IN THE
UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDERBILT UNIVERSITY

Plaintiff,

v.

ICOS CORPORATION,

Defendant.

Civil Action No: 05-506-SLR

PLAINTIFF VANDERBILT UNIVERSITY'S CORRECTED POST-TRIAL REBUTTAL BRIEF

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INTRODUCTION

> *You should use your common sense in weighing the evidence. Consider it in light of your everyday experience with people and events, and give it whatever weight you believe it deserves. If your experience tells you that certain evidence reasonably leads to a conclusion, you are free to reach that conclusion*[1]

ICOS' own expert has acknowledged that the structural features found in the novel PDE5 inhibitor design communicated by Drs. Corbin, Francis and Konjeti to Glaxo are found within the compounds claimed in the Patents-at-Issue. ICOS' claim that the presence of those features in the patented compounds is a mere coincidence, and its explanation of how they got there, simply defy the common sense that the Court, as trier of fact, must apply in weighing the evidence. Application of common sense to the evidence relating to the communication of that design to Glaxo and the appearance of those features in the patented compounds can only reasonably lead to one conclusion: Drs. Corbin, Francis and Konjeti should be added as co-inventors on the Patents-at-Issue.

STATEMENT OF FACTS

Incorporation of Vanderbilt's Design into Compounds Claimed in the Patents[2]

ICOS does not and cannot dispute that: (1) Drs. Corbin, Francis and Konjeti conceived of a novel design theory for PDE5 inhibitors or that their theory was reflected in structure of 8-(4-hydroxy phenylthio)-IBMX; (2) on February 24, 1992 Drs. Corbin, Francis and Konjeti sent the 1992 Research Proposal (PTX 117) to Dr. Barry Ross, Director of Medicinal Chemistry at Glaxo

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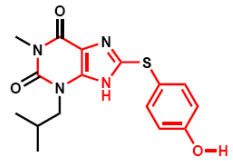
[1] Uniform Jury Instructions for Patent Cases in the United States District Court for the District of Delaware, Instruction 1.5 Consideration of Evidence (Hon. Roderick R. McKelvie, U.S.D.J ET AL., March 1993).

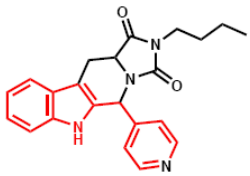
[2] Vanderbilt submits that ICOS has not raised any material dispute to the evidence regarding the Parties, the Nature of the Compounds Claimed in the Patents, the 1988 Research Proposal and 1989 Research Agreement, the history of Glaxo France's PDE Project, Vanderbilt's Design of a New PDE5 Inhibitor, or the Communication of Vanderbilt's New PDE5 Inhibitor Design to Glaxo.

Group Research and head of Glaxo's Cardiovascular Research Management Committee; (3) the 1992 Research Proposal communicated the structure of 8-(4-hydroxy phenylthio)-IBMX and the fact that the attachment of a 4-hydroxy phenylthio group to the 8 position on IBMX resulted in a compound that was 160 times more potent than IBMX in inhibiting PDE5 and 6 times more potent than zaprinast, the most potent PDE5 inhibitor known at the time; (4) on April 8, 1992 Dr. Ross transmitted the 1992 Research Proposal to Dr. Richard Labaudiniere, head of Glaxo France's PDE Project team and lead chemist at the Glaxo France laboratory; (5) as of April 8, 1992, and through the time that Glaxo filed the first patent applications, there was no reference in the published state of the art to the use of 8-(4-hydroxy phenylthio)-IBMX, or any other compound comprised of a 6 member ring fused to a 5 member ring with a 6 member aromatic



8-(4-OH-PT)-IBMX

ring appended at the 8-position ( ), as a PDE5 inhibitor; (6) on April 23, 1992, Glaxo France **for the first time** tested not one, but eleven compounds that included a substructure comprised of a 6 member ring fused to a 5 member ring with a 6 member aromatic



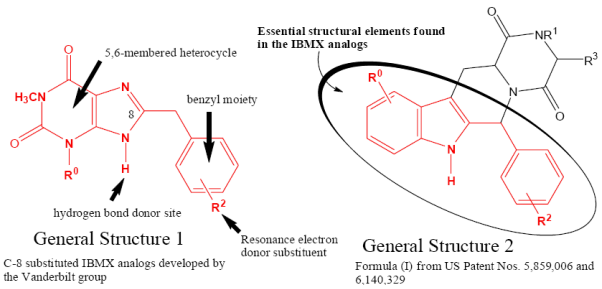
GR 30040X

ring appended at the analogous to 8-position of IBMX[3], including

[3] Like all of the IBMX analogs proposed in the 1992 Research Proposal, the skeletons of 26 of the 29 compounds tested on April 23rd contain that 6- and 5-member ring scaffold with some substitution at the analogous to 8-position of IBMX. (Tr. 672:9-689:9 (Konjeti); PTX 134A, 135A, 136A, 137A, 138A, 139A, 140A, 141A, 142A, 143A, 144A, 145A, 146A, 148A, 149A, 150A, 151A, 152A, 153A, 421A; Tr. 1259:25-1300:23 (Rafferty); PTX 425; PTX 427, p. 3).

and; (7) Starting with that one compound, Glaxo France began to study a new series of PDE5 inhibitors that, by December 1992, led to the synthesis of the first compound that falls within those claimed in the Patents-at-Issue and which, like every other compound claimed in the Patents-at-Issue, contain the substructure reflected in PTX 426:

FIGURE 1



In the face of this evidence, ICOS contends that (1) Dr. Labaudiniere ignored the 1992 Research Proposal; (2) it is purely coincidental that GR30040X and the patented compounds contain the Vanderbilt Structural Elements; (3) GR30040X was identified through a substructure search based upon GR35273X; and (4) the Vanderbilt Structural Features do not significantly contribute to the patented compounds. Such contentions are simply not supported by a common sense review of the evidence in the record before the Court.

The evidence before the Court is that (1) Drs. Corbin and Francis were leaders in the study of PDE5 (Vanderbilt Brief pp. 5-7, 9); (2) Vanderbilt and Glaxo were engaged in a "close" and "substantial" collaboration (Vanderbilt Brief pp. 9-12, 15, 19-22, 24; PTX 67); (3) Glaxo appropriated Vanderbilt's novel cGMP analog design theory and novel cGMP analog designs[4];

This too large a number to be the result of coincidence as contrasted with the fact that only 8 of the 29 compounds contained any kind of carboline structure.

