**IN THE UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

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| ZYMOGENETICS, INC., a Washington Corporation,<br><br>Plaintiff,<br>v.<br><br>BRISTOL-MYERS SQUIBB CO., a Delaware Corporation, and DOES 1 through 100,<br><br>Defendants. | ) | C. A. No: 06-500-SLR-MPT<br><br>**REDACTED PUBLIC VERSION** |

**DECLARATION OF JEFFREY V. RAVETCH, M.D., PH.D. IN SUPPORT OF BRISTOL-MYERS SQUIBB'S RESPONSE TO PLAINTIFF ZYMOGENETICS, INC.'S STATEMENT OF MATERIAL FACTS AS TO WHICH THERE IS NO GENUINE ISSUE TO BE TRIED AND LEGAL ISSUES IN SUPPORT OF PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT OF VALIDITY OF PATENTS-IN-SUIT WITH RESPECT TO THE CAPON PATENTS AND SEED PATENT**

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*Attorneys for Defendant Bristol-Myers Squibb Co.*

Dated: June 2, 2008

1. I provide my expert opinion as set forth in this Declaration of Jeffrey V. Ravetch, M.D., Ph.D, In Support Of Bristol-Myers Squibb's Response To Plaintiff ZymoGenetics Inc.'s Statement Of Material Facts As To Which There Is No Genuine Issue To Be Tried And Legal Issues In Support of Plaintiff's Motion for Summary Judgment of Validity of Patents-In-Suit With Respect to the Capon Patents and Seed Patent ("Declaration") regarding the invalidity of United States Patent Nos. 5,843,725 ("the '725 patent") and 6,018,026 ("the '026 patent").

2. This Declaration is provided to address ZymoGenetics' positions on conception and reduction to practice, which were not articulated until the Disclosure of Rebuttal Expert Testimony of Paul Edward Purdue Ph.D. Pursuant to Fed. R. Civ. P. 26(a)(2) ("Purdue Rebuttal Report"). I was advised by attorneys for Bristol that there was no scheduled opportunity for a reply to the Purdue Rebuttal Report and I did not prepare such a reply. I was advised by attorneys for Bristol that the Motion for Summary Judgment of Validity of Patents-In-Suit With Respect to the Capon and Seed Patents was accompanied by the Declaration of Paul Edward Purdue, Ph.D., In Support of ZymoGenetics, Inc.'s Motion for Summary Judgment of Validity of Patents-In-Suit With Respect to the Capon and Seed Patents ("the Purdue Declaration"), and I was asked to respond to statements made therein regarding conception and reduction to practice. Therefore, I provide below my opinion on conception and reduction to practice as addressed in the Purdue Declaration.

3. I have been advised by attorneys for Bristol that ZymoGenetics has asserted a conception date of no later than January 4th and 5th, 1988 and relied upon the

**REDACTED**

as support for the conception of the invention in the '725 and '026 patents.

**REDACTED**

4. I have been advised by Bristol attorneys that conception is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention as it is to be applied in practice. Conception is complete when the idea is so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation. Under some circumstances, especially in cases where there is no reasonable certainty that the experiment will produce the desired result, conception

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[1] Citations to exhibits with the prefix "Ex." are attached to the Declaration of Hannah Lee In Support of Plaintiff ZymoGenetics, Inc.'s Motion For Summary Judgment Of Validity Of Patents-In-Suit With Respect To The Capon Patents and The Seed Patent filed with the Motion For Summary Judgment Of Validity Of Patents-In-Suit With Respect To The Capon Patents And Seed Patent (D.I. 163-64; 188-89).

does not occur until the inventor has actually reduced the invention to practice through successful experiment. I have been advised by Bristol attorneys that conception must be proven by corroborated evidence which show that the inventor disclosed to others his complete thought expressed in such clear terms as to enable those skilled in the art to make the invention. I have been advised by Bristol attorneys that a showing of actual reduction to practice requires the construction of an embodiment of the invention that meets all of the claim limitations and the determination that the invention would work for its intended purpose.

5.

**REDACTED**

REDACTED

This uncorroborated testimony does not evidence a definite and permanent idea of the complete and operative invention because it does not disclose a biologically active dimerized polypeptide fusion which is a claim limitation of each of the asserted claims of the patents-in-suit.

6.

REDACTED

REDACTED

fails to provide sufficient information to a person of ordinary skill that conception of the '725 and '026 patents was so clearly defined in the inventor's mind that only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation.

7.

REDACTED

REDACTED

8.

does not provide support for the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention claimed in the

'725 and '026 patents as would be understood by one of ordinary skill in the art.

**REDACTED**

provides no support that biologically active dimerized polypeptide fusion proteins were made or contemplated.

9.

**REDACTED**

REDACTED

10. REDACTED

does not provide corroborating evidence that the listed inventors conceived of the invention claimed in the '725 and '026 patents on a date no later than January 4th-5th, 1988.

11.

REDACTED

fails to evidence conception for the limitation that the non-immunoglobulin "requires dimerization for biological activity".

12. REDACTED

does not provide support for the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention claimed in the '725 and '026 patents as would be understood by one of ordinary skill in the art.

