IN THE
UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VANDERBILT UNIVERSITY

Plaintiff

v.

ICOS CORPORATION, et al.

Defendant

Civil Action No: 05-506-SLR

PLAINTIFF, VANDERBILT UNIVERSITY'S CORRECTED POST-TRIAL BRIEF

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INTRODUCTION

The evidence presented at trial clearly and convincingly demonstrated that Vanderbilt's scientists invented a novel structure for a PDE5 inhibitor. The evidence clearly and convincingly demonstrated that Vanderbilt communicated that structure, the theory behind it, and impressive test results in a research proposal sent to the head of Glaxo's Cardiovascular Research Management Committee who, after personally flying from England to Tennessee to hear more about Vanderbilt's ideas, forwarded the research proposal to the Glaxo scientists working on PDE5 inhibitors. The evidence clearly and convincingly demonstrated that within two weeks after receiving Vanderbilt's ideas, Glaxo identified a "new" PDE5 inhibitor, of which the Vanderbilt structure, which had never before appeared in any inhibitors tested by Glaxo, comprised a significant part. Finally, the evidence clearly and convincingly demonstrated that the new inhibitor lead to invention of the PDE5 inhibitor compounds that are claimed in two U.S. patents now held by Defendant ICOS, and that the Vanderbilt structure comprises a significant part of those claimed compounds. Such evidence clearly and convincingly establishes that Vanderbilt's scientists made significant contributions to the conception of the claimed compounds and that they should have been included as joint inventors on the patents.

Despite the fact that these events occurred in the midst of a well-documented close and substantial 6 year collaboration between Vanderbilt and Glaxo, during which Glaxo had already clearly appropriated Vanderbilt's compounds and compound design theories, ICOS would have the Court conclude that it is simply a coincidence that Vanderbilt's novel concepts and structures are a prominent component of the patented compounds, and that, despite the fact that they were communicated by internationally-recognized experts in the field, through the head of Glaxo's Cardiovascular Research Management Committee, to Glaxo scientists anxiously looking for new

leads, Vanderbilt's concepts and structures were completely ignored. In that effort to convince the Court to depart from common sense and accept those conclusions, ICOS posits two alternative explanations, one of which is chronologically impossible, both of which are completely belied by the documents created at and immediately after the time Glaxo identified the "new" inhibitor possessing the Vanderbilt design, and neither of which are persuasive. ICOS further asserts that even if the Court acknowledges the contribution of the Vanderbilt scientists in the conception of the patented compounds, they are not joint inventors because Glaxo did not apprise their Vanderbilt collaborators of what Glaxo was doing with the novel Vanderbilt structure. Thankfully that premise, which would only encourage collaborators to deceive each other, is not consistent with the law of inventorship.

For these reasons, which are more fully set forth below, Vanderbilt submits that the Court should enter judgment in its favor and issue an order directing the Director of the United States Patent and Trademark Office to correct the Patents-at-Issue to add the Vanderbilt scientists as joint inventors.

STATEMENT OF FACTS

Parties

Vanderbilt University ("Vanderbilt") is a Tennessee not-for-profit corporation with its principal place of business in Nashville, Tennessee. (Joint Pretrial Order ("JPTO"), Exh. 1, p.1, ¶ 1). Vanderbilt brought this action pursuant to 35 U.S.C. § 256, requesting that the Court issue an order directing the United States Patent and Trademark Office to correct U.S. Patent Nos. 5,859,006 ("the '006 Patent") (JTX 1) and 6,140,329 ("the '329 Patent") (JTX 2) (collectively, "the Patents-at-Issue") by adding the names of three Vanderbilt professors, Jackie D. Corbin, Ph.D. ("Dr. Corbin"), Sharron H. Francis, Ph.D. ("Dr. Francis") and Sekhar R. Konjeti, Ph.D.

("Dr. Konjeti") as inventors on those patents.[1] Vanderbilt named as defendant ICOS Corporation ("ICOS"), a Delaware corporation, which, by assignment, is the holder of the Patents-at-Issue. (JPTO, Exh. 1 p. 1, ¶ 5)[2]

Nature of Compounds Claimed in Patents

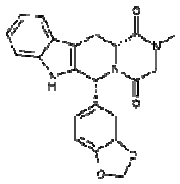
The '006 Patent claims chemical compounds described as being "potent and selective inhibitors of cGMP specific PDE." The '329 Patent claims compositions and methods of treating erectile dysfunction in a male animal involving the administration of at least one of the compounds claimed in the '006 Patent. For the purposes of this action the parties stipulated that claims 1-4, 6-8, 10, 12 and 13 of the '006 patent and claims 1-3, 5-12, and 15-21 of the '329 patent encompass at least the compound known as Tadalafil, which has at least the following chemical names:

A. pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-, (6R-12ar)-;

B. (6R,12ar)-2,3,6,7,12,12a-hexahydro-2-methyl-6-[3,4-(methylenedioxy)phenyl] pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione; and

C. (6R-trans)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione

and has the following structural formula:

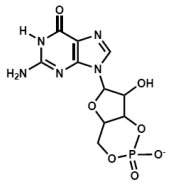


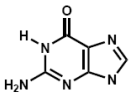
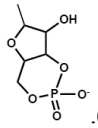
[1] Drs. Corbin, Francis, and Konjeti are, and have been at all times relevant to this case, employees of Vanderbilt University, and consistent with the terms of their employment have assigned all rights that they may have in the Patents-at-Issue to Vanderbilt. (Tr. 240:4-241:19 (Corbin); 709:13-710:18 (Konjeti); 799:24-800:19 (Francis); PTX 4, 6, 7, 8).

[2] During the course of the suit ICOS was acquired by the Eli Lilly Company and its principal place of business shifted to Indianapolis, Indiana. (JPTO Exh. 1, p. 1, ¶ 3).

(JPTO Exh. 1, pp. 2-3 , ¶¶9-10).

Guanosine 3':5'-cyclic monophosphate, or cGMP, is a cyclic nucleotide that has the following structural formula:



It consists of two primary parts, or moieties; a guanine moiety  and a ribose phosphate moiety:  .(Tr. 199:9-18 (Corbin); PTX 14).

cGMP is found in smooth muscle tissues where it is synthesized by an enzyme known as guanylyl cyclase. (Tr. 108:1-4 (Corbin); 1083:5-22 (Cote); PTX 9, DTX SY). cGMP specific PDE, now known as PDE5, is a phosphodiesterase enzyme found in smooth muscle cells that binds to and breaks down GMP. (Tr. 108:5-8 (Corbin); 1084:15-1089:4 (Cote); PTX 9, DTX SY). The introduction of a "first messenger" such as nitric oxide into smooth muscle cells stimulates the guanylyl cyclase and speeds up the synthesis of cGMP. When the level of cGMP in a smooth muscle cell exceeds that which can be immediately hydrolyzed by the PDE5, cGMP begins to bind with and activate a cGMP-dependent protein kinase ("PKG"), which, through the phosphorylation of other proteins, reduces the level of calcium in the cell. The lowering of the calcium level results in the relaxation of the smooth muscle cell. (Tr. 108:16-23 (Corbin), 1083:12-24 (Cote); PTX 9, DTX SY). PDE5 inhibitors, such as the compounds claimed in the

'006 Patent, potentiate smooth muscle relaxation by binding to PDE5, thereby preventing PDE5 from breaking down cGMP. (Tr. 1086:3-11(Cote); PTX 9, DTX SY).

Smooth muscle tissue is present throughout the human body and, through the process of relaxation and contraction, serves an important role in a number of physiological systems, including the digestive system, the respiratory system, and the vascular system. (Tr. 103:6-108:23 (Corbin)). Vascular smooth muscle is found in the walls of arteries and other blood vessels. When vascular smooth muscle tissue relaxes, the channel through which blood flows (the lumen) dilates, thus allowing increased blood flow. (Tr. 108:16-23 (Corbin)).

1988 Research Proposal and 1989 Research Agreement

Dr. Corbin is, and since 1971, has been a professor of molecular physiology in the Department of Molecular Physiology and Biophysics at Vanderbilt University School of Medicine. (Tr. 101:21-102:6 (Corbin); PTX 1).[3] He received his Ph.D. from Vanderbilt in 1968. Upon returning to Vanderbilt in 1971 he focused his research on the molecular aspects of smooth muscle relaxation and, in particular, the role of cGMP in that process. Prior to that time much of the focus in the field had been on the role of adenosine 3',5'-cyclic monophosphate, known as cAMP, and the cAMP-dependent protein kinase, known as PKA. (Tr.112:19-114:19 (Corbin)). Dr. Francis is, and since 1975, has been a professor of molecular physiology in the Department of Molecular Physiology and Biophysics at Vanderbilt University School of Medicine. (Tr. 759:4-74:3; PTX 35, p. VM-000592).[4] Since becoming a professor her work has focused on the

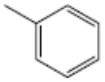
[3] Dr. Corbin became an assistant professor in 1971, was promoted to associate professor in 1975, and became a full professor in 1980. (PTX 1).

[4] Dr. Francis became an assistant professor in 1975, was promoted to research associate professor in 1990, and became a full research professor in 1996. (Tr. 759:4-761:3 (Francis); PTX 35, page VM-000592).

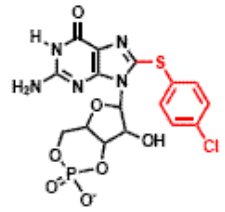
study of cGMP, and its role in the process of smooth muscle relaxation. (Tr. 760:10-761:3 (Francis)).

In the late 1970's Drs. Corbin and Francis collaborated in identifying and studying cellular proteins that bind cGMP and bring about its physiological effects. In the course of this work they discovered that there was another cGMP-binding protein in smooth muscle cells unrelated to PKG. They determined that this protein was a cGMP-specific phosphodiesterase, which they named "cGMP-binding protein PDE," and which has since become known as PDE5 (Tr. 115:16-117:6 (Corbin); 768:16-772:6 (Francis); PTX 25, PTX 420, p. 118).

Drs. Corbin and Francis continued to collaborate with each other and other colleagues at Vanderbilt in the study of smooth muscle relaxation by, among other things, developing cGMP analogs by appending groups of atoms at various locations on the cGMP molecule. They tested these analogs to see which modifications increased potency in stimulating PKG or PKA activity. They also tested the cGMP analogs with living smooth muscle tissue from guinea pig trachea and pig coronary arteries to determine which modifications increased potency to relax smooth muscle. Drs. Corbin and Francis discovered that analogs that were the most potent in stimulating PKG were also the most potent in promoting relaxation of live tissue, with no correlation between stimulation of PKA and relaxation. This strongly suggested that cGMP and PKG were more important to smooth muscle relaxation than cAMP and PKA. Some cGMP analogs designed by Drs. Corbin and Francis included attachment of a relatively bulky and hydrophobic group of atoms, in the form of a six-membered aromatic phenyl ring



at the "8-position" on the guanine moiety of cGMP. Drs. Corbin and Francis discovered that cGMP analogs with such bulky, hydrophobic substitutions at the 8-position tended to resist hydrolysis by PDE. One such analog was 8-(4-chloro-phenylthio)-cGMP:



8-(4-chloro-phenylthio)-cGMP

(PTX 51, p.15570; Tr. 154:2-155:9 (Corbin); 651:22-652:10 (Konjeti); PTX 35, p.VM-000601). Their work and their discoveries were reflected in an article entitled *Relaxation of Vascular and Tracheal Smooth Muscle by Cyclic Nucleotide Analogs That Preferentially Activate Purified cGMP-Dependent Protein Kinase* that was received by the journal Molecular Phamacology on December 5, 1987 and accepted for publication on July 11, 1988. (Tr. 117:7-118:6, 121:13-122:4 (Corbin); PTX 13).

Following submission of their article to Molecular Pharmacology, Drs. Corbin and Francis continued to work on, among other things, the study of PKG and its relationship to smooth muscle relaxation. Among other things, they discovered that there were two distinct forms of PKG, Type Iα and Type Iβ, that different analogs stimulated each form with varying degrees of potency, and that a strong correlation existed between stimulation of Type Iα and smooth muscle relaxation. (Tr. 133:4-134:10 (Corbin); 774:14-24 (Francis); PTX 35, pp. VM-000598-601).

