IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

VANDERBILT UNIVERSITY,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 05-506-SLR
	)	
ICOS CORPORATION,	)	
	)	
Defendant.	)	

Vincent A. Bifferato, Jr., Esquire, Ian Connor Bifferato, Esquire, and Raj Srovatsan, Esquire of Bifferato Gentilotti LLC, Wilmington, Delaware. Counsel for Plaintiff. Of Counsel: Kurt C. Rommel, Esquire of Miles & Stockbridge P.C., McLean, Virginia; Robert S. Brennen, Esquire and Donald E. English, Jr., Esquire of Miles & Stockbridge P.C., Baltimore, Maryland.

Richard K. Hermann, Esquire and Mary B. Matterer, Esquire of Morris James LLP, Wilmington, Delaware. Counsel for Defendant. Of Counsel: Kevin M. Flowers, Esquire, Thomas I. Ross, Esquire, and Matthew C. Nielsen, Esquire of Marshall, Gerstein & Borun LLP, Chicago, Illinois.

OPINION

Dated: January 27, 2009
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

Plaintiff Vanderbilt University ("plaintiff" or "Vanderbilt") brought the present action pursuant to 35 U.S.C. § 256 against defendant ICOS Corporation ("defendant" or "ICOS") on July 20, 2005, requesting that the court direct the United States Patent and Trademark Office ("PTO") to correct U.S. Patent Nos. 5,859,006 ("the '006 patent") and 6,140,329 ("the '329 patent") by adding three Vanderbilt professors as inventors. (D.I. 1) A bench trial was held between January 7, 2008 and January 15, 2008 on the issues of inventorship of the '006 and '329 patents. Post-trial briefing has been completed. (D.I. 153, 150, 154) The court has jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338. Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW[1]

A. The Parties

1. Vanderbilt is a Tennessee not-for-profit corporation with its principal place of business in Nashville, Tennessee. (D.I. 130, ex. 1 at ¶ 1) Vanderbilt brought this action pursuant to 35 U.S.C. § 256, requesting that the court add Jackie D. Corbin, Ph.D., Sharron H. Francis, Ph.D., and Sekhar R. Konjeti, Ph.D. as inventors on the '006 and '329 patents. (D.I. 1) All three scientists are employed as professors at Vanderbilt and, consistent with their terms of employment, have assigned all rights that they may have in the '006 or '329 patents to Vanderbilt. (PTX-6; PTX-7; PTX-8)

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[1]The court is appreciative of ICOS' counsel's submission of DVDs containing the parties' post-trial briefs and exhibits in searchable, hyperlinked format.

2. ICOS is a Delaware corporation with its principal place of business in Bothell, Washington.[2] (*Id.* at ¶ 2) ICOS is the owner by assignment of the '006 and '329 patents (together, the "patents at issue").

3. Glaxo Wellcome Inc. is a North Carolina corporation (hereinafter, "Glaxo").[3] Glaxo Group Limited is Glaxo's English subsidiary (hereinafter, "Glaxo U.K."). In 1991, Glaxo[4] and Glaxo U.K. entered into a collaboration with ICOS, assigning to ICOS the rights, title, and interest in the compounds covered by the patents at issue. (PTX-406) At all times relevant to the present litigation, Glaxo maintained a research facility in Les Ulis, France (hereinafter, "Glaxo France").

B. The Technology at Issue

4. Cyclic guanosine monophosphate ("cGMP") is a chemical messenger in the body that activates cGMP kinase,[5] resulting in the relaxation of smooth muscle tissue. The relaxation of vascular smooth muscles lead to vasodilation[6] and increased blood flow. (103:5-23) Phosphodiesterase-5 ("PDE5") is an enzyme that breaks down cGMP. (Tr. 103:4-5) PDE5 has two different binding sites: one for binding cGMP to regulate it,

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[2]ICOS was acquired by Eli Lilly and Company on January 29, 2007; it is now a wholly-owned subsidiary of that company. (D.I. 130, ex. 1 at ¶ 3)

[3]In 2001, Glaxo merged with SmithKline Beecham to form Glaxo SmithKline.

[4]At that time, Glaxo Wellcome's predecessor, Glaxo, Inc.

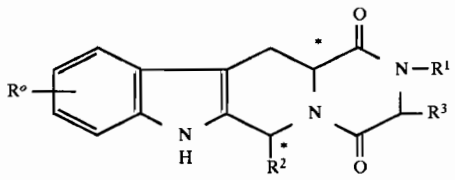
[5]Also called protein kinase G or PKG. Generally, kinases are enzymes that phosphorylate particular target molecules. Protein kinases act on and modify the activity of proteins.

[6]Generally, the widening of blood vessels, resulting from relaxation of smooth muscle cells within the vessel walls.

and another for binding cGMP to break it down. (D.I. 140 at 115:20-116:24) Phosphodiesterase (or "PDE") inhibitors prevent the degradation of cGMP, thereby enhancing and/or prolonging smooth muscle relaxation.

5. The '006 patent claims at issue (claims 1-8, 10, 12 and 13) are directed to chemical compounds and methods for making those compounds. The compounds are tetracyclic derivatives of the following general structure:

A compound of formula (I)

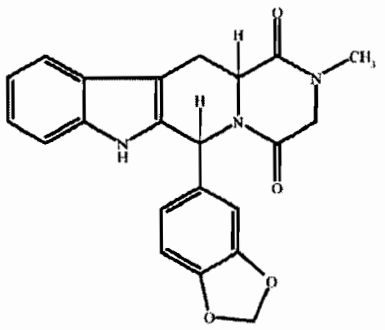


The '006 patent provides that such compounds are "potent and selective inhibitors of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE)." ('006 patent, col. 1, ll. 8-12)

6. The '006 patent teaches that PDE5 inhibition caused by the claimed compounds results in elevated cGMP levels, resulting in, amongst other benefits, improved vasodilation. ('006 patent, col. 5, ll. 15-35) Such compounds are of interest "for the treatment of a variety of conditions where inhibition of [PDE5] is thought to be beneficial," for example, the treatment of cardiovascular disorders. ('006 patent, col. 1, ll. 12-15; col. 5, ll. 9-14)

7. The '329 patent claims at issue (1, 2, 3, 5-12, and 15-21) are directed to compositions and methods of treating impotence, also called erectile dysfunction ("ED"), in a male animal involving the administration of at least one of the compounds

claimed in the '006 patent. One such compound is "tadalafil,"[7] the active ingredient in the prescription ED drug Cialis®. Tadalafil has the following structural formula:



C. Nature of the Dispute

8. Plaintiff asserts that Corbin, Francis and Konjeti conceived of a compound, 8-(4-hydroxy phenylthio)-IMBX (also referred to as 8-(4-OH-PT)-IMBX), which was communicated to Glaxo in 1992 pursuant to a research agreement. According to plaintiff, the disclosure of 8-(4-OH-PT)-IMBX led to Glaxo's development of two molecules incorporating the same molecular scaffold and, ultimately, the general chemical structure of formula 1 of the '006 and '329 patents.

9. Glaxo scientist Dr. Alain Daugan, who began work on Glaxo's PDE inhibitor project in June 1992, is the sole named inventor on the '006 and '329 patents. Defendant asserts that Daughan independently conceived the claimed compounds by conducting a comprehensive medicinal chemistry study between June 1992 and January 1994.

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[7]Tadalafil has the formula $C_{22}H_{19}N_3O_4$ and IUPAC name (6R-trans)-6-(1,3-benzodioxol-5-yl)- 2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1', 2':1,6] pyrido[3,4-b]indole-1,4-dione.

D. Legal Framework

10. 35 U.S.C. § 116 provides that "[w]hen an invention is made by two or more persons jointly, they shall apply for a patent jointly and each make the required oath, except as otherwise provided in this title. Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent."

> All that is required of a joint inventor is that he or she (1) contribute in some significant manner to the conception or reduction to practice of the invention, (2) make a contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and (3) do more than merely explain to the real inventors well-known concepts and/or the current state of the art.

Pannu v. Iolab Corp., 155 F.3d 1344, 1351 (Fed. Cir. 1998). Section 116 "sets no explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor. Rather, a joint invention is simply the product of a collaboration between two or more persons working together to solve the problem addressed." *Fina Oil and Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997) (citing *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1227 (Fed. Cir. 1994)).

11. "A patent is invalid if more or fewer than the true inventors are named." *Gemstar-TV Guide Intern., Inc. v. Int'l Trade Com'n*, 383 F.3d 1352, 1381 (Fed. Cir. 2004) (citing *Jamesbury Corp. v. United States*, 518 F.2d 1384, 1395 (Ct. Cl. 1975)); 35 U.S.C. § 102(f) ("A person shall be entitled to a patent unless . . . he did not himself invent the subject matter sought to be patented[.]") Because patents are presumed

valid, 35 U.S.C. § 282, there is a presumption that the named inventors on a patent are the true inventors. *Gemstar*, 383 F.3d at 1381 (citation omitted). This presumption may be overcome by demonstrating, by clear and convincing evidence, that the alleged omitted inventor "contribute[d] in some significant manner to the conception of the invention" claimed. *Id.* (quoting *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997)).

12. 35 U.S.C. § 256 provides that an error in naming persons who are not inventors or in omitting inventors will not invalidate a patent where a correction is requested (and approved by) the PTO Director, or where "[t]he court before which such matter is called in question [orders] correction of the patent on notice or hearing of all parties concerned[.]" Plaintiff at bar does not seek to invalidate the '006 and '329 patents, but seeks an order directing the Director of the PTO to correct the named inventorship. (D.I. 153 at 50) Regardless of the relief requested, Corbin, Francis, and Konjeti must establish their co-inventorship by facts supported by clear and convincing evidence.[8] *See Gemstar*, 383 F.3d at 1382.

