IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

ZYMOGENETICS, INC., a Washington Corporation, Plaintiff, v. Bristol-MYERS SQUIBB CO., a Delaware Corporation, and DOES 1 through 100, Defendants.	C.A. No. 06-500-SLR **PUBLIC VERSION**

PLAINTIFF ZYMOGENETICS, INC.'S REPLY BRIEF IN SUPPORT OF ITS MOTION FOR SUMMARY JUDGMENT OF VALIDITY OF PATENTS-IN-SUIT WITH RESPECT TO THE CAPON PATENTS AND THE SEED PATENT

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INTRODUCTION

ZymoGenetics, Inc.'s ("ZymoGenetics") Motion for Summary Judgment of Validity of The Patents-In-Suit With Respect to The Capon Patents and The Seed Patents ("Motion") demonstrates there is no genuine issue of material fact that the Capon Patent and the Seed Patents are not prior art to the ZymoGenetics' asserted patents (the "ZymoGenetics Patents"). Bristol-Myers Squibb Company's ("Bristol") Answering Brief Opposing ZymoGenetics' Motion ("Opposition") is notable primarily for what it ***does not*** include. Bristol does not dispute that ZymoGenetics scientists Dr. Andrzej Sledziewski, Dr. Wayne Kindsvogel, and Ms. Lillian Anne Bell, who are the named inventors, were attempting to create a secreted PDGF-receptor ("PDGFR") in 1987 and 1988. Bristol does not dispute that Dr. Sledziewski made a lab notebook entry on January 4-5, 1988 discussing the creation of an embodiment of the invention, PDGFR-Ig and PDGF-invertase fusion proteins, and that the inventors diligently recorded experiments and, thereafter, finally appreciated and recognized that they had created the claimed invention. These facts, combined with expert opinion of Dr. Paul Edward Purdue, one of ordinary skill in the art, demonstrates that the Capon and Seed patents are not prior art. Based on the testimony of the inventors, laboratory notebooks, and the opinion of Dr. Purdue, the evidence indisputably shows the date of the invention was no later than January 4-5, 1988.

Further, Bristol's opposition is based on an incorrect understanding of the law on the conception and reduction to practice of an invention. When the facts contained in ZymoGenetics' Motion are analyzed under the established case law, there can be no reasonable dispute that ZymoGenetics' inventors conceived and diligently reduced to practice the claimed dimerized fusion protein of the ZymoGenetics Patents.

ARGUMENT

I. The Capon and Seed Patents Are Not Prior Art To The ZymoGenetics Patents

Bristol is well-aware that ZymoGenetics disputes that U.S. Patent No. 6,004,781 (the "Seed Patent") and U.S. Patent Nos. 5,336,603, 5,565,335, 6,117,655, and 6,710,169 (the "Capon Patents") (collectively, the "Seed and Capon Patents") are even relevant to the ZymoGenetics Patents for two reasons: (1) the Seed and Capon Patents are not prior art to the patented invention and (2) the Seed and Capon Patents do not disclose the invention of the ZymoGenetics Patents. The second reason is not the subject of ZymoGenetics' Motion. The subject of this Motion is that Bristol is precluded from alleging the Seed and Capon Patents are prior art to the ZymoGenetics Patents. Bristol bears "the burden of persuasion, by clear and convincing evidence," of demonstrating that a particular reference or combination of references are prior art to a patented invention. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996). The undisputed facts demonstrate that the inventors predate the Seed and Capon Patents, such that they are not prior art.

II. It Remains Undisputed That ZymoGenetics Scientists Conceived Of The Invention Of The ZymoGenetics Patents No Later Than January 4-5, 1988

Bristol misinterprets the law of conception by alleging that evidence in the form of documents needs to be corroborated. Rather it is the inventor's testimony that requires corroboration for purposes of establishing conception. *See Izumi Prods. Co. v. Koninklijke Philips Elecs. N.V.*, 315 F. Supp. 2d 589, 607 (D. Del. 2004), *aff'd*, 140 Fed. Appx. 236 (Fed. Cir. 2005) (citations omitted) ("Evidence in the form of documents does not need to be corroborated. Rather, '[o]nly the inventor's testimony requires corroboration before it can be considered'"); *see also Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1230 (Fed. Cir. 1994) ("conception occurs in the inventors' minds, not on paper"). Bristol ignores the testimony of the inventors of the

ZymoGenetics Patents, and improperly looks at Dr. Sledziewski's laboratory notebook page in isolation.

Deposition testimony of Dr. Sledziewski confirms that conception of the claimed invention in the embodiment of PDGFR-invertase and PDGFR-Ig fusion proteins occurred no later than January 4-5, 1988. D.I. 160 (Opening Brief at 2-3). Dr. Sledziewski's testimony is corroborated, as required by the law of inventive conception, by written evidence of the invention. *Id.* Dr. Purdue also confirmed that Dr. Sledziewski's notebook discloses conception of "a secreted, biologically active non-immunoglobulin polypeptide joined to a dimerization partner." *Id.*; D.I. 165 (Declaration of Paul Edward Purdue, Ph.D. (" Purdue Decl."), ¶4).