In 1988, Glaxo Inc. published advertisements seeking applications for a "Cardiovascular Discovery Grant" program through which it proposed to make research grants to various

institutions involved in research relating to prevention and treatment of cardiovascular disease. (Tr. 123:1-126:1 (Corbin); 773:12-776:24 (Francis)). Because they felt their work in the area of smooth muscle relaxation, including vascular smooth muscle relaxation, fell squarely within the ambit of the program, Drs. Francis and Corbin decided that this represented a great opportunity. (Tr. 773:12-774:13 (Francis)). Together they prepared an application seeking a grant to fund their continued research in the relaxation of vascular smooth muscle by cGMP analogs, which they submitted to Glaxo in December 1988. (the "1988 Research Proposal") (Tr. 123:10-134:10 (Corbin); 774:14-777:24 (Francis); PTX 32, PTX 35, p. VM-000589 *et seq.*). Along with the application they submitted their biographical information, an abstract of the research proposal and the research proposal itself. (Tr. 126:3-134:10 (Corbin); PTX 35, p. VM-000589 *et seq.*).

A key feature of the 1988 Research Proposal was the design of new cGMP analogs, based on structures of the analogs that the Vanderbilt lab had already synthesized and a model of the cGMP binding sites on PKG. The latter had been developed at Vanderbilt using a Vax 11/780 computer and a graphic display system and was based on the x-ray crystallographic structure of a bacterial cAMP-binding protein known as "CAP." That model suggested the existence of space that could accommodate large or bulky groups of atoms attached to the 8-position on the guanine moiety of cGMP. The model also predicted the existence of a hydrophobic phenyl group in the same area. As Drs. Corbin and Francis understood that hydrophobic groups tended to bind to each other, this suggested to them that attachment of a phenyl group (which would be both relatively bulky and hydrophobic) at the 8 position on the cGMP molecule would result in an analog that bound more tightly to PKG. (Tr. 126:3-134:10, 149:25-150:10 (Corbin); PTX 35, pp. VM-000596, 599-600). The 1988 Research Proposal included a list of new cGMP analogs that Vanderbilt had already synthesized, including 8-pCl-phenyl-S-cGMP (Tr. 133:4-134:10

(Corbin); 648:6-655:13 (Konjeti); PTX 35, p. VM-000601), as well as other 8-substituted compounds that Vanderbilt proposed to synthesize using its design model, such as 1-naphthyl-S-cGMP. (Tr. 652:24-655:13 (Konjeti); PTX 35, p.VM-000602).

By letter dated March 4, 1989, Dr. Don F. Kirksey of Cardiovascular Development for Glaxo Inc. in Research Triangle Park, North Carolina notified Dr. Corbin that he had been selected as one of twenty recipients of the Glaxo Cardiovascular Discovery Grants. (Tr. 125:12-21 (Corbin); PTX 34).[5] Subsequently Glaxo representatives visited the Vanderbilt lab and met with all who would be involved in the project. (Tr. 125:12-21, 135:3-10 (Corbin); PTX 34). Vanderbilt and Glaxo executed a Research Agreement in June and July 1989 (the "1989 Research Agreement"). (PTX 35, p. VM-000567, 586-587).

On November 1, 1989, Dr. Corbin flew to North Carolina to present the Vanderbilt lab's work to a group of senior Glaxo scientists including Dr. Kirksey, the Director of Glaxo's Discovery Program, Dr. Crist Frangakis, Head of the Biochemical Pharmacology Section, Joel Shaffer, Head of the Cardiovascular Pharmacology Section, Jeff Wiseman, Head of the Enzymology Department, and Dr. Thomas Rimele. (Tr. 136:1-139:8 (Corbin); PTX 37, 41). Dr. Francis assisted Dr. Corbin in the preparation of the presentation. (Tr. 776:25-778:4 (Francis)).

While Dr. Corbin and Dr. Francis were each devoting 25% of their time to the research involving the design, synthesis and testing of cGMP analogs under their research agreement with Glaxo, they continued to do research on the cGMP-binding protein phosphodiesterase (PDE5) that they had earlier discovered. They successfully purified PDE5 from cow lung and determined that PDE5, like PKG, had two regulatory cGMP-binding sites, but, unlike PKG,

[5] Although Dr. Corbin was identified in the 1988 Research Proposal (and the resulting Research Agreement) as the "principal investigator" the proposal made it clear that Drs. Corbin and Francis would be equally responsible for overseeing the research and would devote an equal amount of time to the project. (Tr. 126:14-127:9 (Corbin); PTX 35, pp. VM-000567, 587, 607).

PDE5 also had a catalytic site where cGMP was broken down. Results of this work were published as a chapter in a book, *Cyclic Nucleotide Phosphodiesterases: Structure, Regulation and Drug Action*, and in articles in the Journal of Biological Chemistry. (Tr. 141:7-143:25 (Corbin); 779:1-4 (Francis); PTX 420, PTX 43).

In January 1990 Sekhar R. Konjeti, Ph.D., who had received his doctorate in synthetic organic chemistry from Gulbarga University in India, joined the Vanderbilt lab as a postdoctoral fellow to collaborate with Drs. Corbin and Francis in the design, synthesis and testing of cGMP analogs under the 1989 Research Agreement with Glaxo. (Tr. 645:8-648:23(Konjeti)); 145:18-146:22 (Corbin); PTX 40). To familiarize himself with the project and the role of cGMP in smooth muscle relaxation Dr. Konjeti reviewed many research papers that Drs. Corbin and Francis had published, as well as the 1988 Research Proposal. (Tr. 647:23-648:23 (Konjeti)).

At Dr. Kirksey's invitation, Dr. Corbin attended a "Cardiovascular Discovery Conference" in Tucson, Arizona from March 22 – 24, 1990. (Tr. 134:19-135:16 (Corbin); PTX 36) where he met Dr. Jeff Leighton, Vice President for Pharmacology at Glaxo, Dr. James Chubb, Director of Business Opportunities, Dr. Ross Johnson, Vice President for Chemistry, and Dr. Paul Domanico, a senior Glaxo scientist. Also present were Drs. Kirksey, Shaffer, Rimele and Wiseman, whom Dr. Corbin had met during his visit to Glaxo in November 1989. (Tr. 138:5-24 (Corbin); PTX 41). At that conference in Arizona Dr. Corbin met with Drs. Kirksey, Leighton, Rimele and Domainco from Glaxo, and Dr. Joseph Beavo from the University of Washington ("UW"), to discuss a potential collaboration between the Vanderbilt and UW labs to determine the DNA sequence for and ultimately clone PDE5. This was summarized by Dr. Corbin in a letter to Dr. Kirksey dated March 30, 1990 (Tr. 139:11-23 (Corbin); PTX 42). A

PDE5 clone could be used to produce large quantities of PDE5 for testing. At that time PDE5 was derived, painstakingly, from rat and cow lung. (Tr. 139:24-140:24 (Corbin)).

Following the 1990 Glaxo Discovery Conference Drs. Corbin, Francis and Konjeti submitted a progress report to Glaxo on work that they had performed under the 1989 Research Agreement. The report listed new cGMP analogs that Vanderbilt had synthesized and tested, including 8-napthylthio-cGMP, 8-o-Br-PT-cGMP, and 8-p-OH-PT-cGMP. (Tr. 145:14-17 (Corbin); 650:14-16 (Konjeti); PTX 44). On October 23, 1990 Dr. Kirksey wrote to Dr. Corbin that administration of Glaxo's cardiovascular research programs was being transferred from Glaxo Inc. in North Carolina to Glaxo Group Research in the United Kingdom and requested an updated progress report. (Tr. 146:24-25, 147:1-12 (Corbin); PTX 45, PTX 46).

Under the research agreement Glaxo reserved the right to delay publication and dissemination of the results of Vanderbilt's work relating to the 1989 Research Agreement, if Glaxo believed that such publication might jeopardize its plans to seek patent protection for inventions related to that work. (PTX 35, pp. VM-000577-78). In the fall of 1990, Vanderbilt sought permission to publish the results of its work with cGMP analogs at a Federation of American Societies for Experimental Biology ("FASEB") conference scheduled to be held in 1991. Those results included Vanderbilt's discovery that the potency of the cGMP analogs with derivatized phenylthio groups attached at the 8-position was enhanced by attachment of electron donating groups, such as hydroxy (OH), amino (NH_2) and methoxy (OCH_3) to the phenyl ring. These results were highly significant to Vanderbilt because it validated its cGMP design model. Nonetheless, Vanderbilt was required by Glaxo to withdraw the abstract. (Tr. 148:10-150:12 (Corbin); PTX 47). In 1991 Dr. Corbin requested blanket approval to allow Vanderbilt to

provide samples of the compounds Vanderbilt had developed to third parties. Glaxo denied that request. (Tr. 173:14-24, 174:8- 175-6 (Corbin); PTX 81; JTX 43).

In January 1991 Dr. Kirksey wrote to Dr. Corbin that Glaxo, Inc. (US) and Glaxo Group Research (UK) were looking forward to meeting with him to discuss the progress of Vanderbilt's research. (PTX 49). On March 18, 1991 Dr. Corbin attended a Glaxo Discovery Conference in Pittsboro, North Carolina where he was one of 4 of the 20 Discovery Grant recipients asked to give a presentation.[6] While there he met Dr. Barry C. Ross and Dr. Michael Drew from Glaxo Group Research. (Tr. 151:7-25, 152:1-6 (Corbin); PTX 53).

On the same day that Dr. Corbin presented the results of his research to Drs. Ross and Kirksey, Dr. Rimele of Glaxo Inc. gave Dr. Ross, Dr. Leighton (Vice President for Pharmacology), and Dr. Johnson (Vice President for Chemistry) a status report describing the history and results of Glaxo Inc.'s research in the area of smooth muscle relaxation. (Tr. 152:8-18 (Corbin); (PTX 51). The report included a timeline showing that in March 1990 Glaxo Inc. proposed to the Glaxo Cardiovascular Research Management Committee ("RMC") that Glaxo Inc. study cGMP analogs, and that Glaxo began to synthesize cGMP analogs in April 1990. (p. GLAX15563-4). Dr. Rimele's report also included copies of several status reports corresponding to the timeline. The status report for April 1990 shows that Glaxo took the cGMP analog design model from Vanderbilt's 1988 Research Proposal and employed it in "designing" its own "new" cGMP analogs. (Tr. 152:23-153:23 (Corbin); PTX 51, pp. GLAX15594, 15596; PTX 35, p. VM-000600). Indeed, one of the first "new" cGMP analogs Glaxo synthesized using Vanderbilt's design was 8-(4-chloro-phenylthio)-cGMP, which Glaxo designated as compound GI 118611A, and which was listed on the Table 1 of compounds Vanderbilt had already

[6] Dr. Francis assisted Dr. Corbin in the preparation of the presentation (Tr. 779:15-780:5 (Francis)).

synthesized and tested when it submitted the 1988 Research Proposal. (Tr. 154:2-155:9 (Corbin); 651:22-652:10 (Konjeti); PTX 51, p. 15596, 15570; PTX 35, p. VM-000601). Five (5) of the "new" cGMP analogs Glaxo "designed" using Vanderbilt's design model[7] had been identified for Glaxo by Vanderbilt in either the 1988 Research Agreement or in the 1990 Progress Report, including the two most potent cGMP analogs Glaxo succeeded in synthesizing. (Tr. 651:17-655:13 (Konjeti); PTX 51, pp. 15570, 15571, 15621; PTX 35, pp. VM-000600, 602; PTX 44). Glaxo's own lawyer confirmed that at least three of those Vanderbilt compounds, which Glaxo "re-created" using Vanderbilt's design model, were novel as compared to the published state of the art as of April 1991. (Tr. 162:3-20 (Corbin); 655:14-657:6, 657:18-658:9 (Konjeti); PTX 55, PTX 57).

No one at Glaxo ever advised Dr. Corbin or anyone else at Vanderbilt that Glaxo had co-opted Vanderbilt's cGMP analog design or Vanderbilt's cGMP analogs. No one from Vanderbilt ever had any direct contact with the Glaxo chemists who were responsible for synthesizing Vanderbilt's cGMP analogs at Glaxo. (Tr. 155:10-24 (Corbin); 654:23-655:13, 657:13-17 (Konjeti)).