[4] ICOS' suggestion that this is conjecture simply ignores the evidence. Comparison of Vanderbilt's 1988 Research Proposal (PTX 35) and the March 18, 1991 status report by Dr.

(4) Dr. Ross flew from England to Nashville and specifically asked for the details of Vanderbilt's new design (Vanderbilt Brief pp. 19-22); (5) Dr. Labaudiniere was actively looking for new PDE5 leads;[5] (6) The results reported in the 1992 Research Proposal were impressive enough to warrant the launch of a new lead series, let alone a substructure search. (Tr.1176:14-15, 1256:24-1258:7 (Rafferty); Tr.1067:9-20 (Padwa); PTX 121, p. GLAX02001; DTX RJ, p.ICOS-003008; Tr. 573:17-574:2 (Grondin)).[6] The only reasonable inference that the Court can draw from the record is that Dr. Labaudiniere did not ignore the 1992 Research Proposal, but rather conducted a substructure search based upon 8-(4-hydroxy phenylthio)-IBMX that identified the compounds tested on April 23, 1992.

In and of itself the evidence of the circumstances relating to the communication of the 1992 Research Proposal to Glaxo France and the timing of the identification of GR30040X strongly point to the conclusion that GR30040X was identified as a result of Glaxo France's study of the Vanderbilt compound and design theory, such that Vanderbilt need not prove specifically how that occurred, but simply how it logically could have occurred.[7] The evidence

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Rimele to Dr. Ross (PTX 51) shows conclusively that a year after Vanderbilt submitted that proposal Glaxo employed the design theory developed by Vanderbilt and described in the proposal to synthesize several of the same novel cGMP analogs that Drs. Corbin and Francis had developed. The most potent analogs that Glaxo made were identical to those described in the 1988 Research Proposal and/or the progress reports that Vanderbilt made during the course of the 1989 Research Agreement. Glaxo did not inform Vanderbilt of Glaxo's appropriation, without attribution, of Vanderbilt's theories and designs and would never have done so but for this litigation. (Vanderbilt Brief, pp. 12-13).

[5] Because the proposal was sent directly to Dr. Labaudiniere by Dr. Ross and Dr. Labaudiniere participated in the meeting during which the Cardiovascular Research Management Committee voted to continue the Glaxo/Vanderbilt collaboration, the only reasonable inference is that Dr. Labaudiniere read the proposal.

[6] Indeed, Glaxo apparently considered an IC50 as poor as 40,000 nM to be worthy of a substructure search in the Glaxdatabank. (PTX 167; Tr. 1256:24-1258:7 (Rafferty)).

[7] The Court will no doubt recall that at first ICOS claimed an inability to produce <u>any</u> Glaxo documents and then, only after the originally scheduled closing date for discovery and Vanderbilt's counsel was in Europe for depositions did ICOS *begin* to produce documents

demonstrates that when Dr. Labaudiniere received information that suggested possible new lead compounds he searched the Glaxdatabank to find compounds that contained a common core structure, scaffold, skeleton or chemical motif. (Tr. 431:11-13, 432:1-433:2, 433:25-435:20 (Labaudiniere); 627:6-21, 636:5 (Kadouri)). Given that such a search would take less than two minutes to conduct[8], common sense compels the conclusion that Dr. Labaudiniere conducted substructure searches based upon the Vanderbilt compound. Moreover, as the Court can see from DTX KC, a substructure search of a database containing GR30040X (such as either DTX KC or Glaxdatabank) using the skeleton or scaffold of the Vanderbilt compound would have identified GR30040X as a possible candidate.[9]

Relying primarily upon the testimony of its expert Dr. Rafferty, ICOS asserts that a substructure search, such as Vanderbilt suggested would identify GR30040X from the skeleton of 8-(4-hydroxy phenylthio)-IBMX, simply could not have occurred.[10] However, there are several flaws in Dr. Rafferty's testimony.[11] For example, Dr. Rafferty surmised, based upon his

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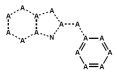
relating to Glaxdatabank and ChemBase, including the thousands of pages of compound data cards and ISIS prints that are in evidence as DTX IT and DTX KB and the PDE database itself, DTX KC.

[8] (Tr. 1288:8-12(Rafferty)). *See also* DTX KC.

[9] For example, as demonstrated at trial, a search based upon the following structure, where "A" represents any atom, and dotted lines represent any bond, would yield GR30040X:  (DTX KC, JTX 40, pp. GLAX18530-35, 861-871, 19010-19032).

[10] ICOS mischaracterizes Dr. Konjeti's testimony. He testified that all of the compounds tested by Florence Godard on April 22, 1992 contained a xanthine "scaffold or skeleton," which is the term used by Drs. Labaudiniere and Kadouri; not the complete xanthine "nucleus." (Tr. 670:25-689:2 756:1-14; PTX 134A-146A, 153A, 421A, 424, 425). Moreover, the fact that, in reviewing whatever limited documentation he was provided by ICOS' lawyers, Dr. Rafferty did not see any documents evidencing a substructure search using 8-(4-hydroxy phenylthio)-IBMX proves nothing. The evidence is that no record was maintained of any such searches and that, to the extent that they ever did, such records no longer exist. (Tr. 635:18-636:24 (Kadouri); Tr. 1007:7-1009:5 (ICOS' Answers to Interrogatories)).

[11] In addition to the flaws explained above, the Court should consider the fact that Dr. Rafferty, whose primary business is to serve the interests of large pharmaceutical companies, was

belief that there would have been as many as 500,000 compounds in the Glaxdatabank as of April 1992, that such a search would have yielded too many results to be practical. (*See* ICOS brief, pp. 21-22, ¶ 25). In fact, there were only 160,180 compounds in Glaxdatabank as of April 21, 1992, or 70% less than Dr. Rafferty predicted. (Tr. 618:5-620:19 (Kadouri); PTX 400; DTX IT, p. GLAX16829). Dr. Rafferty also failed to take into account the fact that if a search was limited to those compounds that were available at Glaxo France for testing the results would have been far fewer in number. (*See* Vanderbilt Brief, p. 26).[12]

Dr. Rafferty also asserts that no Glaxo chemist would have performed a skeletal search such as Vanderbilt suggests because a chemist would never ignore the nitrogen atoms and other substituents found on the guanine moiety of IBMX as would be required for such a search. Such an assertion is inconsistent with the concepts of "scaffold" and "skeleton" to which Drs. Labaudiniere and Kadouri referred to in their testimony, wherein Dr. Labaudiniere specifically distinguished between the core structure of a compound and substituents. More importantly, it is directly contradicted by the evidence of how the Glaxo France scientists viewed such differences. For example, those scientists considered GR35273X to be an analog of zaprinast, even though they did not share several of the same nitrogen atoms, rings, and other groups:

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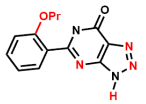
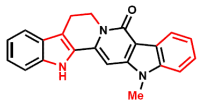
provided some of his opinions by ICOS' lawyers. (Tr. 1225:1-1226:15). By contrast, Vanderbilt's experts were truly independent academic scientists who are not professional witnesses and who possess impeccable credentials in the fields in which they testified. (PTX 413; PTX 415).