Bristol makes the erroneous argument that, if an inventor engages in post-conception experimentation, conception is not complete until the working invention is made. D.I. 246 (Opposition at 14-18). Bristol misinterprets the law by alleging that conception requires an "operative" invention. For conception, "an inventor *need not know that his invention will work for conception to be complete*." *Burroughs*, 40 F.3d at 1228 (citing *Applegate v. Scherer*, 332 F.2d 571, 573 (C.C.P.A. 1964)) (emphasis added). In order to show conception, an inventor "need only show that he had the idea; the discovery that an invention actually works is part of its reduction to practice." *Id.* Post-conception experimentation does not alter the date of conception, and the limited doctrine of "simultaneous conception and reduction to practice" is inapplicable to this case. *Id.*

A. ZymoGenetics Sets Forth Substantial Evidence Demonstrating Conception Occurred No Later Than January 4-5, 1988

Dr. Sledziewski's deposition testimony identifies the claimed invention, which is corroborated by his laboratory notebook. Contrary to Bristol's allegation that "the named inventors did not even know what the problem was," ZymoGenetics was attempting to express a soluble, active form of the PDGF-receptor in 1987, as Dr. Sledziewski testified during his deposition. D.I. 163 (Declaration of Hannah Lee ("Lee Decl."), Ex. 1

(Sledziewski Depo. at 26:1-9)); Opposition at 12-13. Research in the scientific community, including that done by ZymoGenetics' scientists, led to the conclusion that the PDGF-receptor needed to be a dimer in order to exhibit biological activity. *Id.* (Sledziewski Depo. at 27:4-19). Dr. Sledziewski testified "we had a problem how to produce a soluble receptor that would dimerize outside the cell environment. So that was our problem." *Id.* Dr. Sledziewski's testimony of the problem at hand is supported by his laboratory notebook entry, which refers to [redacted] D.I. 163 (Lee Decl., Ex. 2 (Sledziewski notebook at ZG033206) [redacted] *see also* id. (Lee Decl., Ex. 1 (Sledziewski Depo. at 178:9-23 ("it basically outlines the concept that you would need to dimerize PDGF receptor to -- to create high-affinity binding.")).

Dr. Sledziewski's testimony is supported by the testimony of co-inventor Dr. Wayne Kindsvogel, who stated it was known in the scientific community in the late 1980s that the PDGF-receptor was a dimer in its active form. Declaration of Hannah Lee in Support of ZymoGenetics' Reply ("Lee Reply Decl."), Ex. 2 (Kindsvogel Depo. at 18:9-13)). Dr. Kindsvogel confirmed that [redacted] Id. (Kindsvogel Depo. at 15:17-19; 29:10-23).

Dr. Sledziewski's testimony and laboratory notebooks not only identify the problem ZymoGenetics was attempting to solve, they also provide the solution. Dr. Sledziewski's deposition testimony proves that [redacted] Dr. Sledziewski testified "[i]f I could accomplish that by dimerizing two monomers with a single cysteine bond, I think that would solve my problem, provided that I recovered biological activity at the level that I desire." Lee Reply Decl., Ex. 1 (Sledziewski Depo. at 191:11-20). Dr. Sledziewski's lab notebook corroborates his testimony because it contains a statement

[redacted] D.I. 163 (Lee Decl., Ex. 2 (Sledziewski notebook at ZG033206)). Despite Bristol's attempts to confuse the issue, there is no doubt that Dr. Sledziewski had thought of both the problem he was trying to solve, and the solution no later than January 4-5, 1988. This is precisely the "particular solution to the problem at hand" defined by the *Burroughs* court as the hallmark of conception. *Burroughs*, 40 F.3d at 1228 (citations omitted).

Furthermore, Dr. Sledziewski's laboratory notebook was reviewed by Dr. Purdue from the perspective of ordinary skill in the art. Dr. Purdue stated, in both a written declaration and in deposition testimony, that the information contained in Dr. Sledziewski's laboratory notebook discloses the conception of "producing of a secreted, biologically active non-immunoglobulin polypeptide joined to a dimerization partner." D.I. 165 (Purdue Decl., ¶¶2, 4); D.I. 163 (Lee Decl., Ex. 3 (Purdue Depo. at 178:25-179:4)). Dr. Purdue's analysis provides confirmation that one of ordinary skill in the art would have understood that Dr. Sledziewski's notebook contained a "definite and permanent idea of the complete and operative invention." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986).