Glaxo France's PDE Project

Dr. Rimele's March 18, 1991 status report to Dr. Ross also detailed Glaxo's efforts, beginning in April 1990, to study PDE5 inhibitors. The timeline and monthly status reports reflect the fact that those efforts focused on the study of zaprinast and modifications to zaprinast, and later expanded to the study of compounds termed "imidazoles." (PTX 51). Shortly after Dr. Rimele's report Glaxo took steps to shift its study of PDE5 inhibitors from North Carolina to a research facility in France ("Glaxo France"). In June 1991 Dr. Jorge Kirilovsky, a biochemist

[7] Dr. Konjeti identified these as bearing Glaxo registration numbers GI 118611A, GI 120446A, GI 118815A, GI 119889A, and GI 120547A. (Tr. 651:17-654:9 (Konjeti)).

and enzymologist with Glaxo France, traveled to North Carolina for three days of meetings with the Glaxo Inc. scientists, including Drs. Rimele and Domanico (both of whom had direct dealings with Dr. Corbin) in order to take advantage of the work that Glaxo had already done with PDE inhibitors. (Tr. 474:7-19; 475:5-9 (Grondin); PTX 58, PTX 58A).

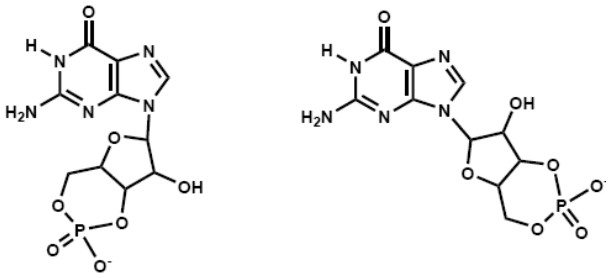
At the time the Glaxo France PDE Project began, Glaxo France had no PDE5 inhibitors to test and no means of testing them for PDE5 inhibition. Following his meetings in North Carolina Dr. Kirilovsky requested that Glaxo Inc. send fifty-nine (59) compounds to Glaxo France. (Tr. 474:20-475:1, 20-25, 478:12-19 (Grondin); PTX 58, p. GLAX15735, 15739-42; PTX 58A, PTX60, PTX61, PTX 62). Dr. Kirilovsky hired Dr. Pascal Grondin, a biochemist, as the first member of the Glaxo France PDE Project Team. (Tr. 473:7-15, 474:1-4 (Grondin)). Dr. Grondin was given the task of maintaining the central file of documents for the PDE Project, developing a process to purify PDE5, and developing a process or assay for testing compounds for potency in inhibiting PDE5. (Tr. 479:2-9, 483:7, 25-484:11 (Grondin); PTX 61, p. GLAX00488; PTX 62, p.GLAX00488; JTX 6; PTX 69; JTX 7; PTX 77). Dr. Grondin did not succeed in creating a PDE5 assay until October 1991 and Glaxo France did not test a single compound for PDE5 inhibition until October 18, 1991. (Tr. 483:7, 25-484:11 (Grondin); JTX 7; PTX 77; PTX 79).

Vanderbilt's Design of a New PDE5 Inhibitor

At about the same time the 5 month old Glaxo France PDE Project team was testing its first compound for PDE5 inhibition, Drs. Corbin, Francis and Konjeti were using their combined decades of experience with PDE5 and smooth muscle relaxation to develop a rational design of a novel PDE5 inhibitor. (Tr.647:21-648:5 (Konjeti)).

Several weeks after his meeting with Dr. Ross and other Glaxo scientists in North Carolina, Dr. Corbin received a letter from Dr. M. W. Elves, Director of Glaxo Group Research's External Scientific Affairs Division in the United Kingdom. In his letter, copies of which were sent to Drs. Ross and Kirksey, Dr. Elves explained that responsibility for oversight of the Vanderbilt/Glaxo collaboration had been shifted to Glaxo Group Research ("GGR") and specifically to its CVS Research Management Committee headed by Dr. Ross. Dr. Elves further explained that "[w]e consider your work to be very close to our own project interests and so we **would like to develop as close a collaboration with you as geography will allow** for the remaining period of the grant.." (Tr. 167:6-18 (Corbin); PTX 59A)(Emphasis supplied). Dr. Corbin responded that he was glad that Glaxo was interested in Vanderbilt's work and made it clear that Vanderbilt was interested in a continuation of the Glaxo/Vanderbilt collaboration beyond the expiration of the 1989 Research Agreement. (Tr. 171:8-15 (Corbin); PTX 71).

The Vanderbilt lab's study of cGMP analogs under the 1989 Research Agreement had been proceeding and had led to additional new discoveries and insights, many of which were reflected in a manuscript that Drs. Corbin, Francis and Konjeti had prepared for publication and provided to Glaxo for approval. (Tr. 162:22-163:8 (Corbin), 657:7-12 (Konjeti); PTX 56. Among these was the apparent preference of the PKG binding site for cGMP to be in the "syn" position, with the guanine and ribose phosphate moieties aligned one above the other, as opposed to the "anti" position in which the two moieties are turned away from each other:



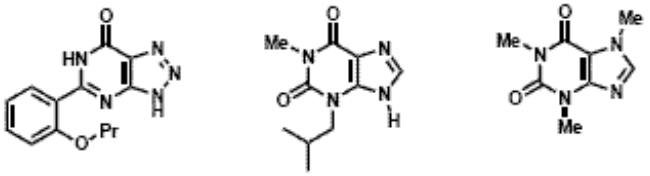
Syn position Anti position

(Tr. 787:11-788:19 (Francis)). Drs. Corbin, Francis and Konjeti theorized that one of the reasons that cGMP analogs with bulky phenyl groups appended at the 8-position were more potent at stimulating PKG was that such groups effectively prevented the ribose phosphate moiety from rotating out of the syn position, so that that the ribose phosphate more consistently bound to the PKG binding pocket. At the same time, such 8-substituted cGMP analogs proved to be very resistant to breakdown by PDE5. This, they surmised, was the result of the fact that the binding site on PDE5 preferred cGMP to be in the anti position. (Tr. 163: 9-165:1 (Corbin); 787:11-788:25, 789:25-791:15 (Francis); PTX 56 at p. VC-000146).

While Drs. Corbin, Francis and Konjeti believed that they had not yet achieved all of the discoveries that could advance the state of the art relating to the study of smooth muscle relaxation through the study of cGMP analogs, they recognized that, in order to make an extended collaboration attractive to Glaxo, they should consider proposing a new or additional area of study. Moreover, during their informal discussions with Glaxo scientists had told Dr. Corbin that because cGMP analogs would break down in the digestive system before reaching targeted smooth muscle cells, they were not good candidates for orally-administered drugs. They also encouraged Dr. Corbin to consider the development of PDE5 inhibitors. For these reasons, as well as the fact that they had already engaged in significant study of PDE5, its binding sites, and PDE5 inhibitors, Drs. Corbin, Francis and Konjeti decided to focus their energies on

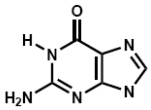
developing a rational design theory for PDE5 inhibitors as they had done for cGMP analogs. (Tr. 171:8-172:20, 178:17-179:23 (Corbin); 662:14-663:11 (Konjeti); PTX71; PTX 106).

Drs. Corbin, Francis and Konjeti began the process of designing a new PDE5 inhibitor by looking at known inhibitors, such as zaprinast, 3-isobutyl-1-methylxanthine ("IBMX"), and caffeine:



Zaprinast IBMX Caffeine

(PTX 20; PTX 21; PTX 51, p. GLAX15632). They observed that each of those inhibitors resembled the guanine moiety of the cGMP molecule, which is built on a scaffold consisting of a 6-member ring fused to a 5-member ring:



However, the existing inhibitors did not contain any structure that could bind to PDE5 in the area where cGMP's ribose phosphate moiety would ordinarily be in contact with the PDE5 catalytic site. Using their knowledge of the PDE5 catalytic site, Drs. Corbin, Francis and Konjeti theorized that existing inhibitors would bind more tightly to PDE5, and thereby more potently inhibit PDE5 from breaking down cGMP, if one attached to those inhibitors groups of atoms that would be in a position to bind to PDE5 at that same location as the ribose phosphate of cGMP. (Tr. 181:9-183:12 (Corbin); 789:25-790:11 (Francis)).

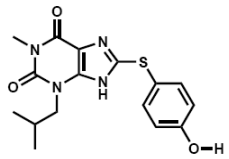
In their work with cGMP analogs Drs. Corbin, Francis and Konjeti had demonstrated that hydrophobic groups of atoms, such as a phenyl ring, with additional electron-donating groups

appended to the ring, appeared to bind well to binding sites on PKG in the vicinity of the cGMP ribose phosphate moiety. (Tr. 148:10-150:12 (Corbin); PTX 47). Because they believed that there may be some common genetic history for PKG and PDE5, they theorized that such groups might also bind well to the catalytic site on PDE5. (Tr. 789:25-794:11 (Francis); 663:17-664:1(Konjeti)).

The ribose phosphate moiety is attached to the guanine moiety of cGMP at what is commonly regarded, using a standard numbering system, to be the "9-position" on its fused 6 and 5 member ring scaffold. (Tr. 191:7-10 (Corbin)). To many chemists it might seem obvious that one would want to attach a group of atoms intended to mimic the binding role of the ribose phosphate moiety to the corresponding position on fused 6 and 5 member ring scaffold of inhibitors. (Tr. 1176:17-1177:6 (Rafferty)). However, because of their years of work with PDE5, Drs. Corbin, Francis and Konjeti believed that catalytic site on PDE5 bound most tightly to the ribose phosphate moiety of cGMP when cGMP was in the anti conformation, and less tightly, and perhaps not at all, when cGMP was in the syn conformation. They knew that a group of atoms attached in the 9-position would be able to swing freely from the anti position into the syn position, as does the ribose phosphate moiety on cGMP. A group of atoms attached at the 8-position, however, would not be able to occupy the same area as the ribose phosphate on cGMP in the syn position. For these reasons the Vanderbilt Inventors theorized that attaching the ribose phosphate mimic to the 8 position on an existing inhibitor would make it a more potent inhibitor of PDE5. (Tr. 193:18-194:23 (Corbin); 664:2-12, 665:17-667:18 (Konjeti)).

Drs. Corbin, Francis and Konjeti decided to test their PDE5 inhibitor design theory on IBMX, a known inhibitor of PDE 5, because it was readily available and it could be easily modified by adding groups of atoms at its 8-position. (Tr. 185:4-17 (Corbin); 785:25-786:21

(Francis); 663:12-16 (Konjeti)). Consistent with their design, they decided to attach a phenyl ring to the 8-position of IBMX, and an electron-donating hydroxy group at the 4 position of that phenyl ring. The result was 8-(4-hydroxy phenylthio)-IBMX:[8]



(Tr. 189:14-190:5 (Corbin); 663:17-664:1, 668:7-13 (Konjeti); PTX 88, p. VK-001737, 57-62; PTX 117, p. VC-00251; PTX 424).

Test results on 8-(4-hydroxy phenylthio)-IBMX demonstrated that Vanderbilt's PDE5 inhibitor design theory was as much or more of a success than its cGMP analog design theory. Addition of the hydroxyl-phenyl resulted in an inhibitor that was 160 times more potent in inhibiting PDE5 than the parent compound, IBMX, without the modifications, and six (6) times more potent than zaprinast, which at the time was the most potent known inhibitor of PDE5. (Tr.184:19-24 (Corbin); JTX 41).

Communication of Vanderbilt's New PDE5 Inhibitor Design to Glaxo

Armed with a new PDE5 inhibitor design and impressive test results, Dr. Corbin had a telephone conversation with Dr. Ross during the last week of December 1991 about the possibility of extending the Glaxo/Vanderbilt collaboration. Based upon what Dr. Corbin reported, Dr. Ross suggested that Vanderbilt put a description of the new research proposal in a letter and Dr. Ross planned a trip from the UK to meet with Dr. Corbin at Vanderbilt in Nashville. (Tr. 668:14-23 (Konjeti); 784:10-785:10 (Francis); JTX 41, pp.VC-000225, 227).

