Patent discovered that 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its derivatives overcame the problems plaguing the prior art, and provided longer-lasting efficacy:

> [T]he present inventors have found that 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ and its derivatives are superior to the known natural $PGF_{2\alpha}$ 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. They are characterized in that they stimulate[] melanogenesis [*i.e.*, melanin production, causing eye discoloration] much less as well as in that their efficacy lasts longer than Latanoprost.

Id. at 2:7-15.

34. In addition to C15 difluorination, the inventors also emphasized a preference for omega chains other than the one present on naturally-occurring prostaglandin: "[A]mong the fluorine-prostaglandin derivatives of the present invention, those having an ω-chain which is not of the naturally occurring type . . . are preferred." *Id*. at 2:59-62. For example, the omega chain of tafluprost terminates with a 16-phenoxy group. *Id*. at 14:25-26 ("**16-phenoxy**-15-deoxy-

15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$, isopropyl ester") (emphasis added).

35. In Example 23, the inventors compared latanoprost against four compounds of the '035 Patent (referred to as Compounds A-D), with respect to IOP-lowering and melanogenesis. *Id*. at 28:1-30:67. The '035 Patent compounds included tafluprost (referred to as "Compound D"), as well as 16-phenoxy-15-deoxy-15,15-difluoro-17,18,19,20-tetranorprostaglandin $F_{2\alpha}$ methyl ester (which shares the same free acid form as tafluprost and is referred to as "Compound A"). *Id*. at 27:7-39.

36. The IOP-lowering efficacy of the tested compounds, after a single administration to macaques, was reported in Table 1:

TABLE 1

			Change in ocular pressure after application (mmHg)		
			4 hours	6 hours	8 hours
Compound A	(0.01%)	[7]	−1.7	−2.3	−2.3
	(0.1%)	[8]	−2.6	−3.0	−3.1
Compound B	(0.01%)	[10]	−0.9	−1.0	−1.0
	(0.1%)	[9]	−1.3	−1.4	−2.0
Compound C	(0.01%)	[9]	−0.6	−1.2	−2.0
	(0.1%)	[9]	−1.0	−0.4	−2.0
Compound D	(0.01%)	[12]	−0.1	−0.8	−1.3
	(0.1%)	[12]	−0.8	−1.6	−2.3
Latanoprost	(0.01%)	[5]	−0.4	−1.2	−0.6
	(0.1%)	[8]	−0.8	−1.3	−0.8

Id. at 28:16-49. The inventors observed that "the intraocular pressure had already started to decrease 4 hours after the application of compounds of the present invention and was still decreasing even 8 hours after the application." *Id*. at 28:50-

53. In comparison to latanoprost, "Compound A lowered the intraocular pressure twice as much as Latanoprost did 6 hours after application, and about 4 times as much 8 hours after application." *Id*. at 28:53-56. Compound D (tafluprost) performed similarly to latanoprost at 4 and 6 hours after application, but at 8 hours, it lowered IOP about 2-3 times more than latanoprost. *Id*. at 28:35-49 (Table 1). This data "proves that the compound of the present invention has a long-lasting effect of lowering intraocular pressure." *Id*. at 28:57-58.

37. With respect to IOP-lowering efficacy after a two week repeated application test in macaques, the results were reported in Table 2:

TABLE 2

			Difference in intraocular pressure between the right and left eyes (mmHg) [(Intraocular pressure of the eye treated with test compound) − (Intraocular pressure of the eye treated with vehicle solution)]				
			1st day	3rd day	7th day	10th day	14th day
Compound A	(0.1%)	[7]	−0.5	−2.7	−3.4	−3.3	−2.6
Compound B	(0.1%)	[7]	−0.5	−2.5	−3.2	−2.8	−1.9
Compound D	(0.01%)	[7]	−2.1	−2.8	−3.0	−2.2	−1.9
	(0.1%)	[7]	−1.6	−4.4	−3.9	−2.7	−2.4
Latanoprost	(0.1%)	[7]	−0.6	−2.1	−1.7	−0.7	−0.3

Id. at 28:59-29:33. For the '035 Patent compounds in general, "the intraocular pressure had remarkably decreased since the 3rd day from the start of the application . . . and kept low till the 14th day." *Id*. at 29:34-37. Tafluprost (Compound D), in particular, "lowered intraocular pressure about 2 to 8 times as much as Latanoprost did." *Id*. at 29:37-38. And, no side effects were noted. *Id*. at

29:39-41 ("When the intraocular pressures were measured, no turbid cornea, abnormal conjunctiva vessels, conjunctivoma or secretions were observed."). As with the data in Table 1 after a single application, the results after the two week repeated application test "proves that the compound of the present invention has an excellent effect of lowering intraocular pressure." *Id*. at 29:42-43.

38. The inventors of the '035 Patent also investigated the effect of their novel compounds on melanogenesis in B16 pigment cells, as compared to latanoprost. *Id*. at 29:44-30:52. The free acid forms (*i.e.*, the active forms in the body) of Compounds A-D were evaluated; because tafluprost (Compound D) and Compound A have the same free acid form, results are only presented for Compound A. *Id*. at 30:35-37, 30:40-41. The results were presented in Table 3:

TABLE 3

	Concentration		
	1 μM	10 μM	100 μM
Compound A	102%	113%	111%
Compound B	110%	122%	107%
Compound C	107%	116%	127%
Latanoprost	109%	136%	224%

Id. at 30:42-52. Each of the tested '035 Patent compounds performed better than latanoprost with respect to avoiding melanogenesis:

> As is evident from Table 3, compounds of the present invention did not have much effect and, the melanin contents in the presence of 100 μM of them were only about 1.1 to 1.3 times higher than that in the absence of them. On the other hand, when Latanoprost was added at

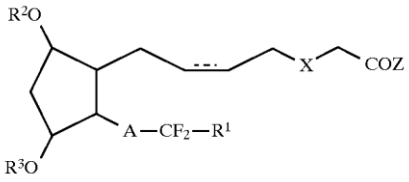
concentrations of 10 μM and 100 μM, the melanin contents were about 1.4 times and about 2.2 times, respectively, higher than that in its absence.

Id. at 30:53-60. "This proves that compounds of the present invention have little effect on melanogenesis and do not cause irid[i]al pigmentation when applied repeatedly." *Id*. at 30:61-63.

39. Overall, "[t]he results of the pharmacological tests clearly indicate that the compounds of the present invention are useful as long-lasting therapeutic medicines for glaucoma, are hardly irritant to the eye and have little effect on melanogenesis." *Id*. at 30:64-67.

40. Consistent with the data of the '035 Patent - demonstrating the advantages of the disclosed compounds over the prior art - independent claim 1 of the '035 Patent recites a genus of 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ analogs, in which the omega chain is terminated by an aryloxyalkyl group:

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



(1)

wherein A is an ethylene group, a vinylene group, an ethynylene group, --OCH_2-- or --SCH_2 --,

R^1 is a substituted or unsubstituted aryloxyalkyl group,

each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is --CH_2 --, --O-- or --S--,

Z is --OR^4, --$NHCOR^5$, --$NHSO_2R^6$ or --SR^7, or forms a single bond together with R^2 or R^3,

each of R^4, R^5, R^6 and R^7 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.

Id. at 31:2-26.

41. Dependent claims 2 and 3 further narrow the genus of claim 1, with claim 3 reciting only three specific compounds, including the tafluprost compound:

> 3. The compound according to claim 1, which is **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 a salt **thereof**.

Id. at 31:27-32:3 (emphasis added).

42. Dependent claims 4-11 are directed to "[a] medicine containing the compound according to claim 1 as an active ingredient." *Id*. at 32:4-21. Claim 5 limits the medicine to "a preventive or therapeutic medicine for an eye disease,"

and claim 6 further limits the eye disease to "glaucoma or ocular hypertension." *Id*. at 32:6-9. Claims 7-11 narrow the genus of claim 1 that is included in the medicine. *Id*. at 32:10-21.

43. The second of two independent claims - claim 12 - recites a medicine with one of three specific compounds, including tafluprost:

> 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 ingredient.

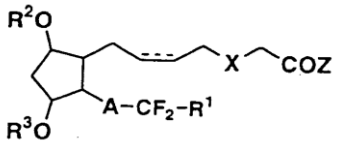
Id. at 32:22-27 (emphasis added). Claim 13 limits the medicine to "a preventive or therapeutic medicine for an eye disease," and claim 14 further limits the eye disease to "glaucoma or ocular hypertension." *Id*. at 32:28-31.

VI. PROSECUTION HISTORY FOR THE '035 PATENT

44. I understand that the '035 Patent issued on March 23, 1999 from an application filed on December 18, 1997, claiming an earliest priority date of December 26, 1996, based on the earlier filing of three Japanese patent applications. Ex. 1001; Ex. 1002.