E. Inventorship Evidence

The court turns now to the findings of fact upon which its ultimate conclusion on inventorship will be based.

1. Pre-collaboration

13. Corbin and Francis have been professors of molecular physiology at

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[8]Despite plaintiff's invitation to apply a lesser standard in view of the fact that the PTO does not verify named inventors, the court declines to apply a preponderance of the evidence standard absent compelling Federal Circuit authority.

Vanderbilt University School of Medicine since the 1970s. Their research focuses on the molecular aspects of smooth muscle relaxation. Francis specifically focuses on cGMP. Corbin and Francis identified PDE5 in the late-1970s. (D.I. 140 at 115:20-116:24)

14. Prior to their collaboration with Glaxo, Corbin and Francis tested several dozen cGMP analogs. (PTX-35 at VM601; D.I. 140 at 133:9-10) They discovered that there were two forms of cGMP kinase, type Iα and Iβ. (D.I. 140 at 133:17-19)

2. Plaintiff's cGMP analog work & the communication of 8-(4-OH-PT)-IMBX to Glaxo

15. On December 16, 1988, Corbin completed an application for a "Glaxo Cardiovascular Discovery Grant." (PTX-32) Along with this application, Corbin and Francis submitted an abstract of their research proposal and the research proposal itself (hereinafter, "the 1988 Research Proposal"). (PTX-35)

16. The objective of the 1988 Research Proposal was described as "develop[ing] cGMP analogs[9], or combinations of analogs, that are potent and specific, and that exhibit an appropriate pattern of reversibility or persistence, in causing relaxation of vascular smooth muscle[.]" (PTX-35, ex. A, p. 10 at VM599) New cGMP analogs would be tested for their activation "of smooth muscle type Iα and Iβ isozymes[10] of cGMP kinase," which isozymes have two specific cGMP binding sites ("site 1 and 2"). (*Id.*) In other words, the team sought to identify compounds that would

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[9]A compound that is similar in structure to cGMP.

[10]Generally, enzyme variants having different amino acid sequences but which catalyze the same chemical reaction (*i.e.*, have the same function).

activate cGMP kinase, just like cGMP would activate cGMP kinase to achieve smooth muscle relaxation, therefore mimicking an increase in cGMP.[11] The proposal provided that combinations of cGMP analogs and specific cGMP PDE inhibitors would be tested for synergistic effects. (*Id.* at VM599) Also included was a list of the new cGMP analogs that had been synthesized by Corbin and Francis: 8-pCL-phenyl-S-cGMP, a compound with an eight-position substitution, as well as several other 8-substituted compounds (e.g., compound GI118611A). (*Id.* at VM601; D.I. 143 at 651:23-652:11)

17. Corbin was selected for a Glaxo Cardiovascular Discovery Grant. Following a visit from Glaxo representatives, plaintiff and Glaxo executed a "Glaxo Cardiovascular Discovery Grants Research Agreement" (hereinafter, "the 1989 Research Agreement") dated July 1, 1989. (PTX-35) The 1988 Research Proposal (and abstract of that agreement) became appendices to the 1989 Research Agreement.

18. The 1989 Research Agreement provided that the project would be funded for a three-year period, and contemplated renewal by mutual agreement of all of the parties. (*Id.* at 2-3) Any inventions made by a participant in the project "and conceived or reduced to practice during the course of and under the project shall be the property of the University subject to the rights agreed herein to be granted to Glaxo under a license agreement to be entered into between the parties." (*Id.* at 3-4) Glaxo retained the right to delay publication and dissemination of the results of plaintiff's work relating to the Agreement for up to three months if Glaxo believed the publication would

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[11]In this regard, the "focus" would be on four analog groups: "(a) analogs that are selective for cGMP-binding site 1 of cGMP kinase; (b) analogs that are selective for site 2; (c) analogs that bind with high affinity to both sites; and (d) analogs that are persistent in causing relaxation of artery strips." (PTX-35, ex. A, p. 10 at VM600)

jeopardize its patent rights. (*Id.* at 12)

19. On November 1, 1989, Corbin presented his group's work to a group of senior Glaxo scientists in North Carolina: Dr. Crist Frangakis, Joel Shaffer, Jeff Wiseman, and Dr. Thomas Rimele. (PTX-37)

20. In January 1990, Konjeti joined the Vanderbilt lab as a postdoctoral fellow to collaborate with Corbin and Francis on cGMP analogs under the 1989 Research Agreement. (647:2-8) Konjeti studied Corbin and Francis's work on cGMP and PDE5 upon his arrival, as well as the research proposal, to familiarize himself with their work. (647:23-648:5)

21. From March 22 to 24, 1990, by the invitation of Dr. Don Kirksey, Director of Glaxo's "Discovery Program," Corbin attended a "Cardiovascular Discovery Conference" in Tucson, Arizona. (D.I. 140 at 134:19-135:4; PTX-36) During the conference, Corbin had a lunch meeting with several scientists: Dr. Joseph Beavo (from the University of Washington ("UW")) and Kirksey, Shaffer, Rimele and Wiseman (all from Glaxo). (PTX-42) The parties discussed a potential collaboration between plaintiff and UW to determine the DNA sequence for and ultimately clone PDE5.[12] (*Id.*)

22. Aside from doing work under the 1989 Research Agreement, Corbin and Francis continued their work on PDE5 during this period, funded by the National Institutes of Health. (D.I. 140 at 141:7-143:5) An article received for publication in the Journal of Biological Chemistry on April 11, 1990 describes Corbin and Francis's

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[12]Cloning PDE5 would avoid the process of purifying PDE5 from rat and cow lung for testing purposes. (D.I. 140 at 139:24-140:24)

purification of PDE5 from cow lung.[13] (PTX-43) This work illustrated that zaprinast[14] was a PDE5 inhibitor. (D.I. 140 at 141:24-142:2) According to Corbin, these results got the team thinking that "the studies of cyclic GMP analogs on [cGMP kinase] that we had already done might apply to PDE5." (*Id.* at 142:7-14)

23. Following the 1990 Cardiovascular Discovery Conference, Corbin, Francis and Konjeti submitted a progress report to Glaxo on work done under the 1989 Research Agreement, entitled "Cardiovascular Discovery Grant 1989-1990 Annual Report" (hereinafter, "the 1990 Progress Report").[15] (PTX-44) The 1990 Progress Report listed newly synthesized cGMP analogs that were tested over the past year for activation of cGMP kinase (both types I[alpha] and I[beta]), including: 8-napthylthio-cGMP, 8-o-Br-PT-cGMP, and 8-p-OH-PT-cGMP. (*Id.* at VC-78) The 1990 Progress Report stated that "[i]t should be noted that the most potent smooth muscle relaxants, 8-Br-PET-cGMP and 8-pOH-PT-cGMP, are ~20 times more potent than the best cGMP analog (8-pCL-PT-cGMP) tested prior to this study." (*Id.* at VC-79)

24. On November 28, 1990, Corbin sent Kirksey at Glaxo U.K.[16] a copy of an

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[13]This PDE5 work was also published in 1990 as a book chapter entitled "Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action." (PTX-420; D.I. 143 at 779:7-14)

Also named on both publications is Melissa K. Thomas, a graduate student at Vanderbilt University.

[14]1,4-Dihydro-5-(2-propoxyphenyl)-7H-1,2,3-triazolo[4,5-d]pyrimidine-7-one. A compound originally developed as an anti-allergy treatment.

[15]Defendant does not contest plaintiff's representation that the 1990 Progress Report was presented following the Cardiovascular Discovery Conference in 1990.

[16]On October 23, 1990, Glaxo informed Corbin that the administration of Glaxo's cardiovascular program was being transferred from North Carolina to Glaxo Group

abstract he sought to be published at a Federation of American Societies for Experimental Biology ("FASEB") conference scheduled in 1991 (hereinafter, the "FASEB abstract"). (PTX-47) The results contained in the FASEB abstract included the discovery that the potency of the cGMP analogs with certain functional groups attached at the 8-position was enhanced by the attachment of electron-donating groups to the phenyl ring. (*Id.*) ("Analogs modified with a derivatized phenyl-activating group at the 8-position were 100-1000 fold more potent in activating [cGMP kinase type Iα] than [cGMP kinase type Iβ]). Electron donating substituents such as OH, NH2 and OCH3 on the phenyl ring enhanced the potencies of these analogs in activating [type Iα].")) Corbin testified that Glaxo required him to withdraw the FASEB abstract. (150:11-12)

25. On March 18, 1991, Corbin made a presentation at the "Glaxo Discovery Conference" in North Carolina on his team's progress to date. (PTX-53) In attendance were Kirksey (Glaxo), Beavo (UW), two Glaxo scientists from the United Kingdom (Barry Moss, Mike Drew), and several others. (*Id.*; D.I. 140 at 151:7-25)

26. Also on March 18, 1991, Rimele authored a "Cardiovascular Status Report" (hereinafter, the "Glaxo CSR") detailing the history and results of Glaxo's research in the area of smooth muscle relaxation. (PTX-51) The Glaxo CSR states that the first examples of cGMP analogs were submitted in May 1990. (*Id.* at GLAX15564) Testing on these analogs began in June 1990. (*Id.*) Among the list of cGMP analogs was GI118611A, Glaxo's designation for 8-(4-chloro-phenylthio)-cGMP, a compound previously listed by plaintiff in the research proposal portion of the 1989 Research

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Research ("GGR") in the United Kingdom. (PTX-45)

Agreement. (*Id.* & GLAX15570; D.I. 143 at 651:22-652:10) In addition to GI118611A, the Glaxo CSR lists four additional cGMP analogs that had been included in either the 1989 Research Agreement or the 1990 Progress Report: (1) GI 120446A, or 1-napthylthio cGMP (D.I. 143 at 652:12-653:12; PTX-51 at GLAX15571; PTX-35 at VM-602[17]); (2) GI 118815A, or napthylthio cGMP; (3) GI 119889A, or 8-octobromo cGMP (D.I. 143 at 653:13-654:1; PTX-51 at GLAX15570; PTX-40 at VK347[18]); and (4) GI 120547A, a hydroxythio cGMP[19] (D.I. 143 at 654:2-654:22; PTX-51 at GLAC15621).[20] Zaprinast and a compound SC-44238 were listed as cGMP PDE inhibitors, and IMBX, caffeine, and theophyline were listed as nonselective inhibitors. (PTX-51 at GLAX15632)

27. The Glaxo CSR described the progress on cGMP analogs, discussed at a May 4, 1990 meeting, as follows:

> The important interactions of the protein with cGMP were presented along with the location of a novel lipophilic binding pocket off of the eight position of the guanine base. This modeling will serve as the basis to design novel cGMP

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[17]The research proposal of the Agreement notes that "[t]he more bulky 1-napthyl-S-cGMP (analog 14) will be made by using 1-napthylenethiol as starting material."