[8] Also sometimes referred to as 8-(4-OH-PT)-IBMX.

Following Dr. Corbin's telephone conversation with Dr. Ross, Drs. Corbin, Francis and Konjeti, consistent with Dr. Ross' suggestion, prepared a letter containing "a general outline of a proposal for an extension of the Corbin/Glaxo collaboration." The letter, dated January 3, 1992, first described Vanderbilt's proposal to continue the development and study of cGMP analogs, some of which had been shown to act as PDE5 inhibitors. The next section of the letter focused upon the design and development of PDE5 inhibitors:

> We will design phosphodiesterase 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 cyclic GMP molecule. The existing inhibitors only resemble the guanine component. Our preliminary results indicate that this strategy works. We have synthesized one compound that is about 160-fold more potent than the parent IBMX, and 6-fold more potent than the best existing inhibitor, zaprinast.

(JTX 41). The letter did not, however, identify the compound nor describe its structure, other than the fact that it was an IBMX analog.

The concept of developing PDE5 inhibitors that more closely resembled the entire cGMP molecule, by adding groups of atoms to mimic the binding function of the ribose phosphate moiety, was not new to Glaxo. Glaxo's scientists had tried to create a "zaprinast-cGMP hybrid" by attaching a "cyclic phosphate ribose surrogate" to zaprinast. However, unlike Vanderbilt, Glaxo had attached its ribose phosphate mimics to the 9-position on zaprinast. (Tr. 191:11-192:2 (Corbin); PTX 51, pp. GLAX 15597, 15598, 15601-604, 15635, 15637). Apparently those efforts were not successful because as of early 1992 Glaxo had abandoned efforts to develop inhibitors that more closely resembled cGMP. (Tr. 405:4-18 (Labaudiniere)).

The final section of the Vanderbilt letter was entitled "Other projects to consider." It stated Vanderbilt's theory that its PDE5 inhibitors should work in connection with corpus cavernosum relaxation, which could have an impact on individuals suffering from male

impotence. Months earlier Drs. Corbin and Francis had developed the theory that the cGMP-PKG pathway was important in the context of the relaxation of the vascular smooth muscle tissue surrounding the corpus cavernosum in the male penis and surmised that agents that enhanced that pathway either through stimulating PKG, as did the Vanderbilt cGMP analogs, or inhibiting PDE5 from breaking down cGMP, could be used to treat male impotence. (Tr. 781:23-782:12 (Francis); 176:17-177:3 (Corbin); PTX 89). As 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. (Tr. 781:23-784:9, 794:24-797:19 (Francis); 1138:13-1139:17 (Cote).[9]

Vanderbilt's January 3, 1992 letter was followed by plans for Dr. Ross, then the head of Glaxo's Cardiovascular Research Management Committee, to visit Vanderbilt to discuss the research proposal described in the letter. (JTX 42; PTX 109; PTX 113). Dr. Ross flew from England and, on February 3, 1992, met with Drs. Corbin and Francis. (Tr. 185:21-22, 187:14-22 (Corbin); 583:10-586:7 (Ross); PTX 118). Dr. Ross told Dr. Corbin to prepare a more detailed research proposal that included more detail regarding Vanderbilt's designs. (PTX 118).[10] On February 24, 1992 Dr. Corbin sent a letter to Dr. Ross, enclosing the more detailed research proposal, and stating:

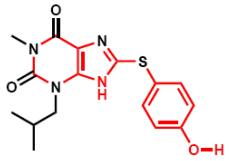
> Based on our discussions during your visit to Nashville this month, I have prepared a final proposal with certain inclusions. More detail of the experimental design is provided, and there is an increased emphasis on use of the newly synthesized compounds to study basic mechanisms of the protein kinase and phosphodiesterase.

[9] According to Dr. Labaudiniere, who headed Glaxo's PDE Project, Glaxo was not researching the use of PDE5 inhibitors as a possible treatment for male impotence (Tr. 407:12-24 (Labaudiniere)).

[10] A little more than a week after Dr. Ross' visit to Nashville, Glaxo France purchased a quantity of IBMX. (PTX 115).

(PTX 118). Accordingly, the research proposal enclosed with the February 24, 1992 letter (the "1992 Research Proposal") identified the compound that had been created using Vanderbilt's design theory and which had been shown to be 160-fold more potent than IBMX and 6 times more potent than zaprinast: 8-(4-OH-phenylythio)-IBMX or 8-(4-hydroxy phenylthio)-IBMX. (Tr. 189:18-190:24 (Corbin)).

It is undisputed that 8-(4-hydroxy phenylthio)-IBMX represented a novel structure for a PDE5 inhibitor at the time that it was developed by Vanderbilt and communicated by Vanderbilt to Glaxo. (Tr. 353:9-354:10 (Crooks)[11]; 1036:10-1037:17 (Padwa); 962:9-14, 974:7-975:1 (Koh)).[12] In fact there was no published reference to any PDE5 inhibitor containing a structure consisting of a 6-member ring fused to a 5-member ring with a phenyl group attached to the 8-position as highlighted here in red, with an electron-donating group attached to the phenyl ring, in this case hydroxy, and a nitrogen-hydrogen group (NH) available at the 9-position. (the "Vanderbilt Structural Features"):



8-(4-OH-PT)-IBMX

(Tr. 358:6-24,376:8-22 (Crooks).

[11] Vanderbilt's expert, Peter A. Crooks, Ph.D., is the George A. Digenis Professor in Drug Design and Discovery at the University of Kentucky, College of Pharmacy. His credentials and experience are described in PTX 413 and illustrated by his testimony. (Tr. 342:5-352:4 (Crooks)). He was accepted by the Court as an expert in medicinal chemistry. (Tr. 352:5-9 (Crooks)).

[12] Vanderbilt's expert, Dr. John T. Koh, is a Professor in the Department of Chemistry and Biochemistry at the University of Delaware. His credentials and experience are described in PTX 415 and illustrated by his testimony (Tr. 947:5-957:21 (Koh)). He was accepted by the Court as an expert in chemistry, organic chemistry, bioorganic chemistry, and chemical biology. (Tr. 958:6-9 (Koh)).

In addition to identifying 8-(4-hydroxy phenylthio)-IBMX, the 1992 Research Proposal included a table of the IBMX and zaprinast analogs that Vanderbilt proposed to synthesize in order to further test its PDE5 inhibitor design theory. Each of the IBMX and all but one of the zaprinast analogs in the table contained a skeleton consisting of a 6-member ring fused to a 5-member ring with some form of substitution at the 8-position. (Tr. 671:1-672:6 (Konjeti); 1239:5-18 (Rafferty); PTX 424).

In addition to describing the novel PDE5 inhibitor structure that Vanderbilt had created, the 1992 Research Proposal explained the rationale behind the hypothesis supported by a very unique finding. Vanderbilt reported that they had found that some of their cGMP analogs were not only PDE resistant, but also acted like methyl xanthine inhibitors of the enzyme by binding tightly to its catalytic site. A finding that the substrate cGMP, which normally would be broken down when modified as Vanderbilt suggested is not getting degraded and, further, that it is acting as a competitive inhibitor would have been surprising to a chemist , and would communicate unique information about the active site. The modifications to the 8-position on the cGMP analogs were preventing the substrate, cGMP, from being degraded. The substitution was affecting the ability of the ribose phosphate on the cGMP to get into the portion of the catalytic site that breaks the bond in the phosphate ring. (Tr. 967:5-968:19 (Koh)). The 1992 Research Proposal would have communicated to a chemist that if he or she attached a "biomimetic" of the ribose phosphate moiety, consisting of groups like 4-hydroxy phenylthio, to the 8-position of existing inhibitors, that biomimetic would bind in the same region of the catalytic site as the ribose phosphate group that it is mimicking, and the result would be increased inhibition. (Tr.963:22-969:3 (Koh)).

On April 8, 1992 Dr. Ross sent copies of the 1992 Research Proposal to six Glaxo scientists who were members of Glaxo's Cardiovascular Research Management Committee, along with a memorandum which explained: "[t]his is **a substantial collaboration** and the only one of the original US CV discovery grants that remains." (Emphasis supplied). The memorandum further explained that one of the four objects of the research would be "Inhibitors of cGMP-binding PDE based on specific design concepts arising from synthesized cGMP derivatives." (PTX 121). One of the six Glaxo scientists to whom Dr. Ross directed his memorandum was Dr. Francois Hyafil, head of the Glaxo France lab. (PTX 121; JPTO, Exh. 1, p. 4 ¶21; Tr. 494:24-495:22 (Grondin); 396:5-12 (Labaudiniere)). Another was Dr. Richard Labaudiniere. Both attended the Glaxo CV RMC meeting on April 9, 1992 where the 1992 Research Proposal was considered and approved. (JTX 22, pp. GLAX25734, 25739).[13]

Incorporation of Vanderbilt's Design into Glaxo's Lead Inhibitor

Dr. Labaudiniere joined Glaxo France in December 1991 as head of chemistry. (Tr. 392:10-19 (Labaudiniere); JTX 8, p. GLAX15826). In that capacity he was solely responsible for supervising and directing the work of the chemists at Glaxo France.[14] He would discuss with the chemists the best approaches to take in their work, and would suggest things Dr. Labaudiniere thought they ought to be trying and modifications that Dr. Labaudiniere thought they ought to be making to particular compounds. (Tr. 393:1-23 (Labaudiniere)).

[13] The other addressees included Dr. Barry Price, Director of Research for Glaxo worldwide, Dr. Malcolm Johnson, a senior pharmacologist for Glaxo in the U.K., Dr. David Middlemiss, a senior medicinal chemist for Glaxo in the U.K., and Dr. Michael Drew, a senior pharmacologist for Glaxo in the U.K. (Tr. 591:12-22 (Ross)). As Dr. Grondin explained, handwritten initials appearing at the top of the memorandum most likely refer to Dr. Grondin, Dr. Kirilovsky, Dr. Anne Charlotte de Gouville, and Dr. Richard Labaudiniere. (Tr. 491:24-492:11(Grondin)).

[14] Dr. Labaudiniere testified that there were approximately six chemists at Glaxo France during the period from 1991 to 1994. (Tr. 394:25-395:9 (Labaudiniere)).

Upon his arrival in December 1991 Dr. Labaudiniere assumed leadership of the PDE Project and directed the research on PDE5 for all of the scientists. (Tr. 392:12-19, 393:1-15, 396:1- (Labaudiniere); 492:12-18(Grondin)). At that time the Glaxo France PDE Project team had been testing compounds for PDE5 inhibition for less than two months. (Tr. 483:7, 25-484:11 (Grondin); JTX 7; PTX 77; PTX 79). At the suggestion of Dr. Rimele and others at Glaxo Inc. in North Carolina, the Glaxo France team had focused their efforts on zaprinast analogs and imidazoles, and in particular, an imidazole quinoxaline that had been designated AH19041XX. (Tr. 475:25-477:8, 482:25-485:1(Grondin); 421:6-13 (Labaudiniere); PTX 58; PTX 58A; PTX 61; PTX 62; JTX 6; PTX 69; PTX 75; JTX 7; PTX 77). Scientific literature studied by the PDE Project team described imidazole quinoxalines as having been developed to have structural and functional features similar to IBMX. (JTX 7; PTX 77; PTX 78, p.GLAX15805).

At the time that Dr. Labaudiniere received a copy of Vanderbilt's 1992 Research Proposal he had access to a database, referred to as Glax or Glaxdatabank that contained information on the structures of all compounds that had been registered by Glaxo scientists at its various research facilities throughout the world. (Tr. 429:25-431:4, 431:21-25 (Labaudiniere); 620:25-621:21 (Kadouri)). Glaxdatabank could be used to perform substructure searches 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)). As Dr. Labaudiniere explained, the core structure is distinguished from the substituted core in the same manner as one would distinguish the part of an automobile that allows it to drive from one place to another from the automobile with its less directly functional accessories. To conduct a substructure search he would simply access the search screen of the software used with

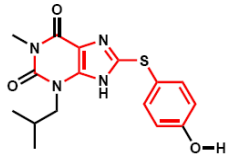
Glaxdatabank, draw the core structure, hit a button, and he would have the results of the search. (Tr. 432:14-433:2 (Labaudiniere)). It is evident from Dr. Labaudiniere's undisputed testimony, that such a substructure search took only a few minutes to perform. (Tr. 1286:19-1288:12 (Rafferty); *See also* DTX KC).

