IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDERBILT UNIVERSITY,	)	
	)	
Plaintiff,	)	
vs.	)	C.A. No. 1:05-cv-00506-SLR
	)	
ICOS CORPORATION,	)	
	)	
Defendant.	)	

ICOS CORPORATION'S RESPONSIVE POST-TRIAL BRIEF

March 26, 2008

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I. INTRODUCTION

Before the trial in January, the Glaxo documents and the testimony of both the Glaxo and Vanderbilt witnesses confirmed that Dr. Daugan independently conceived the compounds and methods claimed in the '006 and '329 patents. Before the trial, there was no evidence, direct or circumstantial, that anyone at Glaxo thought that any information from Vanderbilt was useful for any purpose relating to those compounds or methods, or used any such information for any purpose relating to those compounds or methods.

After seven days of trial, there is even more evidence that Dr. Daugan conceived the claimed inventions himself, and there is still no evidence, direct or circumstantial, that anyone at Glaxo thought that any information from Vanderbilt was useful for any purpose relating to any of those inventions, or used any such information for any purpose relating to those inventions.

The accumulated evidence confirms that in March 1992, a beta-carboline compound called "GR35273x" was identified as a PDE-5 inhibitor. Dr. Labaudiniere used a beta-carboline-based substructure from that compound to search Glaxo's world-wide compound database. That search yielded another beta-carboline compound called "GR30040x," which was shown to be a potent PDE-5 inhibitor in April 1992. Over the next few months, other beta-carboline compounds were found to be PDE-5 inhibitors. Beginning in July 1992, Dr. Daugan used GR30040x as a lead compound in a comprehensive medicinal chemistry project to create chemical compounds that could selectively inhibit the PDE-5 enzyme and could be used as oral drugs to treat hypertension. It is undisputed that over the next eighteen months Dr. Daugan designed and synthesized hundreds of novel beta-carboline-based compounds in his search for a drug candidate. Through designing and testing hundreds of such compounds, Dr. Daugan conceived the family of "Formula (I)" compounds described and claimed in his patents.

As Vanderbilt recognizes, to prove that any of its three scientists co-invented any invention claimed in Dr. Daugan's patents, it had to present clear-and-convincing evidence that Dr. Daugan's inventions were "the product of collaboration of the inventive endeavors"[1] of that Vanderbilt scientist and Dr. Daugan;[2] that they were "working toward the same end and produc[ed] an invention by their aggregate efforts," that they were "work[ing] on the same subject matter" and "ma[de] some contribution to the inventive thought and to the final result" (*i.e.*, that there was "some element of joint behavior");[3] that the Vanderbilt scientist made "a contribution to the conception of the claimed invention that is not insignificant in quality when that contribution is measured against the dimension of the full invention;"[4] and that Dr. Daugan was aware of their alleged contribution when he conceived his inventions.[5]

Vanderbilt has not provided any evidence meeting any of these requirements for even one[6] of its scientists. In its Post-Trial Brief, Vanderbilt says its scientists made a "significant" contribution to Dr. Daugan's conceptions of his claimed compounds by disclosing, in a research proposal sent to Barry Ross (a Glaxo research manager in England), a single PDE-5 inhibition result for an IBMX analog (8-(4-hydroxyphenylthio)-IBMX). Vanderbilt says this Proposal

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[1] Vanderbilt Post-Trial Brief ("Vanderbilt Br.") at 41 (citing *Monsanto v. Kamp*, 269 F. Supp. 818, 824 (D.D.C. 1967) and *Kimberly-Clark Corp. v. Procter & Gamble Dist. Co., Inc.*, 973 F.2d 911, 916 (Fed. Cir. 1992)).

[2] Vanderbilt has never alleged that anyone else at Glaxo (*i.e.*, other than Dr. Daugan) was a co-inventor of any invention claimed in the patents-at-issue.

[3] Vanderbilt Br. at 42 (quoting *Kimberly-Clark*, 973 F.2d at 917).

[4] *Id*. (citing *Eli Lilly & Co. v. Aradigm Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998)).

[5] *Kimberly-Clark*, 973 F.2d at 916 (scientists are not joint inventors if they "had no contact whatsoever and are completely unaware of each other's work"); Fasse, W.F., *The Muddy Metaphysics of Joint Inventorship*, 5 HARV. J.L. & TECH. 153, 171 ("Separate ideas can only be linked in a joint invention if at least one of the inventors, while conceiving or perfecting his ideas, considers the other inventor's ideas. Thus, the minimum required collaboration is some form of communication between two joint inventors.").

[6] Despite its obligation to do so, Vanderbilt never attempted to explain just what contribution each of its three scientists made to the purported "design theory."

somehow communicated what it has finally settled on[7] as a "design theory" consisting of the four "Vanderbilt Structural Features."[8] Vanderbilt hypothesizes that in April 1992, Dr. Labaudiniere read the Proposal, recognized the PDE-5 inhibition result for this IBMX analog as indicating the importance of these four "features" to the potency of any PDE-5 inhibitor, then used some hypothetical substructure consisting of these "features" (rather than a beta-carboline-based substructure) to search Glaxo's compound database and find GR30040x (which Vanderbilt says contains "nearly all" of these features).[9]

Vanderbilt's case fails because Vanderbilt did not provide any direct (or even circumstantial) evidence that any of this happened, or that the four "Structural Features" played any role in Dr. Daugan's conceptions. Vanderbilt has only provided its attorneys' conjecture about how compounds tested on certain days at Glaxo might or might not have been identified. For example, there is no document in which anyone at Vanderbilt referred to the four "Structural

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[7] Vanderbilt Br. at 22. Vanderbilt's arguments about the key "features" of Vanderbilt's IBMX compounds have continually morphed throughout this case, both before trial (*see, e.g.*, D.I. 1 (Complaint) at 6-7, D.I. 130-3 at 4-9, and D.I. 130-11 at 1-2), at trial (*e.g.*, in his opening argument, Mr. Brennen repeatedly argued that Vanderbilt contributed the idea that a potent PDE-5 inhibitor should have a "xanthine" nucleus or scaffold, yet Dr. Konjeti admitted such a structure is not present in the Glaxo compounds that Dr. Labaudiniere supposedly found by conducting searches using such a structure), and now in its Post-Trial Brief (where Vanderbilt has now jettisoned that "feature" in favor of a "feature" consisting solely of a "6-membered ring fused to a 5-member ring").

[8] *Id*. at 22 ("[A] 6-membered ring fused to a 5-member ring with a phenyl group attached to the 8 position . . . with an electron-donating group attached to the phenyl ring, . . . and a nitrogen-hydrogen group (NH) available at the 9-position"). As Drs. Corbin, Padwa, Crooks, and Rafferty explained, in choosing just these four "features," Vanderbilt has selectively ignored the other "Structural Features" of its IBMX ("Iso-Butyl Methyl Xanthine") analogs (particularly the nitrogen and oxygen atoms in the "xanthine" nucleus of the analogs, and the iso-butyl, methyl, and carbonyl groups attached to that xanthine nucleus) (D.I. 141 330:10-24 (Corbin); D.I. 145 at 1038:14-1040:22; and 1042:25-1043:19 (Padwa); D.I. 141 at 360:10-361:14 and 362:23-363:7 (Crooks); D.I. 146 at 1188:21-1189:14; 1189:15-1190:7; and 1208:8-16 (Rafferty)).

[9] *See*, *e.g.*, Vanderbilt Br. at 40 ("The evidence demonstrates that Drs. Corbin, Francis and Konjeti['s] . . . communication of the Vanderbilt Structural Features led to the identification of GR30040x (which contains nearly all of those features) in April 1992.") (emphasis added).

Features" as somehow important to the activity of a PDE-5 inhibitor. Indeed, there is no document in which anyone at Vanderbilt made even a passing reference to these four "Structural Features."

There is no testimony that anyone at Vanderbilt told anyone at Glaxo that the four "Structural Features" were somehow important to the activity of a PDE-5 inhibitor. Nor is there any document or testimony suggesting that anyone at Glaxo thought that these features were somehow important to the activity of a PDE-5 inhibitor. Indeed, there is no document in which anyone at Glaxo made even a passing reference to these features. To the contrary, both Dr. Daugan and Dr. Labaudiniere testified that they never heard of Vanderbilt's design theory.

All of the actual evidence presented at trial (as opposed to the Vanderbilt lawyers' conjecture) confirmed that no one at Glaxo ever recognized or considered Vanderbilt's four "Structural Features" or its "design theory" in designing any compound at Glaxo. All of the evidence presented at trial confirmed that Dr. Daugan, and no one else, conceived his claimed compounds by conducting an independent medicinal chemistry effort to determine the empirical relationship between his compounds' chemical structures and their PDE-5 activity, *i.e.*, an "SAR" study. There simply is no direct or circumstantial evidence that anyone else (including Dr. Labaudiniere, Dr. Ross, Dr. Hyafil, or anyone at Vanderbilt) contributed (much less significantly contributed) to Dr. Daugan's conceptions of his claimed inventions. It is not a question of whether there is clear-and-convincing evidence (or even a preponderance of evidence) of Vanderbilt's contribution; there simply is no evidence even suggesting that anything from Vanderbilt played any role in Dr. Daugan's conceptions of his claimed inventions.

In its Post-Trial Brief, Vanderbilt spends many pages talking about the years Dr. Corbin worked on cyclic nucleotide biochemistry; how Dr. Corbin was the first to isolate the PDE-5

enzyme; how many theories Dr. Corbin has had about how cGMP interacts with PKG or PDE-5 and how those theories purportedly led him to make his cGMP and IBMX analogs; and how Dr. Corbin interacted with a number of Glaxo scientists in the U.S. and England.[10]

Vanderbilt does not, and cannot, show how any of these things contributed in any way to Dr. Daugan's conceptions of his claimed compounds or methods because as Dr. Daugan (and Dr. Labaudiniere) testified, none of these things had anything to do with Dr. Daugan's conceptions of his claimed inventions.

Faced with no actual evidence that Vanderbilt contributed anything to Dr. Daugan's inventions, Vanderbilt's lawyers instead concocted the following theory:

(i) Dr. Labaudiniere read Dr. Corbin's "1992 Research Proposal" in April 1992;[11]

(ii) Dr. Labaudiniere somehow recognized, from the single PDE-5 inhibition result reported for the 8-(4-hydroxy phenylthio)-IBMX compound mentioned in that Proposal, that the four "Structural Features" which Vanderbilt now selects with hindsight could be predictably transferred to any new scaffold, where they would enhance PDE-5 inhibition, regardless of whether other (non-selected) "features" of Vanderbilt's analog were present or not;[12]

(iii) Based on this recognition, in April 1992 Dr. Labaudiniere used a substructure containing only Vanderbilt's four "Structural Features" to search Glaxo's

[10] *See* Vanderbilt Br. at 5-24. Vanderbilt's arguments are similar to those made by the losing party, Dr. Nemerson, in *Scripps Research Institute v. Nemerson*, 78 U.S.P.Q.2D (BNA) 1019, 1044 (Bd. Pat. App. & Interf. 2005) ("In any case, assuming that Nemerson's contribution was truly necessary for Edgington and Morrissey's conception, it does not automatically follow that Nemerson was an inventor. This case is most analogous to *American Bioscience*, in which the university contended that its contributions were necessary to the conception of the invention. Like Nemerson, the university emphasized the considerable expertise and long experience of its scientists as well as their relationship to the named inventors. The court, however, held that even if it assumed the truth about the university scientists' work on related compounds, there was no evidence that they participated in the conception of what was actually claimed. Dr. Nemerson may have been the giant on whose shoulders Edgington and Morrissey stood, but Nemerson has not pointed us to evidence that he contributed to the conception of the invention defined in claim 1.") (internal citations omitted). [11] Vanderbilt Br. at 24, ¶ 1 and 25, ¶ 2.
[12] Vanderbilt Br. at 27.

world-wide "GLAX" compound database to find compounds containing those four "Structural Features";[13]

(iv) This search identified the "GR30040x" compound (which contains only two (which Vanderbilt disingenuously characterizes as "nearly all") of the "Structural Features" ("a 6-membered ring fused to a 5-member ring . . . and a nitrogen-hydrogen group (NH) available at the 9-position"));[14]

(v) Dr. Labaudiniere then directed Dr. Daugan to modify GR30040x to include the two missing "Structural Features" ("a phenyl group attached to the 8 position [*sic*: there is no such 8-position in Dr. Daugan's compounds]. . . with an electron-donating group attached to the phenyl ring");[15]

(vi) Following Dr. Labaudiniere's directions, Dr. Daugan created analogs of GR30040x that he thought "more fully reflected the Vanderbilit [*sic*] design";[16]

(vii) All of the subsequent modifications that Dr. Daugan made to his initial GR30040x analogs (and to his patentably distinct "Formula (I)" compounds claimed in the patents-at-issue) were "obvious;"[17] and

(viii) Vanderbilt's "Structural Features" were a "significant" contribution to Dr. Daugan's conceptions of the structures of those "Formula (I)" compounds.[18]

Accepting Vanderbilt's theory would require this Court to also find the following:

(i) Dr. Labaudiniere, Dr. Daugan, and everyone else at Glaxo France conspired to avoid any mention in any of their PDE-5 Project documents that Dr. Labaudiniere performed his searches using the four "Structural Features"; and

(ii) Dr. Labaudiniere, Dr. Daugan, and everyone else at Glaxo France conspired to avoid any mention in any of their PDE-5 Project documents that Dr. Labaudiniere instructed Dr. Daugan to make GR30040x analog compounds containing all of the four "Structural Features"; and

(iii) In his PDE-5 Project Annual Report for 1992-1993, Dr. Labaudiniere lied to his superiors at Glaxo when he described how he conducted the substructure searches that identified GR30040x.