[18]Konjeti's lab notebook lists 8-napthylthio cGMP and 8-octobromo cGMP as compounds synthesized as of February 13, 1990. (PTX-40 at VK-347; D.I. 143 at 649:12-650:6)

[19]Because the precise nomenclature of this compound does not appear to be of record, the court cannot match up GI 120547A with the 1990 Progress Report as per Konjeti's testimony. Defendant, however, did not contest this point in its answering brief.

[20]Glaxo patent counsel conducted a literature search in April 1991, and concluded that several of these compounds were not previously described. (PTX-57) It is unclear from the record exactly which compounds were deemed novel as of that date.

analogs to synthesize.

(*Id.* at GLAX15594; *see also id.* at GLAX15596 ("Based upon the location of a novel lipophilic binding pocket off the eight position of the guanine base, compounds with bulky groups off the 8-position are being synthesized."))

28. The Glaxo CSR described future work regarding PDE5 as: (1) continu[ing to] develop an SAR of zaprinast[21]; (2) synthesiz[ing] compounds that vary the distance of a particular zaprinast; (3) synthesiz[ing] a substrate for an affinity column for PDE5; (4) develop[ing] syntheses of zaprinast-cGMP hybrids; and (5) validat[ing] the cGMP PDE enzyme assay. (PTX-35 at GLAX15597)

29. In April 1991, Corbin and his group sent a minuscript for Glaxo's approval for publication, entitled "Relaxation of Pig Coronary Arteries by New and Potent cGMP Analogs that Selectively Activate Type Iα Compared to Type Iβ cGMP-Dependent Protein Kinase."[22] (PTX-56) In the article, Corbin et al. hypothesized that the potency of 8-position substituted cGMP analogs was due to the "spacial tolerance of large

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[21]A weak PDE inhibitor known at the time.

[22]This paper was eventually published in 1992. (D.I. 140 at 163:5-8)

substituents at C-8, preference of this binding site for the syn[23] conformation of cyclic nucleotides and the electron-withdrawing/donating properties of the substituent." (*Id.* at VC-146) "It was thus concluded that a bulky halogen substituent with low electron withdrawing power favors the activation of the cGMP kinases." (*Id.*) Corbin testified that analogs with large bulky groups at the 8-position are fixed in the syn position; they cannot rotate to the anti position due to the substituent. (D.I. 140 at 163:9-165:1)

30. On May 29, 1991, Dr. M. W. Elwes of Glaxo's External Scientific Affairs Division, Glaxo U.K., sent Corbin a letter stating the following:

> [Glaxo has] now had time to examine the projects in [ ] light of our new arrangements for supervision of the cardiovascular therapeutic area within the Glaxo research organization. As you will be aware responsibility for this therapeutic area now rests with Glaxo Group research and our CVS Research Management Committee (RMC) is not lead by Dr. Barry Ross. . . . We consider your work to be very close to our own project interests and so we would like to develop as close a collaboration with you as geography will allow for the remaining period of the grant. I would ask you, therefore, to send your reports in the future to Dr. Fiona Roberts, our Academic Liason Manager, at this [U.K.] address . . . .

(PTX-59A)

31. Corbin testified that he and Glaxo representatives engaged in informal

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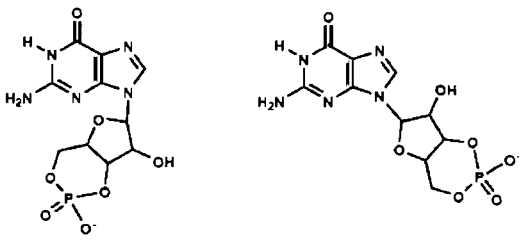
[23]cGMP has two segments which can rotate around a specific point of the molecule, resulting in two 3-D configurations. When cGMP is in the "syn" position, the guanine moiety and the ribose cyclic phosphate moiety are pointed in the same direction. In the "anti" position, the two moieties are turned away from each other.



Syn position Anti position

discussions during that time regarding the continuation of plaintiff's grant. (D.I. 140 at 171:8-172:20) During these discussions, Glaxo indicated a potential bioavailability issue insofar as cGMP breaks down in the stomach and intestines, never reaching its destination tissue. (*Id.*) According to Corbin, Glaxo also indicated that future work should focus more on PDE5 than the original grant did. (*Id.*)

32. Corbin responded to Elwes' letter on July 24, 1991, in which he noted that he was pleased with Glaxo's interest in plaintiff's work, and that it "seems [from previous informal discussions with Glaxo representatives] that any future relationship with Glaxo, following the award termination, would be an open-ended proposition." (PTX-71) Corbin asked to be informed "if there is anything [he] could do now to improve the chances for such a continuation . . . We feel that this particular project is going quite well, and we wish to carry on with it if possible." (*Id.*)

33. Glaxo meeting minutes for the "PDE Project" dated June 3, 1991 state that Glaxo's goal at that time was "[t]o discover a potent specific inhibitor of cGMP-specific ('type V') [PDE] for the treatment of hypertension, angina pectoris, etc." (PTX-62) Some specific "molecules already obtained in the U.S., with some biological results," were "azapurines" and "imidazoles."[24] (*Id.*) Action items included "search[ing] for available molecules." (*Id.*) "The compound that seems to be the most interesting at this point is AH19041xx (azapurine family . . .)." (*Id.*) The following "[o]ther molecules to be studied (various vasodilators and PDE inhibitors" were listed: hydralazine,

[24]Generally, imidazole is a organic compound with the formula $HC_3H_3N_2$. Purine is a heterocycle consisting of a pyrimidine ring fused to an imidazole ring. Azopurines are purine analogs.

dihydralazine, eudralazine, minoxidil, pinacidil, diazoxide, flosequinan, nicotinamide ethers, nitraquazone, imidazolidinones, rolipram analogs, and cicletanine. (*Id.*)

34. From June 17-20, 1991, Dr. Jorge Kirilovsky, a scientist with Glaxo France, traveled to North Carolina for meetings with Rimele, Domanico, and other Glaxo scientists regarding PDE V.[25] (PTX-58; PTX-58A) Glaxo sent compounds listed in the meeting minutes of June 3, 1991 to Glaxo France. (*Id.*; D.I. 142 at 474:20-475:3, 478:12-19) The American scientists proposed to test "AH19041X-type imidazoles fairly soon" to determine any effects on the central nervous system. (PTX-58A at GLAX15734; D.I. 142 at 477:3-8) Glaxo was in discussions with ICOS at this time, which was to clone and express about 30 enzymes which would be used to test different types of compounds developed by Glaxo. "ICOS's priority would be type IV, followed by types V and III." (PTX-58A at GLAX15735-36)

35. Dr. Paul Grondin was hired by Glaxo in June 1991 by George Kirilovsky to carry out experiments for the PDE V project at Glaxo France; he was the first person assigned to do so. (D.I. 142 at 473:7-15, 474:1-4)

36. Minutes of a Glaxo France PDE Project meeting on July 9, 1991 reflect that

> [a] list of model compounds already characterized as PDE inhibitors has been drawn up on the basis of published work and the GI results. These compounds will be analyzed using the various tests currently being set up at Les Ulis: enzymology, isolated artery, isolated heart, whole animal.