Glaxo France did not have samples of every Glaxo compound that might come up in a substructure search of the Glaxdatabank. Thus, Glaxo France's ability to test compounds that were identified through a substructure search of Glaxdatabank was limited to compounds that had been synthesized at Glaxo France or could be obtained from another Glaxo facility. (Tr. 490:19-481:25 (Grondin)). Such limitations are illustrated by the case of compound AH19041XX. AH19041XX had been identified to the Glaxo France PDE Project team by the Glaxo Inc. scientists in mid-June 1991 as the first compound upon which Glaxo France should focus its attention (Tr. 477:3-8 (Grondin); PTX 58 and 58A, pp. GLAX15734, 15759; PTX61, PTX 62), but Glaxo France was apparently unable to obtain the compound from any Glaxo facility. Glaxo France was thus compelled to synthesize AH19041XX, a process that was not completed until September 27, 1991, more than three months after it had been identified as a compound of immediate interest. (Tr. 475:25-477:2 (Grondin); PTX 75). Because of this serious practical limitation, even a broad substructure search in Glaxdatabank could identify only a small number of compounds that Glaxo France would actually be able to test.[15]

On April 23, 1992, a few weeks after Dr. Labaudiniere received a copy of Vanderbilt's 1992 Research Proposal, Florence Goddard, a biologist on the Glaxo France PDE Project team, tested twenty-nine (29) compounds, including zaprinast (GR68801X), for PDE 5 inhibition. (Tr. 493:22-494:8 (Grondin); JTX 39, p. GLAX 22500-501; PTX 134-46, 148-54, 421A). None of

[15] In fact, review of the ISIS prints introduced by ICOS at trial (DTX KB) shows that Glaxo France had only tested 310 compounds for PDE 5 inhibition as of April 22, 1992.

the compounds had originally been developed and registered in Glaxo France, thus they were clearly chosen for testing based upon a substructure search in Glaxdatabank.[16] The skeletons of each of the 29 compounds tested on April 23, 1992 included a 6-member ring fused to a five-member ring. (PTX 427, p. 4). As did 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 8-position. (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). Eleven of the 29 compounds tested on April 23rd contained the Vanderbilt Structural Features shown in red below:



8-(4-OH-PT)-IBMX

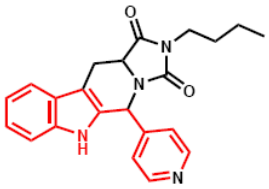
(PTX 425; PTX 427, p. 1). There is no evidence of Glaxo France ever testing, for PDE 5 inhibition, a single compound possessing a substructure comprised of these Vanderbilt Structural Features prior to April 23, 1992. All of these facts, combined with (1) the impressive results reported in the 1992 Research Proposal;[17] (2) the fact that those results came from a source that

[16] As Dr. Kadouri explained, compounds originating at Glaxo France would be given registration numbers with a "GF" prefix; compounds from Glaxo Group Research in the U.K., "GR;" compounds from Glaxo Inc. in the U.S., "GI." (Tr. 619:15-620:24 (Kadouri)).

[17] ICOS' expert, Dr. Rafferty, acknowledged that the 160-fold potency gain reported in the 1992 Research Proposal "is impressive." (Tr.1176:14-15 (Rafferty)). ICOS' other expert, Dr. Padwa, acknowledged that a 100-fold increase of potency "would certainly get my attention," and that an increase of 160-fold "would certainly be interesting." (Tr.1067:9-20 (Padwa)). Dr. Grondin acknowledged that Glaxo had created new chemical programs based upon results that were

was respected by Glaxo and the field at large and whose design and design theories, in prior research proposals Glaxo had successfully adopted in the past; and (3) the ease with which such a search could be performed clearly demonstrate that the April 23, 1992 compounds 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.

One compound tested by Glaxo France on April 23, 1992 that contained nearly all of the Vanderbilt Structural Features was GR30040X:



GR 30040X

(JTX 39, p. GLAX 22500-501; PTX 425). There is no dispute that a search of Glaxdatabank using a generic version of the 8-(4-hydroxy phenylthio)-IBMX skeleton would have yielded GR30040X as a "hit."[18] There is likewise no dispute that the identification of GR30040X led to the development of the compounds claimed in the Patents-at-Issue. (Tr.886:19-21 (Daugan)).

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almost equal to what had been reported in the 1992 Research Proposal. (Tr. 573:4-574:2 (Grondin)).

[18] *See* DTX KC, which consists of the ChemBase software used by Glaxo France from 1991 to 1994 and which includes a database containing information on every compound tested in the PDE Project at Glaxo France, including GR30040X. As Dr. Labaudiniere testified, the ChemBase software has the same substructure search capabilities as that which was used to search Glaxdatabank. (Tr. 429:25-440:24 (Labaudiniere); 626:4-628:25 (Kadouri)). To access the program and run substructure searches a user must copy the ChemBase folder on the disk to a computer hard drive, open the folder, open "CONSULT.BAT," type "consult pde" in response to the DOS prompt, and push enter. The manuals explaining the operation of the program are in evidence at JTX 40, PTX384, and PTX 385. At trial ICOS complained that such a search would disregard substituents of IBMX present in 8-(4-Hydroxy phenylthio)-IBMX that are not present in GR30040X or the patented compounds. However, those substituents, like the "accessories" described by Dr. Labaudiniere, are not part of the core structure or skeleton. The Court need look

In the first few months of the Glaxo France PDE Project Dr. Grondin had developed two tests for testing compounds for inhibition of various phosphodiesterases. The first measured inhibition using a set concentration of the compound, usually 10 micromolar, on a scale from 0% to 100%, with 100% representing complete inhibition. If a compound scored at least a 50% on that test, it would then be re-tested to establish what concentration of the compound was needed to achieve 50% of complete inhibition, which concentration was and is referred to as an "IC_{50}" value. The lower a compound's IC_{50} value, the more potent it is in inhibiting the phosphodiesterase. (Tr. 488:2-489:23 (Grondin)). The test performed on GR30040X and the other compounds tested April 23, 1992 using PDE5 was a 10 micromolar concentration test. Because it scored an 86, GR30040X, along with other compounds that had scored above a 50 in that test, was tested to determine an IC_{50} value on April 24, 1992, and these determinations revealed that GR30040X had an IC_{50} of 0.2 micromolar or 200 nanomolar. (PTX 140).[19] On May 12, 1992 a concentration test was performed on GR30040X using PDE 1, followed by an IC_{50} test on June 3, 1992. (PTX 140).

On June 17, 1992 biologist Valerie Baujet at Glaxo France used PDE5 to perform inhibition concentration tests on 27 compounds that appear to have been selected from a Glaxdatabank search of various substructures of GR30040X. Those compounds that contained the Vanderbilt Structural Features significantly outperformed those that did not. (DTX IG, p. GLAX13261; DTX KB, pp. GLAX14224-26, 14228, 14229, 14232, 142283-87, 14289, 14295,

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no further than the '006 patent itself, which consists of a skeleton in which several different chemical substituents are regarded as equivalents. (JTX 1, p. 1 (abstract), column 49).

[19] As Dr. Grondin explained, documents such as PTX 140 and PTX 79 were printed from a computer system referred to as "ISIS." He also testified that all of data relating to compounds that Glaxo France PDE Project had tested, which had been stored in a ChemBase database, has been transferred into that ISIS system. (Tr. 485:13-17, 486:8-12 (Grondin)). Dr. Grondin further explained what data is reflected in the various columns on the ISIS prints. (Tr. 486:18-488:23 (Grondin)).

14297-99, 15420, 15462, 15480, 15487, 15488, 15495). GR30040X was identified by the Glaxo Project PDE team as a "new inhibitor" of PDE5 at its June 23, 1992 meeting. (JTX 13, p. GLAX15986). The test results for compounds identified as "GR30040X Analogues," including several of the compounds tested on June 17, 1992, were presented. (JTX 13, pp. GLAX15995-960).

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

Dr. Alain Daugan, a Glaxo France chemist who had been assigned to other projects, joined the Project PDE team in June 1992. (Tr. 857:8-9 (Daugan)).[20] He had no prior experience working on phosphodiesterase inhibitors. He did nothing to familiarize himself with the work that the PDE Project team had done prior to his arrival or the state of the art with respect to PDE inhibitors or with respect to the nature of the binding or catalytic sites on PDE5. (Tr. 909:4-14, 914:17-22 (Daugan)).[21] Dr. Labaudiniere initially assigned to Dr. Daugan responsibility for synthesizing compounds in a series of PDE5 inhibitors termed "nitrovinyl indoles." (Tr. 857:22-858:10, 915:2-916:13 (Daugan); JTX 13). Dr. Daugan was later assigned the task of synthesizing compounds related to GR30040X.

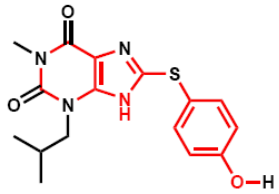
The very first modification that Dr. Daugan made to the GR30040X structure was to replace the pyridine ring ()with a combination of a phenyl ring **and** an electron-donating methoxy substituent:  (DTX GE, p. GLAX00607; Tr.895:23-896:4 (Daugan)).

[20] Dr. Daugan did not actually perform any chemistry for the team until July 2, 1992. (Tr. 914:5-16 (Daugan); DTX GD).

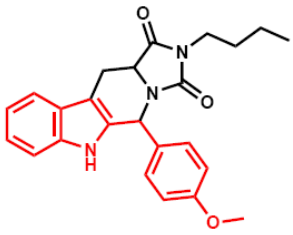
[21] *Compare* (Tr. 647:23-648:23 (Konjeti)). Even ICOS' expert, Dr. Rafferty recognized the importance of learning as much as possible about binding sites in order to design an inhibitor that would bind to those sites. (Tr. 1226:16-1227:4, 1228:20-1232:15 (Rafferty)). Daugan would have the Court conclude that all he needed was his intuition. (Tr.906:6-11, 909:8-14 (Daugan).

Dr. Labaudiniere testified that the decisions with respect to these modifications[22] were the result of a discussion between himself and Dr. Daugan. (Tr. 424:11-425:13 (Labaudiniere); JTX 29, p. VC-00888).[23]

The modifications made to GR30040X by Dr. Daugan, after discussions with Dr. Labaudiniere, had the effect of bringing to bear the only element of the Vanderbilt Structural Features and design that was lacking in GR30040X: the addition of an electron-donating substituent on the phenyl ring. As a result, the new compound, GF173321X, resembled 8-(4-hydroxy phenylthio)-IBMX even more closely than GR30040X and more fully reflected the Vanderbilit design:



8-(4-Hydroxy phenylthio)-IBMX



GF 173321X

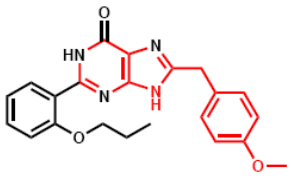
These changes dramatically improved the compound's potency in inhibiting PDE5, dropping from the 200 nanomolar IC_{50} achieved by GR30040X down to 3 or 4 nanomolar. (DTX KB, p. 14607.; JTX 15, p. GLAX16288; PTX 326, p. GLAX25219).

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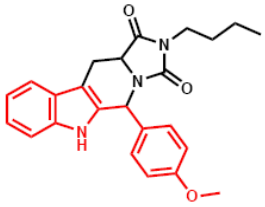
[22] In the context of the GR30040X the phenyl ring was said to be attached at the"C-5" position. (JTX 29, p. VC-00888; Tr. 896:9-897:8, 927:14-928:7(Daugan)).

[23] Dr. Daugan confirmed that Dr. Labaudiniere gave him direction with regard to modifications (Tr. 864:20-865:16 (Daugan)). The evidence shows that, at the same time Dr. Daugan purported to make his first modifications to GR30040X, Dr. Labaudinere also directed Dr. Daugan to append aromatic rings on beta carboline compounds at the position where the resulting compounds more closely resembled GR30040X and thus the Vanderbilt Design Features. (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).