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[13] Vanderbilt Br. at 27-28.
[14] Vanderbilt Br. at 28-29.
[15] Vanderbilt Br. at 30-31.
[16] Vanderbilt Br. at 31 and 34.
[17] Vanderbilt Br. at 34.
[18] Vanderbilt Br. at 40-41.

Vanderbilt's theory fails because there is absolutely no evidence, direct or circumstantial, that even suggests that any of these things happened, and the actual evidence presented at trial showed that they did not happen; rather, as is usually the case in drug discovery efforts, Dr. Daugan created his compounds in an unpredictable, trial-and-error process, driven by empirical results that revealed the unique combinations of structural features that cause a chemical compound to be useful as a drug.

Dr. Labaudiniere's deposition testimony read at trial made clear that no Vanderbilt information was used to design any of Dr. Daugan's compounds. He could not recall ever seeing the 1992 Research Proposal or discussing it with anyone.[19] Moreover, he did not know what compounds the Vanderbilt scientists were developing until Dr. Corbin visited Glaxo France in June 1993 (months after Dr. Daugan conceived his claimed compounds);[20] no one at Glaxo France used any data relating to any IBMX analogs for any purpose;[21] no one at Glaxo France was trying to develop PDE-5 inhibitors that would resemble cGMP;[22] and he was not aware of any outside collaborator having provided Glaxo with any "design theory" for PDE-5 inhibitors.[23]

Dr. Labaudiniere explained how he was first led to investigate beta-carboline compounds as potential PDE-5 inhibitors and to have Dr. Daugan pursue the beta-carboline series, none of which had anything to do with Vanderbilt. The actual evidence presented at trial confirmed that Dr. Labaudiniere's search for new "lead" compounds for Glaxo's PDE-5 Project led him first to GR35273x, which was shown to inhibit PDE-5 in March 1992; he used a beta-carboline-based substructure from GR35273x to search Glaxo's global compound database, which identified

[19] D.I. 141 at 408:2-410:8; D.I. 148-2 (errata).
[20] D.I. 141 at 398:21-399:12. Before that visit in 1993, Dr. Labaudiniere did not know that IBMX was a potential starting point to develop potent PDE-5 inhibitors (D.I. 141 at 407:3-9).
[21] D.I. 141 at 416:8-418:21; D.I. 148-2 (errata).
[22] D.I. 141 at 405:15-18.
[23] D.I. 141 at 411:9-22; D.I. 148-2 (errata).

GR30040x. This beta-carboline compound was shown to inhibit PDE-5 in April 1992. Shortly thereafter, 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. In June 1992, Glaxo tested compounds related to GR35273x and GR30040x against PDE-5.[24] In early July 1992, testing confirmed that β-CCE (designated CCI23002 by Glaxo) inhibited PDE-5. Dr. Labaudiniere selected the most potent of these beta-carboline compounds, GR30040x, as a "lead" compound for Dr. Daugan's research on the beta-carboline series.

In his live testimony, Dr. Daugan explained that when he conceived the compounds claimed in the patents-at-issue, he was completely unaware of the existence of the Vanderbilt scientists, of the nature of their work, of their cGMP or IBMX analogs, of the PDE-5 inhibition results for those analogs, of the 1992 Research Proposal, and of Vanderbilt's purported "design theory."[25] Dr. Daugan explained his understanding of how Dr. Labaudiniere was originally led to the beta-carboline series[26] and how he himself carried out a comprehensive medicinal chemistry program which culminated in his invention of the claimed compounds,[27] none of which had anything to do with Vanderbilt.[28] All of this testimony was confirmed by the contemporaneous Glaxo documents, and further supported by the expert testimony of Drs. Padwa and Rafferty. None of it was rebutted (or even challenged) by any other witness.

In its Post-Trial brief, Vanderbilt simply ignores this evidence, because it has no legitimate response to it. Instead, Vanderbilt offers attorney conjecture about hypothetical searches by Dr. Labaudiniere, using information hypothetically received from Vanderbilt, and

[24] Dr. Labaudiniere was also investigating the PDE-5 inhibitory activities of benzodiazepine ("BZD")-related compounds, including the β-CCE compound described by Elgoyhen.
[25] D.I. 144 at 868:2-870:11; 871:3-21.
[26] D.I. 144 at 885:21-894:22.
[27] D.I. 144 at 879:13-886:6; 895:19-905:17; D.I. 148-2 (errata).
[28] D.I. 144 at 869:2-870:19; 871:3-872:6; 905:18-906:23; 908:24-910:13.

attorney conjecture about Dr. Labaudiniere hypothetically directing Dr. Daugan to make compounds based on such information. Such conjecture cannot possibly constitute the clear-and-convincing, corroborated evidence required to overcome the presumption (confirmed by the undisputed evidence presented at trial) that Dr. Daugan is the sole inventor of the claimed inventions, *i.e.*, that Vanderbilt did not contribute anything (much less the significant contribution required to justify co-inventorship) to Dr. Daugan's conceptions of those inventions.

Consequently, this Court should grant judgment for ICOS on Counts I and II of Vanderbilt's Complaint.

II. COUNTER-STATEMENT OF FACTS[29]

A. The patents and claims at issue

1. The '006 claims-at-issue (claims 1-8, 10, 12 and 13) are directed to specific chemical compounds and compositions comprising those compounds.[30] One of those compounds is "tadalafil," the active ingredient in the prescription impotence drug Cialis® (*see particularly* claim 13).[31]

2. The '329 claims-at-issue (claims 1, 2, 3, 5-12, and 15-21) are directed to pharmaceutical compositions containing some of the specific chemical compounds claimed in the '006 patent, including tadalafil, and methods of using those compounds and compositions to treat impotence.

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[29] Because, contrary to common practice, Vanderbilt did not number its "Statements of Facts," ICOS cannot simply respond *seriatim* to each "fact" alleged by Vanderbilt. Moreover, Vanderbilt cites PTX 20, 21, 60, 154, 204 and 309 in its Post-Trial Brief, but none of those exhibits were admitted in evidence; consequently, ICOS will not address those exhibits here.

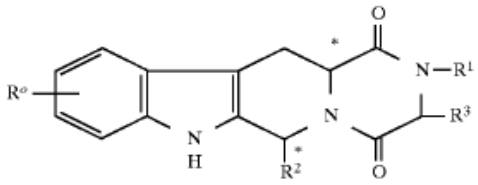
[30] As Exhibit 1 to the Joint [Proposed] Pretrial Order (D.I. 130-2), the parties jointly submitted additional, uncontested facts (Nos. 1-25) regarding the parties, the patents-at-issue, claim construction, the Vanderbilt scientists, the Glaxo research agreements, Glaxo's PDE-5 inhibitor project, and the conception of the inventions claimed in the patents-at-issue, which ICOS hereby incorporates by reference.

[31] JTX 1 at column 52, lines 13-15. The '006 patent describes these compounds as potent and selective inhibitors of PDE-5 (*id*. at column 1, lines 8-15; column 5, lines 15-24) which can alter cGMP levels in cells and therefore are useful in treating diseases such as congestive heart failure. (*id*. at, *e.g.*, column 5, lines 9-35).

These claims derive from the discovery that these compounds are not only useful for diseases like congestive heart failure, but also for "the treatment of impotence."[32]

3. The compounds claimed in the '006 and '329 patents have the general structure referred to and depicted as "Formula (I)" in the patents,[33] with specific substituents (or "side chains") attached at the "R" positions on that scaffold:[34]

A compound of formula (I)



B. Dr. Daugan independently conceived his claimed compounds by conducting a comprehensive medicinal chemistry study

4. As his unrebutted testimony and the contemporaneous documents established, between June 1992 and January 1994, Dr. Daugan carried out a comprehensive medicinal chemistry project in which he designed and synthesized hundreds of different beta-carboline compounds exploring all aspects of the structure-activity relationship ("SAR") of the molecules.[35] At the start, Dr. Daugan's "main mission [was] to begin with a structure that we call a lead and develop an SAR for that lead so as to eventually arrive at a drug candidate," the SAR being "a study that we do systematically on a series, a given series, to understand the information or the elements that are important for biological activity."[36] As Dr. Daugan designed and synthesized novel

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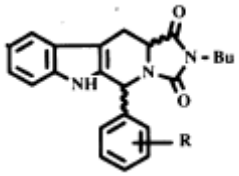
[32] *Id*. at col. 1, lines 7-10 and col. 3, lines 31-35 ("As a consequence of the selective [PDE-5] inhibition exhibited by compounds of the present invention, the subject compounds can elevate cGMP levels, which in turn can mediate relaxation of the corpus cavernosum tissue and consequent penile erection.").
[33] D.I. 146 at 1189:15-22 (Rafferty).
[34] JTX 1 at col. 49, lines 24-67; JTX 2 at col. 10, lines 15-24.
[35] D.I. 144 at 875:12-20; 879:13-886:6; 895:19-905:17 (discussing JTX 4, 29, and 64, and DTX P, SQ, GD, GE, GG, GH, and IT at GLAX 17081 and 25440); D.I. 148-2 (errata).
[36] D.I. 144 at 853:17-854:3 (Daugan); *see also* D.I. 141 at 371:22-372:1 (Crooks); DTX MN at 265-269.

compounds, the Glaxo France biologists working on the PDE-5 project tested those compounds for activity against a PDE-5 enzyme purified from cow lungs. Compounds found to be most potent and selective were then tested *in vitro* to determine whether they altered cGMP levels in smooth muscle cells growing in culture. If so, they were then tested *in vivo* (*i.e.*, in live animals) to determine whether they reduced blood pressure,[37] particularly "when taken orally."[38]

5. Between June and December of 1992, Dr. Daugan's research focused on the design and synthesis of a family of compounds that each contained the four-ring scaffold structure found in GR30040x (consisting of the three-ring tetrahydro-beta-carboline structure fused to a five-member "hydantoin" ring), as shown below:[39]



6. By December 1992, after designing and testing many dozens of such compounds, Dr. Daugan had determined that although his beta-carboline/hydantoin compounds were potent inhibitors of PDE-5 in cellular assays, they were not effective when administered orally.[40] Dr. Daugan then discovered that incorporating a 6-member "piperazinedione" ring in place of the 5-member "hydantoin" ring resulted in improved oral efficacy.[41] His efforts led him to conceive a group of potent, selective, and orally-effective PDE-5 inhibitors having structures that fall within "Formula (I)" (as reflected in the general structure shown below):[42]

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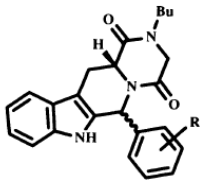
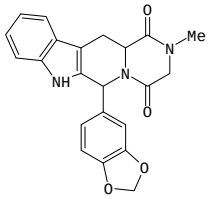
[37] D.I. 144 at 857:10-21; 910:1-13.
[38] D.I. 144 at 857:10-16.
[39] Image from DTX P at GLAX00080.
[40] D.I. 144 at 901:22-903:6; JTX 4 at ICOS000730 (Table 1).
[41] *Id.*; DTX P at GLAX00038 ("Replacement of the hydantoin ring by a 6-membered ring led to potent PDE-5 inhibitors.").
[42] Image from DTX P at GLAX00083.



7. By June 1993, Dr. Daugan had conceived tadalafil,[43] shown below, which was subsequently shown to be a potent PDE-5 inhibitor and a highly effective drug:[44]



8. When Dr. Daugan was designing his compounds, he had never heard of the Vanderbilt scientists, had never seen their results, and had never discussed their work with anyone:

> Q. Before this lawsuit, had you ever read any document that was written by any of those three scientists?
> A. No, never.
> Q. Before this lawsuit, had you ever seen the results of any experiment involving any of those three scientists?
> A. No, never.
> Q. Before this lawsuit, had you ever discussed the results of any experiment involving any of those three scientists with anyone?
> A. No.
> Q. Before this lawsuit, did you have any idea what kind of research Dr. Corbin or his two colleagues worked on?
> A. No, I have never heard of his research.[45]

9. When asked whether the designs of his claimed compounds were influenced in any way by any "design theory" or by the structure of any cGMP or IBMX analog, Dr. Daugan could not have been more clear that they were not:

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[43] D.I. 144 at 859:6-861:5; 905:10-17 (discussing DTX GE and DTX IT at GLAX25440); D.I. 148-2 (errata).
[44] Image from DTX SQ at GLAX12214.
[45] D.I. 144 at 868:17-869:4.

> Q. Doctor, when you designed the beta-carboline compounds claimed in your patents at issue in this case, were you trying to make those compounds resemble any part of the cGMP molecule?
> A. No. Never.
>
> * * * *
>
> Q. When you designed the beta-carboline compounds claimed in your patents, were you aware of any general design concepts that would be applicable to all PDE-5 inhibitors?
> A. No. I used my expertise and my intuition and my knowledge in the area of medicinal chemistry.
> Q. Was your design of your beta-carboline compounds influenced in any way by the design or structure of any IBMX analogue?
> A. No, in no way.
> Q. Was your design of your beta-carboline compounds influenced in any way by the design or structure of any cGMP analogue?
> A. Not at all.
> Q. Was the design of your beta-carboline compounds influenced in any way by the design or structure of any other class of compounds other than beta-carbolines?
> A. No, not at all.[46]
>
> This testimony was not challenged on cross-examination, and went unrebutted.