The "proposed list of model compounds" for a "type V inhibitor" consisted of AH 91041XX, GI 122529X, and zaprinast. (PTX-69) "The second step will be to determine

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[25]"Individuals who have been involved in the PDE V program in the past;" in addition, chemists David Uehling and Paul Feldman. (PTX-58A) Scientists Steve Simpson and Verghese were also listed in the memorandum discussing the trip. (*Id.*)

the lead compounds, drawing from either the PDE inhibitors presented in published work, the known vasodilators, or model compound analogs (above list)." (*Id.*)

37. The Glaxo July 1991 minutes state that a ChemBase computer file was set up to include all of the compounds tested and the results obtained. "Compounds of interest" GI 122529X and AH 19041XX were to be compared to zaprinast. (*Id.*) Neither compound was available in sufficient amounts at that time, and needed to be synthesized for the study. (*Id.*) Glaxo France's "[g]oal for the end of the year [1991]" was "[o]perational enzymology and pharmacology tests with in-house results on compounds chosen as references." (*Id.*)

38. Minutes of a Glaxo PDE Project meeting of August 27, 1991 reflect that Glaxo was, as of that date, "beginning [ ] in vivo testing of zaprinast and rolipram." (PTX-58A at GLAX15759) Dr. Bernard Dumaitre was planning to synthesize AH19041X as a reference compound, which was accomplished in September 1991. (PTX-58A; PTX-75) Compound GI122529X would not be available for six weeks, and GI121730 was to be tested in its stead. (PTX-58A at GLAX15759) Finally, Glaxo noted an "action" item of "[i]mmediate synthesis of rolipram and denbuflyn" by Dumaitre and another scientist. (*Id.*)

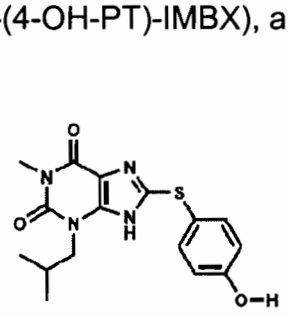
39. A PDE Project meeting was held at Glaxo France on October 9, 1991. (JTX-7; PTX-77) At that time, Glaxo[26] was working to complete an assay to measure PDE5 inhibition. (D.I. 142 at 423:25-484:11) Following completion of the assay, Glaxo's objective was to "develop a specific tool of the zaprinast (asapurinone) type

[26]Glaxo considered the PDE Project to be an international collaboration between Glaxo and Glaxo France. (PTX-77 ("The PDE project is international[.]"))

with 10 times greater activity." (*Id.*; PTX-77) Glaxo expected that in the near future, ICOS would possess a "type V [PDE] (human lung) . . . for screening." (PTX-77)

40. Also in October 1991, Corbin wrote Roberts at Glaxo requesting permission to provide plaintiff's "close collaborators" with the cGMP analogs "for basic research purposes." (PTX-81) Corbin indicated that Glaxo had approved, as of that date, "the publication of the syntheses and properties of the compounds." (JTX-43) Corbin testified that his request for a blanket approval to provide compounds to third parties was denied by Glaxo. (D.I. 140 at 175:4-6)

41. In November 1991, Corbin, Francis and Konjeti synthesized a new PDE5 inhibitor. (PTX-88 at VK-1737, 1757-62) IMBX was chosen as a parent compound for the new PDE5 inhibitor because it was known to work, it was cheap and readily available, and was easily substituted at the 8-position. (D.I. 140 at 185:4-17; D.I. 143 at 663:12-16, 786:2-21) A phenyl ring was attached to the 8-position of IMBX, and an electron-donating hydroxy group at the 4 position of that phenyl ring. The result was 8-(4-hydroxy phenylthio)-IMBX (or 8-(4-OH-PT)-IMBX), a potent PDE5 inhibitor.



42. Also in November 1991, Corbin drafted a letter to plaintiff's General Counsel, Jackie Schrago, with respect to Corbin's request for plaintiff to sponsor the compounds Corbin was developing. (PTX-89; D.I. 140 at 176:17-177:3) Corbin communicated to Schrago possible therapeutic uses for the new analogs, including the

treatment of male impotence. (PTX-89) The treatment of ED with cGMP analogs had not been published in the literature as of this time. (D.I. 143 at 784:1-9, 796:8-25; D.I. 145 at 1139:9-17)

43. In December 1991, Dr. Richard Labaudiniere was hired by Glaxo France as the head of chemistry. (D.I. 141 at 392:10-393:23) Labaudiniere assumed leadership of the PDE5 project. (*Id.*) As head of chemistry, Labaudiniere was involved in all projects of that department and was responsible for discussing the best approaches for chemists' work, including suggesting modifications to compounds. Additionally, Labaudiniere was involved in management and discussed methods of drug development with the head of biology. (*Id.*)

44. Also in December 1991, Corbin spoke with Ross at Glaxo U.K. about the possibility of extending plaintiff's collaboration with Glaxo. (D.I. 143 at 668:19-23, 784:20-785:10; PTX-41) On January 3, 1992, Corbin sent Ross a "general outline of a proposal for an extension of the Corbin/Glaxo corroboration (hereinafter, the "January 1992 general proposal"). (JTX-41) "The major change [of this proposal] is that it emphasize[d] a combined protein kinase/[PDE] approach[.]" (*Id.*) Corbin testified that the "major change" referenced was a focus on PDE5 inhibitors, at the encouragement of Glaxo scientists. (D.I. 140 at 178:17-179:23) Corbin theorized that "cyclic GMP analogs might apply to PDE5 as they applied to PKG" and, therefore, "[w]e could in practical terms even use the same analogs that we already synthesized for PKG to test on PDE5." (*Id.*)

45. The January 1992 general proposal contained three sections: cGMP analogs; "[i]nhibitors of a [cGMP]-binding [PDE]"; and "other projects to consider."

(JTX-41) Regarding cGMP analogs, Corbin stated the following:

> We will expand on our most significant finding that analogs modified at the 1,2- and 8-positions of the guanine moiety of cyclic GMP are the most potent relaxants. We originally proposed to synthesize such analogs because 1,2-modified analogs bind to one cyclic GMP-binding site of the cG kinase and 8-modified analogs bind to the other site. As predicted, when these two structural elements were combined, the resulting compounds were even more efficacious because they bound well to both binding sites. We now believe that the high potencies of these analogs are due not only to the high kinase affinity of 1,2- and 8-modifications, but also to a strong [PDE] resistance due mainly to the 8-modifications. This latter property also contributes to the long-lasting analog effect observed in the intact tissue (and presumably in the intact organism). . . .

(JTX-41 at VC-225-26) Corbin testified that the "persistence" of the analogs, or failure to break down, was believed to be the result of resistence to PDE in the tissue. (D.I. 140 at 180:2-15)

46. With respect to PDE inhibitors, the January 1992 proposal stated the following:

> We will design [PDE] inhibitors based on the theory that the potencies of existing inhibitors, such as 3-isobutyl-1-methylxanthine (IMBX) and zaprinast, could be enhanced by appending groups that would allow the inhibitors to more closely resemble the entire cyclic GMP molecule. The existing inhibitors resemble only the guanine component. Our preliminary results indicate that this strategy works. **We have synthesized one compound that is about 160-fold more potent than the parent IMBX, and 6-fold more potent than the best existing inhibitor, zaprinast**. . . . This section overlaps neither with our NIH grant . . . nor with our ICOS/Glaxo collaboration described above. However, each of these projects should benefit from the others.

(JTX-41 at VC-226-27) (emphasis added) Corbin and Francis testified that they believed that compounds having both the guanine component and an appendage to make contact with the (exposed) ribose phosphate portion would be more potent. (D.I. 140 at 181:21-183:12; D.I. 143 at 790:3-792:9) Notably, Corbin and Francis did not have the genetic sequence of PDE5 at the time and did know the structure of the

catalytic site; their theory was based upon observations of cGMP binding on PKG.[27] (791:23-794:11)

47. Finally, under the "other projects" heading of the January 1992 general proposal, Corbin noted that "the cG kinase has important disease-related functions other than the induction of vascular smooth muscle relaxation." (JTX-41 at VC-227) "Corpus cavernosum relaxation (male impotence)" was listed as an application of interest. (*Id.*) Corbin suggested Glaxo support plaintiff's research for three years starting in July 1992. (*Id.*)

48. Glaxo was not researching male impotence in early 1992. (D.I. 141 at 407:12-24)

49. Ross flew from England for a presentation of the January 1992 general proposal on February 3, 1992. (JTX-42; D.I. 140 at 187:14-22; D.I. 142 at 583:10-19) On February 11, 1992, Glaxo France purchased a quantity of IMBX. (PTX-115)

50. On February 24, 1992, Corbin mailed Ross a final proposal including "[m]ore detail of the experimental design" with "increased emphasis on use of the newly synthesized compounds to study basic mechanisms of the protein kinase and [PDE]"

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[27]That is, as explained in the FASEB abstract, hydrophobic groups of atoms, such as a phenyl ring, with additional electron-donating groups appeared to bind well to binding sites on PKG in the vicinity of the ribose phosphate moiety of cGMP. (PTX-47; D.I. 140 at 149:15-150:12) Francis acknowledged at trial that scientists at the time did not believe that PKG and PDE5 catalytic sites were related. She testified, however, that the team believed a relationship was "plausible" because a new PKG was developed in the lab that was identical in amino acid sequence but differed dramatically in affinity for cGMP, illustrating chemical preferences. (D.I. 143 at 793:4-794:11)

(hereinafter, the "1992 Research Proposal").[28] (PTX-117; PTX-118) Like the January proposal, the 1992 Research Proposal specifically identified 8-(4-OH-PT)-IMBX as a new compound "that is about 160-fold more potent than the parent IMBX, and 6-fold more potent than the best existing inhibitor, zaprinast." (PTX-117 at 3) Other IMBX and zaprinast analogs were also listed. (*Id.* at 4; PTX-424) All but one had 8-position substitutions. (D.I. 143 at 672:3-6)

51. In addition, the 1992 Research Proposal stated that Corbin's team "now believe[d] that the high potencies of these analogs in intact tissues are not only due to the high kinase affinity of the 1,2- and 8-modifications, but also to a strong PDE resistance and antagonism due mainly to the 8-modifications." (PTX-117 at VC250) "[S]ome cGMP analogs are not only PDE-resistent, but they also act like methylxanthine inhibitors of the enzyme by binding tightly to its catalytic site." (*Id.*)

52. On March 11 and 12, 1992, Glaxo tested 26 compounds for PDE5 inhibition, including a compound designated GR35273x, discussed in further detail *infra*. (DTX-IG at GLAX13202)

53. On April 8, 1992, Ross sent copes of the 1992 Research Proposal to six Glaxo scientists, including Dr. Francois Hyafil, head of the Glaxo France lab, and Labaudiniere. (PTX-121; D.I. 130, ex. 1 at ¶ 21) In his cover, Ross stated that Corbin's work on cGMP analogs and "prob[ing] the mechanism and role of smooth muscle protein kinases and [PDEs]" was "a substantial collaboration and the only one of the original US CV discovery grants that remains." (PTX-121) Further, Ross stated that

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[28]Corbin testified that he, Francis, and Konjeti jointly prepared the February 1992 proposal. (D.I. 140 at 190:22-24)

> Corbin is collaborating with the ICOS/Glaxo strategic alliance in the area of type V [PDE] enzyme mechanisms and function. This proposal is distinct from that collaboration and is primarily directed towards the cGMP simulated kinases. As a spinoff some compounds have demonstrated type V PDE inhibitory activity. Results eminating from this collaboration may provide the foundation for a future in-house discovery programme directed towards hypertension and congestive heart failure.