45. The originally-filed application contained 20 claims with two independent claims - 1 and 18:

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



(1)

wherein A is an ethylene group, a vinylene group, an ethynylene group, $-OCH_2-$ or $-SCH_2-$,

R^1 is a substituted or unsubstituted C_{3-8} alkyl group, a substituted or unsubstituted C_{3-8} alkenyl group, a substituted or unsubstituted C_{3-8} alkynyl group, a substituted or unsubstituted C_{3-8} cycloalkyl group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aryloxyalkyl group,

each of R^2 and R^3 which are independent of each other, is a hydrogen atom or an acyl group, or forms a single bond together with Z,

X is $-CH_2-$, -O- or -S-,

Z is $-OR^4$, $-NHCOR^5$, $-NHSO_2R^6$ or $-SR^7$, or forms a single bond together with R^2 or R^3,

each of R^4, R^5, R^6 and R^7 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.

18. 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 ingredient.

Ex. 1002 at 365, 367.

46. The Examiner rejected claims 1-5 and 9-15 as obvious over the prior art, but allowed claims 6-8 and 16-20 (including independent claim 18). *Id*. at 113-116. Claim 6 limited the compound of claim 1 to one in which "R^1 is a substituted or unsubstituted aryloxyalkyl group." *Id*. at 366. Claim 7 depended from claim 6 and further limited R^1 to "a phenoxymethyl group, a 3,5-dichlorophenoxymethyl group or a 3-chlorophenoxymethyl group." *Id*. Claim 8 limited the compound of claim 1 to particular species: "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 a salt thereof." *Id*. Claims 16 and 17 depended from claim 9 (which recited "[a] medicine containing the compound according to Claim 1 as an active ingredient"), and those claims recited the same structural limitations as claims 6 and 7, respectively. *Id*. at 367. Finally, claims 19-20 depended from independent claim 18; claim 19 limited the claimed medicine to "a preventive or therapeutic medicine for an eye disease," and claim 20 further recited that "the eye disease is glaucoma or ocular hypertension." *Id*.

47. In response, independent claim 1 was "amended to include the limitation of [c]laim 6," which the Examiner found to be patentable. *Id*. at 111. Claims 2-6 and 16 were canceled. *Id*. at 110. The Examiner allowed claims 1, 7-15 and 17-20, which issued as claims 1-14 of the '035 Patent. *Id*. at 105-109.

VII. LEVEL OF ORDINARY SKILL IN THE ART

48. I have been informed by counsel and I understand that the '035 Patent was filed on December 18, 1997, but that it claims an earliest priority date of December 26, 1996, based on the earlier filing of three Japanese patent applications. I have been informed by counsel and I understand that Petitioner has not challenged the priority date of December 26, 1996. Therefore, I have been instructed by counsel that, for purposes of this Declaration only, the invention date of the claims of the '035 Patent is December 26, 1996.

49. I have been informed by counsel and I understand that the "POSITA" is a hypothetical person who is presumed to be familiar with the relevant scientific field and its literature at the time of the invention. I additionally understand that this hypothetical person is a person of ordinary creativity in his or her field. The POSITA is assumed to be aware of all relevant prior art at the time an invention took place.

50. I am informed by counsel and I understand that the level of ordinary skill in the art may be determined by reference to certain factors, including (1) the

educational level of the inventor, (2) the type of problems encountered in the art, (3) prior art solutions to those problems, (4) the rapidity with which innovations are made, (5) the sophistication of the technology, and (6) the educational level of active workers in the field.

51. It is my opinion that the claims of the '035 Patent are generally directed to a genus (and particular species) of 15,15-difluoro-15-deoxy-$PGF_{2\alpha}$ analogs, in which the omega chain is terminated by an aryloxyalkyl group, as well as medicines containing one of the claimed compounds as an active ingredient (including medicines for preventing or treating glaucoma or ocular hypertension). Therefore, in my opinion, a POSITA would have been an individual or a team with a Ph.D. degree in medicinal or organic chemistry, 3 years of work experience in medicinal chemistry, and sufficient familiarity interpreting or evaluating studies that use animal models to test for IOP reducing activity and side effects of compounds having the potential to treat glaucoma or ocular hypertension.

52. With respect to Petitioner's proposed definition of a POSITA, I disagree that the ordinary level of skill in the art would have required a chemist with "at least several years of experience researching and developing preventative or therapeutic medicines for treatment of eye diseases." Ex. 1027, ¶ 28; Ex. 1028, ¶ 22. Similarly, I disagree that the ordinary level of skill in the art would have required a chemist with "sufficient familiarity interpreting or evaluating studies

that use animal models to test for IOP reducing activity and side effects of compounds having the potential to treat glaucoma or ocular hypertension." Ex. 1028, ¶ 22. Chemists working on such projects often do not have specific prior experience with eye diseases or animal studies. Rather, as Petitioner concedes, "it would be reasonable that the [POSITA] would be working as part of a multi-disciplinary team with respect to the subject research." Ex. 1027, ¶ 28; Ex. 1028, ¶ 22. Consistent with that understanding in the art, my proposed definition requires an individual **or team** with sufficient familiarity interpreting or evaluating studies that use animal models to test for IOP reducing activity and side effects of compounds having the potential to treat glaucoma or ocular hypertension.

53. I also disagree that that the ordinary level of skill in the art would have required a chemist with "familiarity designing, formulating and evaluating ophthalmic compositions for treatment of eye conditions that include glaucoma or ocular hypertension." Ex. 1027, ¶ 28; Ex. 1028, ¶ 22. Some claims of the '035 Patent (claims 4-14) are generally directed to medicines containing at least one of the novel compounds as an active ingredient, but those claims do not recite any particular formulation details. Ex. 1001 at 32:4-32:31.

VIII. CLAIM CONSTRUCTION

54. I have been informed by counsel and I understand that, in IPR proceedings, claims of unexpired patents are construed under the "broadest

reasonable interpretation" standard. Under this standard, claims are construed according to their broadest reasonable construction in light of the specification as it would be interpreted by a POSITA at the time of the invention.

55. I have been informed by counsel and I understand that, if the patentee has acted as her own lexicographer and has clearly defined a claim term in the patent specification, that definition is applied.

56. I have been informed by counsel and I understand that a patentee's arguments during prosecution will only operate to limit the patent claims if there was a clear and unambiguous disavowal of scope by the patentee.

57. In my opinion, claims 1-14 do not contain any terms that require construction by the Board.

IX. OBVIOUSNESS ANALYSIS

58. I have been informed by counsel and I understand that an obviousness analysis asks if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a POSITA to which said subject matter pertains.

59. I have been informed by counsel and I understand that obviousness is a factual inquiry, where the following factors guide the analysis: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; (4) and the objective secondary

factors of nonobviousness (for example, commercial success, long-felt unmet need, unexpected results, copying).

60. I have been informed by counsel and I understand that obviousness may be shown by a combination of prior art references, but there must be a reason, whether explicit or implicit, to combine elements found in the prior art. I further have been informed and understand that a POSITA must have had a reasonable expectation of success in combining the prior art references.

61. I have been informed by counsel and I understand that, in order to evaluate the obviousness of the '035 Patent claims over a given prior art combination, I should analyze whether the prior art references disclose every limitation of the challenged claims either explicitly or inherently, as those references are read by the POSITA at the time of the invention. Then I am to determine whether that combination makes the claimed invention as a whole obvious to the POSITA by a preponderance of the evidence, at the time of the invention. I understand that the preponderance of the evidence standard is satisfied if the proposition is more likely to be true than not true.

62. I have been informed by counsel and I understand that determining whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds is a two-part inquiry: 1) whether a POSITA at the time of the invention would have selected the asserted prior art compound as a lead

compound, and 2) whether the prior art would have provided a POSITA with a reason or motivation to modify the lead compound to make the claimed compound with a reasonable expectation of success.

63. I have been informed by counsel and I understand that a lead compound is a prior art compound that would be most promising to modify in order to improve upon its activity and obtain a compound with better activity. I further have been informed and understand that lead compound selection is guided by evidence of the compound's pertinent properties, including activity, potency, and toxicity, and that absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.

64. I have been informed by counsel and I understand that although the reason or motivation for modifying a lead compound may come from any number of sources and need not necessarily be explicit in the prior art, pertinent properties guide the analysis. I further have been informed and understand that a reference may be said to teach away from a particular modification when a POSITA, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the inventors.

A. The Claimed Tafluprost Compound Would Not Have Been Obvious to a POSITA as of December 26, 1996

65. Petitioner presents two similar grounds of invalidity, both based primarily on a combination of three prior art references: Klimko (Ex. 1003), Kishi (Ex. 1005) and Ueno Japan (Ex. 1006). According to Petitioner, modification of "Compound C" of Klimko,[2] in view of Kishi and Ueno Japan, yields the tafluprost compound, which is within the scope of each claim of the '035 Patent. Ex. 1027, ¶ 123. Petitioner's second ground adds two additional prior art references, Bezuglov 1982 (Ex. 1007) and Bezuglov 1986 (Ex. 1008), requiring a combination of five prior art references to allegedly arrive at the claimed tafluprost compound. Ex. 1027, ¶ 129.