B. ZymoGenetics' Patented Invention Does Not Require Simultaneous Conception And Reduction to Practice

Bristol's argument that if an inventor must perform any experiments at all, "then conception is not complete until the working invention is actually made" is contrary to the law. D.I. 246 (Opposition at 14). In fact, this very argument is virtually identical to the rejected argument presented by Barr Laboratories and Novapharm, Inc. in the *Burroughs* case, that "[w]ithout some experimental confirmation…the inventor has only a hope or an expectation, and has not yet conceived of the invention…." *Burroughs*, 40 F.3d at 1228. As the *Burroughs* Court unequivocally stated, "this is not the law." *Id.*

While experimental confirmation can be proof of successful reduction to practice, it has no bearing on the topic of conception.

It is true that there is a line of cases, starting with *Smith v. Bousquet,* 111 F.2d 157 (C.C.P.A. 1940), and extending through *Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200 (Fed. Cir. 1991), holding that, in limited circumstances, conception requires reduction to practice. *See Smith*, 111 F.2d at 162-63; *Amgen*, 927 F.2d at 1207. However, "these cases do not stand for the proposition that an inventor can never conceive an invention in an unpredictable or experimental field...." *Burroughs*, 40 F.3d at 1229. Application of the doctrine of simultaneous conception and reduction to practice is the ***exception*** to the general rule on conception, and it is only applied in circumstances when there exists "uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention...." *Id.*, *see also Smith*, 111 F.2d at 162 (neither claimed inventor knew whether, if, or how proposed insecticide would function); *Alpert v. Slatin*, 305 F.2d 891, 894 (C.C.P.A. 1962) (no conception when method for producing titanium involved a series of undirected trial and error experiments); *Amgen*, 927 F.2d at 1207 (no conception when suggested experimental technique failed to achieve desired results and, where inventor claimed unknown DNA sequence as part of invention). In each of these cases, "[i]t is the factual uncertainty, not the general uncertainty surrounding experimental sciences, that bears on the problem of conception." *Burroughs*, 40 F.3d at 1229. As shown above, the invention underlying the ZymoGenetics Patents involved using recombiant DNA technology to find a novel solution for a novel problem.

In the field of chemical substances, conception "includes knowledge of both the specific chemical structure of the compound and an operative method of making it." *Id.* (citations omitted). Conception of the invention underlying the ZymoGenetics Patents involved application of recombinant DNA techniques to create a novel solution for a novel problem. It is undisputed that generating fusion proteins generally was well known

to one of skill in the art by 1988. *See* D.I. 171 (Declaration of Paul J. Andre ("Andre Decl."), Ex. 9 (Ravetch Expert Report at ¶47 [redacted] *see also id.*, Ex. 10 (Capon Expert Report at ¶49 [redacted] It is further undisputed that the DNA and protein sequence for the PDGF-receptor were known at the time of the conception. *See* D.I. 169 (Andre Decl., Ex. 2 ('026 Patent at Fig. 1A-D and col. 8, ll. 6-12)). Accordingly, the limited doctrine of simultaneous conception and reduction to practice does not apply to the ZymoGenetics Patents.

C. Dr. Sledziewski's Conception Evidence Contains All Elements Of The Asserted Claims Of The ZymoGenetics Patents

Bristol's final argument regarding conception of the invention underlying the ZymoGenetics Patents is based on the alleged inadequacy of the disclosure to contain every feature of the claimed invention. D.I. 246 (Opposition at 18-19). Specifically, Bristol claims that "eukaryotic host cells," "transcriptional promoters," "secretory signal sequences" and a polypeptide or receptor requiring dimerization for biological activity are not disclosed. However, Dr. Sledziewski's testimony and laboratory notebook page shows that all the claim elements of the invention of the ZymoGenetics Patents, including these, were conceived no later than January 4-5, 1988.

First, Dr. Sledziewksi's laboratory notebook page explicitly refers to a [redacted] D.I. 163 (Lee Decl., Ex. 2 (Sledziewski notebook at ZG033206)). Moreover, "eukaryotic host cells," "transcriptional promoters" and "secretory signal sequences" are elements that are required to make a fusion protein, which were well-known to those of ordinary skill in the art as required elements in order to create a fusion protein at the time of the invention. *See* D.I. 247 (Declaration of Jason E. Johnson ("Johnson Decl."), Ex. 1 (Sledziewski Depo. at 111:2-13) (showing use of construct including transcriptional promoters and secretory signal sequences for expression of claimed fusion protein)). *See Oka v.*

Youssefyeh, 849 F.2d 581, 583 (Fed. Cir. 1988) ("When, as is often the case, a method of making a compound with conventional techniques is a matter of routine knowledge among those skilled in the art, a compound has been deemed to have been conceived when it was described, and the question of whether the conceiver was in possession of a method of making it is simply not raised."). Simply because the exact terms from the claims were not used in Dr. Sledziewski's notebook does not mean that he did not have these elements in his mind at the time of conception.