10. Dr. Daugan also explained that even if he had known that Vanderbilt's 8-(4-hydroxy phenylthio)-IBMX compound had been a potent PDE-5 inhibitor, it would not have helped him in his work designing beta-carboline compounds, because there is no structural similarity between the two kinds of compounds.[47]

11. The most potent, selective, and orally effective PDE-5 inhibitor compounds invented by Dr. Daugan during this project (including tadalafil), and methods for making and using those compounds, were described, exemplified and claimed in a U.K. patent application that Glaxo filed on behalf of Dr. Daugan in January 1994.[48] That application eventually led to the '006

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[46] D.I. 144 at 905:18-906:23. *See also* D.I. 144 at 875:3-11 (Daugan) ("Q. Did any information from anyone at Vanderbilt University influence your conception of those compounds in any way? A. No, no information and no one influenced me in the design and conception of these compounds. Q. Was your design of any of the compounds described in this patent, the '006 patent, influenced by the design of any other PDE inhibitor compound? A. No.").
[47] D.I. 144 at 873:1-11.
[48] JTX 1 at ICOS00009 ("Foreign Application Priority Data: January 21, 1994 [GB] United

patent that claims those compounds and methods.[49]

12. Vanderbilt relies on the testimony of its retained witnesses, Drs. Crooks and Koh,[50] that Dr. Daugan's claimed compounds all contain the four Vanderbilt "Structural Features,"[51] as if this shows that Dr. Daugan's claimed compounds were specifically designed to contain those "Features." But carefully selecting those few structural aspects that are common between two families of compounds, while selectively ignoring the many structural aspects that differ, is mere hindsight re-construction; it is not evidence that the conception of a later-discovered family of compounds was influenced by knowledge of an earlier family of compounds.[52] Vanderbilt's witnesses admitted they had no idea how Dr. Daugan actually conceived his compounds.[53]

C. Dr. Labaudiniere did not conduct any of Vanderbilt's hypothetical searches

13. At its core, Vanderbilt's co-inventorship argument is based on its attorneys' conjecture that Dr. Labaudiniere saw the 1992 Research Proposal and was so influenced by the single result[54] for 8-(4-hydroxy phenylthio)-IBMX that he could, and did, identify the four "Structural Features" that Vanderbilt now touts as being important, chose two of them to use in a search for a new chemical series, and then directed Dr. Daugan to modify "lead" compounds in that series

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Kingdom 9401090").
[49] JTX 1.
[50] As a graduate student, Dr. Koh was not "a person of ordinary skill" in 1992 (D.I. 145 at 977:12-14).
[51] Vanderbilt Br. at 34-35.
[52] Dr. Koh conceded that he never compared Dr. Corbin's 1992 "design theory" with the actual work that Dr. Daugan did in designing, synthesizing, and testing his beta-carboline compounds in 1992-93 (D.I. 145 at 989:15-990:14; 992:9-993:18). Dr. Crooks admitted that in comparing Dr. Daugan's beta-carboline compounds with Vanderbilt's IBMX analogs, he "didn't consider the actual SAR studies that Dr. Daugan conducted on his beta-carboline compound starting from the beginning and all the way through to the end of the project for all of the claimed compounds in his patents"; he "was just looking for structural commonalities between the IBMX analogues and compounds in the two patents" (D.I. 141 at 371:5-18).
[53] *See*, *e.g.*, D.I. 141 at 272:8-273:22, 275:18-20 (Corbin); D.I. 141 at 370:21-371:24 (Crooks); D.I. 143 at 745:8-15 (Konjeti); D.I. 145 at 977:18-22, 988:7-10, 990:16-991:1, 993:9-18 (Koh).
[54] D.I. 141 at 285:8-15 (Corbin).

to "more closely resemble" the IBMX analog. But a medicinal chemist such as Dr. Labaudiniere would not have considered the structures of any of the IBMX analogs listed in the Proposal, all of which contain a purine ring (specifically xanthine, a derivative of purine), to be relevant or informative regarding the design of unrelated compounds containing an indole ring (such as Dr. Daugan's beta-carboline compounds). As Dr. Rafferty testified, a medicinal chemist knows that arbitrarily omitting certain elements from consideration can yield unpredictable results: "In the absence of any information that would allow one to disregard any of these details in the structure [of the xanthine found in IBMX], the nitrogens at position seven, position three, position one and the carbonyls at position six and position two [which are not present in the indole structure of beta-carbolines], it's simply not appropriate to assume that those functional groups are irrelevant" to the PDE-5 inhibitory activity of Dr. Corbin's proposed IBMX analogs.[55] Indeed, both parties' witnesses agreed that there were many differences between Vanderbilt's IBMX analogs and Dr. Daugan's claimed "Formula (I)" compounds (*e.g.*, the absence in Dr. Daugan's claimed compounds of the three nitrogen atoms, two carbonyl groups, a methyl group, and an isobutyl group that were all present in Vanderbilt's IBMX compounds),[56] and there was unrebutted testimony that medicinal chemists would expect those missing features to have an impact on the biological activity of a compound.[57]

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[55] D.I. 146 at 1188:21-1189:14; 1189:15-1190:7; 1208:8-16; DTX TD.

[56] D.I. 141 at 330:10-24 (Corbin); D.I. 145 at 1038:14-1040: 22; 1042:25-1043:19 (Padwa); D.I. 141 at 360:10-361:14; 362:23-363:7 (Crooks).

[57] D.I. 145 at 1018:10-1023:20; 1038:14-1040:6 (Padwa) ("[C]hemists recognize that the nature of the hetero atoms have incredible importance for their properties, not only their chemical and physical properties, but also how they interface with an active site biologically."); D.I. 148-2 (errata); D.I. 146 at 1190:8-1191:14 (Rafferty) ("So in the absence of any data that would allow a chemist to ignore or disregard any of these structural features, you can't assume that they're not essential. You cannot assume they're not part of the contributing structure for activity."); DTX TE; *see also* D.I. 141 at 306:6-9 (Corbin) ("[A] substituent attached to the ring structure . . . can have significant effects on the function of the molecule."); D.I. 148-2 (errata).

14. The only "design theory" mentioned in the 1992 Research Proposal was the statement "[w]e will design PDE inhibitors based on the theory that the potencies of existing inhibitors, such as 3-isobutyl-1-methylxanthine (IBMX) and zaprinast, could be enhanced by appending groups that would allow the inhibitors to more closely resemble the entire cGMP molecule."[58] However, as Dr. Rafferty explained, the Proposal failed to convey "any meaningful principles" for designing PDE-5 inhibitors.[59] The "design theory" said a PDE-5 inhibitor should "more closely resemble cGMP," but 8-(4-hydroxy-phenylthio)-IBMX "in no way looks like or resembles cGMP"; whereas cGMP "consists of a guanine nucleus with an appended ribose phosphate moiety, which is attached to the N-9 position on the body on the guanine nucleus," 8-(4-hydroxy-phenylthio)-IBMX "is a compound that's modified at the eight position, not the nine position."[60] "IBMX has structural details that are different than -- than what are present on the guanine nucleus [of cGMP]," and in biology, "those differences are important and significant"; therefore, 8-(4-hydroxy-phenylthio)-IBMX was "not a valid test" of Vanderbilt's "design theory."[61] Moreover, the Proposal provided "no specificity [as to] what modifications they believe would work to enhance PDE-5 activity," and "there's only a single example with any data presented in this particular communication and a single example is not sufficient to be of

[58] Both parties' witnesses (and Vanderbilt in its Post-Trial Brief) agreed that modifying an enzyme inhibitor to make it resemble a portion of the substrate was well-known in 1992. D.I. 146 at 1179:4-1180:7 (Rafferty) ("[I]t's well precedented in the history of medicinal chemistry, even up to and before -- well, up to 1992, to start with a natural substrate as a basis for designing inhibitors."); D.I. 141 at 251:17-252:6 (Corbin) (such an approach was "logical"); D.I. 145 at 963:4-964:12 (Koh) (it was "a common strategy used in drug design, which is basically to create a biomimetic"); Vanderbilt Br. at 20 (this concept was "not new to Glaxo" in 1992).
[59] D.I. 146 at 1175:14-1179:3.
[60] D.I. 146 at 1175:14-1176:16 (Rafferty).
[61] D.I. 146 at 1177:7-21 (Rafferty). In 1992, scientists "couldn't be sure how a compound like IBMX would bind in the catalytic site of PDE-5" (D.I. 145 at 978:5-12; 994:13-996:19 (Koh)).

any -- any use to a medicinal chemist."[62] Even Vanderbilt's own witness, Dr. Crooks, admitted that "[t]here was no way to predict the functional aspects of any portion of [Dr. Daugan's compounds] from anything that Dr. Corbin did with IBMX analogues back in 1992."[63]

15. There is no evidence that the identification or testing of beta-carboline compounds in 1992 at Glaxo related in any way to information received from Vanderbilt. For example, Vanderbilt says that 29 compounds tested against PDE-5 on April 23, 1992 (each of which contained one of Vanderbilt's four "Structural Features" ("a 6-member ring fused to a five-member ring")) were "clearly chosen for testing based upon a substructure search in Glaxdatabank" because "[n]one of the compounds had originally been developed and registered in Glaxo France."[64] But this is simply attorney conjecture; there is no evidence that this hypothetical search ever happened.

16. Vanderbilt says that 26 of these 29 compounds contained one of the four "Structural Features" (a "6- and 5-member ring scaffold with some substitution at the 8-position"), and that 11 of those 29 compounds contained two of the four "Structural Features."[65] But Vanderbilt does not even attempt to explain the significance of these unsupported assertions (no witness testified

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[62] D.I. 146 at 1177:22-1179:3 (Rafferty). Vanderbilt's own uncertainty about the purported "design theory" in the 1992 Research Proposal is evident from Dr. Corbin's June 1993 question to Dr. Grondin: "Do our best cGMP analogs and PDE inhibitors compare well with ones that you have available at Glaxo? It would be informative to know the general answer to this question since it would give me a better feeling for whether we are on the right track here." JTX 51; D.I. 141 at 334:3-25 (Corbin).

[63] D.I. 141 at 365:18-21; *see also* D.I. 141 at 365:11-17 (Crooks) ("There was no way that you could have predicted from the 6-5 heterocyclic xanthine core with its attached substituents in Dr. Corbin's IBMX analogues that the piperazinedione structure on the right side of the tetracyclic [structure] of Dr. Daugan's compound would be important for PDE-5 inhibitory activity"); 365:22-366:8 (same for stereochemistry of Dr. Daugan's compounds); 366:20-367:3 (same for piperazinedione structure and stereochemistry of Dr. Daugan's compounds in view of PTX 117).

[64] Vanderbilt Br. at 27. Vanderbilt's assertion on the previous page that "even a broad substructure search in Glaxdatabank could identify only a small number of compounds that Glaxo France would actually be able to test" is pure attorney conjecture. None of the cited documents, or the cited testimony from Dr. Grondin, supports this assertion.

[65] Vanderbilt Br. at 27. This of course means that 18 of those 29 compounds that Vanderbilt says would have resulted from its hypothetical search did not contain the four "Structural Features."

that of any of this was related to Dr. Daugan's conceptions of the claimed compounds).

17. Astonishingly, Vanderbilt then asserts that these purported "facts," along with (i) the "impressive results [*sic*: result]" reported for the 8-(4-hydroxy phenylthio)-IBMX compound in the 1992 Research Proposal; (ii) Vanderbilt's unsupported conjecture that Glaxo had "successfully adopted" Vanderbilt's "design and design theories" in "prior research proposals"; and (iii) Vanderbilt's unsupported conjecture about the "ease" of conducting substructure searches,[66] combine to "clearly demonstrate that the April 23, 1992 compounds [*i.e.*, GR30040x] were derived from a substructure search using the skeleton and motif of 8-(4-hydroxy phenylthio)-IBMX and the other compounds described in the 1992 Research Proposal."[67]

18. Vanderbilt never explains just what the "skeleton and motif" is to which it refers. But while important, that omission is secondary, because there is no evidence that Dr. Labaudiniere used any information derived from this compound to search any database, or for any other purpose,[68] and Dr. Labaudiniere's testimony directly refutes Vanderbilt's theory.

19. Vanderbilt says that "there is no dispute" that searching the "Glaxdatabank" with a

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[66] Vanderbilt Br. at 28. No witness testified that conducting substructure searches was easy. Vanderbilt cites testimony from Drs. Labaudiniere and Rafferty (*see* Vanderbilt Br. at 26), but neither witness said such searches were simple, easy, or "took only a few minutes."

[67] Vanderbilt Br. at 28.

[68] This hypothetical search wasn't even performed at the trial, much less back in 1992. Both during his Opening Statement and at several points in the trial, Mr. Brennen purported to run searches on his laptop computer, using a "substructure" containing some, but not all, of the four Vanderbilt "Structural Features." But Mr. Brennen was conducting those searches in a copy of the "ChemBase" database (DTX KC) used locally at Glaxo France, not in Glaxo's world-wide "Glaxdatabank" database of compounds that was used by Dr. Labaudiniere for his searches in 1992 (D.I. 141 at 437:4-20; 439:15-21 (Labaudiniere)). Vanderbilt tries to discount ICOS's objections to the nature of the searches by suggesting, without any evidentiary support, that the heteroatoms present in the heterocyclic rings of IBMX and the substituents attached to those rings are "not part of the core structure or skeleton" (Vanderbilt Br. at 28, fn. 18). But Drs. Padwa and Rafferty's testimony that Dr. Labaudiniere would have considered those heteroatoms and substituents to be important, and would have included those structures in any search based on IBMX, was unrebutted; Vanderbilt's attorney argument otherwise is not evidence.

"generic version" of the 8-(4-hydroxy phenylthio)-IBMX "skeleton" would have "yielded GR30040x as a 'hit.'"[69] Vanderbilt never explains just what constitutes the "generic version" of the "skeleton" of this compound. This attorney argument is as ambiguous as the rest. But in any event, there simply is no evidence that any of this happened.