[12] While it is not clear what Glaxo records ICOS' lawyers provided to Dr. Rafferty, it is very clear that they did not provide him with all of the documents necessary to ensure the accuracy of his opinions. (Tr. 1240:12-1243:11; 1250:21-25; 1251:23-1252:11 (Rafferty)).

ANALOGIE AVEC LE ZAPRINAST



GR 35273X 

(JTX 13, p. GLAX16000). *See also*, PTX 178, p. GLAX16053).[13] Even Formula 1 of Claim 1 of the '006 patent ignores the differences between benzene , thiophene , furan  and pyridine , treating them as equivalents for the purpose of the R-2 component (JTX 1, p. 1 (abstract), column 49).[14]

Deleted: JTX 14

By far the most significant indication that Dr. Rafferty's opinions are not worthy of consideration by the Court is his testimony that, notwithstanding what he himself characterized as "impressive" results, Dr. Rafferty asserts that the Glaxo scientists would not have taken the less than two minutes necessary to conduct any substructure search based upon the Vanderbilt compound. (Tr. 1289:15-20 (Rafferty)). Vanderbilt submits that, in the context of the record before the Court, such an opinion defies all common sense and reflects the lengths to which Dr. Rafferty is prepared to go to mold his opinions as necessary to support ICOS' defense.

[13] This is not the only incidence in which Dr. Rafferty's opinion of what a chemist *would* do differed from what the Glaxo France chemists *did* do. For example, Dr. Rafferty testified that a chemist working on developing an inhibitor would want to know as much as he could about the structure of the related enzymes, but Dr. Daugan testified that he did nothing of the kind in connection with his work on PDE5 inhibitors. (Tr. 1228:25-1231:1 (Rafferty); Tr: 905:18-906:11, 909:4-19 (Daugan)).

[14] It is worth emphasizing that while he complains that the search suggested by Vanderbilt would ignore substituent atoms attached to the skeleton of IBMX, the searches that Dr. Rafferty suggests might have occurred based upon GR35273X ignore even more components of that compound's structure, including several complete rings of atoms.

For years Glaxo has represented to the scientific community that, after reading Belen Elgoyhen's *Relaxant Effects of β-Carbolines on Rat Aortic Rings* in the May 1992 edition of the Journal of Pharmacology and Experimental Therapeutics, Glaxo identified and tested βCCE and then, conducting a substructure search on the basis of those test results, found GR30040X. (JTX 29, PTX 326, p. GLAX25219-20).[15] As recently as its statement of facts in the Joint Pretrial Order, ICOS told the same story. (JPTO, Exh. 3, pp. 3-4). However, the evidence proves that story is and always was false. Even Dr. Rafferty concedes that a substructure search using the beta carboline scaffold depicted by ICOS in the Joint Pretrial Order would not have yielded a single one of the compounds tested on April 23, 1992, including GR30040X. (PTX 426; Tr. 1273:2-1275:15 (Rafferty); JPTO, Exh. 3, p. 4). GR30040X was identified a month before the Elgoyhen article became publicly available and had already been identified as a "new" PDE5 inhibitor (with no reference to beta carboline) before Dr. Labaudiniere did any substructure searches based upon beta carboline. (JTX 13, PTX 167). Dr. Labaudiniere went out of his way to document a search based upon the non-specific 40,000 nM IC50 reflected in the Elgoyhen article.[16] He directed that βCCE bypass the 10 μM concentration test and go straight to an IC50

[15] ICOS quietly suggests that Dr. Labaudiniere did beta carboline substructure searches based upon a 1983 article referenced in JTX 29. There is no evidence to support such a claim, and the idea that Dr. Labaudiniere coincidently would have stumbled upon a 9-year-old article just after receiving the 1992 Research Proposal and gleaned from it insights into the use of beta carbolines that had escaped the entire scientific community for almost a decade is nearly ridiculous.

[16] As noted, records of substructure searches were not often generated if at all and none were retained by Glaxo. Interestingly, PTX 167, apparently the only document of its kind in existence, was provided to Vanderbilt *by ICOS' counsel* at Dr. Labaudiniere's October 28, 2006 deposition in response to the deposition subpoena duces tecum that was served *upon Dr. Labaudiniere*, who left Glaxo France in 1994 shortly after the first patent application. (Tr.389:1-5, 390:20-22, 392:20-25 (Labaudiniere)). It does not list GR30040X, which had been identified two months before PTX 167 was created. Nonetheless, one must wonder why Dr. Labaudiniere has been holding on to that document for over 14 years after he created it and 12 years after he left the company.

test..[17] The unimpressive 800 nM IC50 that test produced was supposedly used as a basis for pursuing beta carbolines as a separate series of inhibitors. Dr. Labaudiniere then made a point of rewriting the history of the identification of GR30040X to make it appear as though it was identified from the Elgoyhen article and βCCE (PTX 188, p. GLAX00313; Tr. 895:4-6 (Daugan)). Why? The only logical explanation is that Dr. Labaudinere wanted it to appear that GR30040X was identified as a PDE5 inhibitor based upon the published state of the art rather than Vanderbilt's novel conceptions.[18] Regardless of Glaxo's motives, the fact that Elgoyhen/βCCE story was invented, and patently false, casts further doubt on the already questionable, and newly invented, "replacement story."