Second, Dr. Sledziewski specifically testified during his deposition that he knew PDGR-receptor "requires dimerization for biological activity" at the time of conception. D.I. 163 (Lee Decl., Ex. 1 (Sledziewski Depo. at 186:4-17) (testifying with regards to the statement in the January 4-5, 1988 entry [redacted] *Id.*, Ex. 2 (Sledziewski notebook at ZG033206)). Thus, Bristol's arguments fail, and conception of the invention of the ZymoGenetics Patents occurred no later than January 4-5, 1988.

III. It Remains Undisputed That ZymoGenetics' Inventors Acted With Reasonable Diligence To Reduce The Invention To Practice

As set forth in ZymoGenetics' opening brief, incorporated herein, it is undisputed that ZymoGenetics' inventors exercised reasonable diligence in reducing the invention to practice in this case. The argument Bristol raises in its Opposition is disingenuous as Bristol was in possession of many laboratory notebooks evidencing reasonable diligence of the inventors that ZymoGenetics provided to Bristol during discovery. Dr. Sledziewski's laboratory notebook shows several pages with laboratory activity after conception of the idea. Specifically, Dr. Sledziewski's laboratory notebook pages of January 6-8 and 11-13, 1988 document that he was carrying out the idea he outlined in his entry of January 4-5, 1988. *See* Lee Reply Decl., Ex. 3 (Sledziewski notebook at

ZG033206-09, signed and witnessed) (entries as January 6-8 and 11-13). Diligence after conception is further supported by the deposition testimony of Dr. Sledziewski who stated that he believed "that this is a continuation of the experiments from the previous page." *Id.*, Ex. 1 (Sledziewski Depo. at 198:9-10). The many pages of Ms. Bell's laboratory notebooks in the time period after conception also show evidence of diligence to reduction to practice. Dr. Purdue cited to a few exemplary pages of Ms. Bell's notebook in his declaration and expert report to show diligence and reduction to practice. D.I. 165 (Purdue Decl., ¶¶9-10).

Bristol attempts to show that there were "unexplained gaps" between the period after conception and the reduction to practice of the claimed invention. Opposition at 29. However, Bristol does not cite to any authority in support of its allegation that in order for reduction to practice, there must be a ***daily*** record of the reasonable diligence that is exercised. To the contrary, the case law states the exact opposite. In fact, this Court has held to show diligence that "it is not necessary for a party alleging prior invention to drop all other work and concentrate solely on the particular invention involved," and that "there also need not be evidence of activity on every single day if a satisfactory explanation is evidenced. *Izumi Prods.* Co., 315 F. Supp. 2d at 608 (citations omitted); *see also Monsanto Co. v. Mycogen Plant Sci., Inc.*, 261 F.3d 1356, 1369 (Fed. Cir. 2001) (finding "notebook and the discovery responses suggest that the plant transformation work was ongoing without interruption, despite the lack of daily entries"). Bristol's arguments are simply out of touch with how reasonable diligence is carried out in reality.

Bristol also incorrectly applied the law relating to diligence. Bristol attempts to mislead this Court by citing to a blatantly incorrect holding of the case *In re Mulder*. The Federal Circuit in *Mulder* had the exact contrary holding that Bristol alleges and held that the lack of reasonable diligence was caused by a delay of ***many months*** in filing the U.S. patent application, and ***did not*** rely upon a two-day period to determine a lack of reasonable diligence. *In re Mulder*, 716 F.2d 1542, 1545 (Fed. Cir. 1983) (emphasis

added). As described above and as set forth in ZymoGenetics' opening brief, ZymoGenetics has substantial, undisputed evidence that the inventors were exercising reasonable diligence to reduce the claimed invention to practice.

Further, Bristol tediously calculated the number of days between January 4-5, 1988 and September 28, 1988 in an attempt to manufacture an argument that there was no reasonable diligence in reducing the invention to practice. However, Bristol cites to no law that requires that an invention must be completed in a certain amount of time for there to have been reasonable diligence. In fact, as discussed above, Bristol has been in possession of the many laboratory notebook pages of the inventors that document the inventors' experiments and diligence in reducing the invention to practice.

Finally, Bristol fails to recognize that the purpose of the reasonable diligence standard is to balance "the interest in rewarding and encouraging invention with the public's interest in the earliest possible disclosure of innovation." *Griffith v. Kanamaru*, 816 F.2d 624, 626 (Fed. Cir. 1987) (citations omitted). There is no evidence from Bristol that Dr. Sledziewski and the other inventors of the claimed invention were attempting to withhold the invention from the public and not diligently working to reduce the invention to practice. Bristol simply alleges that there was no reasonable diligence while ignoring the detailed entries in Dr. Sledziewski's laboratory notebook and the references in Ms. Bell's laboratory notebook, among other evidence were produced to Bristol during discovery. Thus, a reasonable jury would find that the inventors exercised reasonable diligence in reducing the invention to practice.