66. As summarized here and detailed below, it is my opinion that Petitioner's proposed path to the tafluprost compound would have been entirely counterintuitive to a POSITA. Moreover, a POSITA would not have had a reasonable expectation that the piecemeal combination of features from the 3-5 asserted prior art references would yield a compound that was successful for its intended purpose, *i.e.*, lowering IOP.

[2] The '035 Patent also discloses a "Compound C." Unless otherwise specified, references to "Compound C" are to the compound disclosed in Klimko, not the '035 Patent.

67. As an initial matter, a POSITA would not have considered Compound C of Klimko to be a lead compound, as required for Petitioner's obviousness argument. For this reason alone, Petitioner's obviousness argument is untenable. Compound C of Klimko is the only alleged lead compound identified by Petitioner. But, Klimko **expressly teaches away** from further development efforts with Compound C, because of its unacceptable therapeutic profile, including severe side effects and an initial increase in IOP after administration. Instead, Klimko identifies other compounds with purportedly better IOP-lowering activity and milder side effects. Petitioner's selection of Compound C as a lead compound can only be improper hindsight based on certain structural similarities between Compound C and tafluprost.

68. Similarly, Petitioner's proposed trajectory from Compound C to tafluprost is a convoluted path that could only have been constructed in hindsight:

a. replacing the C15 hydroxyl with a hydrogen to diminish side effects (based on Kishi), despite an expected reduction in IOP-lowering activity;

b. replacing the C15 hydrogen of Kishi with fluorine (based on Bezuglov 1982, Bezuglov 1986 and/or Ueno Japan), in order to mimic the hydroxyl group that had just been removed and thereby restore the

IOP-lowering activity (while somehow not also reinstating Compound C's severe side effects); and

c. choosing **two** fluorines at C15 (based on Ueno Japan), even though the difluoride bears little (if any) resemblance to the **one** hydroxyl that the modification is meant to mimic.

A POSITA would not have been motivated to undertake the sort of elaborate and unpredictable combination that Petitioner suggests, especially since none of the asserted prior art references disclose any fluorinated compound with demonstrated IOP-lowering activity or an acceptable ocular side effect profile.

69. Importantly, the only asserted prior art reference that discloses difluorination of a prostaglandin - Ueno Japan - has nothing to do with IOP-lowering, and would not have motivated a POSITA to difluorinate the C15 position of Compound C of Klimko. Ueno Japan is directed to histamine antagonism in allergic and inflammatory diseases, and to treating liver and biliary tract diseases; in both cases the mechanism of action is undisclosed. There is no mention of using the disclosed difluorinated compounds to lower IOP, and there is no discussion of ocular side effects. Indeed, it was known that the assignee of Ueno Japan (R-Tech Ueno) had been marketing isopropyl unoprostone - **a non-fluorinated compound** - for IOP reduction in Japan since 1994.

70. Petitioner's only other alleged motivation to difluorinate Compound C at position 15 is based on supposed practical considerations, *i.e.*, that a C15 difluorinated compound - without a stereogenic center at position 15 - would have been easier to manufacture and analyze than a C15 monofluorinated compound. However, this argument is belied by the fact that, as of December 26, 1996, latanoprost (which has a stereogenic center at C15) had already been licensed. Petitioner's argument also begs the question as to whether C15 difluorination would have been expected to provide a suitable therapeutic profile, especially since the original therapeutic profile of Compound C was unacceptable. As of December 26, 1996, there was no evidence whatsoever that a C15 difluorinated prostaglandin derivative would perform as well as, or better than, a C15 monofluorinated prostaglandin derivative (nor was there any evidence that a C15 monofluorinated prostaglandin derivative would perform better than an unfluorinated prostaglandin derivative).

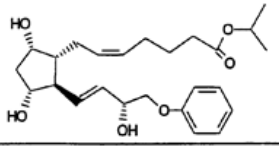
71. Finally, Petitioner's reliance on the unpublished Klimko '671 patent application (Ex. 1012) is misplaced. According to Petitioner, Klimko '671 demonstrates that POSITAs as of December 26, 1996 monofluorinated the C15 position of prostaglandin analogs for purposes of IOP-lowering. But, I understand from counsel that Klimko '671 is not prior art in this proceeding. And, contrary to Petitioner's argument, the inventors of Klimko '671 state that the prior art did not

teach C15 monofluorination for IOP-lowering. Importantly, Klimko '671 expressly excludes difluorination at the C15 position of a prostaglandin analog. It affirmatively establishes that it would **not** have been obvious to C15 difluorinate Compound C of Klimko.

1. A POSITA Would Not Have Considered Compound C of Klimko as a Lead Compound

72. Petitioner's obviousness argument depends on the selection of "Compound C" of Klimko as the lead compound in the development of tafluprost. Ex. 1027, ¶¶ 103-109, 124; Ex. 1028, ¶ 70. Petitioner has not identified any other alleged lead compounds. In my opinion, Petitioner's obviousness argument is fatally flawed because a POSITA would not have considered Compound C of Klimko to be a lead compound. To the contrary, Klimko **expressly teaches away** from further development of Compound C.

73. Compound C of Klimko is 16-phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$ isopropyl ester:

	COMPOUND NAME	COMPOUND STRUCTURE
C	16-Phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester	

Ex. 1003 at 15:1-50 (Table 2).

74. The "Background of the Invention" of Klimko explains that Compound C is a compound that had been previously shown to be unacceptable.

In particular, Klimko cites to European Patent Application No. 0364417 A1 ("Stjernschantz") (Ex. 2017) for its assessment of "16-phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$ isopropyl ester," *i.e.*, Compound C of Klimko. Ex. 1003 at 2:54-56, 3:38-39. As expressly recognized by Klimko, the testing of Compound C in Stjernschantz demonstrated that it had an "unacceptable therapeutic profile":

> The IOP data revealed by Stjernschantz et al. for **16-phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester [i.e., Compound C]** (see Stjernschantz et al, page 17, Table V) indicate an initial increase in IOP (1-2 hours after administration) followed by a decrease. Moreover, this compound displays unacceptable hyperemia (see Stjernschantz et al., Table IV, line 40). In short, data from Stjernschantz et al. demonstrate that the oxygen-interrupted omega chain subgeneric class of compounds (see formula 2) **displays an unacceptable therapeutic profile**.

Id. at 3:39-44 (underlining in original, bold added).

75. Stjernschantz evaluated 11 different derivatives, numbered (1) - (10) and (20), with a ring structure in the omega chain. Ex. 2017 at 4:8-20. Stjernschantz identified Compounds (3), (6), (7) and (9) as the "most preferred" derivatives - all of which were **17-phenyl**-18,19,20-**trinor** analogs. *Id*. at 4:21-24. This led to the further development and eventual commercialization of latanoprost, *i.e.*, Compound (9) of Stjernschantz. In contrast, Compound (4) of Stjernschantz -

the same compound as Compound C of Klimko - was a **16-phenoxy**-17,18,19,20-**tetranor** analog. *Id*. at 4:13.

76. As highlighted by the inventors of Klimko, Compound (4) in Stjernschantz caused a high degree of hyperemia (2.3±0.3), nearly as high as for naturally occurring prostaglandins (2.8±0.2). *Id*. at 15:1-42 (Table IV).

77. The inventors of Klimko also emphasized that Compound (4) in Stjernschantz caused an unacceptable initial **increase** in IOP following its administration. In particular, Table V reports that, at 1-2 hours after administration of Compound (4), experimentally-treated cat eyes (group "E") exhibited an increase in IOP from 20.5±1.2 mmHg to 25.7±1.2 mmHg, which was also higher than the value in control (group "C") eyes of 22.7±1.1 mmHg. *Id*. at 16:1-17:55 (Table V).

78. In contrast to the unacceptable therapeutic profile of Compound C, Klimko identifies other compounds - namely cloprostenol and fluprostenol - which add "a chlorine atom or a trifluoromethyl group to the meta position on the phenoxy ring at the end of the omega chain":

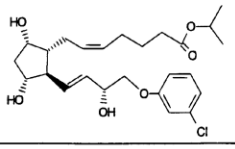
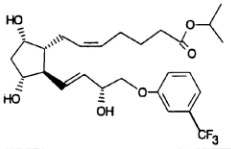
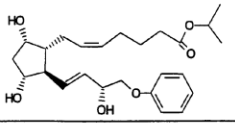
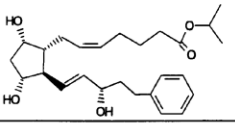
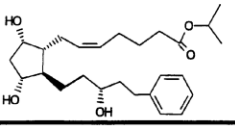
> It has now been unexpectedly found that cloprostenol, fluprostenol, and their pharmaceutically acceptable salts and esters show significantly greater IOP reduction than the compounds of Stjernschantz et al., while having a similar or lower side effect profile. In particular, it appears that the addition 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.

Ex. 1003 at 3:48-53.

79. Klimko evaluated Compound C against other compounds, and confirmed that Compound C exhibits the unacceptable therapeutic profile discussed above.