Further evidence of Dr. Labaudiniere's role in directing the modifications made to GR30040X is reflected in the fact that several weeks later, Nerina Dodic, another chemist working under his supervision, but on unrelated zaprinast analogs, suddenly synthesized a zaprinast analog with the exact same structure:



GF 178534X



GF 173321X

(JTX 36, p. GLAX 07657; PTX 222; Tr. 1240:8-1241:24 (Rafferty)).

Before Drs. Daugan and Labaudinere had made their first modification to GR30040X, Dr. Hyafil, head of Glaxo France, was making plans to fly from France to meet with Drs. Corbin, Francis and Konjeti in Nashville.[24] Shortly after Glaxo formally accepted the 1992 Research Proposal, Dr. Ross told Dr. Corbin, in a letter dated July 31, 1992, that Dr. Hyafil wanted to meet with Dr. Corbin. (PTX 165; PTX 179). Arrangements were made for a meeting on September 30, 1992. (PTX 180-84). Drs. Corbin, Francis and Konjeti took the opportunity to explain to Dr. Hyafil all aspects of their work under the 1992 Research Proposal, including their design theories for creating potent PDE5 inhibitors. (Tr. 201:11-16, 207:14-25 (Corbin); 690:8-694:1

[24] Dr. Daugan's notebook pages suggest that he first began to make the modifications to GR30040X that resulted in GF173321 on September 23, 1992, but the pages were not signed and the new compound was not registered until October 7, 1992, a week after Dr. Hyafil met with the Vanderbilt Inventors. (DTX GE, p. GLAX00607; DTX IT, p. GLAX17081). His own testimony demonstrates that his notebooks are less than completely trustworthy and do not reflect all of the information that he used in deciding what modifications to make. (Tr. 910:14-913:19 (Daugan)).

(Konjeti); PTX 193).[25] Minutes of the next PDE Project meeting show that upon Dr. Hyafil's return to France 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. As Dr. Corbin explained, those minutes include data, albeit without proper attribution, taken from a number of publications authored by Drs. Corbin and Francis. (Tr. 210:12 -211:8, 212:13-215:9 (Corbin); JTX 5, p.16301-16311; PTX 25; PTX 119; PTX 420; PTX 208).

The Glaxo/Vanderbilt collaboration continued for another 2 ½ years. During that time Vanderbilt continued to supply Glaxo France with the test results on Vanderbilt's PDE5 inhibitors and samples of those inhibitors for Glaxo France to test, as well as quantities of cGMP analogs and purified PKG, and PKG antibody for testing.[26] (Tr. 200:5-12, 208:4-210:1, 218:4-220:19, 221:10-16, 23-222:2, 222:21-223:1, 223:22-224:5, 227:12-228:13, 229:1- 13, 231:3-233:4(Corbin); 694:15- 707:25 (Konjeti); PTX 185; PTX 187; PTX 201; PTX 205; JTX 17; PTX 228; JTX 45; PTX 223; PTX 224; PTX 225; PTX 226; JTX 59; JTX 60; JTX 47; JTX49; PTX 231; PTX 253-55; PTX 298; JTX 52; PTX 300; JTX 61; JTX 62; PTX 308, PTX 310; JTX 53; PTX 312; PTX 313; PTX 315; PTX 321-322; PTX 337; PTX 343; PTX 348-350; JTX 56; PTX 355; PTX 197-200; PTX 203; PTX 212; PTX 267-277; PTX 281-286). At Dr. Hyafil's invitation Dr. Corbin visited Glaxo France in June 1993, gave a presentation to the PDE Project team about the Vanderbilt lab's work, and shared meals with most of its members as well as higher ranking Glaxo personnel. (Tr. 223:10-14, 224:13, 225:14 (Corbin); PTX 250; PTX 257; PTX 265; PTX 291; PTX 292; PTX 294-296; JTX 60). Later Dr. Grondin traveled from Glaxo

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[25] Notes that ICOS suggested were made by Dr. Hyafil during his visit to Vanderbilt indicate that there was discussion regarding Vanderbilt's theories about the binding sites on the PDE5 molecule. (Tr. 570:2-571:9 (Grondin); PTX 194, p. 2).

[26] Dr. Koh testified that the test results reflected in PTX 225 and PTX 253 reinforced the efficacy of the design and design theory described in the 1992 Research Proposal and that Vanderbilt's inhibitors were indeed binding to the active site on PDE5. (Tr.969:10-973:13 (Koh)).

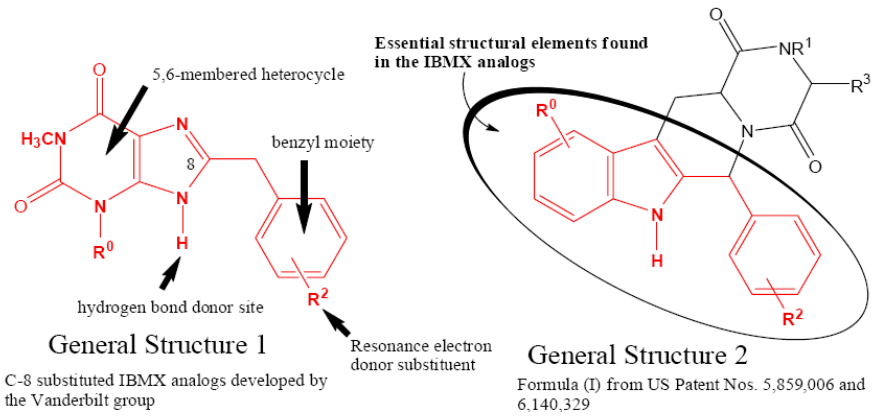
France to meet with the Vanderbilt Inventors in Nashville, Tennessee. (Tr. 229:21-230:20 (Corbin); PTX 329-330; PTX 332-33). Dr. Grondin later submitted a poster for a conference on second messengers and phosphoproteins that Dr. Corbin chaired and hosted in Nashville, and then co-authored a book chapter with Drs. Corbin, Francis and Konjeti about the Vanderbilt design for PDE5 inhibitors. (Tr. 235:13-22 (Corbin); JTX 27; PTX 366).

In the meantime, Drs. Daugan and Labaudinere, having completely absorbed the Vanderbilt design and Vanderbilt Structural Features with the synthesis of GF173321X, continued to make changes to the compound, all of which Dr. Labaudinere characterized as "obvious" modifications, including the replacement of the 5-member hydantoin ring with a 6-member piperazinedione ring. (Tr. 426:18-427:18, 428:12-429:16 (Labaudiniere); JTX 29). Dr. Daugan testified about synthesizing and testing a number of different substituents, but the Vanderbilt Structural Features persisted throughout. By December 3, 1992, just over two months after Dr. Daugan and Dr. Labaudiniere began to work together on modifications to GR30040X, Glaxo France succeeded in synthesizing the first compound that contained all of the features described in Formula 1 of Claim 1 of the '006 Patent, GF178899X. (DTX GE, p. GLAX 00626; DTX IT, p. GLAX17240).

On January 21, 1994, Laboratoires Glaxo S.A. filed a patent application in the U.K. patent office for "tetracyclic derivatives; process of preparation and use," naming Dr. Daugan as the sole inventor. The '006 patent claims the priority of that application. On July 14, 1995, Laboratoires Glaxo S.A. filed a second patent application in the U.K. patent office, entitled "use of cGMP-phosphodiesterase inhibitors to treat impotence," again naming Dr. Daugan as the sole inventor. The '329 patent claims the priority of that application. (JPTO, Exh. 1, p.1-2, ¶¶ 4-8). The compounds claimed in Formula 1 of Claim 1 of both the '006 Patent and the '329 Patent

contain the Vanderbilt Structural Features. (Tr. 355:14-25 (Crooks); 975:15-976:23 (Koh)). ICOS' expert, Dr. Padwa, conceded that Plaintiff's Exhibit 422 accurately reflected the structures in the General Formula 1 of Claim 1 and examples described in the '006 patent, including Example 78/1, the compound that had been registered as GF196960X and which is now the active ingredient in the prescription medication *Cialis*®:

FIGURE 1



(PTX 426; Tr. 1061:11-1064:21(Padwa)).

Glaxo Group Limited and Glaxo Inc. entered into a "Collaboration Agreement" with ICOS in October 1991 in connection with their work on phosphodiesterases and agreed to share profits on any commercial products generated by that work. (PTX 406, pp. 1, 31, 35, 36). The agreement was amended in January 1997 to reflect the fact that Glaxo Inc. had been succeeded by Glaxo Wellcome Inc. and to expressly assign to ICOS Glaxo Wellcome Inc. and Glaxo Group Limited's right, title and interest in the lead compounds covered by the '006 and '329 Patents, including GF196960, along with the rights to those patents, as well as other compounds. (PTX 406, p. ICOS002231-32). Included among the compounds the Glaxo entities purported to assign

to ICOS were 17 IBMX analog PDE5 inhibitors that Vanderbilt synthesized and sent to Glaxo France for testing.[27]

At no time did anyone at Glaxo France, Glaxo Group Research or Glaxo Inc. inform Vanderbilt that Glaxo had filed a patent application for a PDE5 inhibitor incorporating Vanderbilt's design, or that Glaxo had sold intellectual property rights relating to Vanderbilt's compounds to ICOS. (Tr. 235:23-236:13 (Corbin); 798:4-14 (Francis)).

In 1998, ICOS and Eli Lilly and Company ("Eli Lilly") established Lilly ICOS LLC to develop and globally commercialize tadalafil as the active ingredient in the composition sold in the U.S. as Cialis® as an oral therapeutic agent for the treatment of impotence and other potential indications. (JPTO, Exh. 1, p. 1, ¶ 6).

When they first became aware of the existence of tadalafil around 2000 or 2001 the Vanderbilt Inventors believed that it had been developed by ICOS, with which they had never shared their PDE5 design or design theories. (Tr. 237:9-20 (Corbin)). Then, in 2004, they saw articles entitled *The Discovery of Tadalafil: A Novel and Highly Selective PDE5 Inhibitor* published in the Journal of Medicinal Chemistry and that the co-authors included Dr. Grondin, Dr. Hyafil and Dr. Labaudiniere. It was then that Drs. Corbin, Francis and Konjeti realized that tadalafil had been developed at and patented by Glaxo France at the same time that Vanderbilt had provided its novel design structure, which was contained within tadalafil. (Tr. 238:19-239:23 (Corbin); 708:1-709:12 (Konjeti); 798:15-799:14 (Francis); JTX 29; JTX 4).

[27] (PTX 406, pp. ICOS002261 (GF190126X, GF190127X, GF190128X, GF190129X, GF190131X, GF190133X, GF190134X, GF190136X, GF190137X, GF190138X), ICOS002272-73 (GF223707X, GF223719X, GF223720X, GF223721X, GF223722X, GF223723X), ICOS002283 (GF190133X). These are identified as Corbin compounds in Glaxo France's Register of Commercial Products, JTX 35, pp. GLAX24682, 24703-704, 24738. *See also* Tr. 694:2-696:9 (Konjeti); PTX 197-200, 267-77, 281-86.

The *Discovery of Tadalafil 1* article suggests that GR30040X was identified as a novel PDE5 inhibitor as a result of an article published in the Journal of Pharmacology and Experimental Therapeutics entitled *Relaxant Effects of β-Carbolines on Rat Aortic Rings* in May, 1992 by Belen Elgoyhen, *et al...* That article purportedly led Glaxo to test β-carboline-3-carboxylate (β-CCE), which Glaxo had in its possession. When the tests on β-CCE displayed modest inhibitory activity, Glaxo used the β-carboline scaffold as the basis for a substructure search that identified GR30040X as a possible PDE5 inhibitor. (JTX 29, p. VC-000886).[28] That story is consistent with Dr. Labaudiniere's testimony, and is consistent with presentations made by Dr. Hyafil to decision makers at Glaxo. (Tr. 420:23-421:5, 421:16-423:14, 441:7-442:4, 446:7-448:23 (Labaudinere); PTX 326, p. GLAX25219). However, that story does not withstand scrutiny in the face of the contemporaneous documents. The Elgoyhen article became publicly available in mid-May 1992 (Tr. 1254:20-1256:23 (Rafferty); DTX RJ). The article does not suggest that β-carboline is a potent inhibitor of PDE5, but rather that β-carboline, which was described in the article as acting like another family of compounds termed "BZDs," is a very weak inhibitor of a non-specific cGMP PDE, with an IC_{50} of approximately 40,000 nanomolar. [29] (DTX RJ, p.ICOS-003008 ; Tr.1256:24-1258:7 (Rafferty)). On June 25, 1992 Dr. Labaudinere generated a list of "BZD" analogs for testing for PDE5 inhibition, which included β-CCE (designated CCI23002), but not GR30040X. (Tr. 390:7-391:22; PTX 167). Contrary to the

[28] Dr. Daugan, who wrote that historical portion of the article, acknowledged that he was not involved with the PDE Project at the time and had no personal knowledge of how GR30040X was identified as a possible PDE5 inhibitor.