(*Id.*)

54. On April 23, 1992, Glaxo tested the PDE5 inhibitory capacities of 29 compounds. (PTX-425) Among these were zaprinast, and a molecule designated GR30040x, discussed in detail *infra*. (PTX-140) There is no evidence of record demonstrating the date GR30040x was identified by Glaxo for the purpose of this testing.

55. Plaintiff asserts 11 of these 29 compounds contain what it calls the "Vanderbilt Structural Features," or "a 6-member ring fused to a 5-member ring, with some substitution at the 8-position." (D.I. 153 at 27)

3. The identification of GR30040x preceded the discovery of tadalafil

56. This case pivots around GR30040x, a beta-carboline[29] compound having the following four-ring scaffold structure.

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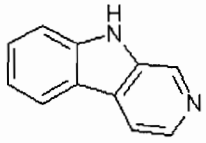
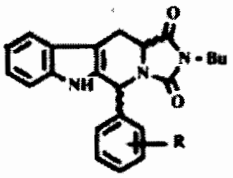
[29]Beta-carbolines are compounds comprising the following general (three-ringed) structure.





(D.I. 150 at 11)

57. There is no dispute that Labaudiniere identified GR30040x as a "lead" compound for research regarding PDE5 inhibition. Following its identification, Daugan conducted research on GR30040x. Through the course of this research, Daugan discovered tadalafil.[30]

58. Plaintiff asserts that Labaudiniere used the "Vanderbilt Structural Features" for two purposes. First, plaintiff claims that the disclosure of 8-(4-OH-PT)-IMBX led to the discovery of the lead compound GR30040x. Second, plaintiff asserts that its disclosure of 8-(4-OH-PT)-IMBX contributed to the course of the modifications to GR30040x performed by Daugan.[31] The court addresses the facts relevant to each assertion in turn.

59. Plaintiff asserts that the "only logical source for the identification of GR30040x and the inclusion of the Vanderbilt Structural Features in the patented compounds" was the 1992 Research Proposal. (D.I. 154 at 12) To give context to

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[30]The compounds of formula 1 of the patents at issue are beta-carboline/piperazinedione compounds; GR30040x and GF173321x are beta-carboline hydantoin compounds, and are not part of the claimed inventions.

[31]The parties debate the sequence of modifications to GR30040x performed by Daugan, as it relates to this argument.

plaintiff's claim, and in view of the presumption that Daugan invented the compositions and methods claimed in the patents at issue, the court first addresses Glaxo's evidence regarding how GR30040x was identified as the lead compound for Daugan's research.

a. Glaxo's evidence regarding the identification of GR30040x

i. Elgoyhen

60. In its pretrial disclosure, Glaxo asserted that Labaudiniere became aware in early 1992 of literature suggesting that beta-carbolines could alter cGMP levels, which caused him to use the "basic beta-carboline structure" of the prior art compounds to conduct a substructure search. (D.I. 130, pt. 4 at 3) When these compounds were tested, some were found to be fairly potent PDE5 inhibitors. Labaudiniere then asked Daugan to pursue the modification of these "lead compounds," including GR30040x. (*Id.*)

61. This theory is reflected in a paper received by the Journal of Medicinal Chemistry on February 5, 2003, entitled "The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor[.]" (hereinafter, the "Tadalafil Paper"). (JTX-29) As reflected in the Tadalafil Paper, "β-carbolines had been previously found to increase basal level of cGMP in rat cerebellum . . . [and] were also reported to inhibit crude rate aortic cyclic nucleotide [PDE] activity." Two references are cited: (1) a 1983 article in the European Journal of Pharmacology by B. Koe et al. entitled "Contrasting Effects of Ethyl β-Carboline-3-Carboxylate and Diazepam on Cerebellar Cyclic GMP Content and Antagonism of Both Effects by Ro 15-1788, A Specific Benzodiazepine Receptor Blocker" (hereinafter, "Koe"); and (2) a May 1992 article in the Journal of Pharmacology and Experimental Therapeutics by B. Elgoyhen et al. entitled "Relaxant Effects of β-

Carbolines on Rat Aortic Rings" (hereinafter, "Elgoyhen"). (JTX-29 at ICOS737 & n.10 & n.11) The Tadalifil Paper proceeds to state that "[t]he β-carboine scaffold was then used as a basis for substructure searching in our internal database to find novel type 5 [PDE] inhibitors (chart 1)." (*Id.* at ICOS737)

62. Of record is a Glaxo document entitled "PDE V Inhibitors Project Annual Report for the Year Ending 30/4/93" (hereinafter, the "1992-93 Annual Report"). (DTX-P) The 1992-93 Annual Report reflects that Koe and/or Elgoyhen led Labaudiniere to beta-carbolines generally, while substructure searches on the tetrahydro beta-carboline portion of GR35273[32] led to the identification of GR30040x in particular:

> 4. 7. a- GR30040 analogues
>
> It is a new series of compounds we began to study last year starting from literature data on β-carboline and benzodiazepine derivatives having some vasorelaxant effect on precontracted rat aortic rings. These compounds displayed in our hand some PDE V inhibition activities. Substructure searches from β-CCE[[33]] and GR35273 on tetrahydro-β-carboline analogues in GLAX led to the idenfification of GR30040, a specific PDE V inhibitor, with activities similar to zaprinast (see figure 11). Studies have been performed to improve potency.

(*Id.* at GLAX00037)

63. Glaxo's internal testing record indicates that GR30040x was subjected to a 10 micromolar concentration test[34] on April 23, 1992, scoring an 86 for inhibition. (PTX-

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[32]A beta-carboline compound. (D.I. 143 at 891:22-892:9)

[33]β-CCE or βCCE, chemical name ethyl beta-carboline-3-carboxylate (or beta-carboline-3-carboxylic acid ester), is a benzodiazepine antagonist and a member of the beta-carboline chemical family.

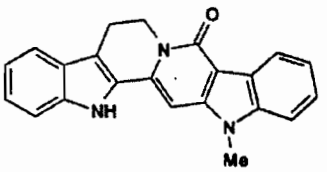
[34]Plaintiff represents that this test measures inhibition using a set concentration of the compound, usually 10 micromolar, on a scale from 0-10%, with 100% representing complete inhibition. (D.I. 153 at 29)

140) GR30040x was then tested to determine an IC_{50}[35] value on April 24, 1992, which revealed a value of 0.2 micromolar. (*Id.*) Tests on GR30040x using PDE1, or a type 1 PDE inhibitor, were performed on May 12 (10 micromolar concentration test) and June 3, 1992 (IC_{50} = 2.0 micromolar, a poor result). (*Id.*) Additional IC_{50} tests were performed on GR30040x (PDE5) on June 9 and 10, 1992 (IC_{50} = 0.6 and 0.15 micromolar, respectively). (*Id.*) A IC_{50} test was performed on βCCE on July 3, 1992, revealing a IC_{50} value of 0.8 micromolar. (PTX-170; D.I. 146 at 1215:18-1216:2)

64. Rafferty conceded that any searches conducted by Glaxo based on Elgoyhen or βCCE would have had to have occurred after Elgoyhen was published on May 8, 1992. (DTX-RJ; D.I. 146 at 1256:2-23) In short, GR30040x was not identified following Labaudiniere's reading of Elgoyhen.

ii. Substructure searches

65. Glaxo distanced itself from Elgoyhen at trial, asserting that GR30040x was identified through a substructure search of GR35273, a beta-carboline compound having the following structure.[36]



[35] IC_{50} is a measure of the biochemical function of a compound, indicating the quantity of the drug required to inhibit a biological process (or component of a process, *i.e.*, an enzyme, cell, cell receptor or microorganism) by half. *See gen.* www.wikipedia.org/wiki/IC50.

[36]Glaxo argues in its papers that "in May 1992, the Elgoyhen publication **reinforced** Dr. Labaudiniere's interest in beta-carbolines as potential PDE-5 inhibitors by showing that they could relax blood vessels." (D.I. 150 at 8) (emphasis added)

66. Rafferty opined at trial that Labaudiniere identified GR35273, a compound of interest taken from Glaxo's "APOB100"[37] program, "another internal discovery program in Glaxo," in an effort to identify new leads for the PDE5 program. (D.I. 146 at 1202:5-18) GR35273 was tested on March 11 and 12, 1992, and was identified as an "impressive" PDE5 inhibitor. (*Id.*; DTX-IG at GLAX13202) According to Rafferty, Labaudiniere then undertook substructure searches based on the tetrahydro beta-carboline fragment[38] of GR35273, leading to the identification of GR30040x (among other compounds), which was tested on April 23, 1992. (D.I. 146 at 1202:5-18, 1204:15-1206:14) Rafferty explained that, among the compounds tested by Glaxo between March and July 1992, there are "a rather disproportionate number of tetrahydro beta-carbolines, which suggests [ ] a search was conducted . . . and that Dr. Labaudiniere was exploring possibilities that turned up from that search." (*Id.* at 1299:1-5)

a. Documentary evidence

67. Minutes of a meeting held by Glaxo's Cardiovascular Research Management Committee on April 9, 1992 describe GR35273 as a compound synthesized by Prof. Campbell of Bath University that "selectively down-modulates

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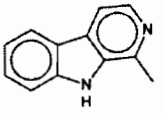
[37]APOB-100 is one of the two main isoforms of apolipoprotein B, the primary apolipoprotein of low-density lipoproteins ("LDL", commonly referred to as "bad cholesterol"). *See gen.* www.wikipedia.org/wiki/apolilipoprotein_B.