80. Specifically, Klimko "compared the IOP lowering activity and side effects of five compounds," including Compound C and the isopropyl esters of cloprostenol (Compound A) and fluprostenol (Compound B):

	COMPOUND NAME	COMPOUND STRUCTURE
A	Cloprostenol, isopropyl ester	
B	Fluprostenol, isopropyl ester	
C	16-Phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester	
D	17-Phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester	
E	13,14-Dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester	

Id. at 14:47-51, 15:1-50 (Table 2).

81. With respect to side effects, Compounds A-E were tested for conjunctival hyperemia - eye redness due to excess blood flow, an important side effect in glaucoma patients being treated with prostaglandin analogs. *Id*. 16:1-18:6 (Example 5). Guinea pigs treated with the compounds were scored for hyperemia at 1, 2, 3 and 4 hours after dosing. *Id*. at 16:16-17. The results were presented in Table 3 as the percent frequency of each score:

Table 3: Guinea Pig Conjunctival Hyperemia**

Compound (isopropyl ester)	Prostaglandin Dose																			
	0.03 µg					0.1 µg					0.3 µg					1.0 µg				
	Score				N*	Score				N*	Score				N*	Score				N*
	0	1	2	3		0	1	2	3		0	1	2	3		0	1	2	3	
A (Cloprostenol)	40	60	0	0	5	60	33	7	0	23	23	61	13	3	21	18	59	19	4	23
B (Fluprostenol)	17	70	13	0	6	12	88	0	0	6	17	50	29	4	6	21	60	13	6	12
C (16-Phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$)	33	54	13	0	6	4	71	25	0	6	0	0	62	38	6	0	4	33	63	6
D (17-Phenyl-18,19-20-trinor $PGF_{2\alpha}$)	46	54	0	0	6	23	62	13	2	12	10	61	27	2	12	15	56	17	12	12
E (13,14-Dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$)	80	20	0	0	5	75	25	0	0	5	40	60	0	0	5	39	56	6	0	9

* Number of animals tested
**Numbers indicate percent incidence for that score

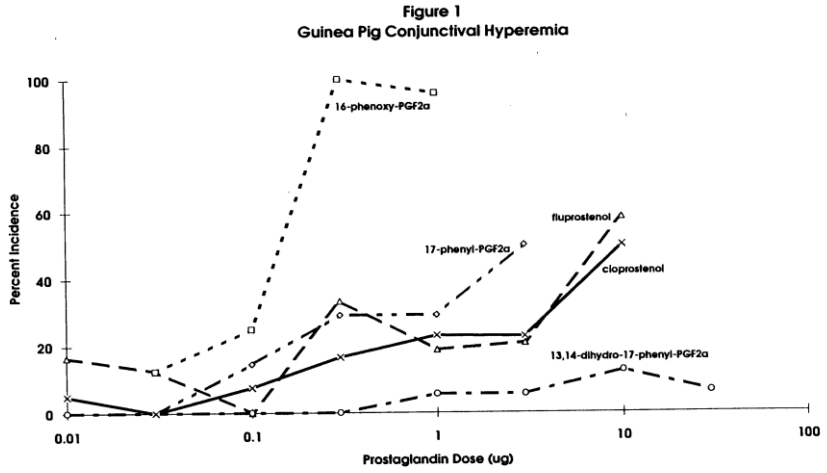
Id. at 17:1-55 (Table 3).

82. Compound C was singled out as producing the highest levels of conjunctival hyperemia: "Compound C (16-phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$, isopropyl ester) produces significant hyperemia at low doses, and at 0.3 and 1.0 µg doses, all eyes received one or more scores of +3 [on a scale of 0 to +4, with +4 being worst]." *Id*. at 17:57-18:1. On the other end of the spectrum, Compound E (latanoprost, a licensed prostaglandin analog) caused only "mild hyperemia," and the other compounds likewise caused less hyperemia than Compound C:

> Compound D (17-phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester) produces less hyperemia than compound C, but significantly more than compound E (13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$, isopropyl ester), which produces only mild hyperemia. The hyperemia produced by compound A (cloprostenol, isopropyl ester) and compound B (fluprostenol, isopropyl ester) 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 18:1-6.

83. Figure 1 of Klimko, which depicts the percent incidence of a score of +2 or +3, demonstrates the vast difference in hyperemia produced by Compound C ("16-phenoxy-PGF2α"), as compared to every other compound studied:



Id. at 29 (Figure 1).

84. To assess the efficacy of Compounds A-E in lowering IOP, the compounds were administered in five doses to cynomolgus monkey eyes in which

hypertension had been previously induced. *Id*. at 18:8-19:35 (Example 6). IOP was then measured "from 1 to 7 hours after the first dose, 16 hours after the fourth dose, and 1 to 4 hours after the fifth dose." *Id*. at 18:18-20. The percent IOP reduction was presented in Table 4:

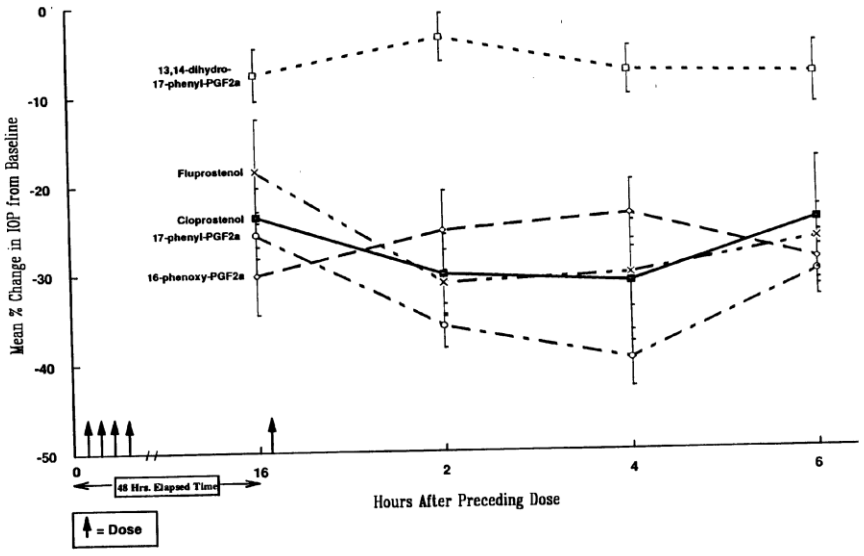
Table 4: Percent IOP Reduction in Lasered Cynomolgus Monkeys

Compound (isopropyl ester)	Baseline IOP (mm Hg)	Percent IOP Reduction (Hours after Last Dose/Dose#)			
		16/4	2/5	4/5	6/5
A (Cloprostenol)	36.9	23.6 ± 3.3	30.2 ± 4.5	31.2 ± 6.8	24.4 ± 6.9
B (Fluprostenol)	41.6	18.4 ± 5.9	31.2 ± 3.7	30.3 ± 3.8	26.6 ± 3.6
C (16-Phenoxy-17,18,19,20-tetranor $PGF_{2\alpha}$)	38.2	30.2 ± 4.4	25.3 ± 4.5	23.6 ± 3.8	28.9 ± 3.0
D (17-Phenyl-18, 19,20-trinor $PGF_{2\alpha}$)	40.8	25.6 ± 2.6	36.0 ± 2.4	39.8 ± 3.1	30.3 ± 2.8
E (13,14-Dihydro-17-phenyl-18,19, 20-trinor $PGF_{2\alpha}$)	39.7	7.6 ± 2.9	3.6 ± 2.7	7.5 ± 2.7	8.0 ± 3.4

Id. at 18:28-50 (Table 4).

85. The results of Table 4 were graphed in Figure 2:

Figure 2
Monkey Intraocular Pressure
Prostaglandin Dose = 0.3 ug



Id. at 30 (Figure 2).

86. As an initial matter, I note that Klimko does not disclose whether differences in the data for the above IOP-lowering experiment are statistically significant. And, it is impossible to assess the significance of the data, because important details regarding the experiment are omitted. For example, Klimko does not disclose the number of monkeys in each group. Further, Klimko does not provide data regarding the normal untreated left eyes or any time point prior to 16 hours after the fourth dose, but does disclose that such measurements were taken. *Id*. at 18:16-20.

87. With the above qualifications, in my opinion, the data in Table 4 and Figure 2 for Compound C is consistent with Klimko's earlier characterization, *i.e.*, there is an unacceptable initial **increase in IOP** after administration of the fifth dose. The increase in IOP is reported as a decrease in percent IOP reduction from 30.2±4.4 (before the fifth dose) to 25.3±4.5 (2 hours after the fifth dose) to 23.6±3.8 (4 hours after the fifth dose). *Id*. at 18:28-50 (Table 4). At 6 hours after the fifth dose, the IOP appears to be returning to the treated baseline level prior to administration of the fifth dose. *Id*. As with the severe hyperemia observed with Compound C, the increased IOP due to Compound C also teaches away from the selection of Compound C as a lead compound.