[29] As Vanderbilt had reported that it was 6 times more potent than Zaprinast, Dr. Labaudinere would have expected 8-(4-hydroxy phenylthio)-IBMX to have an IC50 of approximately 33 nanomolar. (PTX 121, p. GLAX02001; Tr. 573:17-574:2 (Grondin)). Common sense dictates that if a report of a 40,000 nanomolar IC_{50} was enough to merit a substructure search by Glaxo scientists, surely a 33 nanomolar IC50 for the Vanderbilt compound would have as well, and more so.

testing protocols set up by Dr. Grondin, β-CCE was not first subjected to a concentration test but went straight to an IC_{50} test, which yielded an unimpressive IC_{50} of 800 nanomolar. (PTX 170).[30] However, as noted above, GR30040X was first identified and tested in April 1992, prior to the publication of the Elgoyhen article and more than two months before β-CCE was tested. It had been identified as a "new" inhibitor of PDE5 (with no reference to β-CCE or β-carbolines or BZD) before Dr. Labaudiniere created his list of BZD analogs. (JTX 13, p. GLAX15987). Thus that identification could not have been the result of either the Elgoyhen article or the β-CCE test results.[31]

In lieu of the chronologically impossible Elgoyhen/ β-CCE story, ICOS has asserted that GR30040X was identified through a substructure search based upon elements of another compound, GR35273X. That assertion is not simply unsupported by the contemporaneous documents, it is entirely belied by them. GR35273X does contain elements of the Vanderbilt Structural Features and was apparently "re-identified" through the same substructure search that led toGR30040X because GR35273X was also tested on April 23, 1992.[32] However, it is very clear that GR30040X was never considered to be an analog of or otherwise structurally related to

[30] *See* note 19 above. The fact that Glaxo would violate its own protocols in order to push through a test on a compound purportedly identified as the result of a report that similar compounds were very weak inhibitors suggests that Glaxo was anxious to go out of its way to find a published prior art basis for its lead compound.

[31] Moreover, a substructure search using the β-CCE structure would not have yielded any of the April 23, 1992 compounds. (PTX 426; Tr. 1273:2-1275:6 (Rafferty), 928:22-929:13, 934:8-936:15 (Daugan)).

[32] *See* PTX 425. GR35273X was first tested with PDE5 at Glaxo France along with a number of other non-Glaxo France compounds on March 11 and 12, 1992. A review of the structures of those compounds indicates that GR35273X was initially identified through substructure searches exploring various modifications on the compounds containing variations of nitrovinyl structures: . (DTX IG, pp. GLAX13199-200, DTX KB, pp. GLAX14235, 14236, 14261, 14262, 14272, 14281, 14282, 14293, 14294, 14296, 14360, 14353, 14368, 14336, 15441-443, 15446, 15448, 15454, 15463, 15483, 15491, 15497, 15483, 15509, 15519, 15520, 15280, 15319, 15332, 15334, 15335, 15341, 15482, 15560, 15326, 15327, 15342, 14450, 14451, 15345, 15390, 15452, 14346, 14452).

GR35273X. The contemporaneous documents show that the PDE Project team regarded GR35273X as a "conformationally constrained analog of zaprinast," rather than a carboline or tetrahydro β-carboline (JTX 24, p. GLAX10365), because GR35273X contains certain structural features----not found in GR30040X---that were considered to be related to zaprinast. (JTX 13, p. GLAX16000; PTX 428).[33] Both compounds are mentioned, in separate sections, in the PDE Project team's June 1992 meeting minutes, along with analogs, and neither is identified as the analog of the other. (JTX 13, p. GLAX15986, 15995-996, 15999-601).[34] The same is true with respect to the July 1992 minutes (PTX 178, p. GLAX16026, 16053-54, 16059-61).[35] Dr. Daugan, who was responsible for pursuing the development of GR30040X never did any work with GR35273X. (Tr. 916:14-917:11). 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.[36]

[33] 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). It was not until October 1992 that the Project PDE team first began to question its hypothesis that GR35273X should be considered a Zaprinast analog and began to consider it as a carboline. (JTX 15, pp. GLAX16277-280).

[34] There is likewise no mention of GR30040X in the June 11, 1992 report to the CV RMC on GR35273X. (JTX 24, p.GLAX10365).

[35] Dr. Labaudiniere's handwritten annexes to the September 1992 minutes that ICOS suggested as reflecting the genesis of GR30040X from the study of β-CCE likewise make no reference to GR35273X. (PTX 188, p. GLAX00313; Tr. 895:4-6 (Daugan)).

[36] Neither Dr. Hyafil's presentation on GF19690X in January of 1994 nor the *Discovery of Tadalafil* articles make any reference to GR35273X, but rely instead on the demonstrably impossible Elgoyhen/β-CCE story, suggesting that anything other than documents contemporaneous to the identification of GR30040X in April 1992 is of highly questionable reliability. (PTX 326, p. GLAX25219; JTX 29, p. VC-000886). It 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.

ARGUMENT

35 U.S.C. §256 provides, in pertinent part:

> The error of omitting inventors or naming persons who are not inventors shall not invalidate the patent in which such error occurred if it can be corrected as provided in this section. The court before which such matter is called in question may order correction of the patent on notice and hearing of all parties concerned and the Director shall issue a certificate accordingly.

As discussed above, the evidence demonstrates that Drs. Corbin, Francis and Konjeti conceived of the use of the compounds incorporating the Vanderbilt Structural Features as PDE5 inhibitors and that their communication of the Vanderbilt Structural Features led to the identification of GR30040X (which contains nearly all of those features) in April 1992. However, Dr. Alain Daugan, who (1) came to the Glaxo France PDE Project in June 1992, (2) had never worked on PDE5 inhibitors or smooth muscle relaxation prior to the time, (3) did nothing to educate himself about the nature of PDE5 or its binding sites, (4) modified GR30040X, in consultation with Dr. Labaudiniere, to create a compound that more fully reflected the Vanderbilt Structural Features, and, (5) made additional obvious changes, also in consultation with Dr. Labaudinere, to arrive at the first compound covered by Patents-at-Issue within six months of joining the PDE Project team, is currently the sole named inventor on the '006 Patent. The evidence also demonstrates that Drs. Corbin, Francis and Konjeti were the first people to conceive of the use of PDE5 inhibitors incorporating the Vanderbilt Structural Features and design for the treatment of male erectile dysfunction. Yet Dr. Daugan, who clearly was not even the first person at Glaxo to determine that such inhibitors could be used for that purpose[37] is the sole named inventor on the '329 Patent. Because it is clear that they made significant contributions to the conception of the

[37] Tr. 907:7-24; 908:13-23, (Daugan).

inventions claimed in those patents, the Court should order that the Patents-at-Issue be corrected to name them as joint inventors.

The Court in *Monsanto v. Kamp*, 269 F.Supp. 818, 824 (D.D.C.1967) described the principles of joint inventorship:

> A joint invention is the product of collaboration of the inventive endeavors of two or more persons working toward the same end and producing an invention by their aggregate efforts. To constitute a joint invention, it is necessary that each of the inventors work on the same subject matter and make some contribution to the inventive thought and to the final result. Each needs to perform but a part of the task if an invention emerges from all of the steps taken together. It is not necessary that the entire inventive concept should occur to each of the joint inventors, or that the two should physically work on the project together. One may take a step at one time, the other an approach at different times. One may do more of the experimental work while the other makes suggestions from time to time. The fact that each of the inventors plays a different role and that the contribution of one may not be as great as that of another does not detract from the fact that the invention is joint if each makes some original contribution, though partial, to the final solution of the problem.

Congress codified those principles of *Monsanto* when it amended 35 U.S.C. §116, which, in pertinent part states:

> When an invention is made by two or more persons jointly, they shall apply for patent jointly and each make the required oath, except as otherwise provided in this title. Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent.

Kimberly-Clark, Corp. v. Procter & Gamble Dist. Co., Inc., 973 F.2d 911, 916 (Fed. Cir. 1992); Fasse, W.F., *The Muddy Metaphysics of Joint Inventorship: Cleaning up after the 1984 amendments to 35 U.S.C. §116*, 5 Harv. J.L. & Tech. 153, 185 (*Monsanto* represents concrete application of principles of amendments to Section 116).

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. *Fina Oil v.*

Ewen, 123 F3d 1466, 1473 (Fed. Cir. 1997)(provision sets no explicit lower limit on the quantum or quality of inventive contribution required for a person to qualify as a joint inventor). *See also Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1997) (co-inventor need not make a contribution to every claim of a patent; a contribution to one claim is enough); *Kimberly-Clark*, 973 F.2d at 916. (not necessary that the entire inventive concept should occur to each of the joint inventors), *Rodgard Corp. v. Miner Enterprises, Inc.*, 12 U.S.P.Q.2d 1353, 1989 WL 41727 (W.D.N.Y. 1989)(if the conceptions of one supplement and complement the conceptions of the other, the result might be invention and therefore joint invention). Nor is one precluded from being a joint inventor simply because her contribution to a collaborative effort is experimental. *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1229 (Fed. Cir. 1994). However, in order to be a co-inventor a person must make 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. *Eli Lilly v. Aradigm Corp.*, 376 F.3d 1352, 1359 (Fed Cir. 2004). *See also Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998)(individual who conceived significant aspects of invention was co-inventor). Moreover, while it is clear under Section 116 that persons may be joint inventors even though they did not physically work together or at the same time, there must be "some element of joint behavior." *Kimberly-Clark,* 973 F.2d at 917.

Vanderbilt has demonstrated through clear and convincing evidence[38], including their testimony and a number of corroborating documents, that during their close and substantial six year collaboration with Glaxo, Drs. Corbin, Francis and Konjeti made significant contributions to the conception of the inventions claimed in the '006 and '329 Patents.[39] The evidence that they conceived of a novel structure for PDE 5 inhibitors, and that the structure and design theory were communicated to Glaxo scientists directly involved in the development of the claimed compounds is substantial and largely undisputed. *See supra.*, pp. 14-25. It is undisputed that at the time the information was received by scientists at Glaxo France, its PDE Project team had never tested a compound containing the novel Vanderbilt Structural Features. It is likewise undisputed that within two weeks of that communication, Glaxo identified a new lead compound that contains nearly all of the novel Vanderbilt Structural Features, and that all of those features are reflected in the compounds claimed in the patents. *See supra.*, pp. 25-36. Glaxo's own records demonstrate that the structural features conceived by Drs. Corbin, Francis and Konjeti

[38] There is a presumption that inventors named on an issued patent are correct and courts have held that misjoinder or nonjoinder of inventors must be proven by clear and convincing evidence. *Fina Oil and Chemical Co. v. Ewen*, 123 F.3d 1466, 1472 (Fed. Cir. 1997). Notwithstanding the general principles regarding the burden of proof discussed in *Fina Oil* and certain other cases, 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. ICOS has stipulated that the patent review process generally and the review of the applications for the '006 and '329 patents specifically does not and did not involve any verification by the USPTO of the accuracy of the inventorship representations. (Document No.133). Thus there is no factual basis for such a presumption or heightened burden.