20. Vanderbilt says that "there is likewise no dispute" that GR30040x "led to" the development of the compounds claimed in the Patents-at-Issue."[70] ICOS does not dispute that GR30040x was one of the "lead" compounds in the beta-carboline series, such that Dr. Daugan considered it in designing his other beta-carboline/hydantoin compounds, and that he considered the structures of those compounds in designing the beta-carboline/piperazinedione "Formula (I)" compounds claimed in his patents. But that did not make GR30040x part of the conception of any of the claimed compounds; as the contemporaneous documents establish, several compounds containing the tricyclic beta-carboline structure led Dr. Labaudiniere to ask Dr. Daugan to pursue the beta-carboline series. Furthermore, Dr. Daugan's claimed "Formula (I)" compounds are not simply analogs of GR30040x. While it has the same tricyclic beta-carboline substructure present in the claimed "Formula (I)" beta-carboline/piperazinedione compounds, GR30040x and the other beta-carboline/hydantoin compounds that Dr. Daugan initially developed (including the compounds tested on April 23 and June 17, 1992, and GF173321x) are not claimed in the patents-at-issue; they are not the inventions at issue here.[71]

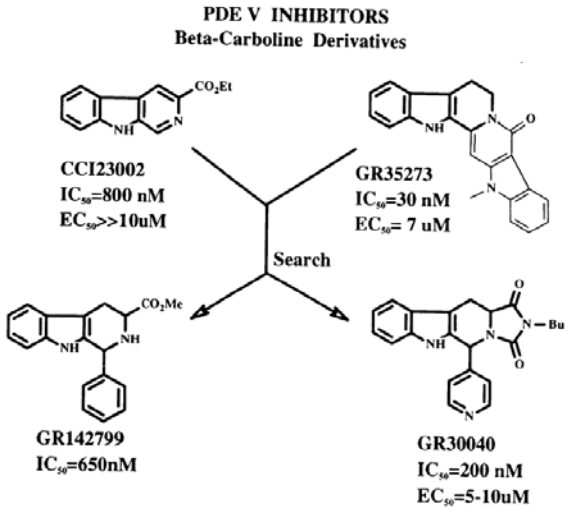
D. Dr. Labaudiniere used a beta-carboline-based substructure to identify GR30040x

21. The reality, as established by both the unrebutted testimony of Drs. Labaudiniere, Daugan and Rafferty and the Glaxo documents, is that Dr. Labaudiniere did not use any information from

[69] Vanderbilt Br. at 28.
[70] *Id*.
[71] D.I. 146 at 1173:3-21; 1221:6-10; 1302:25-1303:5 (Rafferty).

Vanderbilt to search the Glaxo database or identify GR30040x. Rather, as Dr. Labaudiniere stated in the 1992-1993 Annual Report, he identified GR30040x by searching Glaxo's "GLAX" database using a beta-carboline-based substructure present in two previously identified compounds, β-CCE and GR35273x: "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)."[72]

22. In his deposition, Dr. Labaudiniere confirmed that he used the "GLAX" database to "identify analogues with the beta-carboline core structure,"[73] and that he had identified both β-CCE (designated as "CCI23002" by Glaxo[74]) and GR35273x "through the search and the connection of beta-carbolines with [their] vasorelaxation effect."[75] Dr. Labaudiniere illustrated his search strategy and results in Figure 11 in the 1992-1993 Annual Report: [76]



23. Dr. Daugan confirmed that this diagram and the corresponding text in the 1992-1993

[72] DTX P at GLAX00037.
[73] D.I. 141 at 436:23-437:3; 437:21-25.
[74] It was standard practice at Glaxo to give compounds – whether internally-developed, obtained from third parties, or synthesized at Glaxo based on published reports – an internal Glaxo identification number (PTX 400; D.I. 143 at 618:5-620:24; D.I. 141 at 429:25-430:9).
[75] D.I. 141 at 441:7-442:4.
[76] DTX P at GLAX 00054 (bold emphasis in original); *see also* D.I. 141 at 441:7-25 (Labaudiniere); DTX SU at GLAX16455.

Annual Report are consistent with his understanding of how GR30040x was identified.[77] Dr. Rafferty, an expert in medicinal chemistry and drug discovery[78] who reviewed the Glaxo documents from this time period,[79] provided expert testimony supporting this.[80] In contrast, Vanderbilt did not present a single witness who had reviewed these documents, who could otherwise dispute these facts, or who could provide any support for Vanderbilt's hypothetical alternative; instead, Vanderbilt provided only attorney conjecture.

E. A medicinal chemist at Glaxo would not have conducted Vanderbilt's hypothetical searches

24. The information in the 1992 Research Proposal would not have led to Dr. Labaudiniere's identification of β-CCE or GR35273x. Dr. Rafferty testified that neither β-CCE nor GR35273x would have been identified by searches using a substructure based on Vanderbilt's 8-(4-hydroxy-phenylthio)-IBMX compound,[81] and that a medicinal chemist like Dr. Labaudiniere would not have conducted such a search:[82] "[b]ased on what was available in terms of information at the time," Vanderbilt's hypothetical searches take "inappropriate liberties . . . in terms of eliminating portions of the [IBMX] structure."[83]

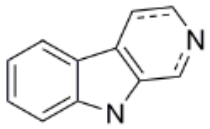
25. As Dr. Rafferty explained, the "generic" 6,5 ring structure in Vanderbilt's purported "Structural Features" was a "common" motif found in many drugs (including zaprinast and caffeine), and are found in "as many as 20 percent of the compounds in nature." [84] By 1992 "it's easily possible that Glaxo would have had as many as 250,000, maybe as many as half a million

[77] D.I. 144 at 890:12-894:22; DTX P; DTX AQ.
[78] D.I. 146 at 1166:20-23.
[79] D.I. 146 at 1170:18-1171:14.
[80] D.I. 146 at 1193:13-1196:24; D.I. 148-2 (errata).
[81] D.I. 146 at 1200:22-1201:4; 1206:15-1207:3; DTX TB; DTX TC.
[82] D.I. 146 at 1206:15-1207:3 (Rafferty); DTX TB (Rafferty demonstrative showing potential substructure searches based on GR35273X); DTX TC (Rafferty demonstrative showing potential substructure searches based on β-CCE).
[83] D.I. 146 at 1297:5-1298:4 (Rafferty).
[84] D.I. 146 at 1300:13-1301:3; 1302:9-15; PTX 427; Vanderbilt Br. at 17.

compounds in their collection."[85] If Dr. Labaudiniere had searched the "GLAX" database for all compounds containing this generic "Structural Feature," the search would likely have yielded hundreds of thousands of compounds.[86] Consequently, "Dr. Labaudiniere would never have conceived of a search like [Vanderbilt's hypothetical search], simply because the enormity of the hit list that he would have had to then wade through and make judgments on and select a handful of compounds for evaluation for PDE-5 activity . . . would have just been impractical."[87]

26. Contrary to Vanderbilt's conjecture, the compounds tested on April 23, 1992 – including GR30040x – would not have been identified using any reasonable substructure search based on Vanderbilt's 8-(4-hydroxy-phenylthio)-IBMX compound.[88] None of those compounds – as Dr. Konjeti admitted one-by-one on cross-examination[89] – contained the "xanthine scaffold" or the "8-substituted xanthine scaffold" found in 8-(4-hydroxy-phenylthio)-IBMX.[90]

27. Rather, the "disproportionate number of tetrahydro-beta-carbolines" that were tested in March and April 1992 leads to only one reasonable conclusion supported by the actual evidence: Dr. Labaudiniere conducted his searches using the tricyclic beta-carboline substructure (shown below, and shown in bold in Figure 11 in DTX P), rather than any combination of the "Structural Features" found in 8-(4-hydroxy-phenylthio)-IBMX.[91]



[85] D.I. 146 at 1301:4-1302:8.
[86] D.I. 146 at 1296:1-1302:24.
[87] D.I. 146 at 1302:16-24.
[88] D.I. 146 at 1212:19-1213:4 (Rafferty); D.I. 148-2; PTX 134A-146A, 148A-153A, 421A.
[89] D.I. 143 at 720:19-722:15; 728:1-735:15; PTX 22; PTX 366; *see also* D.I. 143 at 725:18-727:25 (Konjeti unable to identify essential structural elements of a xanthine nucleus).
[90] D.I. 146 at 1207:19-1213:4 (Rafferty); D.I. 148-2; PTX 134A-146A, 148A-153A, 421A.
[91] D.I. 146 at 1298:17-1299:5 (Rafferty); DTX TC.

28. In its Post-Trial brief, Vanderbilt spends several pages rehashing the argument Mr. Brennen made (for the first time in this case)[92] in his opening statement, *i.e.*, that the "contemporaneous documents" show that Dr. Labaudiniere's "identification [of GR30040x] could not have been the result of either the Elgoyhen article [apparently published on May 1, 1992, a week after GR30040x was identified][93] or the β-CCE test results [which were generated on July 3, 1992[94]]."

29. Vanderbilt's entire argument on this point simply ignores the evidence presented at trial (and discussed above), and misrepresents that Dr. Labaudiniere testified that the Elgoyhen article alone was the impetus for his initial investigation of beta-carboline compounds. But Dr. Labaudiniere testified that he became interested in beta-carboline compounds because there had been "several" reports in the literature of beta-carboline compounds having vasorelaxant properties (including, but not limited to, the Elgoyhen article).[95] Consequently, the Elgoyhen article was not the lone basis for Dr. Labaudiniere's initial interest in beta-carboline compounds. As he testified, there was nothing about the beta-carboline structure itself that led Dr. Labaudiniere to select them for study,[96] except that the beta-carboline structure "was a new structure for PDE-5 not really looking like other PDE-5 [inhibitors]."[97]

30. In March 1992, Glaxo France was testing a number of different families of compounds for activity against PDE-5.[98] For example, on March 11 and 12, 1992, Glaxo tested GR35273x (a

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[92] Vanderbilt Br. at 38. Pursuant to Fed. R. Civ. P. 37(c), the Court should not consider this argument.
[93] DTX ES.
[94] D.I. 146 at 1214:4-1216:2 (Rafferty); DTX P at GLAX00037; PTX 170.
[95] D.I. 141 at 422:19-423:14; D.I. 148-2 (errata); 446:7-448:23 (discussing DTX ES).
[96] D.I. 141 at 422:21-423:14.
[97] D.I. 141 at 422:7-18; D.I. 148-2 (errata).
[98] *See generally, e.g.*, DTX IG at GLAX13188-GLAX13201 and DTX ID at GLAX01084-GLAX01089. *See also* DTX P at GLAX00034-39 (indicating that Glaxo France was

beta-carboline), some "nitrovinyl indole-type compounds," and "quite a number of structures that are completely unrelated to anything that was being pursued within the PDE-5 project at the time."[99] GR35273x had been synthesized at Glaxo as part of the separate "ApoB100" project,[100] and was shown to be a potent inhibitor of PDE-5 in the March tests.[101]

31. Vanderbilt argues that GR35273x contains "elements" of the Vanderbilt "Structural Features" and was "apparently 're-identified' through the same substructure search that led to GR30040x because GR35273x was also tested on April 23, 1992."[102] Vanderbilt also asserts that "a review of the structures of those compounds [tested on March 11 and 12, 1992] indicates that GR35273x was initially identified through substructure searches exploring various modifications on the compounds containing variations of nitrovinyl structures."[103] In addition to this unsupported attorney argument, Vanderbilt also points out that (i) in June 1992, someone at Glaxo France speculated about whether GR35273x might be an analog of zaprinast,[104] a hypothesis that wasn't finally rejected until a few months later,[105] (ii) GR35273x and GR30040x are discussed in separate sections of PDE-5 Project documents,[106] and (iii) Dr. Daugan, "who was responsible for pursuing the development of GR30040x," did not work on GR35273x

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investigating zaprinast, nitrovinyl-indol, azapurinone, pyrimidopyrimidone, thienopyrimidone, isothiazolo, isoxazolopyrimidone, pyrazolo[3,4-d]pyrimidone, and benzylimidazole compounds). In 1992-93, there were six medicinal chemists at Glaxo France investigating these series (D.I. 141 at 392:10-19; 394:25-395:9 (Labaudiniere)).

[99] D.I. 146 at 1197:19-1200:21 (Rafferty); D.I. 148-2 (errata); DTX SZ; D.I. 144 at 937:14-939:11 (Daugan); DTX KB at GLAX15452; DTX IG at GLAX13199; GLAX13202.

[100] JTX 24 at GLAX10365.

[101] Vanderbilt Br. at 38; JTX 24 at GLAX10365; DTX KB at GLAX15452; DTX IG at GLAX13202.

[102] Vanderbilt Br. at 38.

[103] Vanderbilt Br. at 38, fn. 32.

[104] *See* JTX 13 at GLAX16000.

[105] Vanderbilt Br. at 38-39.

[106] Vanderbilt Br. at 39 (citing JTX 13 and PTX 178).

analogs.[107] From this, Vanderbilt concludes "there is simply no indication whatsoever from the documents created at, around or immediately after the identification of GR30040x that suggest that Glaxo France considered there to be any connection between GR30040x and GR35273x."[108]

32. This assertion by Vanderbilt simply ignores the Glaxo documents created in 1992 and 1993 (particularly the 1992-1993 Annual Report, in which Dr. Labaudiniere explained and illustrated the exact "connection between GR30040x and GR35273x"), and the unrebutted testimony of Drs. Labaudiniere, Daugan and Rafferty discussed above, all of which establish:

> (i) GR35273x was found to be a PDE-5 inhibitor on March 11, 1992;
>
> (ii) Dr. Labaudiniere's subsequent searches of the world-wide Glaxo database using various substructures found in GR35273x (including the tricyclic beta-carboline-based substructure highlighted in Figure 11 of the PDE-5 Project Annual Report for 1992-1993) led to the identification of GR30040x; and
>
> (iii) GR30040x, along with GR35273x, was tested against PDE-5 on April 23, 1992, and both were confirmed as PDE-5 inhibitors worthy of further study (which was carried out as separate projects by separate medicinal chemists).