88. Taken together, Klimko expressly teaches that Compound C was previously known to have an unacceptable therapeutic profile (severe hyperemia and an initial increase in IOP after administration), and Klimko's own data is consistent with that teaching away from Compound C as a lead compound.

89. Petitioner argues that a POSITA would have understood the data in Klimko as demonstrating longer-lasting IOP-lowering efficacy for Compound C, compared to Compounds A, B and D. Ex. 1027, ¶¶ 61-65, 70, 105; Ex. 1028, ¶¶ 56-59, 63. Petitioner argues that Compound C provided an uptick in the percent IOP reduction at the last time point (relative to the previous time point), while the efficacy of the other compounds was diminishing at the last time point. Ex. 1027, ¶ 62; Ex. 1028, ¶ 56-57. According to Petitioner, "if the data is extrapolated past 6 hours after the fifth dose it is only compound C that would be reasonably expected to exhibit less diminishment in IOP-reducing effectiveness." Ex. 1027, ¶ 64.

90. In my opinion, Petitioner's analysis of the Klimko data is flawed. As explained above, to the extent the data of Table 4 and Figure 2 conveys anything regarding the IOP-lowering activity of Compound C, it is that there is an **unacceptable initial increase** in IOP after administration of the fifth dose. The uptick in percent IOP reduction at the last time point reflects nothing more than a return toward the IOP level prior to administration of the fifth dose; it does not in any way reflect a longer-lasting IOP reduction.

91. Moreover, the percent IOP reduction for Compounds A-D is similar at the last measured time point, *i.e.*, there is no actual data establishing that any of Compounds A-D have longer-lasting efficacy than the others. Indeed, Klimko expressly notes that "Table 4 shows that compounds A, B, C, and D produce similar degrees of IOP reduction with 0.3μg doses; however, compound E is essentially inactive at this dose." Ex. 1003 at 19:29-30. To the extent Petitioner would ignore Klimko's express disclosure and argue that the small differences in IOP-lowering at the last time point in Table 4 and Figure 2 are somehow significant, I also note that the mean percent IOP reduction is highest at that time point for Compound D (30.3%), not Compound C (28.9%). Ex. 1003 at 18:28-50 (Table 4).

92. Still further, I disagree that a POSITA would rely on a single time point (the last time point measured after administration of the fifth dose) to "extrapolate" the trajectory of the IOP-lowering efficacy of the tested compounds. This is especially true here, where the IOP-lowering efficacy of Compound C had been **reduced** after administration of the fifth dose.

93. Petitioner further argues that a POSITA would have selected Compound C as a lead compound because it exhibited "the greatest mean % change in IOP from baseline 16 hours after administration of the fourth dose (16/4) compared to all other compounds." Ex. 1027, ¶ 65; *see also* Ex. 1027, ¶¶ 70, 107-

108; Ex. 1028, ¶¶ 58-59, 63. In my opinion, even if the data relied on by Petitioner demonstrated a significant difference over all of the other tested compounds (a conclusion that cannot be drawn with the information provided in Klimko), a POSITA would not have been motivated to select Compound C based on its reported performance at one isolated time point, 16 hours after the fourth dose, without any data for the previous time points. This is especially true, given that Klimko specifically discloses that Compound C had been known to exhibit an initial **increase** in IOP following administration (which also is consistent with Klimko's own data after administration of the fifth dose). And, the reported mean percent IOP reduction for Compound C is lower than other compounds at every other time point; it is lower than Compounds A, B and D at 2 and 4 hours after the fifth dose, and lower than Compound D at the last time point, 6 hours after the fifth dose. Ex. 1003 at 18:28-50 (Table 4).

94. Finally, Petitioner argues that a POSITA would have set aside any concerns regarding the unacceptable therapeutic profile of Compound C, because the asserted Kishi prior art reference discloses a modification (removal of the C15 hydroxyl) that purports to alleviate hyperemia in certain prostaglandin derivatives. Ex. 1027, ¶¶ 76, 109; Ex. 1028, ¶¶ 68-70. I disagree that the Kishi disclosure would have motivated a POSITA to discount the severe hyperemia of Compound

C, especially when other disclosed compounds reportedly exhibited much milder hyperemia without any further modification at C15. Ex. 1003 at 17:57-18:6.

95. In any event, Petitioner ignores that Compound C also displayed an unacceptable increase in IOP after administration, a deficiency that would not have been addressed by the Kishi modification. To the contrary, the prevailing view in the art was that removal of the C15 hydroxyl would have been expected to further diminish IOP-lowering activity. In fact, as of December 26, 1996, the field was aware of the Kishi reference, but was skeptical of its teaching, because of the concern that removal of the C15 hydroxyl would abolish IOP-lowering activity. For example, Dr. Stjernschantz, an expert in the field who developed latanoprost, explained that the Kishi modification would make for "less interesting . . . drug candidates":

> Recently 15-deoxyprostaglandin derivatives were described as IOP depressants in a patent application by Kishi et al (see EP 471856). Even if it is claimed that these analogs exert less side effects in the eye it must be pointed out that they exhibit much less biologic activity in general compared to the naturally occurring prostaglandins, making them less interesting as drug candidates for ophthalmic use.

WO 1995/026729 (Ex. 2022) at 3. Petitioner concedes that there was concern that removal of the C15 hydroxyl would diminish IOP-lowering activity. Ex. 1027, ¶

113 ("Pharmacological testing in Kishi indicated that . . . the corresponding 15-deoxy derivative exhibited less activity."); Ex. 1028, ¶ 67 (same).

96. In sum, it is my opinion that, without the benefit of hindsight, a POSITA as of December 26, 1996 would not have considered Compound C to be a suitable lead compound. Klimko **expressly teaches away** from further development efforts with Compound C, because of its unacceptable therapeutic profile, including severe side effects and an initial increase in IOP after administration. Accordingly, I disagree with both grounds of Petitioner's obviousness argument, each of which requires the selection of Compound C as a lead compound and its modification to obtain the claimed tafluprost compound.

2. It Would Not Have Been Obvious to Modify Compound C of Klimko by C15 Fluorination

97. Even if a POSITA were to begin with Compound C as a lead compound, Petitioner's proposed development path from Compound C to a C15 fluorinated compound is incredibly elaborate and fraught with unpredictability all along that path. In my opinion, without improper hindsight, a POSITA would not have been motivated with a reasonable expectation of success to undertake the piecemeal combinations of 3-5 prior art references to arrive at a C15 fluorinated compound, as Petitioner proposes.

98. Initially, Petitioner's arguments require replacing the C15 hydroxyl of Compound C with a hydrogen to diminish side effects, based on the Kishi

reference. Ex. 1027, ¶¶ 110-111. However, as I explain above, the field was skeptical about such modifications as of December 26, 1996, because they were expected to diminish biologic activity. I note again that Petitioner concedes that there was concern that removal of the C15 hydroxyl would diminish IOP-lowering activity. Moreover, a POSITA would have understood that chemical modifications of prostaglandins were unpredictable, and Kishi only discloses replacing the C15 hydroxyl with hydrogen for a subset of prostaglandins that does not include Compound C. In particular, Kishi only discloses prostaglandin derivatives in which the omega chain is a 6-12 carbon chain. *See, e.g.,* Ex. 1005 at Abstract ("The present invention relates to a method for treating hypertension or glaucoma in the eye comprising contacting the surface of the eye with a therapeutic amount of a 15-deoxyprostaglandin derivative . . . in which . . . R^2 [omega chain] is C6 - C12 alkyl, C6 -C12 alkenyl or C6 -C12 alkadienyl . . ."). Kishi does not disclose any embodiment with the 16-phenoxy group that is present on the omega chain of Compound C. This is a significant structural difference, making it impossible to predict with any reasonable level of certainty that the reported results would carry over to removal of the C15 hydroxyl of Compound C. As noted in Petitioner's primary prior art reference (Klimko), "seemingly slight structural differences produce greatly different IOP-lowering effects and levels of hyperemia." Ex. 1003 at 15:54-56. For all of these reasons, a POSITA would not have been motivated

with a reasonable expectation of success to apply the modification of Kishi to Compound C of Klimko.

99. In any event, Petitioner's arguments require yet further modifications to Compound C to arrive at the claimed tafluprost compound. Specifically, Petitioner argues that it would have been obvious to not only replace the C15 hydroxyl with a hydrogen (based on Kishi), but it also would have been obvious to replace the new C15 hydrogen with fluorine (based on one or more of the Bezuglov 1982, Bezuglov 1986 and Ueno Japan references). Ex. 1027, ¶¶ 114-119, 124-128. Petitioner's proposed rationale for such a development path is simply too convoluted to have been considered by a POSITA, let alone to have been reasonably expected to succeed. According to Petitioner, a POSITA would have been motivated to fluorinate the C15 position in order to mimic the hydroxyl group that had just been removed, in the hopes of restoring the IOP-lowering activity that was supposedly unique and desirable at the start, but which was expected to be lost when removing the C15 hydroxyl. *Id*., ¶ 126 ("As discussed previously, the POSA would recognize that fluorine is a particularly suitable surrogate for the hydroxyl group."); *see also id*., ¶¶ 115, 124. In my opinion, a POSITA would simply have chosen a different lead compound, rather than embarking on the "see-saw" development effort suggested by Petitioner, where IOP-lowering is at one end of the see-saw, side effects are on the other, and a

POSITA makes one modification after another that does nothing other than move the see-saw up and down. Indeed, fluorination at C15 (in the hopes of restoring IOP-lowering activity) could have also restored the side effects that were present with Compound C initially, thereby accomplishing nothing more than swinging the "see-saw" back to its original position.