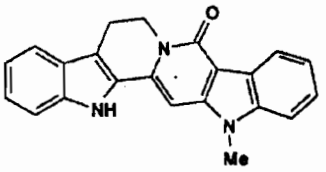
[38]Tetrahydro beta-carboline has the following structure.



apoB-100 production."[39] (JTX-22 at GLAX25738) Notes from that same committee's meeting on June 11, 1992 reflect that

> GR35273x, a compound coming from our APOB100 screen[,] displayed a high PDE V inhibition activity (IC50=30nm). A closed analogue AH20905xx displayed a similar activity (IC50=50nm). These compounds can be considered as conformationally constrained analogues of zaprinast, which are not patented as PDE V inhibitors. We are starting now a chemical programme on GR35273x analogues.

(JTX-24 at GLAX10365) Minutes from Glaxo's PDE Project meeting of June 23, 1992 (hereinafter, the "June 23, 1992 minutes") also list GR35273x as an analog of zaprinast, having the following structure[40]:



(JTX-13 at GLAX16000) At this same meeting, GR30040x was characterized as a "new" PDE5 inhibitor.[41] (*Id.* at GLAX15986)

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[39]This mention of GR35273 occurred in the section entitled "Status Reports" and subtitled "6.1 Atherogenic and Thrombogenic Risk Factors." (JTX-22 at GLAX25738) Aside from an appendix containing its structure, the document does not appear to mention GR35273 elsewhere. (*Id.*)

[40]Plaintiff points to JTX-15 at GLAX16277-80, an untranslated version of minutes from an October 1992 Glaxo France strategy meeting, in support for the proposition that the PDE Project team "debated and concluded [in October 1992] that GR35273x was more appropriately considered a carboline than a zaprinast analog." (D.I. 154 at 10) No English translation appears to have been admitted and the court is not in the position to judge this statement. The court does note, however, that GR35273x appears to contain the beta-carboline core (three-ringed) structure.

[41]Plaintiff does not point to an English translation of JTX-13. It is clear from the transcript that GR30040x was characterized as a "new" PDE5 inhibitor, though little else from this document is readily discernable. (D.I. 146 at 1250:1-15)

68. Also of record are the untranslated minutes of a PDE Meeting held at Glaxo France on September 9, 1992. (DTX-AQ) Among these minutes appears a "β-carbolines" chart, handwritten by Labaudiniere. (*Id.* at GLAX16099) GR30040 is structurally depicted among several compounds related to βCCE[42] (including a compound designated as GR142799); structure-activity relationships between the various compounds are noted. (*Id.*; D.I. 144 at 894:17-22)

69. Glaxo's "PDE V Inhibitors Project Annual Report for the Year Ending 30/4/03" (hereinafter, the "1992-93 Annual Report"), issued April 30, 1993,[43] discusses results of zaprinast analogues as well as "[a] new series of PDE V inhibitors . . . based on [a] tetrahydro-β-carboline structure," the best of which was identified as GF185990. (DTX-P, abstract) Additionally, the 1992-93 Annual Report states as follows:

> 4. 7. β-Carboline Series
>
> 4. 7. a- GR30040 analogues
>
> It is a new series of compounds we began to study last year starting from literature data on β-carboline and benzodiazepine derivatives having some vasorelaxant effect on precontracted rat aortic rings. These compounds displayed in our hand some PDE V inhibition activities. Substructure searches from β-CCE and GR35273 on tetrahydro-β-carboline analogues in GLAX led to the identification of GR30040, a specific PDE V inhibitor, with activities similar to zaprinast (see figure 11). Studies have been performed to improve potency.

(DTX-P at 9) Figure 11, as referenced above, is reproduced below. Compound

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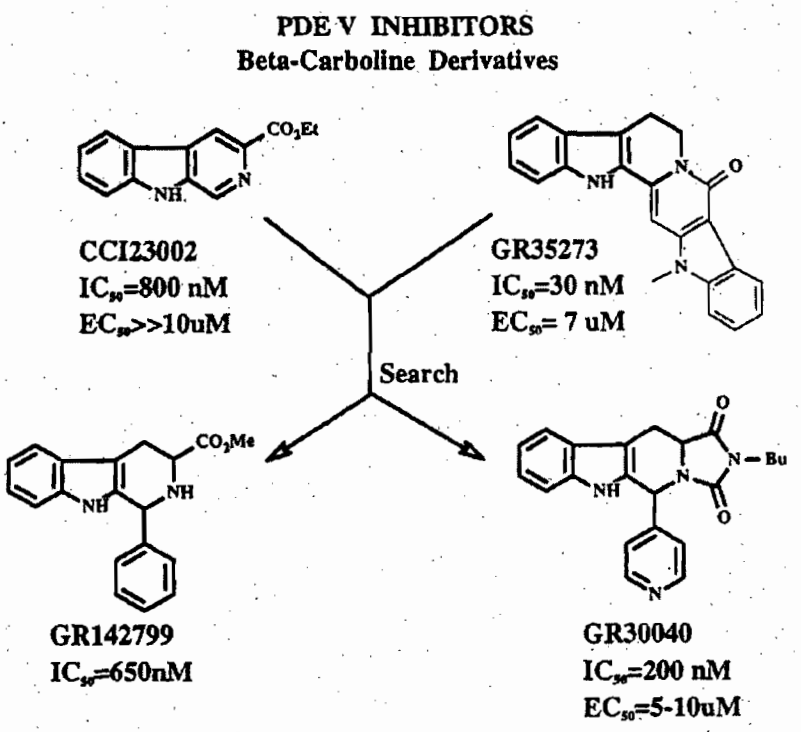
[42]The precise nature of the relationship (analogs, derivatives, etc.) is unclear.

[43]The 1992-93 Annual Report is in memorandum format, addressed from Labaudiniere to Drs. Baxter, Finch, and Johnson of Glaxo France, with distribution to Glaxo's central files, 30 other employees (presumably scientists), and a department titled "Science Information, Les Ulis." (DTX-P)

CC123002 is βCCE.



70. A 2003 Glaxo document also contains the same illustration (hereinafter, the "Beta-Carboline Derivatives Chart"). On February 24, 2003, Labaudiniere sent a report entitled "Progress in the Chemistry and Biology of PDE V Inhibitors" to Dr. Steve Stimpson at Glaxo.[44] (DTX-SU) This report identified three compounds, including βCCE, for "evaluation as PDE V inhibitors."[45] (*Id.* at GLAX16454) The Beta-Carboline Derivatives Chart was provided. (*Id.* at GLAX16455)

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[44]"Enclosed are the acetates of the last ICOS [meeting] for the overview presentation and the cellular biology working session where all the data relevant for PDE V inhibition were presented." (DTX-SU)

[45]Several tetrahydro-beta-carboline PDE5 inhibitors (GF169502; GF171885; GF173322; GF173321) were also identified. (DTX-SU at GLAX16456)

b. Testimony

71. Labaudiniere testified that the term "search" in the Beta-Carboline Derivatives Chart indicates that GR142799 and GR30040x were identified through a substructure search. (D.I. 141 at 441:7-25) Labaudiniere testified that he used Glaxo's ChemBase system to "identify analogues with the beta-carboline core structure." (*Id.* at 436:23-437:3, 437:21-25) Daugan corroborated this testimony. (D.I. 144 at 891:12-892:24)

72. Elgoyhen published prior to the June 1992 testing of βCCE. There was some debate at trial regarding whether a substructure search of βCCE would yield the compounds tested by Glaxo on April 23, 1992, including GR30040x (as indicated by the Beta Carboline Derivatives Chart). Rafferty testified that substructure searches based on the βCCE scaffold, removing the ethylcarboxylate ester from the six-membered notrogen-containing ring (and leaving open the possibility for either single or double bonds on that ring), would have retrieved GR148799 as a result. (D.I. 146 at 1271:21-1272:25; DTX-TC) Plaintiff emphasizes that a substructure search based on the complete βCCE molecule, without modification, would not have returned any of the compounds tested on April 23, 1992. (D.I. 153 at 38, n. 31; D.I. 146 at 1274:3-11)

b. Plaintiff's challenges to Glaxo's inventorship theory based on GR35273x

73. Plaintiff challenges Glaxo's position that GR30040x was gleaned from substructure searches on GR35273x (rather than from substructure searches based on the Vanderbilt Structural Features contained in 8-(4-OH-PT)-IMBX) in several additional ways. First, plaintiff points out that the documents do not seem to connect GR30040x

and GR35273x. (D.I. 153 at 39) GR30040x is not described as a GR35273x analog in the foregoing meeting notes and minutes. Analogs of GR30040x were listed in the June 23, 1992 minutes, but GR35273x was not among them. (*Id.* at GLAX15995-96) GR30040x was characterized as a "new" PDE5 inhibitor. (*Id.* at GLAX15986)