33. In a footnote,[109] Vanderbilt argues that because GR35273x was not mentioned by Dr. Hyafil in a document in 1994,[110] or by Dr. Daugan in his publications in 2003, "anything other than documents contemporaneous to the identification of GR30040x in April 1992 is of highly questionable reliability." This thinly-veiled attack on Dr. Labaudiniere's honesty is of course unfounded: the "contemporaneous" documents, such as the Annual Report for 1992-1993, show that it is not true. Dr. Hyafil's decision not to mention GR35273x in a document in 1994, or Dr. Daugan's decision not to specifically identify that compound in an article in 2003, do not negate Dr. Labaudiniere's earlier description of his searches in the 1992-1993 Annual Report, a "contemporaneous" document he prepared to describe for Glaxo management what was done on

[107] Vanderbilt Br. at 39.
[108] *Id.*
[109] Vanderbilt Br. at 39, fn. 36.
[110] PTX 326, about which there was no testimony at trial.

the PDE-5 Project in 1992.[111]

34. Vanderbilt also argues that "[i]t is likely no coincidence" that "all of the documents upon which ICOS relies in support of the GR35273x story were created *after* Glaxo had succeeded, through the use of the Vanderbilt Structural Features, in reaching PDE5 inhibition potencies below 10 nanomolar and *after* Glaxo had succeeded in synthesizing the first compound covered by Formula 1 in Claim 1 of the '006 and '329 Patents."[112] This argument is blatantly false: the reality of how GR30040x was identified is shown by documents created at Glaxo France in March through July of 1992, as well as the 1992-1993 Annual Report submitted in April 1993, and is confirmed by the testimony of Drs. Labaudiniere, Daugan and Rafferty. Vanderbilt's conjecture and its thinly-veiled attacks on Dr. Labaudiniere's integrity do not rebut any of this.

35. Vanderbilt says that 27 compounds tested against PDE-5 on June 17, 1992 "appear to have been selected from a Glaxdatabank search of various substructures of GR30040x."[113] This attorney conjecture is not corroborated by any evidence. Vanderbilt also says that of the 27 compounds tested against PDE-5 on June 17, 1992, "[t]hose compounds that contained the Vanderbilt Structural Features significantly outperformed those that did not."[114] This is more uncorroborated attorney conjecture, unsupported by testimony. In any event, Vanderbilt does not explain how this testing is relevant to Dr. Daugan's conceptions of his claimed compounds.

F. Dr. Labaudiniere did not contribute to Dr. Daugan's conceptions

36. In June 1992, Dr. Labaudiniere asked Dr. Daugan to explore the structure-activity

[111] The absence of a reference to GR35273x in Dr. Daugan's 2003 publications is not suspect: in their unrebutted testimony, Drs. Daugan and Rafferty explained that it is common when describing a medicinal chemistry project in a publication to omit some information about the discovery of lead compounds. D.I. 144 at 876:23-877:11 (Daugan); D.I. 146 at 1221:11-1223:7 (Rafferty).
[112] Vanderbilt Br. at 39, fn. 36.
[113] Vanderbilt Br. at 29.
[114] *Id*.

relationship of the beta-carboline series. The goal was to design compounds that were more active against PDE-5, more specific for PDE-5 than for other PDEs,[115] and orally effective in lowering blood pressure in animals.

37. Vanderbilt says that "[t]he very first modification that Dr. Daugan made to the GR30040x structure was to replace the pyridine ring with a combination of a phenyl ring **and** an electron-donating methoxy substituent" (citing a page from Dr. Daugan's laboratory notebook dated September 23, 1992, showing his synthesis of the compound later designated GF173321x).[116] Again, that is simply not true. In the testimony cited by Vanderbilt as putative support for this assertion, Dr. Daugan actually said "[t]he first thing I did in this series was explore the replacement of the [pyridinyl] moiety with other heterocyclic or aromatic moieties."[117] As Dr. Daugan explained, his exploration of this position was reflected in part by the compounds listed in Table 1 in his 2003 publication[118] and in Table 15 in the 1992-1993 Annual Report.[119] As can be seen in those Tables, Dr. Daugan explored a large number of different "aromatic moieties" to replace the pyridinyl ring in GR30040x. Contrary to Vanderbilt's assertion, Dr. Daugan's first laboratory notebook recording his work on the beta-carboline series shows that, on August 6, 1992, the "very first" modification that he made in exploring that position was to replace the pyridinyl ring of GR30040x with an unsubstituted phenyl ring,[120] not a methoxy-phenyl ring.

38. Vanderbilt says that "Dr. Labaudiniere testified that the decisions with respect to these

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[115] *See* D.I. 143 at 745:24-746:11 (Konjeti) (Vanderbilt's IBMX analogs were not selective for PDE-5); D.I. 148-2 (errata); D.I. 141 at 252:7-20; 254:24-258:22 (Corbin) (same); D.I. 144 at 857:10-21 (Daugan).
[116] Vanderbilt Br. at 30 (citing DTX GE at GLAX00607) (emphasis in original).
[117] D.I. 144 at 895:23-896:4.
[118] D.I. 144 at 896:5-22 (Daugan) (discussing JTX 29).
[119] D.I. 144 at 896:23-897:8 (discussing DTX P at GLAX00079); D.I. 148-2 (errata). This was also described in the October 1992 PDE-5 Project Monthly Meeting Minutes (JTX 15 at GLAX16288-90; D.I. 146 at 1185:22-1186:22).
[120] *See* DTX GD at GLAX12570; DTX KB at GLAX14635.

modifications, were the result of a discussion between himself and Dr. Daugan"[121] (implying that Dr. Labaudiniere directed Dr. Daugan to modify GR30040x to include "a phenyl ring and an electron-donating methoxy substituent" based on Vanderbilt's 8-(4-hydroxy phenylthio)-IBMX compound). What Dr. Labaudiniere actually said (in the testimony following that cited by Vanderbilt) was that he could not remember who came up with the specific modifications, and that decisions regarding modifications (including the incorporation of the 4-methoxy-phenyl group at the "C-5" position in GF173321x) were the result of trying to "identify what's good for potency" using "a standard group of substitutions or additions" in a "trial-and-error process," not the result of seeing any information from Vanderbilt.[122]

39. Vanderbilt repeatedly asserts that Dr. Daugan admitted that Dr. Labaudiniere "gave him direction" or "directed" him to append certain groups at certain positions on his beta-carboline compounds.[123] Dr. Daugan said no such thing. Rather, Dr. Daugan testified that he was solely "the one responsible for the development of the SAR of this [beta-carboline] chemical series" -- he was "the one who designed all of the products belonging to this series": he decided which compounds to make, when to make them, and how to make them, and he analyzed the biological testing results, whereas Dr. Labaudiniere would "simply give me general information on what there was to be done on a given series. . . . He could, for example, ask me to explore a part of the molecule or region on the molecule."[124] This testimony was not challenged on cross-examination, and was not rebutted by any other witness.

40. Vanderbilt says that Dr. Dodic's "sudden" synthesis of an 8-(4-methoxy benzyl)-zaprinast analog (GF178534x) "several weeks" after Dr. Daugan synthesized GF173321x is "further

[121] Vanderbilt Br. at 31 (citing D.I. 141 at 424:11-425:13 (Labaudiniere)).
[122] D.I. 141 at 424:19-426:17; D.I. 148-2 (errata).
[123] Vanderbilt Br. at, *e.g.*, 31, fn. 23.
[124] D.I. 144 at 864:6-865:16.

evidence" that Dr. Labaudiniere "directed" the modifications Dr. Daugan made to GR30040x.[125] It is nothing of the sort. There is no evidence whatsoever that Dr. Labaudiniere had anything to do with Dr. Dodic's decision to synthesize GF178534x. Moreover, as the very laboratory notebook page cited by Vanderbilt clearly shows, Dr. Dodic synthesized GF178534x on November 23, 1992, two months (not "several weeks") after Dr. Daugan synthesized GF173321 (on September 23, 1992),[126] and more than a month after GF173321 was shown to be a potent PDE-5 inhibitor.[127] Dr. Dodic did not "suddenly" synthesize GF178534; in the two months between Dr. Daugan's synthesis of GF173321 and her synthesis of GF178534, she synthesized two other 8-substituted zaprinast analogs, and neither of them had an 8-phenyl group with an electron-donating substituent (which directly contradicts Vanderbilt's argument).[128]

G. Dr. Hyafil did not contribute to Dr. Daugan's conceptions

41. Vanderbilt says that when Dr. Hyafil visited Dr. Corbin's laboratory on September 30, 1992, the Vanderbilt scientists "explained all aspects of their work under the 1992 Research Proposal, including their design theories for creating potent PDE-5 inhibitors."[129] Vanderbilt cites testimony from Drs. Corbin and Konjeti as putative support for this assertion, but in reality neither of them testified that they discussed "all aspects of their work" or any generalized "design theories" with Dr. Hyafil, and Dr. Corbin admitted they did not discuss applying "concepts of hydrophobicity, electron donation, [or] mimicking cGMP to any compounds other than IBMX, zaprinast, or cGMP."[130]

42. Vanderbilt says that upon Dr. Hyafil's return to France, "minutes of the next PDE Project

[125] Vanderbilt Br. at 32.
[126] DTX GE at GLAX00607.
[127] DTX KB at GLAX14607.
[128] *See* DTX KB at GLAX14653, GLAX14664, GLAX14676; JTX 36 at GLAX07648, GLAX07654, GLAX07657.
[129] Vanderbilt Br. at 32.
[130] D.I. 141 at 293:18-294:25.

meeting" show that there was "much interest within the PDE Project team in Drs. Corbin and Francis' work in the study of smooth muscle relaxation, cGMP analogs and phosphodiesterase inhibitors," and that those minutes include data from the Vanderbilt scientists' publications "without proper attribution."[131] Vanderbilt does not cite any evidence that supports any of this attorney argument: the testimony and documents it cites relate to a March 1991 Glaxo U.S. "Cardiovascular Status Report" for a project regarding the modulation of PKG, not to any PDE-5 Project Team meeting in 1992.

43. Vanderbilt admits that Dr. Daugan's laboratory notebook shows that he began synthesizing GF173321 before Dr. Hyafil met with the Vanderbilt scientists. However, it then asserts that Dr. Daugan's testimony somehow suggests that his laboratory notebooks "are less than completely trustworthy." This is apparently an attempt to get the Court to infer that Dr. Daugan falsified the dates in his laboratory notebook to hide some information he received from Dr. Hyafil after the visit to Vanderbilt. This is ludicrous, of course. Dr. Daugan's testimony does not suggest in any way that the information in his laboratory notebooks is "less than completely trustworthy."[132] In any event, none of this has anything to do with Dr. Daugan's conceptions of his claimed compounds and methods; he testified that he never discussed medicinal chemistry with Dr. Hyafil, and Dr. Hyafil never gave him any advice about modifying his beta-carboline compounds.[133] There is no evidence suggesting otherwise.

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[131] Vanderbilt Br. at 33.
[132] The only thing Dr. Daugan said was that he occasionally crossed out information in his notebooks (D.I. 144 at 911:2-8).
[133] D.I. 144 at 865:17-866:1.

H. Dr. Daugan did not use any information from Vanderbilt to conceive the methods claimed in the '329 patent[134]

44. Referring to Dr. Corbin's January 1992 letter to Dr. Ross, Vanderbilt contends that "[a]s of January 3, 1992, no scientist working in the field had ever published anything that expressly proposed that PDE5 inhibitors could be used to treat male impotence."[135] Vanderbilt fails, however, to explain how Dr. Daugan used any information in the letter to conceive any invention claimed in the '329 patent.[136] Contrary to Vanderbilt's conjecture, the evidence at trial showed that the Vanderbilt scientists were not the first to recognize that PDE-5 inhibitors might be a cure for male impotence because, while it may not have been "expressly" stated in a prior publication, the evidence at trial showed that the concept was self-evident to those in the art by January 1992, and that Dr. Daugan learned of this use for PDE-5 inhibitors from the literature in the field.

45. On December 22, 1994, an international patent application filed by Pfizer was published which expressly disclosed the use of particular PDE-5 inhibitors to treat male impotence.[137] Dr. Francis admitted that this publication would have "indicat[ed] to scientists in the field that PDE-5 inhibitors are an indicated treatment for male impotence."[138] Dr. Daugan and others at Glaxo France discussed this concept.[139] Following these discussions, Dr. Daugan realized that his claimed PDE-5 inhibitors (which at that time were still not publicly known) could be used to

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[134] Vanderbilt argues in a footnote that its scientists made significant contributions to Dr. Daugan's conceptions of the compounds claimed in both the '006 and '329 patents. *See* Vanderbilt Br. at 44, fn. 41. The proposed findings of fact regarding the compounds claimed in the '006 patent apply equally to rebut Vanderbilt's contention regarding the '329 patent.
[135] Vanderbilt Br. at 20-21; *see also id*. at 40-41.
[136] Vanderbilt should not be permitted to rely upon any additional arguments provided for the first time in its Reply brief.
[137] DTX RQ.
[138] D.I. 143 at 810:12-812:12; 813:12-815:7.
[139] D.I. 144 at 907:7-24; 908:13-19 (Daugan) ("It was known that PDE-5 inhibitors could be used to treat impotence, and these were discussions that occurred within the PDE team at Les Ulis," and he first realized that his compounds could treat impotence "following these discussions that we had . . . .") (discussing JTX 2).

treat impotence.[140]Accordingly, in July 1995, Glaxo filed another U.K. patent application on Dr. Daugan's behalf describing and claiming the use of some of his PDE-5 inhibitor compounds to treat male impotence. This application led to the '329 patent-at-issue.