100. Still further, I disagree that a POSITA would have reasonably expected fluorination at C15 to restore IOP-lowering activity. The Bezuglov 1982 and 1986 references themselves illustrate the unpredictability of C15 fluorination. Bezuglov 1982 emphasizes that a C15-fluorinated $PGF_{2\alpha}$ is structurally different from naturally-occurring $PGF_{2\alpha}$; antibodies against naturally-occurring $PGF_{2\alpha}$ have much lower affinity for C15 fluorinated $PGF_{2\alpha}$: "The introduction of fluorine in place of hydroxyl in the prostaglandin molecule changes its immunological properties. For example, 15-fluoro-15-deoxyprostaglandin $F_{2\alpha}$ binds 520 times less actively than prostaglandin $F_{2\alpha}$ with prostaglandin $F_{2\alpha}$ antiserum." Ex. 1007 at 10. Bezuglov 1982 explicitly notes that "[w]hen the 15-hydroxyl group is replaced with fluorine, the activity is generally reduced in a test of contraction of the smooth muscle of the intestines. Meanwhile, the effect on blood pressure either increases or remains unchanged." *Id*. at 9-10. Similarly, Bezuglov 1986 explains that "substitution of 15-hydroxyl for fluorine in $PGF_{2\alpha}$ enhanced pressor action and sharply lowered the spasmogenic effect on uterus muscles (Table III)." Ex. 1008 at

6. And, as I discuss below, the difluorination disclosed in Ueno Japan (Ex. 1006) is one feature of many of a large genus of prostaglandins (that are not directed to IOP-lowering); the purpose or effect of fluorination is not emphasized or even discussed in Ueno Japan. None of the Bezuglov 1982, Bezuglov 1986 and Ueno Japan references are directed to fluorination in the context of IOP-lowering, and a POSITA would not have formed a reasonable expectation of success in IOP-lowering based on prostaglandin activity in wholly different contexts.

101. Taken together, it is my opinion that a POSITA would not have had a reasonable expectation that the piecemeal combination of features from the 3-5 asserted prior art references would yield a prostaglandin derivative that was successful for its intended purpose, *i.e.*, lowering IOP. As of December 26, 1996, medicinal chemistry was a highly unpredictable art, and it remains so to this day. This is especially true with respect to prostaglandins - a large class of compounds with very different, but overlapping, receptor profiles, which generate various distinct biological activities. Structural modifications to a prostaglandin can affect not only the binding to its target receptor, but also its interactions with other receptors - potentially leading to serious consequences (*e.g.*, side effects or loss of efficacy). Coleman 1994 (Ex. 2007) at 20.

102. For the reasons above, even if Compound C had been considered a suitable lead compound as of December 26, 1996 (which it was not), it would not

have been obvious to make the various modifications proposed by Petitioner to arrive at a C15 fluorinated compound. Petitioner's obviousness argument is tainted by hindsight and trivializes the significant undertaking in developing a useful IOP-lowering prostaglandin derivative.

3. It Would Not Have Been Obvious to Difluorinate Compound C of Klimko

103. Even if a POSITA had decided to pursue all of the above modifications, a POSITA would not have been motivated with a reasonable expectation of success to include **two** fluorines at the C15 position of Compound C to restore IOP-lowering activity, while avoiding the side effects of the starting Compound C. The IOP-lowering efficacy and desirable side effect profile of tafluprost was unpredictable as of December 26, 1996. I disagree with Petitioner's arguments that (1) Ueno Japan would have motivated a POSITA with a reasonable expectation of success to difluorinate Compound C at the C15 position, or (2) a POSITA would have sought to difluorinate (rather than monofluorinate) the C15 position to make production of a commercial drug easier by not creating a stereogenic center. Ex. 1027, ¶¶ 114-118. As detailed below, Ueno Japan is not directed to IOP-lowering; it does not disclose or suggest that C15 difluorination would restore IOP-lowering activity (or any biological activity) that is lost due to removal of a C15 hydroxyl. Nor does Ueno Japan disclose or suggest that C15 difluorination of Compound C would avoid the significant hyperemia of the

starting compound. Indeed, it was known that the assignee of Ueno Japan (R-Tech Ueno) had been marketing isopropyl unoprostone - **a non-fluorinated compound** - for IOP reduction in Japan since 1994.

104. And, in my opinion, Petitioner vastly overstates the potential advantages of avoiding a stereogenic center in terms of ease of production; in fact, latanoprost has a stereogenic center at the C15 position and it had already been licensed as of December 26, 1996. Finally, Petitioner completely ignores the potential disadvantages of difluorination over monofluorination, which would be entirely unpredictable, especially since the difluoride bears little (if any) resemblance to the **one** hydroxyl that the modification is meant to mimic.

105. Initially, Ueno Japan is not directed to IOP-lowering. Rather, Ueno Japan is directed to antagonism of the biological effects of histamine in allergic and inflammatory diseases, and to treating liver and biliary tract diseases; for those specific purposes, Ueno Japan discloses an extremely broad and non-specific genus of prostaglandins that lack hydroxyl or oxo groups at positions 15 and 16:

> As a result of continued research related to new applications for 15-dehydroxy-PG compounds that do not have a hydroxyl group or an oxo group at position 15 or position 16, including new compounds, the present inventors discovered that these compounds have superior antagonistic effect toward histamines, and therefore are useful for treating patients with allergies and inflammatory diseases, and thus the present invention was achieved. Furthermore, the present

> inventors also discovered that the compound was useful for treating liver and biliary tract diseases, and thus the present invention was achieved. . . . In other words, the present invention provides a new 15-dehydroxy-PG compound and an allergic disease treating agent, inflammatory disease treating agent, antihistamine agent, a bronchial and tracheal dilating agent, and a hepatic and biliary tract disease treating agent containing a 15-dehydroxy-PG compound as an active ingredient.

Ex. 1006 at 48 (underlining in original to indicate amendment to application). With respect to IOP-lowering, it was known that the assignee of Ueno Japan (R-Tech Ueno) had been marketing isopropyl unoprostone - **a non-fluorinated compound** - in Japan since 1994. *See, e.g.*, Qiu, "Revisit Rescula and Cystoid Macular Edema and Refractory Glaucoma," *J. Clin. Exp. Ophthalmol.* 6:5 (2015) (Ex. 2018) at 1; "R-Tech Ueno Starts Early Phase II Clinical Trial For RK-023" (2009) (Ex. 2019).

106. Ueno Japan explains that its disclosed genus includes a laundry list of possible derivatives, which includes fluorination (mono- or difluorination) at any of a number of positions on the omega chain:

> Examples of typical compounds of the present invention include 15-dehydroxy-PGEs, 13,14-dihydro-15-dehydroxy-PGEs and Δ^2 derivatives, 3-methyl derivatives, Δ^5 derivatives, 11-dehydroxy derivatives, 11-dehydroxy-11-methyl derivatives, Δ^{13} derivatives, Δ^{14} derivatives, 15-mono- or di-methyl derivatives, **15-mono- or di-**

> **fluoro derivatives**, 16-mono-or di-methyl derivatives, **16-mono- or di-fluoro derivatives**, 17 mono- or di-methyl derivatives, **17 mono- or di-fluoro derivatives**, 18 mono- or di-methyl derivatives, **18-mono- or di-fluoro derivatives**, 19-mono- or di-methyl derivatives, **19-mono- or di-fluoro derivatives**, 17,18,19,20-tetranol derivatives, 17,18,19,20-tetranol-16-ethoxy-derivatives, 17,18,19,20-tetranol-16-cyclopentyl derivatives, 17,18,19,20-tetranol-16-phenyl derivatives, 17,18,19,20-tetranol-1,6-phenoxy derivatives, 18,19,20-trinor derivatives, 18,19,20-trinor-17-methoxy derivatives, 18,19,20-trinor-17-cyclohexyl-derivatives, 18,19,20-trinor-17-phenyl derivatives, 18,19,20-trinor-17-phenoxy-derivatives, 19,20-dinor derivatives, 19,20-dinor-18-methoxy-derivatives, 19,20-dinor-18-cyclopentyl derivatives, 19,20-dinor-18-phenyl derivatives, 19,20-dinor-18-phenoxy derivatives, 20-nor derivatives, 20-nor-19-methoxyderivatives, 20-phenyl derivatives, 20-methoxy derivatives, 20-methyl derivatives, 20-ethyl derivatives, 20-propyl derivatives, 20-butyl derivatives, 20-phenyl derivatives and the like.