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REDACTED

REDACTED

does not provide support for conception of the invention, because it provides no guidance to one of skill in the art of a definite and permanent idea of the complete and operative invention. REDACTED does not contain any evidence that biologically active dimerized polypeptide fusions were made or contemplated.

13. REDACTED

does not provide corroborating evidence that the listed inventors conceived of the invention claimed in the '725 and '026 patents on a date no later than January 4th-5th, 1988.

14.

REDACTED

REDACTED

15. In the late 1980's, construction of mammalian fusion proteins involved extensive experimentation. Design of expression plasmids required skilled technicians and involved a great degree of uncertainty. Achievement of a desired result involved more than a mere schematic drawing of a proposed expression vector or thoughts on a page as to how to design and express a mammalian fusion protein. Given the great degree of uncertainty involved in mammalian fusion protein plasmid design and expression therefrom in the late 1980's, it is my opinion that the listed inventors could not have had conception at least until there was a practical demonstration of reduction to practice of the claimed inventions of the '725 and '026 patents, i.e. expression of a secreted, biologically active dimerized non-immunoglobulin requiring dimerization for biological activity joined to a dimerizing protein. To show reduction to practice of the claimed invention of the '725 and '026 patents, I am informed that the support must demonstrate actual expression of a non-immunoglobulin polypeptide fusion and include evidence in support for the expressed protein's dimerization state and biological activity.

16. I have been advised by Bristol's attorneys that ZymoGenetics has asserted a reduction to practice date prior to September 28, 1988 and

REDACTED

REDACTED

I disagree that these notebook pages and expert opinions provide support for conception and/or reduction to practice of the invention in the '725 and '026 patents and discuss each cited document in the paragraphs below.

17. REDACTED does not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents.

REDACTED cannot demonstrate that the listed inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

[3] All Bristol Exhibits ("BMS Ex.") may be found attached to the Declaration of Dana Lau In Support of Bristol-Myers Squibb Company's Response to ZymoGenetics, Inc.'s Statement Of Undisputed Material Facts And Legal Issues Upon Which Judgment Is Sought In Support Of Summary Judgment Of Validity Of Patents-In-Suit.

18. REDACTED do not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents.

REDACTED

cannot demonstrate that the listed inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

19. REDACTED does not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents

REDACTED

cannot demonstrate that the listed

inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

20. REDACTED

do not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents.

REDACTED

REDACTED

cannot demonstrate that the listed inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein because

REDACTED

21.

do not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents.

REDACTED

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22. REDACTED cannot demonstrate that the listed inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

22. REDACTED do not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents.

REDACTED

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6

REDACTED

cannot demonstrate that the listed inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

REDACTED

23.

does not provide support for conception or reduction to practice of the complete and operative invention claimed in the '725 and '026 patents.

REDACTED

REDACTED

: cannot

demonstrate that the listed inventor had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

24.

REDACTED

:annot demonstrate that ZymoGenetics had

reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

25.

REDACTED

None of the cited laboratory notebook pages and oligonucleotide request forms, as discussed in detail above, demonstrate that ZymoGenetics had reduced to practice a

biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

26.

**REDACTED**

None of the cited laboratory notebook pages, as discussed in detail above, demonstrates that ZymoGenetics had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

**REDACTED**

BMS Ex. 4, Kern 1992 does not demonstrate that the PDGF receptor/invertase fusion protein expressed from pBTL26 was a dimer. Instead, BMS Ex. 4, Kern 1992 discloses that active glycosylated invertase expressed in the eukaryotic cells used to express ZymoGenetics' PDGF receptor/immunoglobulin and PDGF receptor/invertase soluble fusion proteins is a mixture of dimers, tetramers and octamers.[8] Moreover, a publication by BMS Ex. 5, Esmon 1987 disclosed that active glycosylated invertase is primarily in the form of an octamer. Therefore, BMS Ex. 4, Kern 1992 cannot evidence that the PDGF receptor/invertase soluble fusion protein expressed from BTL26 was a dimer. As such, BMS Ex. 4, Kern 1992 cannot demonstrate

[7] See also FN 6.

[8] **REDACTED**

that ZymoGenetics had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

27.

**REDACTED**

None of the cited laboratory notebook pages and oligonucleotide request forms, as discussed in detail above, demonstrates that ZymoGenetics had reduced to practice a biologically active non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein.

I declare under penalty of perjury under the laws of the United States that all statements made herein of my own knowledge are true and correct, and that all statements made on information and belief are believed to be true.

Jeffrey V. Ravetch, M.D., Ph.D.

Date: 6/02/08

**UNITED STATES DISTRICT COURT**
**DISTRICT OF DELAWARE**

**CERTIFICATE OF SERVICE**

I HEREBY CERTIFY that on June 2, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF and caused the same to be served on the plaintiff at the address and in the manner indicated below:

**BY HAND DELIVERY AND E-MAIL**

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**UNITED STATES DISTRICT COURT**
**FOR THE DISTRICT OF DELAWARE**

**CERTIFICATE OF SERVICE**

I hereby certify that on June 6, 2008, I electronically filed the foregoing document with the Clerk of the Court using CM/ECF which will send notification of such filing to the following and which has also been served as noted:

**BY HAND DELIVERY**

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I hereby certify that on June 6, 2008, the foregoing document was sent to the following non-registered participants in the manner indicted:

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