IV. It Remains Undisputed That Reduction To Practice Of The Claimed Invention Occurred Prior To September 28, 1988

ZymoGenetics' inventors successfully produced a fusion protein prior to September 28, 1988 that satisfied all the limitations of the claimed invention of the ZymoGenetics Patents. Bristol, in its Opposition, argues only that two elements, "dimerization of the fusion protein" and "biologically active," were not reduced to

practice. Its argument fails because of the substantial, undisputed evidence showing that, prior to September 28, 1988, (1) ZymoGenetics' inventors produced a dimerized polypeptide fusion; and (2) this dimerized polypeptide fusion was also biologically active.

A. Substantial Undisputed Evidence Shows Dimerized Polypeptide Fusions Of The Patented Invention Were Reduced To Practice Prior To September 28, 1988

Bristol's argument that ZymoGenetics' inventors failed to reduce the claimed invention to practice prior to September 28, 1988 rests upon the faulty claim that ZymoGenetics' inventors created tetrameric or octomeric fusion proteins instead of dimerized polypeptide fusions. However, this argument fails for the following reasons. First, Dr. Sledziewski testified during his deposition that he created dimerized polypeptide fusions based on experiments and laboratory notebooks. Second, Dr. Purdue confirmed Dr. Sledziewski's testimony that the claimed invention, dimerized polypeptide fusions were reduced to practice prior to September 28, 1988 based on laboratory notebooks of the named inventors of the ZymoGenetics Patents, pondering his opinion from the perspective of one of ordinary skill in the art. Third, tetrameric or octomeric fusion proteins are merely multiples of dimeric fusion proteins to one of ordinary skill in the art. Thus, there is substantial, undisputed factual evidence that ZymoGenetics' inventors reduced the claimed invention to practice prior to September 28, 1988.

1. Dr. Sledziewski Testified He Created A "Dimerized Polypeptide Fusion" Prior To September 28, 1988

It is well established that where testing is required to determine whether the invention works for its intended purpose, the inventor must have "contemporaneously appreciate[d] that the embodiment worked and that it met all the limitations" of the claimed invention. *Cooper v. Goldfarb*, 240 F.3d 1378, 1382 (Fed. Cir. 2001) (quotation omitted). Bristol does not even address Dr. Sledziewski's testimony identified in ZymoGenetics' opening brief regarding reduction to practice of the claimed invention.

Thus, Dr. Sledziewski's testimony regarding reduction to practice as set forth in ZymoGenetics' opening brief, remains undisputed.

Furthermore, additional testimony from Dr. Sledziewski shows that he appreciated that he had obtained the "dimerized polypeptide fusion" of the claimed invention in the 1988 time frame as a result of successful testing and experimentation. He testified that he obtained the claimed invention by performing "standard sort of experiments that you do in the lab by looking at the molecule or size of the produced protein and determining…that [the product] would correspond to dimer size." D.I. 163 (Lee Decl., Ex. 1 (Sledziewski Depo at 83:4, 19-22). He also testified that "all the experiments that were carried out [had] demonstrated that what we [had] produc[ed] [was] a dimer." *Id.* at 83:14-16. Thus, Dr. Sledziewiski's substantial testimony regarding reduction to practice shows that he "contemporaneously appreciate[d] that the embodiment worked and that it met all the limitations" of the claimed invention. *Cooper*, 240 F.3d at 1382 (quotation omitted).

2. Dr. Purdue's Opinion As One of Ordinary Skill In The Art Shows Reduction To Practice Of Dimerized Polypeptide Fusions Occurred Prior To September 28, 1988

Dr. Purdue provided his expert opinion that Dr. Sledziewski reduced to practice the claimed invention from the perspective of one of ordinary skill in the art. Bristol mischaracterizes Dr. Purdue's deposition testimony by alleging that Dr. Purdue "speculated" there was invertase activity by showing Dr. Purdue used the words "think" and "interpretation" in his testimony. However, the citations only provide support that Dr. Purdue was thinking through his opinions, and interpreting the facts using sound reasoning. Bristol, notably, does not dispute the actual substance of Dr. Purdue's testimony.

As explicitly identified in Dr. Purdue's declaration and expert report, Dr. Purdue relied upon ***multiple*** notebook pages of Ms. Bell and Dr. Sledziewski which contradicts

Bristol's incorrect assertion that Dr. Purdue only relied upon a single notebook page for his opinion. *See* D.I. 165 (Purdue Decl., ¶9 and Ex. 1, ¶5). Dr. Purdue cited, as evidence of the first successful reduction to practice, Ms. Bell's notebook entry dated September 1, 1988 which stated [redacted] D.I. 165 (Purdue Decl., ¶¶10-11). Thus, according to Dr. Purdue, the "dimerized polypeptide fusion" of the claimed invention had been formed as of September 12, 1988. Based on an entry dated September 14, 1988, Dr. Purdue opines that the successful expression of the claimed dimerized polypeptide fusion was repeated by ZymoGenetics' scientists. *Id.* (Purdue Decl., ¶11).