[39] Evidence of invention must be independently corroborated. *Fina Oil* at 1474. Corroborating evidence may take many forms, including documents prepared by a putative inventor. Circumstantial evidence about the inventive process and/or oral testimony of someone other than the alleged inventor may also serve as corroborating evidence. *Ethicon, Inc. v. United States Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1997). *See also Medtronic Vascular, Inc. v. Advanced Cardiovascular Systems,* 2005 WL 46553 (D. Del. January 5, 2005).

significantly contribute to the ability of the claimed compounds to inhibit PDE5.[40]This evidence compels the conclusion that Drs. Corbin, Francis and Konjeti are joint inventors of the inventions claimed in the '006 and '329 Patents.[41]

Relying on the Federal Circuit's decision in *Bd. of Educ. v. American Bioscience*, 333 F.3d 1330 (Fed. Cir. 2003), ICOS has asserted that, contrary to 35 U.S.C. §116 and the other authorities cited above, in order to be a joint inventor of a chemical compound one must conceive all elements of a claimed chemical compound. It is clear from the outcome of that case however, that the Federal Circuit could not have intended to establish such a rule. It is clear from subsequent opinions that *American Bioscience* did not change the legal principles of joint inventorship embodied by Congress in Section 116. Finally, it is clear that a rule such as that espoused by ICOS would run counter to Congress' intent in amending Section 116.

The patent at issue in *American Bioscience* claimed three specific compounds consisting of modified versions of taxotere that could be used as radiosensitizing agents in the treatment of cancer.[42] As the Judge Lourie of the Federal Circuit explained:

> The three claimed compounds all have the 10-hydroxy group of taxotere, as well as a 3 -(4-nitrophenyl) group. The first compound additionally has the N-(tert-butoxycarbonyl) group of taxotere. The second and third compounds have isopropoxycarbonyl (-$COOCH(CH_3)_2$, abbreviated as "-COO-iPr") and isobutoxycarbonyl (-$COOCH_2CH(CH_3)_2$, abbreviated as "-COO-iBu") groups, respectively, in place of the tert-butoxycarbonyl group of the first compound.

[40] *See e.g.*, PTX 326, p. GLAX25219, PTX 140, PTX 204, JTX 15, pp.16286-288.
[41] Vanderbilt submits that it has clearly and convincingly proven that Drs. Corbin, Francis and Konjeti conceived of the use of PDE5 inhibitors comprised of their novel design, including the compounds claimed in the '006 Patent, and that they communicated that conception to Glaxo. Thus, they are legitimately co-inventors of the inventions claimed in the '329 Patent as well. Moreover, ICOS has conceded that if Drs. Corbin, Francis and Konjeti are co-inventors of the compounds claimed in the '006 Patent they are necessarily co-inventors of the inventions claimed in the '329 Patent.
[42] In contrast, Formula of Claim 1 of the '006 Patent describes thousands of different chemical compounds that contain the Vanderbilt Structural Features.

333 F.3d at 1336. The named inventors on the patent were American Bioscience employees Chunlin Tao, Neil Desai, Patrick Soon-Shiong, and Paul Sandford. *Id.* at 1332. A group of scientists employed by Florida State University led by Professor Robert Holton (the "Holton Group"), with whom Tao had worked as a post-doctoral research assistant, claimed that they should be named as co-inventor on the patent and Desai, Soon- Shiong and Sanford removed. The Holton Group had a long history of working with taxol, of which taxotere is considered an analog,[43] FSU claimed that in conceiving the claimed compounds Tao had used information that he had learned while with the Holton Group. The District Court agreed and issued an order directing the removal of Desai, Soon- Shiong and Sanford from the patent and the addition of Holton and his colleagues as joint inventors.

There was no research agreement, communication or collaboration whatsoever between the Holton Group and American Bioscience. There was no evidence that the Holton Group sent any information to American Bioscience regarding any novel structures, designs or design theories.[44] Thus there were no novel structures within the three claimed compounds that had been conceived by the Holton Group. At most the Holton Group imparted to Tao the general knowledge that compounds related to taxol could be used as radiosensitizing agents, a concept that was already part of the published

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[43] As the Court explained, the two compounds differ in two respects:

> First, taxotere has a 10-hydroxy (-OH) group in place of taxol's 10-acetoxy (-$OCOCH_3$, also abbreviated as "-OAc") group. Second, taxotere has a tert-butoxycarbonyl (-$COOC(CH_3)_3$, abbreviated as "-COO-tBu") group attached to its 3 nitrogen atom, in place of taxol's benzoyl (-COC_6H_5) group.

Id. at 1332-33.

[44] Unlike the novel PDE5 inhibitor structure communicated by Vanderbilt to Glaxo, both taxol and taxoltere were well-known in the state of the art and, taxol had been identified in the published art as a radiosensitizing agent. *Id*. at 1330-33.

art. In reversing the lower court's finding that Professor Holton and his colleagues were joint inventors of the taxotere compounds, the Federal Circuit confirmed that "general knowledge regarding the anticipated biological properties of groups of complex chemical compounds is insufficient to confer inventorship status with respect to specifically claimed compounds "(citing *Amgen Inc. v. Chugai Pharmaceutical Co.,* 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed.Cir.1991)), and that "'[o]ne 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'" (quoting *Ethicon,* 135 F.3d at 1460). 333 F.3d at 1340-41.

The evidence showed that Desai and Soon- Shiong conceived the idea of making taxol analogs having both a 10-hydroxy group (i.e., taxoteres) and a nitro functional group, structures that were contained within each of the three compounds. *Id*. at 1339. It also showed that Tao chose the attachment point for the nitro group for all three compounds, and introduced the idea of incorporating the tert-butoxycarbonyl, isobutoxycarbonyl, and isopropoxycarbonyl groups into the first, second and third compounds, respectively. *Id*. Because each had made separate contributions to the conception of the three compounds, the Federal Circuit held that all three should be joint inventors on the patent---even though not one of the three had himself individually conceived of all of the components of those compounds. At the same time, the Court noted that one of the FSU scientists, Dr. Hossein Nadizadeh, who conceived of *none* of the components of the claimed compounds, but conceived of a method of making taxol derivatives, could nonetheless have been a joint inventor:

> If Tao, Soon-Shiong, and Desai had conceived the structures of the claimed compounds, but were then unable to make them without Nadizadeh's help, Nadizadeh might have been a coinventor.

Id. at 1342.. Thus, *American Bioscience* simply cannot stand for the rule espoused by ICOS.

There have been two Federal Circuit cases on joint inventorship since *American Bioscience* and, although Judge Lourie sat on the panels of each, neither cites *American Bioscience* in discussing the standards for joint inventorship. *Eli Lilly v. Aradigm*, 376 F3d 1352, 1358-9 (Fed. Cir. 2004) cites *Fina Oil* and *Burroughs Wellcome* for the rule that a joint inventor "…need not demonstrate that he made a contribution equal in importance to the contribution made by the listed inventors to claim his right to joint inventor status." *Cook Biotech, Inc. v. Acell, Inc.* 460 F.3d 1365, 1373 (Fed. Cir. 2006) simply cites *Eli Lilly* (and thus also adopts the pre-*American Bioscience* formulations).

The only Court that has thus far considered *American Bioscience* in a case involving questions of joint inventorship did not interpret that case as changing the law as suggested by ICOS. After discussing *American Bioscience* the Court went on to describe the joint inventorship standard as follows:

> To make a case for joint inventorship, the inventor must show that he made a "contribution to the claimed invention that is not insignificant in quality, when that contribution is measured against the dimension of the full invention, and [did] more than merely explain to the real inventors well-known concepts and/or the current state of the art." *Pannu v. Iolab Corp.*, 155 F.3d 1344, 1351 (Fed. Cir. 1998). Each inventor must work on the "same subject matter and make a contribution to the inventive thought and to the final result." *Monsanto Co. v. Kamp*, 269 F.Supp. 818, 824 (D.D.C. 1967). The contribution of each inventor, however, need not be the same type or amount, and a joint inventor must make such a contribution only to one claim of a patent. *Id*. at 824. **A joint inventor need not have had the definite and permanent conception of the full invention--otherwise he would be the sole inventor.**[45]

[45] This reasoning is antithetical to ICOS' reading of *American Bioscience* and entirely consistent with Vanderbilt's.

Regents of the University of Michigan v. Bristol-Myers Squibb Co., 301 F.Supp.2d 633, 642 (E.D. Mich. 2003)(Emphasis supplied).

The rule espoused by ICOS is not only inconsistent with the established law that preceded *American Bioscience,* the outcome of *American Bioscience*, and the case law that has come after, it is flatly inconsistent with Congress' intent in enacting the current version of 35 U.S.C. Section 116. As one commentator explained:

> The desire to encourage team research that motivated the amendment to section 103 was also largely responsible for the amendment to section 116. The biggest hindrance to team research efforts under prior section 116 was the "all claims rule" imposed by some courts. This rule required named joint inventors to have contributed jointly to every aspect of an invention and every claim of a resulting patent. In the House Subcommittee Hearings on Innovation and Patent Law Reform, Gerald J. Mossinghoff, Commissioner of Patents and Trademarks, testified:
>
> > Complying with this requirement is sometimes difficult and at times impossible. Scientists or researchers in an organization often work on a particular aspect or embodiment of the invention, or on only a portion of the invention, while others work on different aspects, embodiments or portions. Scientists are continually added to a research team, while other scientists leave the team. Concepts and development plans generated through brainstorming cannot always be accurately attributed.

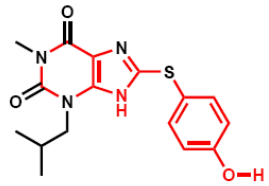
Fasse, W.F., *The Muddy Metaphysics of Joint Inventorship: Cleaning up after the 1984 amendments to 35 U.S.C. §116*, 5 Harv. J.L. & Tech. 153, 178-179. The practical difficulties identified by Commissioner Mossinghoff in his testimony before Congress about the "all claims rule" would apply equally to a rule that required every joint inventor to conceive of all aspects of every claimed chemical compound and the rule espoused by ICOS would undermine Congress' intent that the law of joint inventorship be interpreted to foster collaboration and communication between joint inventors. Indeed, the ICOS rule would encourage unscrupulous behavior, such as this Court observed with respect to Dr. Housey in *Bayer AG, et al. v. Housey Pharmaceuticals,*

Inc., 2003 WL 22953187 (D.Del.), p. 14, in which collaborators would intentionally conceal from each other the work that they were doing in an effort to keep all patent rights flowing from a collaboration to themselves.

The contributions that the Vanderbilt scientists made to the compounds in the Patents-at-Issue are far more significant than those that were found to be sufficient to make Soon-Shiong, Desai and Tao joint inventors in *American Bioscience*. Drs. Corbin, Francis and Konjeti 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. Thus, contrary to ICOS' assertions, the result in *American Bioscience* compels the conclusion that Drs. Corbin, Francis and Konjeti should be added as joint inventors on the '006 and '329 Patents.

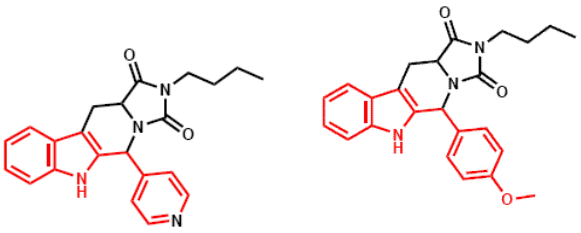
CONCLUSION

As set forth above, the evidence introduced at trial clearly and convincingly demonstrated that Drs. Corbin, Francis and Konjeti conceived of



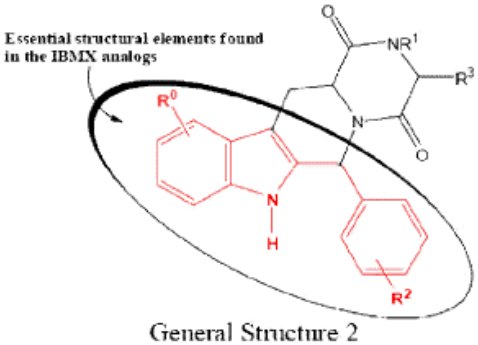
8-(4-OH-PT)-IBMX

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

As this Court stated in *Medtronic Vascular, Inc. v. Advanced Cardiovascular Systems,* 2005 WL 46553 (D. Del. January 5, 2005), "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." That is precisely what occurred here. Vanderbilt significantly contributed to the conception to the inventions claimed in the Patents-At-Issue. 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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