In light of the evidence, ICOS has now effectively abandoned the Elgoyhen/βCCE story that Glaxo published in 2003 and has thrown itself behind the replacement story that GR30040X was identified through a substructure search of beta carboline structures contained within GR35273X, a compound invented by a Professor Campbell at Bath University that Glaxo France had identified as a possible PDE5 inhibitor in March 1992.[19] If such were the case, common sense would lead one to expect that GR35273X would have been identified as a beta carboline in March, April, May or June 1992 and that GR30040X would have been identified not only as a beta carboline, but as an analog of GR35273X as well. Yet GR35273X was identified in June

[17] As Dr. Grondin testified, the concentration test was established to weed out poor candidates before proceeding to an IC50 test. (Tr. 488:2-489:23).Dr. Labaudiniere's apparent fears that βCCE would not pass this test were well founded. Only one of the rest of the beta carbolines (all of which were subjected to the concentration test) passed that test, and barely so. The rest did not come close. (DTX KB, pp. GLAX14341, 14347-49, 15440, 15533).

[18] That Glaxo would actively seek to establish a source other than Vanderbilt for the presence of the Vanderbilt Structural Features in GR30040X and the patented compounds is not surprising in light of the fact that Glaxo had earlier appropriated Vanderbilt's cGMP analog design and designs and subsequently purported to sell the rights to 8-(4-hydroxy phenylthio)-IBMX to ICOS, without disclosing either action to Vanderbilt. *See* Vanderbilt Brief, p. 36, n. 27.

[19] JTX 22, p. GLAX25738.

1992 in both a report to the Cardiovascular Research Management Committee (JTX 24, p. GLAX10365) and minutes of the Glaxo France Project PDE meeting (JTX 13, p. GLAX16000) as a zaprinast analog based upon a structure that is neither a carboline nor found in GR30040X (JTX 13, p. GLAX16000; PTX 428). Both documents identified analogs of GR35273X, but neither listed GR30040X among those analogs. GR30040X was identified in the June 1992 minutes, not as a carboline or a GR35273X analog, but simply as a "new" inhibitor. (JTX 13, p. GLAX15986). Analogues of GR30040X were also identified, but did not include GR35273X. (JTX 13, p.GLAX15995-96). Glaxo France first labeled GR30040X and its analogues as carbolines in July 1992. The September 1992 minutes indicated, albeit inaccurately, that GR30040X was derived from the study of βCCE, but made no reference to GR35273X. (PTX 188, p. GLAX00313; Tr. 895:4-6 (Daugan)). It was not until October 1992 that PDE Project team debated and concluded that GR35273X was more appropriately considered a carboline than a zaprinast analog . (JTX 15, pp. GLAX16277-280). It would simply make no sense whatsoever for such a debate to have occurred in October 1992 had Dr. Labaudiniere concluded in April 1992 that the most important substructure of GR35273X was carboline.

The allegation that the compounds tested on April 23, 1992 compounds were identified through a search based upon GR35273X is itself demonstrably false. A substructure search of the structural elements the Glaxo scientists found important in GR35273X would have identified only one compound among the April 23rd compounds other than GR35273X itself. (PTX 428; JTX13, p.GLAX16000). Had Dr. Labaudiniere conducted a substructure search in April 1992

based upon the structures that had been deemed important by Glaxo France,[20] it would have yielded and Florence Godard would have tested on April 23, 1992 the very same GR35273X analogs that were identified when such searches were actually conducted in June. (JTX 13, p. GLAX15999, 16001). She did not. By the same token, had the search been performed using a beta carboline scaffold, the April 23, 1992 list of compounds would have included most or all of the carboline compounds that were identified when Dr. Labaudiniere performed such a search two months later.[21] They did not.

Perhaps the most conclusive evidence that GR30040X was not identified through a substructure search based upon GR35273X is the fact that the *Discovery of Tadalafil* articles published in 2003 credit the Elgoyhen article as the inspiration for that search. (JTX 29, p. VC-000886)[22] There is simply no rational reason why Glaxo would want or need to fabricate and

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[20] GR35273X contains indole , pyrrole , tetrahydropyrrolopyridine , pyridone , tetrahydro β-carboline , piperidine  and many more ring combination systems. As there had been no SAR study conducted with respect to GR35273X in April 1992 Dr. Labaudiniere would have had no way of knowing which of the many components of the particularly large compound were responsible for its inhibition of PDE5. Indeed, by suggesting that GR35273X would have led Dr. Labaudiniere to conduct a search based on just 3 of the compound's 6 rings, ICOS is guilty of that which it accuses Vanderbilt: "carefully selecting those few structural aspects that are common." (ICOS Brief, p. 14, ¶12). Because Glaxo France was well familiar with zaprinast as an inhibitor, it was only natural for Glaxo France to look for and focus on structures within GR35273X that were believed to be analogous to zaprinast as being the source of GR35273X's inhibitory qualities.

[21] PTX 167. It is clear that at least one of those carboline compounds, CCI23009, was available for testing as of April 23, 1992. Glaxo U.S. had identified CCI23009 as a "Zaprinast Analog" and Glaxo France had included it in the first batch of compounds that were requested from Glaxo U.S. at the beginning of the Glaxo France PDE Project. (PTX 51, p. GLAX15574, PTX 61, p. GLAX00501). In fact, although it was not tested with PDE5 until July 7, 1992 along with the other "Analogues 'BZD'" identified by Dr. Labaudiniere (DTX KB, p. GLAX14348; PTX 167), Glaxo France had a supply of CCI23009 in its storeroom since October 22, 1990. (DTX IT, p. GLAX18454).

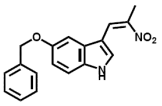
[22] Dr. Hyafil's January 1994 presentation does likewise, as well as falsely reporting that GR30040X achieved a 200nM IC50 in July 1992. (PTX 326, p. GLAX25219; PTX 140).

publicize the Elgoyhen\βCCE\GR30040X story if the true explanation was that one of Glaxo's own scientists had independently identified beta carboline as a potential inhibitor prior to Elgoyhen's publication. Indeed, it only makes sense that Glaxo would have wanted to tell the GR35273X story---if it were true---rather than the demonstrably false Elgoyhen\βCCE story. GR35273X was far more potent with an IC50 of 30 nM than the 40,000 nM Elgoyhen reported for beta CCE, the 800 nM for βCCE, and even the 200nM for GR30040X, and yet GR35273X is not even mentioned in the articles. Of course, the only reasonable explanation is that the GR35273X story is no more true than the Elgoyhen\βCCE story, which leaves Vanderbilt's 1992 Research Proposal and 8-(4-hydroxy phenylthio)-IBMX as the only logical source for the identification of GR30040X and the inclusion of the Vanderbilt Structural Features in the patented compounds.