Ex. 1006 at 54 (emphasis added). Consistent with this disclosure of fluorination virtually anywhere on the omega chain, the specific examples of Ueno Japan involve 15-dehydroxy PGE derivatives that are difluorinated at C15, C16 or C17, with the vast majority of examples being C16 or C17 difluorination. *Id*. at 54-57, 59-65. Given the nonspecific nature of the disclosed fluorination in Ueno Japan, a POSITA would not have associated the disclosed fluorination with C15-specific biological activity (or any specific biological activity). Indeed, Ueno Japan does

not attribute any specific role to the fluorines in the disclosed compounds. A POSITA would not have been motivated to difluorinate at C15 for increased biological activity.

107. Additionally, Ueno Japan does not test any C15 fluorinated (let alone C15 difluorinated) compounds, and **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**. *Id*. 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. The only mention of IOP reduction in Ueno Japan is in the "Background Technology" section, in which Ueno Japan cites to other literature for the proposition that 15-dehydroxy prostaglandins (not C15 difluorinated prostaglandins) can have biological activity. *Id*. at 48 ("It 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 (WO 91/13869).").

108. Still further, Ueno Japan provides no assessment (nor any other disclosure) of ocular side effects with respect to the disclosed compounds. A

POSITA would not have had any understanding from Ueno Japan as to the side effect profile of a C15 difluorinated Compound C; this is especially critical here because of the unacceptable side effects of the supposed lead compound.

109. For the above reasons, it is my opinion that a POSITA would not have been motivated by Ueno Japan to C15 difluorinate Compound C. It is also my opinion that a POSITA would not have had a reasonable expectation of success in achieving an acceptable therapeutic profile with a C15 difluorinated Compound C.

110. Petitioner's only other alleged motivation to difluorinate Compound C at position 15 is based on supposed practical considerations, *i.e.*, that a C15 difluorinated compound - without a stereogenic center at position 15 - would have been easier to manufacture and analyze than a C15 monofluorinated compound. I disagree. It was well known how to manufacture and analyze a prostaglandin derivative with a stereogenic center at C15. Indeed, as of December 26, 1996, latanoprost (which has a stereogenic center at C15) had already been FDA-approved and marketed. Xalatan 1996 (Ex. 2004).

111. Petitioner's argument also begs the question as to whether C15 difluorination would have been expected to provide a suitable therapeutic profile, especially since the original therapeutic profile of Compound C was unacceptable. As of December 26, 1996, there was no evidence that a C15 difluorinated prostaglandin derivative would perform as well as, or better than, a C15

monofluorinated prostaglandin derivative. Petitioner's argument completely ignores the potential disadvantages of adding multiple fluorines, which would be entirely unpredictable, especially since the difluoride bears little (if any) resemblance to the **one** hydroxyl that the modification is meant to mimic.

112. As of December 26, 1996, it was well-known that C15 hydroxyl, monofluorinated C15, and difluorinated C15 are quantifiably different with respect to, for example, electronegativity (the tendency to attract electrons in chemical bonds - an important factor in receptor binding and biological activity) and lipophilicity (the ability to cross lipid-based membranes in the eye, measured by the partition coefficient, log*P*). In the original Compound C, the C15 hydroxyl was well-known to have an electronegativity of ~3.5 (*see* Bezuglov 1986 (Ex. 1008) at 4), and the compound would have been predicted (in ChemDraw software, which was available as of December 26, 1996) to have a log*P* of ~3.2. In contrast, fluorine was well-known to have the highest electronegativity of any element (4.0, *see* Bezuglov 1986 (Ex. 1008) at 4), and a monofluorinated C15 derivative of Compound C would have been predicted to have a log*P* of ~3.9, which is ~5 times higher lipophilicity than the original Compound C. *See also id*. at 3 ("[S]uch [fluorine] substitution increases lipophili[ci]ty of the molecule."). In turn, a difluorinated C15 derivative of Compound C would have been predicted to have a log*P* of ~4.3, which is ~2.5 times higher lipophilicity than the

monofluorinated C15 version, and ~12.5 times higher lipophilicity than the original Compound C. Importantly, it was also well-known as of December 26, 1996 that too much lipophilicity could negatively impact the ability of a compound to cross hydrophilic tissue of the eye, limiting its efficacy in treating glaucoma or ocular hypertension. *See, e.g.*, Schoenwald and Ward, "Relationship between Steroid Permeability across Excised Rabbit Cornea and Octanol-Water Partition Coefficients, " *J. Pharm. Sci.* 67(6):786-788 (1978) (Ex. 2020) at 2 ("Figure 2 predicts a decrease in permeability once a partition coefficient of 2.9 is reached."). Because a POSITA as of December 26, 1996 would have known that C15 hydroxyl, monofluorinated C15, and difluorinated C15 are not fungible, a POSITA would not have had been motivated (let alone with a reasonable expectation of success) to pursue a C15 difluorinated Compound C, merely to avoid the creation of a stereogenic center.

113. In sum, it is my opinion that, a POSITA would not have been motivated with a reasonable expectation of success to include two fluorines at the C15 position of Compound C.

4. Klimko's Own Inventors Specifically Excluded C15 Difluorinated Compounds from the Scope of Their Work

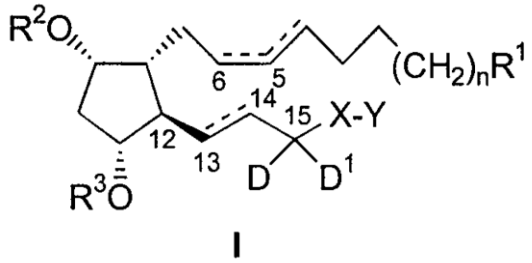
114. Notably, Petitioner has relied on PCT/US97/20671 ("Klimko '671" (Ex. 1012)) as evidencing the state of the art as of December 26, 1996, including a purported motivation to fluorinate the C15 position of Compound C of Klimko.

Ex. 1027, ¶¶ 44-47. As detailed below, I disagree that Klimko '671 is indicative of the relevant state of the art with respect to fluorination of prostaglandins. Moreover, I note that Klimko '671 expressly excludes difluorination at the C15 position of a prostaglandin analog. To the extent Klimko '671 is relevant to these proceedings, it establishes that C15 difluorination would not have been obvious, even to the inventors of the supposed lead compound, Compound C of Klimko.

115. In my opinion, Klimko '671 would not have represented "the general thinking of those skilled in the art" as of December 26, 1996, as claimed by Petitioner. Ex. 1027, ¶ 46. I understand that the disclosure of the Klimko '671 was not made public until May 22, 1998; a POSITA would not have been aware of that disclosure as of December 26, 1996. Contrary to Petitioner's argument, the inventors of Klimko '671 believed their monofluorinated compounds were different from, and novel over, "the general thinking of those skilled in the art": "While 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." Ex. 1012 at 3:18-23.

116. In any event, Klimko '671 expressly excludes difluorination at the C15 position of a prostaglandin analog. Specifically, Klimko '671 discloses that

"[t]he substituted $PGF_{2\alpha}$ analogs of the present invention have the following formula I":



I

Id. at 4:15-5:26. Klimko '671 discloses that, in formula I above, "D, D^1 = **different** = H and fluorine." *Id*. at 5:8 (emphasis added); *see also id*. at 27-38 (all claims contain same monofluorination limitation). In other words, Klimko '671 is limited to monofluorination. And consistent with that limitation, there is no disclosure in Klimko '671 of any genus or specific compound in which the C15 position (or any position) of a prostaglandin is occupied by two fluorines.

117. Still further, the subject matter of Klimko '671 was also published in a scientific journal in 2004 (years after the filing of the '035 Patent). Klimko *et al.*, "15-Fluoro prostaglandin FP agonists: a new class of topical ocular hypotensives," *Bioorg. Med. Chem.* 12:3451-3469 (2004) ("Klimko 2004") (Ex. 2021). Like Klimko '671, the disclosure of Klimko 2004 is limited to monofluorinated prostaglandins. *Id*. at 2 ("We now report the synthesis and pharmacological characterization of a series of 15-fluoro-16-aryloxy-ω-tetranor-$PGF_{2\alpha}$ analogs I (Fig. 3)."). The only mention of a difluorinated prostaglandin is an endnote

referencing **the '035 Patent and Patent Owner's corresponding publications**. *Id*. at 19 n. 12.

118. Klimko '671 is not representative of the state of the art as of December 26, 1996 (as it was not yet published), but its explicit exclusion of C15 difluorination from its scope **does** establish that it would not have been obvious to C15 difluorinate Compound C of Klimko.

X. SECONDARY CONSIDERATIONS

119. Given my opinions above, tafluprost would not have been obvious over the asserted prior art references. I reserve the right to supplement my opinion with respect to secondary considerations should this proceeding be instituted.

DECLARATION

I declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed in Charlottesville, VA on this 6th day of September 2017.