In fact, Dr. Purdue reasonably found that there was active invertase activity from the laboratory notebook page of Ms. Bell on September 19, 1988. Dr. Purdue opined that Ms. Bell's notebook showed "the secretion of active invertase following transformation into yeast" on September 19, 1988. *Id.* In her laboratory notebook page dated September 15-19, 1988, [redacted] D.I. 163 (Lee Decl., Ex. 4 (Anne Bell notebook at ZG 040527)). Thus, there is reliable evidence in Ms. Bell's notebook that there was invertase activity. As stated by Dr. Purdue in his deposition, Scott Emr was a "prominent research in the field," and his data was reliable to those of ordinary skill in the art, including Ms. Bell. D.I. 247 (Johnson Decl., Ex. 2 (Purdue Depo. at 235:3-5).

Furthermore, Dr. Purdue specifically stated during his deposition that the Kern article shows "native internal invertase is a dimer" and "dimerization is required and sufficient to generate enzymatic activity." Lee Reply Decl., Ex. 4 (Purdue Depo. at 183:21-184:9). Bristol attempts to show that Dr. Purdue could not definitively conclude whether tetramers or octomers were also obtained by ZymoGenetics' scientists in

addition to dimers. However, this is irrelevant because for invertase activity to exist, it is undisputed that there were dimerized polypeptide fusions present, according to the scientific data shown in the Kern article that Dr. Purdue cites to in his declaration and expert report. *See* D.I. 165 (Purdue Decl., ¶11). Bristol also fails to mention that Dr. Purdue testified "when we talk about tetramers here, this would be two dimers. And octomers would be two tetramers." Lee Reply Decl., Ex. 4 (Purdue Depo. at 185:20-22). To one of ordinary skill in the art, tetrameric or octomeric form was construed as simply a multiple of a dimeric form.

Bristol's attempt to use Dr. Ravetch's opinions as support for their arguments also fail. Dr. Ravetch opined that because the "primary" form of active invertase is octomeric, or that there could have been a mixture of "dimers, tetramers, and octomers," there was no dimeric form.[1] However, notably, in that same statement, Dr. Ravetch admits that dimers ***were*** present, even if there was a mixture. Thus, Dr. Ravetch did not opine that there was ***absolutely no*** dimeric form present, and he did not dispute that the Kern article specifically states that the "native internal invertase is a dimer." Lee Reply Decl., Ex. 5 (Kern article at 120). Thus, Dr. Ravetch does not undermine Purdue's opinions regarding reduction to practice of the claimed invention, and the material facts showing reduction to practice of the claimed invention remain undisputed by Bristol.

3. Dr. Levin's Opinion Does Not Disprove The Substantial, Undisputed Evidence That Dimerized Polypeptide Fusions Were Obtained Prior To September 28, 1988

Bristol also mischaracterizes the testimony of Dr. Levin, a scientist who worked for Dr. Kindsvogel. Dr. Levin specifically testified that he believed pBTL26 data showed successful expression of the dimerized polypeptide fusion, consistent with Dr. Purdue's opinions. Lee Reply Decl., Ex. 6 (Levin Depo. at 74:19-75:1); D.I. 165 (Purdue Decl.,

[1] Dr. Ravetch's opinions set forth in his declaration in support of Bristol's Opposition statement should be excluded for the reasons set forth in Section V. *See also* D.I. 160 (Opening Brief).

¶10). Bristol tries to make great significance out of the fact that Dr. Levin stated there was no ***explicit*** mention of the size of the proteins from Ms. Bell's laboratory notebook pages, but Dr. Levin never stated that there was no dimerized polypeptide fusion created. Simply because there was no explicit writing of the words "dimerized polypeptide fusion" in the laboratory notebook pages of Ms. Bell did not mean that the dimerized polypeptide fusion was not obtained. *See Mycogen Plant Science v. Monsanto Co.*, 243 F.3d 1316, 1336 (Fed. Cir. 2001) (citation omitted) ("[t]he invention is not the *language* of the count, but the subject matter thereby defined."). Though there was no specific use of the exact term "dimerized polypeptide fusion," [redacted] show that there was reduction to practice of the claimed invention prior to September 28, 1988 according to one of ordinary skill in the art. *See* D.I. 165 (Purdue Decl., ¶¶10-12).