46. In a sworn affidavit he signed in 2006, Dr. Corbin stated:[141]

> In 1990, thousands of scientists working in the field of cAMP or cGMP, including those investigating . . . PDEs, . . . would be well aware that demonstration that an agent would cause elevation of cAMP or cGMP meant that an accompanying PDE inhibitor would help elevate cAMP or cGMP much more. . . . It would be inconceivable that a person skilled in the art would fail to realize that a PDE inhibitor, such as sildenafil [i.e., Viagra], developed to inhibit cGMP PDE in the smooth muscle in general should inhibit cGMP PDE in the cavernosum and therefore stimulate penile erection.

47. Dr. Corbin further admitted that in the early 1990's, "there were a number of pharmaceutical companies pursuing PDE-5 as a target."[142] In his video, Dr. Corbin explained:

> "[T]he thinking was at that time that if that [PDE-5] enzyme could be inhibited by some pills that could lower blood pressure and maybe relieve chest pain for men with chest pain and women with chest pain," but "[w]e had no idea that it could have other effects. It was actually the drug companies that discovered that an inhibitor of that [PDE-5] enzyme could actually cause penile erection. . . . [T]he pharmaceutical companies developed inhibitors of that enzyme, Cialis being one of those . . . ."[143]

48. Dr. Francis admitted that the scientific literature available by January 1992, principally publications by the group headed by Dr. Ignarro, had disclosed the use of PDE-5 inhibitors to treat impotence as a "working hypothesis."[144] Dr. Corbin admitted that Dr. Ignarro and his co-workers were the first to publicly disclose that hypothesis;[145] indeed, in his January 1992 letter to Dr. Ross, he stated that the idea "was well known from the work of many groups."[146] And Drs.

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[140] D.I. 144 at 907:19-24.
[141] DTX OV at ¶ 55.
[142] D.I. 141 at 250:12-15.
[143] D.I. 141 at 301:21-302:24; D.I. 148-2 (errata); DTX NU.
[144] D.I. 144 at 822:9-24; 826:16-828:10; 837:3-839:7 (Francis); D.I. 148-2 (errata); PTX 420.
[145] D.I. 141 at 282:8-19; 298:13-20; D.I. 148-2 (errata).
[146] D.I. 141 at 297:23-299:12; PTX 107 at VC-000227.

Corbin and Francis both admitted that the statement in the letter about the potential use of PDE-5 inhibitors to treat impotence was also a hypothesis.[147]

49. Dr. Rick Cote, a professor of biochemistry at the University of New Hampshire and a PDE expert, [148] directly refuted Dr. Francis's testimony about what was known in early 1992 about using PDE-5 inhibitors to treat impotence.[149] Based on numerous studies, "it would have been evident to people in the field that PDE-5 inhibitors . . . would be, indeed, an excellent avenue to approach for the treatment of impotence."[150]

50. For example, long before 1992, the scientific literature had established "that zaprinast was not only potent but a selective inhibitor of PDE-5 . . . ."[151] From 1990 to 1992, Dr. Ignarro's group published papers showing that zaprinast enhanced relaxation of the corpus cavernosum tissue and consequent penile erection.[152] In particular, Dr. Ignarro published an article in the January 9, 1992, issue of the *New England Journal of Medicine*[153] that referred to this effect of zaprinast on the corpus cavernosum and thus indicated to one of ordinary skill that "a suitable PDE-5 inhibitor would be a strategy worth pursuing for the treatment of impotence."[154] Referring to this article,[155] Dr. Corbin stated in his affidavit that "[p]ersons skilled in the art would have appreciated, without more ado, that compounds which produced relaxation of the corpus

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[147] D.I. 141 at 307:11-309:10; D.I. 143 at 784:10-786:4; 794:24-796:7; D.I. 148-2 (errata).
[148] D.I. 145 at 1075:7-1076:16; 1077:1-1080:17; D.I. 148-2 (errata).
[149] D.I. 145 at 1089:9-1090:16.
[150] D.I. 145 at 1090:4-16; D.I. 148-2 (errata).
[151] D.I. 145 at 1090:19-1091:1; 1092:5-1095:25 (Cote); D.I. 148-2 (errata); DTX KO, LD, KJ, LE, KQ. As Dr. Cote explained, the nomenclature and properties cited in the literature for PDE-5 changed over the years until the field adopted the term "PDE-5" as representing an enzyme with specific functionality in 1994. D.I. 145 at 1101:17-1112:14; D.I. 148-2 (errata).
[152] DTX KV, LA and LH; D.I. 145 at 1112:23-1121:15 (Cote); D.I. 148-2 (errata).
[153] DTX LH. This article was publicly available at least as early as January 6, 1992. A *New York Times* article describing this article was itself published on January 9, 1992 (D.I. 144 at 840:18-841:12; 842:13-843:8 (Francis); D.I. 148-2 (errata); D.I. 145 at 1130:19-1131:1 (Cote)).
[154] D.I. 145 at 1125:2-1127:6 (Cote); D.I. 148-2 (errata).
[155] DTX LH.

cavernosum through the NO-cGMP pathway [*i.e.*, PDE-5 inhibitors] would be useful for the treatment of erectile dysfunction."[156]

51. The Ignarro group published additional papers in 1992 directly linking PDE-5 inhibition to treating impotence;[157] indeed, one such publication in mid-1992 said it very plainly: "treatment of impotence might effectively be carried out by administering . . . cyclic GMP phosphodiesterase inhibitors."[158]

52. As the above proposed findings of fact confirm, Vanderbilt failed to present any direct or circumstantial evidence that suggests that any information it provided to anyone at Glaxo was used in Dr. Daugan's conceptions of his claimed inventions.

III. ARGUMENT

1. This Court must begin with the presumption that Dr. Daugan invented the compounds, compositions and methods claimed in the patents-at-issue.[159] To overcome this heavy[160] presumption, Vanderbilt has to prove, by clear and convincing evidence,[161] that one of its

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[156] DTX OV at ¶¶ 65-66; D.I. 143 at 804:7-19; 805:23-807:10; 807:22-808:11; 809:1-14 (Francis); D.I. 141 at 283:2-8 (Corbin).
[157] DTX LI and LJ; D.I. 145 at 1131:2-1133:23 (Cote).
[158] DTX LJ at ICOS001810; D.I. 145 at 1133:24-1135:13 (Cote); D.I. 148-2 (errata).
[159] *Medtronic Vascular, Inc. et al. v. Adv. Cardiovascular Systems, Inc. et al.*, 2005 WL 46553 (D. Del. January 5, 2005) (Robinson, J.) at *5 (citing *Bd. of Educ. v. American Bioscience, Inc.*, 333 F.3d 1330, 1337 (Fed. Cir. 2003)); *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998).
[160] *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 980 (Fed. Cir. 1997).
[161] In a footnote (Vanderbilt Br. at 43, fn. 38), Vanderbilt suggests that, while "there is a presumption that inventors named on an issued patent are correct and courts have held that misjoinder or nonjoinder must be proven by clear and convincing evidence," Vanderbilt's burden to prove co-inventorship here should only be by a preponderance of the evidence. It is not; as the Federal Circuit, this Court, and other courts have repeatedly held, the burden to prove that the listed inventorship on a patent is incorrect is by clear-and-convincing evidence. *Medtronic Vascular*, 2005 WL 46553 at *5 (citing *American Bioscience,* 333 F.3d at 1337); *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1358 (Fed. Cir. 2004); *Hess*, 106 F.3d at 980 (the clear-and-convincing evidence standard "applies without regard to the circumstances of a particular case."). Vanderbilt's reliance on a concurring opinion in *Eli Lilly v. Aradigm* (376 F.3d at 1370), which was limited to a situation involving competing patent applications, is wholly unavailing.

scientists significantly contributed to Dr. Daugan's conception of his claimed inventions.[162]

2. Conception is "'the touchstone of inventorship."[163] It occurs only when the inventor(s) have in mind "a definite and permanent idea of the complete and operative invention" such that "only ordinary skill would be necessary to reduce the invention to practice," without "extensive research or experimentation."[164] With respect to co-inventorship of specifically claimed chemical compounds, "conception does not occur unless one has a mental picture of the structure of the chemical . . . or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property . . . ." General knowledge regarding the anticipated biological properties of groups of complex chemical compounds is insufficient to prove conception with respect to specifically claimed chemical compounds.[165]

3. Most importantly, "[h]aving in mind specific portions of a claimed compound is not the same as conceiving the compound with all of its components. One must have a conception of the

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See Fasse, *The Muddy Metaphysics of Joint Inventorship*, 5 HARV. J.L. & TECH. 153, 173 n.10 ("Patents are generally presumed to be valid because of the technical expertise of the patent examiners who review the applications. . . . This rationale does not hold for the inventorship designation, because the examiners do not question the applicants' assertions. Instead, the 'presumption of proper inventorship is based on the strong 'temptation for honest witnesses, who have worked years with a patentee to implement his ideas, to forget whose ideas they were.'' *U.S. Surgical Corp. v. Hospital Prod. Int.*, 701 F. Supp. 314, 340 (D. Conn. 1988) (citing *Acme Highway Prods. v. D. S. Brown Co.*, 431 F.2d 1074, 1083 (6th Cir. 1970), *cert. denied*, 401 U.S. 956 (1971)). *See also Amax Fly Ash Corp. v. United States*, 514 F.2d 1041, 1047 (Ct. Cl. 1975).").

[162] *Medtronic Vascular*, 2005 WL 46553 at *5 (citing *American Bioscience*, 333 F.3d at 1337); *Fina Oil and Chem. Co v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997).

[163] *American Bioscience,* 333 F.3d at 1337 (citing *Ethicon*, 135 F.3d at 1460).

[164] *Medtronic Vascular*, 2005 WL 46553 at *5 (citing *Ethicon*, 135 F.3d at 1460); *Burroughs Wellcome Co. v. Barr Labs.*, 40 F.3d 1223, 1227-28 (Fed. Cir. 1994) ("An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue."); and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986)); *American Bioscience,* 333 F.3d at 1338 (quoting 1 ROBINSON ON PATENTS 532 (1890)).

[165] *American Bioscience,* 333 F.3d at 1340 (citing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991)).

specific compounds being claimed, with all of their component substituents . . . ."[166]

4. Joint invention occurs when more than one individual significantly contributes to the conception of a solution to a problem and it is this solution that becomes the subject matter of a patent claim.[167] "Because co-inventors need not 'make a contribution to the subject matter of every claim of the patent,' 35 U.S.C. § 116, inventorship is determined on a claim-by-claim basis" and "compare the alleged contributions of each asserted co-inventor with the subject matter of the properly construed claim to then determine whether the correct inventors were named."[168]

5. An alleged co-inventor's testimony stating that he contributed to the conception at issue is not, by itself, enough to support a finding of co-inventorship.[169] Rather, proof of conception requires "corroborating evidence of a contemporaneous disclosure that would enable one skilled in the art to make the invention."[170]

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[166] *American Bioscience,* 333 F.3d at 1340.
[167] *Medtronic Vascular,* 2005 WL 46553 at *5 (citing 35 U.S.C. § 116 (2004), *Fina Oil and Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997), and CHISUM ON PATENTS § 2.02[2]).
[168] *Trovan v. Sokymat SA*, 299 F.3d 1292, 1302 (Fed. Cir. 2002) (internal citations omitted).
[169] *Medtronic Vascular,* 2005 WL 46553 at *5 (citing *Ethicon*, 135 F.3d at 1461); *Burroughs Wellcome*, 40 F.3d at 1228; *Medichem v. Rolabo*, 437 F.3d 1157, 1171 (Fed. Cir. 2006) ("The requirement of independent knowledge remains key to the corroboration inquiry. . . . One consequence of the independence requirement is that testimony of one co-inventor cannot be used to help corroborate the testimony of another.").
[170] *BJ Services Co. v. Halliburton Energy Services, Inc.*, 338 F.3d 1368, 1373 (Fed. Cir. 2003) (citing *Burroughs Wellcome*, 40 F.3d at 1228); *Finkelstein v. Mardkha*, 495 F. Supp. 2d 329, 343 (S.D.N.Y. 2007) (granting summary judgment based on lack of corroboration) ("Without corroborating evidence, a trial would devolve into [the named inventor] and plaintiff both contending that the triangular facets were their idea. In such a case, plaintiff must lose as a matter of law."); *Stern v. Trustees of Columbia Univ*., 2005 WL 398495, at *7 (S.D.N.Y. Feb. 18, 2005) (granting summary judgment based on "lack of any clear and convincing corroborating evidence"), *aff'd*, 434 F.3d 1375 (Fed. Cir. 2006) ("Stern did not have an understanding of the claimed invention" and "there was no collaboration between Stern and [the inventor] in developing [the claimed inventions]"); *Linear Tech. Corp v. Impala Linear Corp*., 2001 U.S. Dist. LEXIS 25905 at *91 (N.D. Cal. Sept. 21, 2001) (same), *aff'd, vacated on other grounds*, 379 F.3d 1311 (Fed. Cir. 2004).