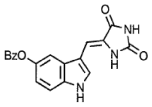
While GR30040X embodied nearly all of the elements of the Vanderbilt PDE5 inhibitor design exemplified by 8-(4-hydroxy phenylthio)-IBMX, it lacked an electron donating substituent on the aromatic ring, which in the case of GR30040X is a pyridine ring as opposed to a phenyl ring in the Vanderbilt compound.[23] (Vanderbilt Brief, p.31). Vanderbilt also proved that the very first modifications that Dr. Daugan made to the GR30040X structure included the simultaneous replacement of the pyridine with a phenyl ring and the attachment of an electron donating methoxy group at the 4 position on that phenyl ring, resulting in the far more potent GF173321X. (Vanderbilt Brief, pp.30-31). ICOS has responded that, in fact, Dr. Daugan made other earlier changes to the GR30040X structure that clearly have nothing to do with the

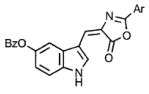
[23] Because Dr. Daugan did not join the Glaxo PDE Project team until after the compound embodying nearly all of the novel Vanderbilt Structural Features, GR30040X, had been identified using Vanderbilt's PDE5 design theory and PDE5 design, there is no need for Vanderbilt to demonstrate any further link between Drs. Corbin, Francis and Konjeti with Dr. Daugan with regard to the communication of those features.

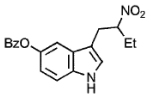
Vanderbilt Structural Features. Review of the compounds to which ICOS is referring, however, demonstrates that they do not reflect efforts to modify the GR30040X structure.

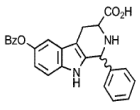
As Dr. Daugan acknowledged, his first assignment upon joining the Glaxo France PDE Project was the "nitrovinyl indole" series exemplified by GR104983X: 

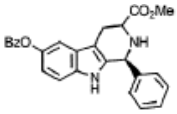
GR104983X

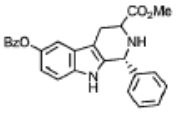
(Tr. 857:22-858:10, 915:15-916:13 (Daugan); JTX 13, pp. GLAX15985-86. 16004). Dr. Daugan's notebooks reveal that the first compounds that he synthesized were in this nitrovinyl indole series, including: 

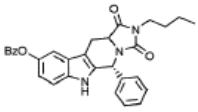
on July 2, 1992, 

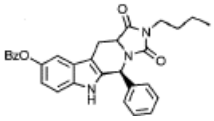
on July 6, 1992, and 

on July 24, 1992. (DTX GD, pp. Glax12565-67. Dr. Daugan then began to synthesize compounds that combined components of both the nitrovinyl indoles, such as the benzyloxy substituent,[24] and features of the series that had recently been designated "beta carbolines." Those hybrids included 

on July 30, 1992, and 

and 

on August 3, 1992 and 

and 

on August 6, 1992. (DTX GD, p. GLAX12568-570). While ICOS asserts that the compounds that the August 6, 1992 compounds reflected efforts to revise, prior to the synthesis of GF173321X, the

[24] Identified here and in Dr. Daugan's notebook as "BzO" and represented in the diagram of GR104983X as .

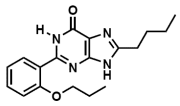
structure of GR30040X, it is clear from the these notebook pages and the minutes of the September 1992 PDE Project team that these compounds were, in fact, synthesized for the purpose of comparing components of the nitrovinyl indoles to those of the beta carbolines. (PTX 188, p. GLAX000309; PTX 189 p. VU000222)("By comparison with the nitrovinylindole series, a benzyloxy group was introduced . . ."). [25] Thus, as Vanderbilt stated, the first revisions Dr. Daugan made specifically to the structure of GR30040X included the simultaneous substitution of the pyridine with a phenyl ring and the attachment of an electron donating methoxy group at the 4 position on that phenyl ring. It is indisputable that these changes, as reflected in GF173321X, resulted in both a compound that embodied all of the Vanderbilt Structural Features as well as in greatly enhanced potency to inhibit PDE5 when compared to GR30040X, exactly as Vanderbilt's conceptions predicted. The fact that they were the first changes made to GR30040X compels the conclusion that Dr. Labaudiniere directed Dr. Daugan to make them as a direct result of Dr. Labaudiniere's knowledge of the Vanderbilt design from the 1992 Research Proposal. [26]

As further evidence of Glaxo France's efforts, through Dr. Labaudinere, to employ the Vanderbilt design in Glaxo's compounds, Vanderbilt pointed out that Nerina Dodic, another Glaxo France PDE Project chemist under Dr. Labaudiniere's supervision, made modifications,

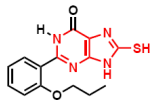
[25] Although they were synthesized more than a month prior to GF173321X, both of the August 6, 1992 compounds (GF176735X and GF176737X) were registered after and first tested a month after GF173321X. (DTX KB pp. GLAX14635-56). The fact that these compounds were not truly part of any SAR with respect to GR30040X is further demonstrated by the absence of any reference to them within the *Discovery of Tadalafil* articles. (JTX 29, 4).

[26] While it also can be confirmed with reference to the related compound data cards, ISIS prints and research notebook pages, it is clear by its registration number alone that GF173321X was the first of the variations referenced in the *Discovery of Tadalafil* articles to be synthesized. It is also clear from those articles and a number of other Glaxo documents that GF173321X was the next and crucial link in the chain leading to the completed conception of the patented compounds two months after GF173321X was tested.

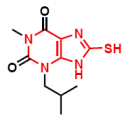
similar to those reflected in GF173321X, in the context of Glaxo France's zaprinast analog series. (PTX 222). Again, ICOS asserts that Vanderbilt has overstated the significance of those facts on grounds that Ms. Dodic had synthesized prior 8-subsituted zaprinast analogs before employing a methoxy benzyl substitution. To the contrary, ICOS simply ignores or fails to understand the significance of those facts. Indeed, ICOS concedes that earliest synthesis of any of the three compounds, and thus the first time that Glaxo France ever synthesized an 8-substituted zaprinast analog, was November 18, 1992,[27] after Dr. Hyafil's meeting with Drs. Corbin, Francis and Konjeti at Vanderbilt. The 8-substitution on that compound, consisting of a butyl group, was clearly intended to mimic the similar group appended on the right of



GR30040X: GF177222X (DTX IT, p. GLAX17173). The second compound bears the same 8-substitution as the first compound listed on Table one of Vanderbilt's 1992 Research Proposal:

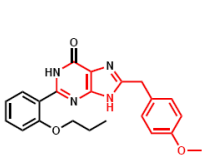


GF177704X

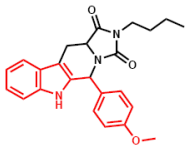


8-SH-IBMX (DTX IT, p. GLAX 17194, PTX424). And the third contains an 8-substitution that, like the substitution made to GF173321, brings it squarely within the

[27] GF177222X was registered on November 18, 1992 and tested for the first time on November 25, 1992 (DTX IT, p. GLAX 17173, DTX KB, p. GLAX14653); GF177704X was registered on November 25, 1992 and first tested on November 27, 1992 (DTX IT, p. GLAX17194, DTX KB, p. GLAX14664); and GF178534X was registered on December 4, 1992 and first tested on December 9, 1992 (DTX IT, p. GLAX17221, 17081).