Timothy L. Macdonald, Ph.D.

EXHIBIT A

CURRICULUM VITAE

Timothy L. Macdonald

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University of Virginia
Charlottesville, VA 22904
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PERSONAL

Birthdate:	March 12, 1948
Birthplace:	Long Beach, California
Marital Status:	Married, two children

PROFESSIONAL EXPERIENCE

University of Virginia, September 1, 1982 – present
- Associate Professor of Chemistry, 1982-1988
  - Member, University of Virginia Cancer Center (1991 - present)
  - Member, Molecular Pharmacology Training Program (1995 - present)
  - Member, Biotechnology Training Program (1998 - present)
  - Member, Board of Directors, Faculty Entrepreneurial Network (2000 -)
- Professor of Chemistry, September 1988 – present
- Chair of Chemistry, July 1, 1997 – August 31, 2003
- Professor of Pharmacology--secondary appointment, September 2003-present

Vanderbilt University, September 1, 1977 - August 31, 1982
- Assistant Professor Chemistry
  - Member, Center in Molecular Toxicology

EDUCATION

Stanford University, October 1, 1975 - August 31, 1977
- National Research Service Award Postdoctoral Fellow
- Advisor: William S. Johnson. Enantioselective synthesis of tetracyclic natural products via the cationic cyclization of polyolefins

Columbia University, Ph. D. September 1975
- George B. Pegram Distinguished Fellow in the Faculty of Science
- Advisor: Gilbert Stork. Thesis: Approaches to Large Carbocycles

University of California, Los Angeles, B. S. Honors, September 1971
- National Science Foundation Undergraduate Research Fellow, 1970-71.
- Advisor: Christopher Foote
- Foreign Study-Travel Fellowship at Lund Universitet, Lund, Sweden, 1968-69

UNIVERSITY AND NATIONAL AWARDS

Research Fellow of The Alfred P. Sloan Foundation, 1981-1983
Young Investigator Grant Awardee from Eli Lilly and Company, 1981-1983
American Cyanamid Award for Excellence in the Advancement of Chemical Synthesis, 1987
Henderson Inventor of the Year Award, University of Virginia, 1997
Edlich-Henderson Inventor of the Year Award, University of Virginia, 2010
Virginia Bio, 20th Anniversary Celebration of Bioscience Award, 2013

AWARDS FROM AND SERVICE TO NATIONAL INSTITUTES OF HEALTH

National Research Service Award from the National Institutes of Health, 1975-1977

Ad Hoc Member, NIH BioOrganic and Natural Products Study Section (1982, 1984, 1986, 1992, 1993, 1994, 1998) and Neurological Sciences Study Section (1989, 1990, 1992, 1996, 1997); participant in numerous NIH site visits.

RECOGNITION FOR PAPERS OF SCIENTIFIC SIGNIFICANCE

Two publications published in 1984 (*Accts. Chem. Res.* 16, 9) and 1985 (*J. Org. Chem*. 50, 422) were among the 100 most cited articles published in the physical sciences in their respective years as determined by three year retrospective surveys conducted by the Institute for Scientific Information.

RESEARCH SUPERVISION

Sixty-three graduate students have received the doctorate degree under my supervision and (approximately) thirty five postdoctoral associates have studied under my direction. Since arriving at Virginia, I have averaged approximately 2 graduating Ph. D. students and one departing postdoctoral associates per year. Approximately 80% of my former associates work in the pharmaceutical industry; the remaining 20% are in academic or government positions. Co-workers in academia currently hold positions at the University of Vermont, Virginia Tech, Michigan State University, Ohio State University, University of Kansas, SUNY Binghamton, Mississippi State University, Georgetown University, Univesity of Redlands, University of Texas, Arlington, Mary Washington College, the College of William and Mary, Lafayette College and Bates College.

ENTREPRENEURIAL ACTIVITIES

I am a founding scientist of six biotechnology companies: Adenosine Therapeutics LLC, AlGlutamine LLC, Tau Therapeutics LLC, Catena Pharmaceuticals, Inc., SphynKx Therapeutics LLC and Xdynia LLC. These companies arose from discoveries made in my laboratory and those of my collaborators at the University of Virginia. Adenosine Therapeutics LLC began operations in 1998, AlGlutamine LLC in 1999, Tau Therapeutics, LLC in 2005, Catena Pharmaceuticals in 2007, SphynKx Therapeutics in 2010 and Xdynia in 2011 following their capitalization and the in licensing of their underlying technologies from the University of Virginia Patent Foundation. Adenosine Therapeutics and AlGlutamine have been sold to larger pharmaceutical companies. Catena Pharmaceuticals has folded. Tau Therapeutics and Xdynia have merged to form Cavion LLC, which is currently sponsoring two clinical trials in oncology and a third in neurological disease. SphynKx Therapeutics' research is directed at identifying and enabling a clinical candidate for the treatment of autoimmune and fibrotic diseases. I serve on the Board of Directors of Cavion LLC and SphynKxTherapeutics LLC and hold equity positions in these companies.

Cavion is focused on targeting calcium T-channels for the treatment of cancer and neurological diseases. The company has in-licensed technology from the University of Virginia that enables and protects a unique strategy for cancer treatment discovered at UVA. In addition, the company has developed new therapeutic agents, treatment protocols and diagnostic materials for cancer and other hyper-proliferative diseases. Cavion initiated its first clinical phase 1/2 trial in *glioblastoma multiforme* with its lead candidate, mibefradil, using a combinational chemotherapy regimen in May 2012. This trial has closed exceeding its target endpoints and further trials are anticipated. An additional phase 1/2 trial in combination with radiation for the treatment of high-grade gliomas began in Q2 2015. Additional clinical trials for pancreatic cancer, ovarian cancer, triple negative breast cancer and/or metastatic melanoma are being explored. Cavion also holds the core technology for the former Xdynia. This is based on the therapeutic modulation of T-type calcium channel signaling for the treatment of neuropathic pain and other neurological disease states. Colleagues at UVA have found that aberrant levels, location or activation of T-type calcium channel proteins (known as Cav 3.1, 3.2 and 3.3) are associated with a number of neurologic conditions. Cavion's neurology-targeted compounds are directed at the selective inhibition of the T-type calcium channel proteins, Cav3.1, 3.2 and 3.3, in a state-dependent fashion. A clinical evaluation in essential tremor is anticipated to begin Q2 2017.

SphynKx Therapeutics is based on technology developed jointly with Kevin Lynch of the Department of Pharmacology and is focused on modulating a growth factor and signaling molecule called sphingosine 1-phosphate. This growth factor is essential for normal function of a wide variety of cells and aberrant signaling occurs in a number of disease states, including cancer, neurological diseases and autoimmune diseases, such as multiple sclerosis. The company is an early stage venture directed at discovering novel therapies for a number of these diseases.

PUBLICATIONS

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3. T. L. Macdonald and W. C. Still, *J. Amer. Chem. Soc*. 1975, **97**, 5280. Organocuprates. A stereoselective synthesis of axial alcohols

4. W. C. Still and T. L. Macdonald, *J. Org. Chem*. 1976, **41**, 3620. Allyloxy carbanions. Synthesis of 3,4-dihydroxy-1-olefins from carbonyl compounds

5. T. L. Macdonald and W. C. Still, *Tetrahedron Letters* 1976, 2559. Organocuprates..II Reaction of trialkylcuprates with saturated and unsaturated carbonyl compounds

6. T. L. Macdonald, *J. Org. Chem*. 1978, **43**, 2559. Regiospecific α-tropolone synthesis. Selective preparation of the isomeric thujaplicins

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INTELLECTUAL PROPERTY

The first four patents were based on my Ph. D. thesis studies conducted under Professor Gilbert Stork at Columbia University. All of the additional patents and patent applications are based on research at the University of Virginia or on research conducted by a UVA spin-out biotechnology company of which I was a founder. I currently have 59 issued US patents (*Issued Patents*) and another dozen or so pending applications that remain under review (*Pending Patents*). Most of the issued US patents have been nationalized in a number of additional countries.

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EXHIBIT B

List of Materials Considered

Exhibit No.	Document
N/A	Petition for *Inter Partes* Review of U.S. Patent No. 5,886,035 by Micro Labs Ltd. (IPR2017-04343)
1001	U.S. Patent No. 5,886,035
1002	File History of U.S. Patent No. 5,886,035
1003	EP0639563A2 to Klimko *et al.*
1005	U.S. Patent No. 5,292,754 to Kishi *et al.*
1006	JP-A-7070054 to Ueno Japan *et al.*
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1008	Bezuglov, Vladimir V. "Fluorodeoxy Prostaglandins, Synthesis and Perspectives" in Prostaglandins and Cardiovascular Diseases (Takayuki Ozawa et al. eds., 1986)
1012	PCT/US97/20671 to Klimko *et al.*
1026	Nelson, N.A. "Prostaglandin Nomenclature," *J. Med. Chem.* 17(9):911-918 (1974)
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2017	European Patent Application No. 0364417 A1
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