4. Schendel Is Not Persuasive Authority

Bristol makes a failed attempt to analogize this case to the facts of *Schendel v. Curtis*. 83 F.3d 1399 (Fed. Cir. 1996). Contrary to *Schendel*, there is sufficient evidence in this action to show the inventors created a dimerized polypeptide fusion. First, unlike the case in *Schendel*, complete plasmids were created to express the dimerized polypeptide fusion, not just "portions" of plasmids. 83 F.3d at 1403; D.I. 165 (Purdue Decl., ¶10). Second, unlike the case in *Schendel* where there was no indication that the inventor used primers that he had ordered to prepare the necessary plasmid, the inventors in this case actually used the same primers that they had ordered to create their necessary plasmid. *Id.* Third, unlike the case in *Schendel* where the inventor failed to show he obtained fusion of individual components of the fusion protein, there is no evidence in this case to support a finding that the actual product was a mixture of the individual PDGF-R and immunoglobulin components rather than a fusion of the two molecules. Rather, it is clear that there was a dimerized polypeptide fusion based on the testing that

was completed by ZymoGenetics' scientists. D.I. 165 (Purdue Decl., ¶¶10-12). Because *Schendel* is distinguishable from this case, it is not persuasive authority. Based on these reasons, Bristol's arguments fail to dispute the substantial evidence that dimerized polypeptide fusions (dimeric fusion proteins) were created by ZymoGenetics scientists prior to September 28, 1988. A reasonable jury would have to find based on the testimony of the inventor of the claimed invention, and corroborating laboratory notebook pages that dimerized polypeptide fusions were reduced to practice before September 28, 1988.

B. It Remains Undisputed That "Biologically Active" Fusion Proteins Of The Patented Invention Were Reduced To Practice Prior To September 28, 1988

The undisputed evidence set forth by ZymoGenetics shows that there was reduction to practice of a "biologically active" dimerized polypeptide fusion prior to September 28, 1988. The term "biologically active" means "exhibits one or more biological activities of its native counterpart."[2] D.I. 169 (Andre Decl., Ex. 1 ('725 Patent, at col. 9, ll. 44-45); *id.*, Ex. 2 ('026 Patent, col. 9, ll. 61-63). [redacted][3] *See* D.I. 163 (Lee Decl., Ex. 4 (Bell notebook at ZG 040518-22, 040523-25)); see also D.I. 165 (Purdue Decl.,¶¶9-12).

Bristol mischaracterizes the testimonies of Dr. Levin and Dr. Purdue. Though Dr. Levin testified that he "ha[d] not seen anything to address" whether the PDGFR portion or Ig portion of the fusion protein was competing binding assays, Dr. Levin never stated that binding of the PDGFR portion never occurred prior to September 28, 1988. Rather,

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[2] As stated in ZymoGenetics' rebuttal claim construction brief, if the Court chooses to construe the term "biologically active," ZymoGenetics does not dispute Bristol's proposed claim construction.

[3] This argument is consistent with ZymoGenetics' infringement arguments regarding "biological activity."

based on the substantial evidence, it is evident that the PDGFR portion of the fusion protein was binding ligand. For example, these assays were cited to by Dr. Purdue as evidence to one of ordinary skill in the art that the dimerized polypeptide fusions were exhibiting biological activity. *See* D.I. 165 (Purdue Decl., ¶11). Also, the laboratory notebook entries subsequent to the binding assays show [redacted] and the claimed fusion protein was, therefore, biologically active. *Id.*

Dr. Purdue based his opinion that the fusion protein was "functional" and "biologically active" based on the data on the particular page of [redacted] in Ms. Bell's notebook on [redacted] ***as well as*** subsequent experiments that he observed in her notebook. [redacted] *See* Lee Decl., Ex. 4 (Bell notebook at ZG 040525). Thus, prior to September 28, 1988, there was substantial, undisputed evidence that ZymoGenetics' scientists had produced a "biologically active" dimerized polypeptide fusion.

As required for there to be reduction to practice, Dr. Sledziewski also "contemporaneously appreciated that the embodiment met all the limitations" of the claimed invention, including being "biologically active." *Cooper*, 240 F.3d at 1382 (citation omitted). Bristol does not even attempt to dispute Dr. Sledziewski's testimony. Dr. Sledziewski stated in his deposition that he used "standard tools" in the laboratory in order to determine whether he had obtained biological activity of the claimed fusion protein: "[We used] [a]ll the standard molecular biology toolbox to help you determine that what you are making is what you expect to make, and then you measure biological activity of what you are making and that adds on the top of what you are observing and concluding that this is what you generated." Lee Decl., Ex. 1 (Sledziewski Depo. at 84:23-85:3); *see also* D.I. 247 (Johnson Decl., Ex. 1 (Sledziewski Depo. at 90:21-23)).

Dr. Sledziewski also testified that reduction to practice occurred in the 1988 time frame. D.I. 163 (Lee Decl., Ex. 1 (Slewziewski Depo. at 83:4; *see also* 77:3-4; 81:24-82:22)).

Dr. Ravetch's conclusory opinion that the construction of fusion proteins in the late 1980s involved extensive experimentation and involved a great degree of uncertainty contradicts that generating fusion proteins, generally, was well known to one of ordinary skill in the art by 1988. *See supra,* § II.B. Based on all the corroborating evidence and inventor testimony, it cannot be disputed that ZymoGenetics' inventors reduced all the limitations of the claimed invention to practice prior to September 28, 1988.