GF 178534X



GF 173321X

Vanderbilt design theory: . (DTX IT, p. GLAX17221, 17081). If anything, the facts with respect to the synthesis of the two other 8-substituted zaprinast analogs identified by ICOS only lends greater weight to the evidence that, contrary to Dr. Daugan's testimony and ICOS' argument, communication and exchange of ideas between Dr. Labaudinere and the PDE Project chemists was significant and on-going.

ICOS asserts the Vanderbilt Structural Features do not make a significant contribution to the compounds claimed in Formula 1 of Claim 1 of the Patents-at-Issue. Glaxo's documents clearly show otherwise. For example, there are many Glaxo documents that demonstrate that the the aromatic ring at the "C-5" position (referred to as "R-2" in the Patents-at-Issue), consistent with the "ribose phosphate mimic" component of the Vanderbilt design, is important for PDE5 inhibition. For example, results of the June 17, 1992 testing of GR30040X analogues show that those analogs that possessed the aromatic ring significantly outperformed those that did not. (DTX IG, p. GLAX13261; DTX KB, pp. GLAX14224-26, 14228, 14229, 14232, 142283-87, 14289, 14295, 14297-99, 15420, 15462, 15480, 15487, 15488, 15495; JTX 13, pp. GLAX15995-960). Most significantly, AH14917XX, which reflects all of the components of GR30040X except for the aromatic ring, performed so poorly on the 10 μM concentration test that it never progressed to the IC50 test. (DTX KB, p. GLAX14229; PTX 140).[28] While not accurately reflecting the history GR30040X's identification, the test data presented in the *Discovery of*

[28] *Compare also* (DTX KB, pp. GLAX14607 and 14612). The addition of aromatic rings---at Dr. Labaudinere's direction---at the C-5 position on other carboline compounds also resulted in marked increases in inhibitory activity. (Tr. 895:4:-18; 924:9-14, 926:12-928:20 (Daugan); PTX 188, p. GLAX 00318, 309, 314-17; DTX AQ, p. 16103; JTX 15, p. GLAX16286-87).

Tadalafil articles and in Dr. Hyafil's January 1994 presentation also show that the inclusion of the Vanderbilt Structural Features contribute significantly to potency of the compounds for PDE5 inhibition. (JTX 29, JTX 4; PTX 326, p. GLAX25219).[29] Thus, while the extensive SAR of the C-5 position did not dislodge GF173321X as the direct successor to GR30040X as the lead compound progressing toward the patented compounds, it did confirm the importance of the Vanderbilt Structural Features to the potency of the patented compounds. As Dr. Labaudiniere testified, all of the modifications that occurred on the way to the patented compounds after the inclusion of the Vanderbilt Structural Features would have been obvious to any chemist trained in the relevant state of the art. (Vanderbilt Brief, p. 34).

Finally, ICOS goes to great lengths to discredit Dr. Francis and Corbin's discovery and communication to Glaxo of the concept that PDE5 inhibitors reflecting the Vanderbilt design could be used to treat male erectile dysfunction. However, there is no dispute that the concept was communicated to Glaxo in both the January 3, 1992 letter (JTX 41) and the 1992 Research Proposal (PTX 117), and there is no evidence in the record of the concept being discovered by Glaxo or communicated to it by another source prior to January 3, 1992. It is likewise indisputable that Dr. Daugan did not conceive such an application himself. In any event, ICOS asserts that Dr. Daugan is legitimately named as an inventor on the '329 Patent solely by virtue of his participation in the conception of the compounds claimed in the '006 Patent. Therefore, ICOS cannot deny that if Drs. Corbin, Francis, and Konjeti are found to be co-inventors of the '006 Patent compounds, they must also be added as co-inventors on the '329 Patent.

[29] *See also* JTX 15, p. GLAX16288.

ARGUMENT

The evidence at trial clearly proved[30] that Vanderbilt scientists invented a novel structure for a PDE5 inhibitor and communicated that structure to Glaxo, that Glaxo used that structure to identify a new lead compound that included that structure, and that the new lead compound lead to the conception of the compounds claimed in the Patents-at-Issue, which contain Vanderbilt's novel structure. ICOS argues that Vanderbilt nevertheless cannot prevail because (i) Vanderbilt did not conceive of any of those compounds in their entirety, and (ii) Vanderbilt did not collaborate with Dr. Daugan. ICOS is wrong on both issues. There is no requirement that Vanderbilt conceive of the entire compound in order to be a joint inventor and the record clearly establishes that the Vanderbilt scientists and Dr. Daugan were engaged in a "close and substantial" collaboration that produced the inventions.

I. There is no requirement that Vanderbilt Conceive of the Entire Compound.

ICOS continues to argue that in order to be a joint inventor Vanderbilt had to have conceived of the entire chemical compound. (See e.g. ICOS Brief at 41 ¶ 22; 42 ¶ 25; 43 ¶ 26) In support of that contention, ICOS relies entirely on a sentence from *Bd. of Educ. v. American Bioscience*, 333 F.3d 1330 (Fed. Cir. 2003). For the reasons discussed at length in Vanderbilt's opening brief, ICOS has taken that statement out of context and misapplied it. There simply is no requirement in the law that a joint inventor must conceive of the entire compound. ICOS

[30] ICOS maintains that the clear and convincing evidence standard should be applied and that the presumption that the inventor is correctly identified should be given great weight. For the reasons expressed by Judge Lourie in his concurring opinion in *Eli Lilly and Co. v. Aradigm*, 376 F.3d 1352, 1370 (Fed. Cir. 2004), and asserted by Eli Lilly in that case , the appropriate burden of proof under the facts and circumstances of this case is the preponderance of the evidence standard. Moreover, the presumption is entitled to little if any weight where the US Patent and Trademark Office did not conduct an investigation into whether the inventorship identified on the Patents-at-Issue was correct and simply accepted the representation that the identified inventor was appropriate. ICOS has stipulated that is what occurred here. (Document 133, filed December 21, 2007)

persists in this untenable position despite that fact that it concedes, as it must, that *American Bioscience* did not change the law of joint inventorship regarding chemical compounds. (ICOS Brief at 47 ¶36).