6. To be a joint inventor, one must have had "some open line of communication during or in temporal proximity to [the named inventor's] inventive efforts . . . ."[171] Disclosure of information to a company is not sufficient to establish that information was disclosed to an employee inventor associated with the company.[172]

7. Joint inventorship requires that a co-inventor do more than simply explain "concepts that are well known and the current state of the art."[173] "One who simply provides the inventor with well-known principles or explains the state of the art without ever having 'a firm and definite idea' of the claimed combination as a whole does not qualify as a joint inventor."[174]

8. A contribution to conception is not sufficiently significant to qualify one as a co-inventor if that contribution is "too far removed from the real-world realization of an invention."[175]

A. Vanderbilt has to prove that its scientists made a significant contribution to Dr. Daugan's conceptions of his claimed inventions

9. To prove that the Vanderbilt scientists are co-inventors on the '006 and/or '329 patents, Vanderbilt had to present clear-and-convincing evidence that, at the least:

> (1) the Vanderbilt scientists made a specific, concrete, and significant contribution to Dr. Daugan's conception of a specific chemical compound claimed in the '006 patent (or to his conception of a specific method claimed in the '329 patent); and
>
> (2) the Vanderbilt scientists' contribution was communicated, directly or indirectly, to Dr. Daugan.

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[171] *Cook Biotech, Inc. et al. v. ACell Inc. et al.*, 460 F.3d 1365, 1373 (Fed. Cir. 2006) (quoting *Eli Lilly v. Aradigm*, 376 F.3d at 1358-59).
[172] *Beall v. Ormsby*, 154 F.2d 663, 665-66 (C.C.P.A. 1946).
[173] *Medtronic Vascular,* 2005 WL 46553 at *5 (quoting *Fina Oil*, 123 F.3d at 1476).
[174] *American Bioscience,* 333 F.3d at 1338 (quoting *Ethicon*, 135 F.3d at 1460). Moreover, in order for a contribution to conception to rise to the level of joint invention, it must be "reasonably concrete and specific." Fasse, *Muddy Metaphysics*, 5 HARV. J.L. & TECH. at 193 (*citing*, *e.g.*, *Jamesbury Corp. v. United States*, 518 F.2d 1384, 1394 (Ct. Cl. 1975); *Garrett Corp.*, 422 F.2d at 881).
[175] *Eli Lilly v. Aradigm*, 376 F.3d at 1359 (citing *Garrett Corp. v. U.S.*, 422 F.2d 874, 880 (Ct. Cl. 1970) ("One who merely suggests an idea of a result to be accomplished, rather than means of accomplishing it, is not a joint inventor.")).

10. The record in this case does not contain any evidence that would allow Vanderbilt to prove ***any*** of these requirements under the appropriate clear-and-convincing evidence standard (or even under Vanderbilt's desired "preponderance" standard). Vanderbilt cannot prove co-inventorship because its theories and conjecture about what Drs. Labaudiniere and Daugan *might* have done with Vanderbilt information that they *might* have seen does not constitute evidence.

11. The only actual evidence Vanderbilt offered at trial consisted of uncorroborated testimony from its three scientists that they conceived a "design theory" for improving the potency of cGMP and IBMX analogs, and that they talked about those analogs with Drs. Ross and Hyafil. Beyond that, the only thing Vanderbilt offered at trial and in its Post-Trial Brief was its lawyers' conjecture that Dr. Labaudiniere (i) saw and recognized some value in the Vanderbilt "design theory" in the 1992 Research Proposal; (ii) purposely used some portion of the structure of a single IBMX analog described in that Proposal to search for and find a beta-carboline "lead" compound in Glaxo's world-wide compound database; and (iii) directed Dr. Daugan to modify that "lead" compound to create compounds more closely resembling Vanderbilt's IBMX analog.

12. There simply was no evidence presented at trial that Dr. Labaudiniere or Dr. Daugan saw, understood, recognized the purported import of, or in any way used any information relating to Vanderbilt's purported "design theory." The Vanderbilt scientists' uncorroborated testimony about their "design theory" and their lawyers' speculation about what might have happened does not and cannot constitute clear-and-convincing evidence that any information from Vanderbilt contributed in any way to Dr. Daugan's conceptions of the claimed inventions, much less the significant contributions that are required to find co-inventorship.[176]

B. *American Bioscience* controls here

13. The question of whether the Vanderbilt scientists could be co-inventors of any of the

[176] *BJ Services*, 338 F.3d at 1373 (citing *Price v. Symsek*, 988 F.2d 1187, 1194 (Fed. Cir. 1993)).

compounds claimed in the patents-at-issue is directly controlled by the decision of the Court of Appeals for the Federal Circuit in *Bd. of Educ. ex rel. Bd. of Trs. of Fla. State Univ. v. American Bioscience, Inc.*, 333 F.3d 1330, 1340 (Fed. Cir. 2003), and cases cited therein.

14. In *American Bioscience*, the Federal Circuit was reviewing a decision by the district court in a 35 U.S.C. § 256 case. In the district court, Florida State University ("FSU") obtained a judgment that three scientists (collectively "the ABI inventors") were incorrectly listed as inventors on the patent, which contained claims directed to analogs of the chemical compound generically known as "taxotere," and that three of FSU's scientists should instead have been named as inventors on the patent.[177]

15. The FSU scientists had conducted significant research with the naturally occurring anti-cancer agent, taxol.[178] That research included synthesizing taxol and its analogs and looking for analogs having increased radiosensitivity (which would make them more effective drugs).[179]

16. One of the ABI inventors (Tao) had worked as a research assistant in the laboratory of one of the FSU scientists (Holton), where he learned the methods of synthesizing taxol that he later used to synthesize the taxotere compounds claimed in the patent-at-issue.[180] Tao had also learned about another compound ("PNIP") from the FSU scientists. PNIP was the most effective taxol analog, and differed only slightly from one of the three claimed taxotere compounds.[181]

17. Despite the structural and functional similarities between the claimed taxotere compounds and the taxol compounds developed at FSU, the similarity of their methods of manufacture, and the fact that the ABI inventors knew about, and even participated in, the FSU research on taxols,

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[177] *American Bioscience,* 333 F.3d. at 1331.
[178] *Id*. at 1332.
[179] *Id*. at 1333-1334.
[180] *Id*. at 1339.
[181] *Id*. at 1338-1339.

the Federal Circuit held that no one at FSU was a co-inventor of the taxotere compounds.[182]

18. The Federal Circuit held that even though the scaffold of the taxol analogs was virtually identical to the taxotere scaffold, and even though the ABI inventors attached substituents to their taxotere analogs because of what they had learned about the effect of those substituents on the taxol analogs developed at FSU, the FSU scientists were not co-inventors of the taxotere compounds because the FSU scientists never had a mental picture of the complete structure of any of those analogs ("Having in mind specific portions of a claimed compound is not the same as conceiving the compound with all of its components. One must have a conception of the specific compounds being claimed, with all of their component substituents.").[183]

19. The fact that the FSU scientists had developed the methods that the ABI inventors later used in manufacturing the claimed compounds was not relevant to the inventorship issue, because the claims at issue were directed to the compounds *per se*, not to their method of manufacture ("[O]nly ABI's inventors were in possession of both the structure of the claimed compounds and an operative method of making those compounds.").[184]

20. Even though the ABI inventor's choice of side chains for the claimed taxotere compounds was informed by their conversations with the FSU scientists about the effect of adding those side chains on the effectiveness of taxol analogs, that did not make the FSU scientists co-inventors of the claimed compounds ("Although [the ABI inventor's] choice of side chains may have been informed by his earlier conversations with [an FSU scientist] regarding the efficacy of PNIP, that

[182] *Id*. at 1342.
[183] *Id*. at 1340.
[184] *Id*. at 1342 ("The fact that similar compounds had been made at FSU in the past by using essentially the same method is of no consequence, because neither that method nor those similar compounds themselves are claimed in the [patent-at-issue].").

alone does not make [the FSU scientist] a coinventor of the claimed compounds.").[185] It was also significant that those side chains were known in the prior art.[186]

21. The fact that the FSU scientists had many scientific achievements in the relevant field and had conceived and synthesized a great number of taxol analogs, that "[t]he sum total of Tao's knowledge and experience with taxol and taxanes was gained in the laboratories of FSU," and that Tao had created taxol analogs containing the claimed side chains while working at FSU was not sufficient to qualify the FSU scientists as co-inventors of the taxotere analogs containing those side chains.[187]

C. The Vanderbilt scientists were not co-inventors of any of Dr. Daugan's claimed compounds

22. The '006 claims-at-issue recite specific chemical compounds *per se*. In *American Bioscience*, the Federal Circuit held that one cannot be a co-inventor of a chemical compound unless one had "a conception of the specific compounds being claimed, with all of their component substituents . . . ."[188] As the '006 patent makes clear (*see, e.g.,* column 1 at lines 16-25), the chemical compounds that Dr. Daugan invented, described and claimed in that patent (and in the '329 patent) all share the beta-carboline/piperazinedione-based "Formula (I)" structure shown below (image from JTX 1, cover page):

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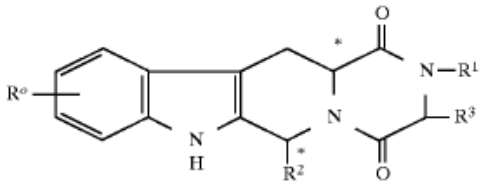
[185] *Id*. at 1342.
[186] *Id*. at 1341 ("[T]the . . . side chains of those compounds did not originate in FSU's laboratories, but are common branched alkyl groups. . . . and there is no serious dispute that the nitrophenyl substituent was also in the prior art.").
[187] *American Bioscience*, 333 F.3d at 1341 ("FSU's arguments and the district court's findings together fall short of meeting the clear and convincing evidence standard required for finding that Holton was a coinventor of the three specific compounds claimed in the 653 patent. While Holton may have invented many of the compounds synthesized in his laboratory, including PNIP, there is nonetheless no evidence of conception by Holton or anyone else at FSU of analogs having the [claimed] substituent[s]. . . . Thus, even assuming that Holton himself conceived all of the compounds synthesized within his laboratory, about which we express no opinion, there is no evidence of Holton's conception of the three [claimed] compounds . . . .").
[188] *Id*.

A compound of formula (I)



23. In its responses to ICOS's Requests for Admissions (which were admitted as DTX RD and RG), Vanderbilt admitted that none of its scientists ever met or communicated with Dr. Daugan.[189] Vanderbilt also admitted that prior to January 21, 1994 (the date on which Glaxo filed Dr. Daugan's first U.K. application), the Vanderbilt Scientists were not aware of the existence of (*i.e.*, the structure of) any of the claimed compounds.[190]

24. Because the Vanderbilt scientists were not aware that Dr. Daugan was working with any compound containing the "Formula (I)" structure, they could not have communicated anything about such structure(s), or modifying such structures, to Dr. Daugan (or Dr. Labaudiniere).

25. Thus, Vanderbilt has admitted that its scientists did not "have a conception of the specific compounds being claimed, with all their component substituents."[191] Under the holding in *American Bioscience* (and the cases cited therein), Vanderbilt's written admissions are alone

[189] DTX RG at Response Nos. 23-26. Likewise, Dr. Corbin admitted that he "never met Dr. Daugan," he "d[id]n't have any direct connection with Dr. Daugan," he "never worked together with Dr. Daugan to solve any kind of a problem," and he and Dr. Daugan "were working independently." D.I. 141 at 275:4-276:5 (Corbin). Dr. Konjeti similarly admitted he "didn't know that Dr. Daugan existed" and he "never had any collaboration" or "interaction" with him. D.I. 143 at 745:16-23 (Konjeti).

[190] DTX RG, at Response Nos. 13-22. Likewise, Dr. Corbin admitted that he "didn't know that anyone in the world was working on beta-carboline compounds to make PDE-5 inhibitors" in 1992 or 1993, and he "didn't think of using beta-carboline compounds" at that time (D.I. 141 at 271:12-14), and Dr. Konjeti admitted that he "didn't know that Glaxo was working on beta-carbolines at the time," he "didn't know that beta-carboline compounds could inhibit PDE" (D.I. 143 at 742:5-743:20), he wasn't aware of the structure of any of the "Formula (I) compounds claimed in the patents," and he "hadn't thought of any methods for making the Formula (I) compounds claimed in the patents" (D.I. 143 at 744:16-745:2).

[191] *American Bioscience,* 333 F.3d at 1340.

sufficient to reject Vanderbilt's allegations of co-inventorship and grant judgment for ICOS.[192]

26. Vanderbilt characterizes ICOS's view of the holding in *American Bioscience* as "in order to be a joint inventor of a chemical compound one must ***conceive*** all elements of a claimed chemical compound."[193] But while *American Bioscience* can be interpreted to support such a rule, such an interpretation is not necessary to reject Vanderbilt's co-inventorship claims here.

27. Vanderbilt argues that *American Bioscience* actually supports its co-inventorship arguments. Vanderbilt says that the contributions that its scientists made "to the compounds in the Patents-at-Issue" were "far more significant than those that were found to be sufficient" to make the ABI scientists (Drs. Soon-Shiong, Desai and Tao) inventors in *American Bioscience*[194] because its scientists "not only identified the substituents to be added to a scaffold (as Soon-Shiong, Desai and Tao did) and identified the attachment point for the substituents (as did Tao), the Vanderbilt scientists *identified the scaffold itself* and *proposed an entire structure for a PDE-5 inhibitor* that was previously unknown in the art."[195]

28. None of this is true. First, the Vanderbilt scientists may have "identified the substituents to be added to a scaffold," but that "*scaffold itself*" (the two-ring xanthine nucleus of IBMX) was not the "scaffold" in Dr. Daugan's claimed compounds (the four-ring tetrahydro-beta-carboline/piperazinedione "Formula (I)" structure). Just as for the FSU scientists in *American Bioscience*, the Vanderbilt's scientists' "design theory" about adding substituents to one compound (IBMX) does not make them co-inventors of a ***very*** different family of compounds

[192] *See also* Dr. Corbin's admissions that the Vanderbilt scientists did not conceive the structure of any compounds claimed in the '006 patent (D.I. 141 at 263:14-21), how to make any of those compounds (D.I. 141 at 265:22-266:11), any pharmaceutical composition containing any of those compounds (D.I. 141 at 267:19-268:2), or a method of using those compounds to treat impotence (D.I. 141 at 270:7-13).
[193] Vanderbilt Br. at 44 (emphasis added).
[194] Vanderbilt Br. at 49.
[195] Vanderbilt Br. at 49 (emphasis in original).