74. Plaintiff also argues that, while Glaxo's internal 1992-93 Annual Report specifically ties the identification of GR30040x to a substructure search on GR35273, Glaxo held out to the scientific community in the Tadalafil Paper that GR30040x was identified through substructure searching using "the β-carboline scaffold" based upon the disclosures of Koe and/or Elgoyhen. (JTX-29 at ICOS737)

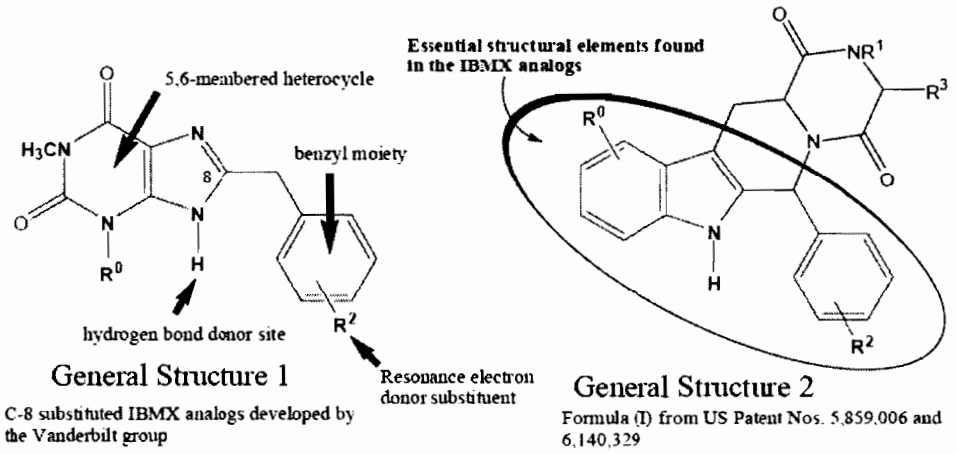
75. Finally, plaintiff argues, without testimonial support, that a substructure search based on "the structural elements the Glaxo scientists found important in GR35273x would have identified only one compound among the April 23rd compounds other than GR35273x itself." (D.I. 153 at 39, n.33; D.I. 154 at 10[46])

c. Plaintiff's theory that its disclosure of 8-(4-OH-PT)-IMBX led to the identification of GR30040x

76. Plaintiff asserts that 8-(4-OH-PT)-IMBX and the claimed compounds share a common scaffold. The portion of the compound of formula 1 corresponding to the asserted "Vanderbilt Structural Features" is circled below.

[46]The exhibits cited by plaintiff do not support this representation.

FIGURE 1



General Structure 1

C-8 substituted IBMX analogs developed by the Vanderbilt group

General Structure 2

Formula (I) from US Patent Nos. 5,859,006 and 6,140,329

(D.I. 153 at 35)

77. As noted previously, the 1992 Research Proposal disclosed that some of the cGMP analogs plaintiff had created were not only PDE resistant, but acted like inhibitors of the enzyme by binding tightly to its catalytic site. (PTX-117 at VC250) Plaintiff asserts that the 1992 Research Proposal would have communicated to a chemist that the 8-position modification of the cGMP analogs prevented the cGMP from being degraded; attaching a "'biomimetic' of the ribose phosphate moiety, consisting of groups like 4-hydroxy phenylthio, to the 8-position of existing inhibitors, that biomimetic would bind in the same region of the catalytic site as the ribose phosphate group that it is mimicking, and the result would be increased inhibition." (D.I. 153 at 23, citing D.I. 145 at 963:22-969:3)

78. Plaintiff asserts that Labaudiniere, upon receiving a copy of plaintiff's 1992 Research Proposal, conducted a substructure search based upon the Vanderbilt

Structural Features contained in 8-(4-OH-PT)-IMBX. Plaintiff admits that no direct evidence supports its theory that such a search occurred.[47] Plaintiff relies on the following circumstantial evidence in order to demonstrate the likeliness of its hypothesis: (1) the 1992 Research Proposal contained impressive and stand-out results for 8-(4-OH-PT)-IMBX; (2) these results came from a respected source; (3) a substructure search based on the Vanderbilt Structural Features could have been performed with ease in only a few minutes; (4) On April 23, 1992, a few weeks after Labaudiniere received the 1992 Research Proposal, Glaxo tested 29 compounds for PDE5 inhibition including zaprinast; (5) none of these 29 compounds had originally been developed and registered in Glaxo France; and (6) each compound had a skeleton including a "6-membered ring fused to a 5-membered ring"; (7) 26 of the 29 compounds tested had "some substitution at the 8-position," as did the IMBX analogues identified by plaintiff in the 1992 Research Proposal; and (8) 11 of the 29 compounds contained both "a 6-member ring fused to a 5-member ring, with some substitution at the 8-position" (*i.e.*, the so-called "Vanderbilt Structural Features"). (D.I. 153 at 26-28)

79. Upon Glaxo's identification of GR30040x, plaintiff asserts that Daugan incorporated into that compound "the only element of the Vanderbilt Structural Features and design that was lacking in GR30040x," electron-donating substituent on the phenyl ring. (D.I. 153 at 31) The result was GF173321x, having the following structure (as compared to 8-(4-OH-PT)-IMBX):

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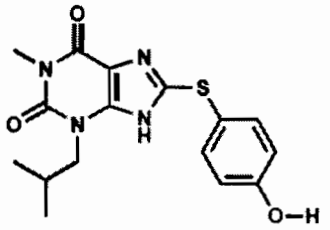
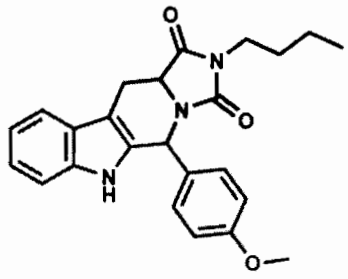
[47](D.I. 154 at 4 ("Vanderbilt need not prove specifically how that occurred, but simply how it logically could have occurred."))



8-(4-Hydroxy phenylthio)-IBMX



GF 173321X

(*Id.*) According to plaintiff, Daugan and Labaudiniere "completely absorbed the Vanderbilt design and Vanderbilt Structural Features with the synthesis of GF173321x."[48] (*Id.* at 34)

4. Modifications to GR30040x

80. According to plaintiff, the methoxy substituent, or the "electron-donating substituent on the phenyl ring," was "the only element of the Vanderbilt Structural Features and design that was lacking in GR30040x." (D.I. 153 at 31) Plaintiff asserts that the first modification made by Daugan to GR30040x was to replace the pyridine ring with a combination of a phenyl ring and an electron-donating methoxy substituent. (D.I. 153 at 30) Plaintiff asserts that these changes occurred simultaneously, "conpel[ling] the conclusion that Dr. Labaudiniere directed Dr. Daugan to make them as a direct result of Dr. Labaudiniere's knowledge of the Vanderbilt design from the 1992

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[48]On or about November 23, 1992, another Glaxo chemist synthesized a zaprinast analog, GF178534x, incorporating the alleged "Vanderbilt Structural Features," which plaintiff asserts is "[f]urther evidence of Dr. Labaudiniere's role in directing the modifications made to GR30040x[.]" (D.I. 153 at 32)

To be clear, plaintiff does not assert in this litigation that Labaudiniere should be named as a co-inventor on either the '006 or '329 patents.

Research Proposal." (D.I. 154 at 14) In support for its assertion that both modifications occurred together, plaintiff cites to Daugan's testimony. (D.I. 153 at 30) Daugan, however, stated only that "[t]he first thing [he] did in this series was explore the replacement of the pyridinyl[ ] moiety with other heterocyclic or aromatic moieties." (896:2-4)

81. Plaintiff asserts that Daugan next continued to make "obvious" modifications to GF173321x, "the Vanderbilt Structural Features persist[ing] throughout," including "the replacement of the 5-member hydantoin ring with a 6-member piperazinedione ring," and eventually synthesized the first compound with all of the features of formula 1 of the '006 patent. (D.I. 153 at 34) In support, plaintiff relies upon the testimony of Labaudiniere. (*Id.*) Labaudiniere stated that modifying the phenyl ring at C5 would have been an obvious location to modify the GR30040x molecule. (D.I. 141 at 424:11:425:18) Labaudiniere also testified that there are a "standard group of substitutions or additions" that would be tried with any molecules of interest, in a "trial-and-error" fashion. (*Id.* at 426:2-17) He stated that the "n-substitution on the hydantion ring," as discussed in the Tadalifil Paper, was an "obvious place to make a modification." (*Id.* at 426:18-24) Because the hydantion series of molecules had poor oral pharmokinetics, meaning that they were generally ineffective oral drugs, further modifications to the hydantion were made leading eventually to the 6-member piperazinedione ring. Labaudiniere characterized the 6-member piperazinedione ring as "a possibility among others." (*Id.* at 427:6-428:24) There was no specific motivation to move from a 6-member ring from the 5-membered ring, only to find an orally active compound. (*Id.*)

F. Discussion

82. As noted previously, 35 U.S.C. § 116 sets "no explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor." *Fina Oil*, 123 F.3d at 1473. Federal Circuit jurisprudence makes clear, however, that a person is a joint inventor "only if he contributes to the conception of the claimed invention." *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1358-59 (Fed. Cir. 2006) (collecting cases). "The line between actual contributions to conception and the remaining, more prosaic contributions to the inventive process that do not render the contributor a co-inventor is sometimes a difficult one to draw." *Id.* at 1359.