In order to be a joint inventor, the individual must have made an independent conceptual contribution to **any** element of **any** claim on the patent. *Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1997)(emphasis added). Persons may be joint inventors even though each did not make the same type or amount of contribution, or each did not make a contribution to the subject matter of every claim of the patent. 35 U.S.C. §116; *Ethicon* at 1460. One may conceive a general or imperfect outline of an entirely novel thing, which, without the conception of another developing it and giving it body, might never amount to invention; but if the **conceptions of one supplement and complement the conceptions of the other**, the result might be invention and therefore joint invention. *Rodgard Corp. v. Miner Enterprises, Inc.*, 12 U.S.P.Q.2d 1353, 1989 WL 41727 (W.D.N.Y. 1989)(emphasis added) citing *Monsanto Company v. Kamp*, 269 F.Supp. 818, 824 (D.D.C.1967).

The Federal Circuit has emphasized that Section 116's definition of joint inventorship does not require a particular level of contribution to the conception of an invention:

> This provision sets no explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor. Rather, a joint invention is simply the product of a collaboration between two or more persons working together to solve the problem addressed. *Burroughs Wellcome*, 40 F.3d at 1227, 32 USPQ2d at 1919. The determination of whether a person is a joint inventor is fact specific, and no bright-line standard will suffice in every case.

Fina Oil and Chemical Co. v. Ewen, 123 F.3d 1466, 1473 (Fed. Cir. 1997). A person is a co-inventor if he made a contribution to the conception of the claimed invention that is not insignificant in quality then that contribution is measured against the dimension of the full invention. *Eli Lilly*, 376 F.3d at 1359. As this Court has held, "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." *Medtronic Vascular, Inc. v. Adv. Cardiovascular Sys., Inc.*, No. Civ. 98-80-SLR, 2005 WL 46553 *5 (D.Del. Jan. 5, 2005).

Joint inventorship law embraces the "modern paradigm of the research and development team." *Searching for an Efficacious Joint Inventorship Standard*, 44 B.C. L. Rev. 245, 254 (2002). "[R]esearch teams, particularly in the biomedical industry, are often large in number and develop products that may take years to mature." *Id*. Through the 1984 Amendments to 35 U.S.C. § 116, the joint inventorship statute, Congress encouraged and recognized team research by **codifying the expansive definition of joint inventorship in *Monsanto v. Kamp* and lowering the bar for joint inventorship**. 1984 U.S.C.C.A.N. 5827, 5833-34 (reprinting Comm. of the Judiciary, 98th Cong., Section-By-Section Analysis of H.R. 6286, Patent Law Amendments Act of 19984, 130 Cong. Rec. 28,069 (1984)).

Contrary to ICOS' misreading of *American Bioscience,* it is clear that it is **not** necessary that the entire inventive concept should occur to each of the joint inventors. *Kimberly-Clark Corp. v. Procter & Gamble Distributing Co.,* 973 F.2d 911, 916 (Fed. Cir. 1992). A joint invention occurs when two or more persons, collaborating together, each contribute to the conception of the solution to a problem that constitutes the invention. *Id.* at 917. It is unnecessary that the joint inventor conceive of the entire invention as long as the contribution is a significant part of the invention. In *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998) the Federal Circuit stated the proposition succinctly:

> Because it is undisputed that the invention was conceived while Link and Pannu were engaged in a collaborative enterprise and it is furthermore undisputed that Pannu **conceived significant *aspects* of the invention**, Pannu is **certainly a least a co-inventor**. (emphasis added).

In this case, Vanderbilt's novel structure has been clearly shown to be a significant part of the patented compounds.

As its fallback position, ICOS argues repeatedly that what distinguishes Vanderbilt's status from that of a joint inventor is that the Vanderbilt scientists were not "aware of" the complete compound and presumably, if they had such "awareness," the Vanderbilt scientists *could* be joint inventors. (See, e.g., ICOS Brief at 42 ¶¶23, 24; 44 ¶ 32). The problem with ICOS' position is that there is absolutely no basis in the law for an "awareness" standard. There are no cases to support such a distinction and ICOS cites none. Moreover, such a construct would reward dishonesty and deceit and encourage an inventor to keep the last changes to an invention from his collaborator in order to strip him of joint inventor status. That is not the law and should not be the law. Under long established and existing law, the Vanderbilt scientists are joint inventors of the inventions in the Patents-at-Issue.

II. Vanderbilt and Daugan were engaged in a Collaboration that Produced the Inventions.

There was a six (6) year paid collaboration between Vanderbilt and Glaxo which even Glaxo described as "close" and "substantial." The evidence clearly established that Glaxo representatives repeatedly visited Vanderbilt, Dr. Corbin repeatedly visited Glaxo locations including Glaxo France, and ultimately the Vanderbilt scientists and Glaxo scientists co-wrote a book chapter on PDE inhibitor design. There was a long series of frequent correspondence and regular reports of research results and scientific records which document and corroborate this collaboration.

During the collaboration, Vanderbilt invented a novel structure and hypothesized that incorporating that structure would make the resulting inhibitors more closely resemble cGMP by adding a ribose phosphate surrogate. The Vanderbilt structure placed the surrogate at a novel

location on the molecule that Vanderbilt reasoned would allow the compound to better bind in the active site of PDE-5 and thus increase the potency of the inhibitor. Using this hypothesis, the Vanderbilt scientists conceived of a specific compound which included the specific structure. Vanderbilt tested this novel compound and the resulting compound was very potent, showing what ICOS' own expert called "impressive" increases in potency over the parent compound and over the best known inhibitor, zaprinast. Vanderbilt communicated this information to Glaxo.