(tetrahydro-beta-carboline/piperazinediones), even where the same substituent is added to that second family of compounds.

29. Second, the Vanderbilt scientists may have "identified the attachment point" for a phenyl group in their IBMX analogs (the "8-position"), but as Dr. Rafferty testified, that "attachment point" does not exist in Dr. Daugan's claimed compounds, so a communication about the "attachment point" for IBMX analogs cannot constitute a contribution to conception of the claimed compounds.

30. Third, the Vanderbilt scientists may have "proposed an entire structure for a PDE-5 inhibitor" (*i.e.*, 8-(4-hydroxy phenylthio)-IBMX), and that structure may even have been "previously unknown in the art."[196] But that compound was not a compound that Dr. Daugan ever used in developing the beta-carboline series or in designing his claimed compounds, and its structure and functional characteristics are not analogous to Dr. Daugan's compounds. Consequently, even if it had been communicated to Dr. Daugan (which it was not) it could not have been a contribution to his conceptions of his claimed compounds.

31. There is a critical distinction between the ABI inventors' contributions to their claimed taxotere analogs and the Vanderbilt scientists' alleged contribution to Dr. Daugan's conceptions of his claimed compounds. In *American Bioscience*, the claimed taxotere analogs were nearly identical in structure to the taxol compounds developed by the FSU scientists. Yet the Federal Circuit held that the FSU scientists' communication of ideas regarding the effects of adding specific substituents to those nearly-identical taxol compounds to the ABI scientists was not a contribution to the ABI scientists' conceptions of the taxotere compounds containing those same

[196] Vanderbilt says that "unlike the novel PDE5 inhibitor structure [8-(4-hydroxy phenylthio)-IBMX] communicated by Vanderbilt to Glaxo, both taxol and taxoltere [*sic*: taxotere] were well-known in the state of the art . . ." (Vanderbilt Br. at 45, fn. 44). But, like taxol and taxotere, there is no dispute that IBMX was "well-known in the state of the art."

substituents. The situation is even more pronounced here: as Drs. Padwa and Rafferty explained, the IBMX analogs that the Vanderbilt scientists disclosed to Glaxo were quite different in structure to Dr. Daugan's claimed "Formula (I)" compounds.

32. Moreover, the ABI inventors in *American Bioscience* (Drs. Desai, Soon-Shiong and Tao) were at least aware that their separate contributions were being made part of the claimed taxotere analogs, and were aware of all the "component substituents" on those claimed analogs, prior to the filing of the patent application. As a result of this awareness, they each possessed a definite and permanent idea of the complete and operative invention as claimed. In contrast, the FSU scientists were not co-inventors because they were working on taxol compounds; they never contemplated making the claimed substitutions on taxotere analogs. Similarly, as Vanderbilt readily admits, the Vanderbilt scientists were completely unaware that anyone at Glaxo was working on compounds having a beta-carboline scaffold until they saw the '006 patent in 2001; they were working on IBMX analogs, and never contemplated making substitutions on beta-carboline compounds.

33. The Vanderbilt scientists' alleged contribution to the claimed "Formula (I)" compounds here is analogous to that of Dr. Holton, who was found ***not*** to be a co-inventor in the *American Bioscience* case. While working in Dr. Holton's laboratory at FSU, Dr. Tao learned about the effect of adding certain substituents to taxol analogs. After leaving FSU for Vivorx (*i.e.*, ABI), Dr. Tao had the idea to add these same substituents to the novel taxotere analogs synthesized by Drs. Desai and Soon-Shiong. Although he may have conceived adding certain substituents to taxol analogs, Dr. Holton was not involved in the conception of adding the substituents to the novel taxotere analogs synthesized at Vivorx. Consequently, the Federal Circuit held that Dr. Holton was not a joint inventor with Drs. Tao, Desai, and Soon-Shiong, because he had no

awareness of the specific compounds being claimed, with all of their component substituents.[197] The Vanderbilt scientists cannot be co-inventors because, like Dr. Holton, they did not conceive adding substituents to the scaffold of the claimed beta-carboline/piperazinedione compounds, and certainly did not have a conception of the claimed compounds with all of their component substituents.

34. Consequently, under *American Bioscience*, even if there was evidence that Dr. Daugan had known of the effect of Vanderbilt's four "Structural Features" on Vanderbilt's IBMX analog (and there is no such evidence), his decision to incorporate any similar "feature" into his novel "Formula (I)" compounds would not qualify the Vanderbilt scientists as co-inventors of his novel compounds.

35. Vanderbilt points to the *American Bioscience* court's treatment of Dr. Nadizadeh, who contributed a method of making the claimed compounds but was held not to be a co-inventor, as somehow supporting Vanderbilt's argument. It does not. The *American Bioscience* court held that Nadizadeh could only have been a co-inventor if the other ABI inventors had been unable to make the claimed compounds without his help, but that "this is not this case."[198] Instead, the court reiterated that, as for the FSU scientists, Nadizadeh was not a co-inventor because "here, there is no evidence in the record that Nadizadeh knew that Tao, Soon-Shiong, and Desai were attempting to make any of the claimed compounds, or even that Tao, Soon-Shiong, or Desai had any contact at all with Nadizadeh after the claimed compounds were conceived. Nadizadeh neither made the claimed compounds nor attempted to make them, and he did not have 'a firm and definite idea' of the claimed combination as a whole."[199] Far from supporting Vanderbilt's

[197] *American Bioscience*, 333 F.3d at 1341.
[198] *Id.* at 1342.
[199] *Id*.

argument, this is why the Vanderbilt Scientists cannot be co-inventors of the compounds conceived by Dr. Daugan – they "neither made the claimed compounds nor attempted to make them," and they "did not have 'a firm and definite idea' of the claimed combination as a whole."

36. Vanderbilt says that "the only court that has thus far considered *American Bioscience* in a case involving questions of joint inventorship[200] did not interpret that case as changing the law as suggested by ICOS."[201] But ICOS does not suggest that *American Bioscience* "changed the law" of joint inventorship regarding chemical compounds. The *American Bioscience* court found that the FSU scientists were not inventors because they only contemplated adding their side chains to taxol compounds, whereas the ABI scientists conceived adding those side chains to taxotere compounds. Despite the fact that the taxol "scaffold" is, structurally, virtually identical to the taxotere "scaffold," even the two minor differences in their structures meant that the FSU scientists could not have made the requisite contribution to conception of the claimed taxotere analogs. Here, as Drs. Crooks, Padwa and Rafferty explained at trial, there are very substantial structural differences between Vanderbilt's IBMX analog and Dr. Daugan's claimed beta-carboline/piperazinedione compounds.

37. Vanderbilt implies that Dr. Daugan selected certain substituents for his claimed "Formula (I)" beta-carboline/piperazinedione compounds because the Vanderbilt scientists had

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[200] Vanderbilt continues to ignore this Court's consideration of *American Bioscience* in *Medtronic Vascular v. Adv. Cardiovascular Sys*., 2005 WL 46553 (D. Del. January 5, 2005).

[201] Vanderbilt Br. at 47. The case Vanderbilt cites, *Regents of the University of Michigan v. Bristol-Myers Squibb, Co.*, 301 F. Supp. 2d 633 (E.D. Mich. 2003), indeed did not view *American Bioscience* as changing the law. In the passage from this case quoted by Vanderbilt, the *Regents* court was addressing the well-established law that a joint inventor need only make a contribution to a single claim. As regarding joint conception of a claimed compound, the *Regents* court expressly followed the holding in *American Bioscience*, stating "[T]here is no suggestion that Dr. Thompson concelved [*sic*] of the complete molecule claimed with all of its component constituents. Accordingly, Dr. Thompson is neither the sole inventor of the '095 Patent nor a joint inventor." *Id*. at 646 (citing *American Bioscience*, 333 F.2d at 1340) (emphasis added).

communicated to Glaxo that those same substituents could increase the potency of an IBMX compound against PDE-5. The evidence at trial showed unequivocally that Vanderbilt's assertion is not true. But even if it were true, it would not support Vanderbilt's case. Just as the Federal Circuit rejected FSU's argument that its scientists contributed to the conception of ABI's taxotere compounds because those compounds had the same "side chains" as FSU's taxol compounds, Vanderbilt cannot establish co-inventorship here even if Dr. Daugan's claimed compounds had some of the same side chains as Vanderbilt's IBMX analogs.

38. In short, every "fact" asserted by Vanderbilt is of the same type as, but is factually weaker than, those rejected by the Federal Circuit in *American Bioscience*. Therefore, there is no factual or legal basis on which the Vanderbilt scientists could be named as co-inventors of any of the chemical compounds recited in the '006 or '329 patents.

39. Co-inventorship also requires some communication of an idea between the co-inventors. In the *Kimberly-Clark* case,[202] the Federal Circuit held that two inventors cannot be joint inventors "if they have had no contact whatsoever and are completely unaware of each other's work."[203] Joint inventorship requires that the inventors must "have some open line of communication during or in temporal proximity to their inventive efforts . . . ."[204] Moreover, disclosure of information to one person in a company is not sufficient to establish that the information was disclosed to an employee inventor associated with that company.[205]

40. Irrespective of what Vanderbilt's scientists might believe they conceived, the record is devoid of any evidence of any communication of any information from Vanderbilt to Dr.

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[202] *Kimberly-Clark Corp. v Procter & Gamble Dist. Co., Inc.*, 973 F.2d 911 (Fed. Cir. 1992).
[203] *Id*. at 916.
[204] *Cook Biotech, Inc. et al. v. ACell Inc. et al.*, 460 F.3d 1365, 1373 (Fed. Cir. 2006) (citing *Eli Lilly v. Aradigm*, 376 F.3d at 1358-59).
[205] *Beall v. Ormsby*, 154 F.2d 663, 665 (C.C.P.A. 1946).

Daugan, directly or indirectly, for any purpose, at any time.

41. Vanderbilt relies on the 1992 Research Proposal submitted to Dr. Ross at Glaxo in England, and its speculation that Dr. Labaudiniere read that Proposal and communicated that information to Dr. Daugan. But there is no evidence of this. Dr. Labaudiniere could not recall even having seen the Proposal, or being involved in any discussion thereof. More importantly, there is no evidence that Dr. Daugan ever saw or heard about the Proposal or anything in it. There certainly is no evidence that Dr. Daugan heard about Vanderbilt's "design theory"; to the contrary, he testified that he never contemplated making compounds that "more closely resemble the entire cGMP molecule." Because Dr. Daugan did not know about any information originating at Vanderbilt, Vanderbilt cannot satisfy the "communication" requirement for co-inventorship, and its claims fail as a matter of law.

D. The Vanderbilt scientists were not co-inventors of any of Dr. Daugan's claimed methods

42. Vanderbilt's argument that its scientists told Dr. Ross that PDE-5 inhibitors might be useful to treat impotence fails as a matter of law to qualify the Vanderbilt scientists as co-inventors of any method claimed in the '329 patent.

43. This issue is controlled by cases such as *Hess v. Advanced Cardiovascular Systems, Inc.*, 106 F.3d 976 (Fed. Cir. 1997). In *Hess*, the inventors consulted with Mr. Hess to find a suitable material for a catheter. Hess suggested an approach he found in the literature, which the inventors then followed.[206] When Hess sued to be added as a co-inventor, the court rejected his claim because he was "doing nothing more than explaining to the inventors what the then state of the art was," and the Federal Circuit affirmed on that basis.[207]

44. Vanderbilt says it communicated a "theory" in the January 1992 letter to Dr. Ross that "its

[206] *Id*. at 977-78.
[207] *Id*. at 981.

PDE5 inhibitors should work in connection with corpus cavernosum, which could have an impact on individuals suffering from impotence," and that this "theory" had not been "expressly" proposed in the scientific literature before that time. But there is no evidence suggesting that Dr. Daugan saw the January 1992 letter, that any information therein was communicated to him, or that he used any such information in his conception of the methods claimed in the '329 patent.

45. Moreover, as Dr. Francis, Dr. Cote, and Dr. Daugan testified, and as Dr. Corbin's sworn affidavit[208] confirmed, the theory that a PDE-5 inhibitor could treat impotence was already known in the art by the time Dr. Daugan conceived using his compounds for such a purpose, and even before Dr. Corbin sent his letter to Dr. Ross. Consequently, under *Hess* and *Fina Oil* (and many other cases),[209] any communication of that theory from Vanderbilt to Glaxo could not qualify the Vanderbilt scientists as co-inventors of any method claimed in the '329 patent.

IV. CONCLUSION

Vanderbilt cannot show that any of its scientists contributed to Dr. Daugan's conception of any compound claimed in the '006 or '329 patent, because Dr. Daugan was not aware of any information from Vanderbilt when he conceived those compounds. Because the Vanderbilt scientists were unaware of the claimed compounds, they could not possibly have conceived the use of those compounds to treat impotence, as claimed in the '329 patent. Moreover, the concept of using PDE-5 inhibitors to treat impotence had already been publicly disclosed by others before Dr. Daugan conceived the methods claimed in the '329 patent. Consequently, Vanderbilt cannot establish co-inventorship for either patent, under any standard of proof, and this Court should enter judgment for ICOS on Counts I and II of the Complaint.

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[208] DTX OV at ¶¶ 55, 65.

[209] *See, e.g., Applied Elastomerics, Inc. v. Z-Man Fishing Prods., Inc*., 521 F. Supp. 2d 1031, 1040-43 (N.D. Cal. 2007) (granting summary judgment where alleged co-inventor "contributed only 'well-known principles'").

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