83. The Federal Circuit has provided clear guidance in the context of claims to chemical compounds. "Conception of a chemical substance includes knowledge of both the **specific chemical structure of the compound** and an operative method of making it," unless "a method of making a compound with conventional techniques is a matter of routine knowledge among those skilled in the art, [in which case] a compound has been deemed to have been conceived when it was described." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1230 (Fed. Cir. 1994) (emphasis added); *Oka v. Youssefyeh*, 849 F.2d 581, 583 (Fed. Cir. 1988). That is, "[c]onception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its biological activity[.]" *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991).

84. Indeed, on facts analogous to those at bar,[49] the Federal Circuit in *The Board of Education of the Board of Trustees of Florida State University v. American Bioscience, Inc.*, 333 F.3d 1330 (Fed. Cir. 2003) (hereinafter, "*American Bioscience*"), declined to add as inventors scientists who contributed the "starting materials" for a chemical compound. The Court there held that conception of a chemical compound requires "a conception of the specific compounds being claimed, with all of their component substituents." *Id.* at 1340. To put the point another way, "[h]aving in mind specific portions of a claimed compound is not the same as conceiving the compound with all of its components." *Id.*

85. The same result is compelled in the case at bar. The "Vanderbilt Structural Features" constitute no more than a "specific portion[ ] of a claimed compound" in the

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[49]The patent at issue in *American Bioscience* claimed three compounds which are analogs of docetaxel, an anticancer drug (similar to the natural compound paclitaxel) having two distinct substituents: (1) a 10-hydroxy group; and (2) a tertbutoxycarbonyl group attached to its 3' nitrogen atom. 333 F.3d at 1332-33. Scientists at Florida State University ("FSU"), including Robert Holton ("Holton") and Chunlin Tao ("Tao"), made paclitaxel analogs, including "PNIP," a promising anticancer compound having a 10-acetoxy group substituent. *Id.* at 1334. Following an industry conference at which Holton spoke regarding the synthesis of paclitaxel, scientists at VivoRx Pharmaceuticals, predecessor to American Bioscience, Inc., hired Tao and assigned him the task of creating docetaxel analogs using 10-deacetyl baccatin, a compound similar to that (baccatin III) used at FSU to synthesize paclitaxel but having a 10-hydroxy group. Tao made several compounds and a patent application was filed. Issuing were claims to three docetaxel analogs having the 10-hydroxy group. Because there was "no evidence of record that the idea of making [paclitaxel] analogs having a both a 10-hydroxy group (*i.e.*, [docetaxels]) and a nitro functional group came from anyone other than [ABI's inventors]," or any "evidence of conception by Holton or anyone else at FSU of analogs having the combination of a 10 hydroxy group, a nitrophenyl group, and an N-alkoxy-carboyl (*i.e.*, tertbutoxycarbonyl, isopropoxycarbonyl, or isubutoxycarbonyl) substituent," FSU's arguments fell short of meeting the clear and convincing standard of proof required to prove inventorship. *Id.* at 1339, 1341.

language of *American Bioscience*. The record is devoid of evidence that Corbin, Francis, and/or Konjeti communicated to Glaxo a compound of the general structure of Formula 1 of the patents at issue. Plaintiff concedes that, prior to January 21, 1994 (the priority date for Glaxo's U.K. application), its scientists were not aware of the existence of (or structure of) any of the claimed compounds. (DTX-RG at Response Nos. 13-22) There is no indication that Corbin, Francis, and Konjeti were working with beta-carbolines.

86. Because there is no evidence that Corbin, Francis and Konjeti ever conceived the "specific chemical structure of the compound" claimed, *Burroughs Wellcome,* 40 F.3d at 1230, or "the compound with all of its components," *American Bioscience*, 333 F.3d at 1340, or communicated that compound to Glaxo,[50] plaintiff has failed to demonstrate, by clear and convincing evidence, that Corbin, Francis and Konjeti are coinventors of the patents at issue.

87. This is not to say that Corbin, Francis and Konjeti did not make contributions to Daugan's inventive process; only that, under the applicable law, these contributions fall more into the category of "prosaic" contributions because they did not conceive the invention as claimed. *Eli Lilly*, 376 F.3d at 1358-59.

88. Notwithstanding the result compelled by Federal Circuit precedent in this

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[50]Defendant points out that plaintiff admitted that Corbin, Francis and Konjeti never had any direct communication with Daugan regarding this subject matter. (DTX-RG at Response Nos. 23-26) Plaintiff seeks an inference that Labaudiniere communicated the "Vanderbilt Structural Features" to Daugan, and directed Daugan to incorporate them into his research. Notwithstanding the lack of evidence in this regard, even had Corbin, Francis or Konjeti communicated 8-(4-OH-PT)-IMBX to Daugan directly, plaintiff could not demonstrate on this record that Corbin, Francis or Konjeti ever conceived a compound within the family of claimed compounds.

case, the court notes that it finds defendant's litigation position troubling. Defendant submits that Glaxo made no use of plaintiff's disclosure that 8-(4-OH-PT)-IMBX was "160-fold more potent that the parent IMBX and 6-fold more potent than the best existing inhibitor, zaprinast" – a position that this court deems untenable. (D.I. 150 at 3 ("[Plaintiff] did not provide any direct (or even circumstantial) evidence that . . . the four "Structural Features" played **any** role in Dr. Daugan's conceptions.") (emphasis in original))

89. By the spring of 1992, of the twenty original Glaxo Cardiovascular Discovery grants, only one remained – and plaintiff was its recipient. (PTX-121) It is difficult to imagine that Glaxo maintained this particular relationship for no particular benefit. Defendant loses credibility in the court's view for failing to acknowledge that Glaxo made any use of plaintiff's disclosure. There was a consensus among the witnesses at trial that the 160-fold result would have commanded attention. (D.I. 145 at 1067:9-20 (acknowledging result was "interesting"); D.I. 146 at 1233:1-4 (acknowledging that result was "significant," despite denying that a single test result would have been "particularly useful") (Rafferty))

90. Defendant's position is also untenable in view of the fact that, although they are (in whole) different molecules having different properties, 8-(4-OH-PT)-IMBX, GR30040x, GF173321x, and the claimed compounds share a common scaffold having a common shape (three-dimensional configuration). It is the court's understanding that the shape of an inhibitor is directly related to its ability to bind to the enzyme. Corbin communicated to Glaxo on several occasions the importance of the spacial relationships of the substituents he was investigating: for example, Corbin's April 1991

minuscript, discussing the 8-position substituent (*supra* no. 29), and the 1992 Research Proposal, discussing the affinity of the 1,2 and 8-position modifications (*supra* nos. 51, 77).

91. Further, there is a close proximity in time of the relevant events which renders plausible plaintiff's theory that Glaxo did take note of 8-(4-OH-PT)-IMBX and incorporated the "Vanderbilt Structural Features" into the beta-carboline research it was conducting.[51] The court notes that nowhere in its papers did defendant articulate why Labaudiniere selected tetrahydro beta-carbolines (more specifically, the tetrahydro beta-carboline fragment of GR35273) for his substructure searches.[52] (*See supra* no. 66) Notwithstanding, the court views plaintiff's theory (which is devoid of evidence regarding the alleged substructure searches based on 8-(4-OH-PT)-IMBX) and defendant's story (which is devoid of the aforementioned foundation) equally plausible with respect to the identification of GR30040x.[53]

92. Ultimately, even if the court were to find that plaintiff's disclosure of 8-(4-OH-PT)-IMBX led to the identification of GR30040x and the subsequent discovery of

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[51]To summarize, the 1992 Research Proposal was dated February 24, 1992. GR35273X was first tested with PDE5 at Glaxo France on March 11 and 12, 1992. Labaudiniere was sent a copy of the 1992 Research Proposal on April 8, 1992. A 10 micromolar concentration test was performed on GR30040x on April 23, 1992, followed by PDE5 inhibition testing on April 24, 1992. Further testing of GR30040x occurred alongside 26 other compounds on June 17, 1992. GR30040x was identified as a "new" PDE5 inhibitor during the June 23, 1992 meeting.

[52]Glaxo's 1992-93 Annual Report states only that the literature suggested the use of beta-carbolines generally. (DTX-P at 9)

[53]Notably, even if GR30040x were the invention, the balance would not so tip in favor of plaintiff such as to constitute clear and convincing evidence.

tadalafil, *American Bioscience* precludes the result plaintiff seeks: namely, that the contribution of a molecular scaffold in the context of one molecule (here, 8-(4-OH-PT)-IMBX) renders the disclosing party or parties inventors of a different family of molecules containing the same scaffold (here, the compounds of Formula I, including tadalafil). The chemical arts have frequently been characterized by the courts as "unpredictable." Minor modifications to a compound may drastically alter its properties and effectiveness; when isolated, particular portions of a molecule are likely to exhibit different chemical properties. For these reasons, the Federal Circuit has indicated that inventorship must be measured in terms of the complete chemical structure claimed as compared to its functional components, just as the validity and the scope of claims to chemical compounds are measured in terms of the complete chemical structure (and very close structural equivalents).[54] The court declines to expand the reach of 35 U.S.C. § 116 in the manner espoused by plaintiff.

III. CONCLUSION

93. For the reasons discussed above, the court concludes that plaintiff has failed to prove, by clear and convincing evidence, that Corbin, Francis, or Konjeti are

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[54] *See, e.g., PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996) ("In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim."); *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1125 (Fed. Cir. 2004) ("[I]f the art is unpredictable, then disclosure of more species is necessary to adequately show possession of the entire genus") (citations omitted); *see also In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) (noting that "particular types or categories of structural similarity without more" may give rise to *prima facie* obviousness, but "generalization is to be avoided insofar as specific structures are alleged to be prima facie obvious one from the other").

inventors of the '006 or '329 patents. Therefore, judgment shall be entered in favor of defendant and against plaintiff. An appropriate order shall issue.