While it is true that there was no personal communication between the Vanderbilt scientists and Dr. Daugan, the direct and circumstantial evidence clearly established that Vanderbilt's concepts and structure were passed to Dr. Daugan by others at Glaxo who clearly did receive them. Dr. Ross, of Glaxo in England, transmitted Vanderbilt's proposal containing these conceptions to Dr. Richard Labaudiniere, Dr. Daugan's supervisor. His covering Memorandum (PTX 121) highlighted that Vanderbilt's research would be "directed toward…4) Inhibitors of c-GMP-binding PDE **based on specific design concepts** arising from synthesized cGMP derivatives**."** (emphasis added).

It is uncontroverted that Vanderbilt's concepts and structure were received by Dr. Daugan's "boss," Dr. Richard Labaudiniere. The evidence also clearly showed that Dr. Labaudiniere directed Dr. Daugan's work. Dr. Labaudiniere gave him the lead compound that had been identified through the use of Vanderbilt's structure.[31] Daugan admitted that Dr. Labaudiniere told him what parts of the molecule or region of the molecule to modify. (Tr. 865:9-16) Dr. Labaudiniere testified that he directed the Glaxo chemists work and even told them what specific modifications to make to particular compounds. (Tr. 393:16-23)

[31] The identification of the lead compound GR30040X, which embodied nearly the entire Vanderbilt design, occurred before Dr. Daugan joined the PDE Project team at Glaxo France.

In addition, the Vanderbilt scientists had many meetings and other communications with Dr. Francois Hyafil, the head of Glaxo France and Dr. Labaudiniere's boss. As evidenced by the contemporaneous Glaxo documents, including reports and minutes of meetings, the work that Vanderbilt was doing was discussed at meetings that all researchers attended, including Dr. Daugan.

While the record does not establish that Dr. Daugan *knew* that the source of what Labaudiniere told him was Vanderbilt[32], the record nevertheless is conclusive that Dr. Daugan received Vanderbilt's conceptions. There are direct links, in the persons of Drs. Hyafil and Labaudiniere, and in the reports of meetings that Dr. Daugan attended, to connect the communication of Vanderbilt's concepts directly to Dr. Daugan.

The "close and substantial" collaboration between Vanderbilt and Daugan is more than sufficient to constitute them joint inventors. Persons may be co-inventors even though they did not physically work together or at the same time. 35 U.S.C. §116; *Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1997). All that is required is that there must be "some element of joint behavior, such as collaboration or working under common direction, **one inventor seeing a relevant report and building upon it or hearing another's suggestion at a meeting**." *Kimberly-Clark* 973 F.2d at 917 (emphasis added). All there must be, at the least, is "some quantum of collaboration or connection." *Id.*

Vanderbilt and Daugan worked together under a formal, paid, contractual collaboration between Glaxo and Vanderbilt. Both the Vanderbilt scientists and Dr. Daugan worked under Glaxo France's common direction. Daugan heard Vanderbilt's suggestions from Labaudiniere in their frequent one-on-one meetings and attended group meetings at which Vanderbilt's ideas

[32] Indeed, the record is replete with examples of Glaxo failing to attribute Vanderbilt's work to Vanderbilt.

were discussed.[33] While the Vanderbilt scientists never talked directly to Dr. Daugan, there was an "open line of communication" from Vanderbilt to Dr. Daugan "during or in temporal proximity to their inventive efforts", which is all that is required in the Federal Circuit's most recent decision on the question, *Cook Biotech, Inc. v. Acell, Inc.*, 460 F.3d 1365, 1373 (Fed. Cir. 2006), citing *Eli Lilly v. Aradigm*, 376 F.3d 1352, 1358-59 (Fed. Cir. 2004).

While the Vanderbilt scientists admittedly never heard Dr. Daugan's name during the collaboration and while Dr. Daugan, as he claims, may never have heard the names of the Vanderbilt scientists, those facts have no legal significance. Under the clearly established precedents, they were nevertheless engaged in a close collaboration in which Vanderbilt shared its conceptions with Dr. Daugan. That collaboration produced the inventions claimed in the Patents-at-Issue. Under the law of joint inventorship, Drs. Corbin, Francis and Konjeti are joint inventors and should be added as named inventors on the Patents-at-Issue.

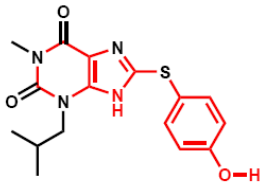
CONCLUSION

> *Clear and convincing evidence is evidence that produces an abiding conviction that the truth of a factual contention is highly probable.*[34]

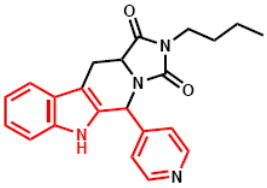
[33] Although ICOS repeatedly cites *Beall v. Ormsby*, 154 F.2d 663 (C.C.P.A. 1946) for the proposition that communication to a company is not sufficient to establish communication to an employee inventor (See, e.g., ICOS Brief at 48 ¶39), that case in inapposite here. In *Beall*, it was suggested that the putative inventor communicated his idea to someone in the corporation and there was no evidence that it got to the inventor. Here there is a clear and proven communication of Vanderbilt's conceptions through Drs. Hyafil and Labaudiniere directly to Dr. Daugan.

[34] Uniform Jury Instructions for Patent Cases in the United States District Court for the District of Delaware, Instruction 1.3 Burden of Proof (Hon. Roderick R. McKelvie, U.S.D.J ET AL., March 1993).

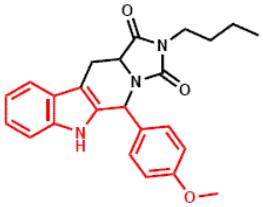
As set forth above and in Vanderbilt's opening brief, the record before the Court contains clear and convincing evidence that that Drs. Corbin, Francis and Konjeti conceived of



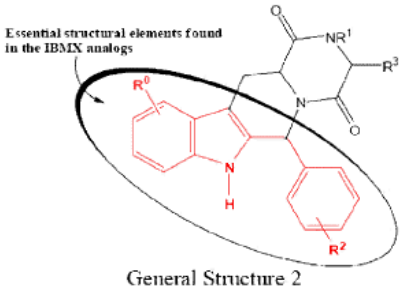
8-(4-OH-PT)-IBMX, which was communicated to Glaxo and led to



GR 30040X and



GF 173321X, and ultimately



General Structure 2

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

Therefore, the Court should enter an order directing the Director of the United States Patent and Trademark Office to correct U.S. Patents 5,859,006 and 6,140,329 by adding Jackie D. Corbin, Ph.D., Sharron H. Francis, Ph.D. and Sekhar R. Konjeti, Ph.D. as joint inventors on each of those patents.

Respectfully submitted,

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