V. Dr. Ravetch's Declaration Is Highly Prejudicial And Should Not Be Considered

Where expert opinions, or supplements thereto, are submitted after the close of discovery, the court may refuse entry of the report or of any new material under Federal Rule 37 (b) 2(B). *See Trilogy Commc'ns, Inc. v. Times Fiber Commc'ns, Inc.,* 109 F.3d 739, 745 (Fed. Cir. 1997) (upholding the denial of expert's reports and affidavit submitted after the close of discovery). Bristol's reliance on Dr. Ravetch's declaration of June 2, 2008 containing opinions that were never disclosed during expert discovery is improper and highly prejudicial to ZymoGenetics. This declaration regarding conception and reduction to practice came after the close of fact and expert discovery, and after ZymoGenetics had submitted this motion, foreclosing a fair opportunity for ZymoGenetics to cross-examine Dr. Ravetch on these new opinions. Indeed, Dr. Ravetch did not testify on the subject matter disclosed in his declaration when he was deposed on May 20, 2008.

Bristol claims that it was unreasonable for Dr. Ravetch to address conception and reduction to practice in a detailed fashion in his opening expert report because there were too many laboratory notebook pages for Dr. Ravetch to review. However, this argument is merely an excuse for the improper belatedness of Dr. Ravetch's declaration. Before the date that Dr. Ravetch had drafted his opening expert report on invalidity,

ZymoGenetics had complied with Magistrate Thynge's order, prompted by Bristol's request, to reduce the number of laboratory pages identified in response to Bristol's interrogatory concerning conception and reduction to practice. D.I. 109 (October 4, 2007 Hearing Transcript at 43-44); D.I. 125 (October 18, 2007 Hearing Transcript at 6:3-14). In fact, the Court pushed back the submission deadline for Dr. Ravetch's opening report regarding invalidity because Bristol's counsel alleged that "the invalidity report hinge[s] on the experts' analysis of the lab notebook pages and the testimony relating to reduction to practice." D.I. 125 (October 18, 2007 Hearing Transcript at 28:14-16). Yet, even after extended time was afforded to Dr. Ravetch and the number of laboratory notebook pages was reduced by ZymoGenetics, Dr. Ravetch did not provide a substantive opinion on conception or reduction to practice in his opening report, and his opinions were extremely bare-boned and conclusory.[4] D.I. 171, Ex. 9 (Opening Ravetch Expert Report); *see also* D.I. 158, 223 (ZymoGenetics' Motion to Exclude Testimony of Bristol-Myer Squibb Co.'s Experts). If Bristol had truly felt that ZymoGenetics' subsequent reduction of pages was inadequate in response to Bristol's interrogatory, it could have complained, but it did not do so.

Even if Dr. Ravetch had desired to supplement his expert report subsequent to Dr. Purdue's rebuttal report, he did not do so. Subsequent to Dr. Purdue's expert report on conception and reduction to practice on January 25, 2007, Dr. Ravetch had about three and a half months to rebut Dr. Purdue's opinions before expert discovery closed, but he did not. Instead, Dr. Ravetch submitted a supplemental expert report on April 24, 2008

[4] Contrary to Bristol's representation, ZymoGenetics did not "dump" documents upon Bristol in response to Bristol's interrogatory regarding reduction to practice. Rather, Bristol requested in its broad interrogatory that ZymoGenetics identify "***all*** supporting documents" for "the date and location where the subject matter was (i) conceived (ii) first observed experimentally, (iii) first described in a document, (iv) first reduced to practice, and (v) first disclosed to a person other than the inventors." Bristol's Interrogatory No. 4 (emphasis added). Pursuant to Magistrate Thyne's order that was prompted by Bristol's request, ZymoGenetics reduced the number of documents in a subsequent supplemental response. *See* D.I. 125 (October 18, 2007 Hearing Transcript at 6:3-14).

related to Bristol's noninfringement arguments, but he failed to include any opinion whatsoever regarding conception or reduction to practice in that supplemental report. Dr. Ravetch's new opinions in his declaration comes four months from the submission of Dr. Purdue's report, six months from the submission of his original expert report on conception and reduction to practice, and weeks after his deposition. Because Dr. Ravetch's belated declaration is unfairly prejudicial to ZymoGenetics, it should not be considered.

CONCLUSION

For the reasons set forth in ZymoGenetics' opening brief and herein, the Court should grant ZymoGenetics summary judgment that the ZymoGenetics Patents are valid over the Capon and Seed patents because they are not prior art.

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FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Philip A. Rovner, hereby certify that on September 2, 2008, the within document was filed with the Clerk of the Court using CM/ECF which will send notification of such filing(s) to the following; that the document was served on the following counsel as indicated; and that the document is available for viewing and downloading from CM/ECF.

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