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-MPT **PUBLIC VERSION**

PLAINTIFF ZYMOGENETICS, INC.'S RESPONSE STATEMENT OF MATERIAL FACTS AS TO WHICH THERE IS A GENUINE ISSUE TO BE TRIED AND LEGAL ISSUES IN OPPOSITION TO DEFENDANT BRISTOL-MYERS SQUIBB COMPANY'S MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

Philip A. Rovner (#3215)
POTTER ANDERSON & CORROON LLP
Hercules Plaza
P. O. Box 951
Wilmington, DE 19899
(302) 984-6000
provner@potteranderson.com

Attorneys for Plaintiff ZymoGenetics, Inc.

OF COUNSEL:

Paul J. Andre
Lisa Kobialka
KING & SPALDING LLP
1000 Bridge Parkway
Suite 100
Redwood Shores, CA 94065
(650) 590-0700

Dated: June 2, 2008
Public Version: June 9, 2008

ZymoGenetics, Inc. ("ZymoGenetics") has asserted that Bristol-Myers Squibb Co. ("Bristol") infringes Claims 1-3, 5, 6, 21, 22, 24, 25, 50, and 51 of U.S. Patent No. 5,843,725 ("the '725 Patent") and Claims 1-4, 7, and 30 of U.S. Patent No. 6,018,026 ("the '026 Patent") (collectively, "Patents-in-Suit"). In accordance with Paragraph 3 of the Court's Revised Scheduling Order of March 13, 2008 (D.I. 148), ZymoGenetics submits this Response Statement of Material Facts As To Which There is a Genuine Issue to Be Tried and Legal Issues in Opposition to Defendant Bristol-Myers Squibb Company's Motion for Summary Judgment of Noninfringement. With reasons set forth below, ZymoGenetics states whether the facts set forth by Bristol in its Statement are "undisputed" or "disputed." Bristol seeks to include opinion testimony and legal conclusion as alleged undisputed fact, including arguments and responses to hypothetical questions. In addition, Bristol refers to nonexistent claim limitations of the Patents-in-Suit as undisputed fact. Bristol also improperly attempts to characterize opinion testimony as fact by using the word "admitted" throughout its statement.

Pursuant to the Court's Revised Scheduling Order dated March 13, 2008, Paragraph 3, the record evidence cited by ZymoGenetics below constitutes only that evidence which directly rebuts the facts which Bristol alleges are undisputed in its underlying summary judgment motion. Bristol's statement of undisputed facts in support of its summary judgment motion is not comprehensive, and therefore the evidence cited below is not exhaustive of the evidence which ZymoGenetics would include in any opposition to Bristol's summary judgment motion. ZymoGenetics reserves the right to rely on record evidence not cited below in any such opposition. These disputed facts pertain to the legal issue of whether Orencia satisfies the claim elements in the asserted claims of the Patents-in-Suit.

STATEMENT OF DISPUTED FACTS

I. "dimerizing protein"

1. Not disputed. This is a legal contention, not a factual statement, and is not in dispute. The claim term "dimerizing protein" should be construed as the Patents-in-Suit have explicitly defined them. *See* Joint Claim Construction Chart (D.I.153), Ex. A at 3-4; *see also* ZymoGenetics' Opening Claim Construction Brief (D.I. 156) at 11-12.

2. Disputed. ZymoGenetics' expert, Dr. Nicholas Gascoigne, [redacted] *See* Declaration of John W. Kirkland in Support of Bristol-Myers Squibb Company's Motion for Summary Judgment of Noninfringement ("Kirkland Decl."), Ex. 22 (Deposition of Nicholas Gascoigne ("Gascoigne Tr.")) at 204:2-11 (emphasis added). Dr. Gascoigne and others have testified [redacted] *See* Ex. 1 attached hereto ZymoGenetics' Response Statement of Material Facts ("Resp.") (Disclosure of Expert Testimony for Nicholas R. J. Gascoigne ("Gascoigne Report") at ¶17; Ex. 2 (Disclosure of Expert Testimony for David A. Ostrov ("Ostrov Report")) at ¶20; Ex. 3 (Dr. Linsley Deposition Testimony) at BMS004256417-418 (69:24-70:10); Ex. 4 [redacted] at BMS003504382-84; Ex. 5 [redacted] at BMS001596163-64; Ex. 6 [redacted] at BMS001463910; Ex. 7 (Hollenbaugh Reference) at BMS003700192-198[1]; *see also* Declaration of Paul J. Andre in Support of ZymoGenetics' Motion for Summary Judgment of Infringement of the Patents-in-Suit ("Andre Decl."), Ex. 14 (Deposition of David A. Ostrov ("Ostrov Tr.") at 262:24-264:1, 271:14-17; Resp. Ex. 12 (Ostrov Tr.) at 274:8-14; Andre Decl., Ex. 6 (Deposition of Kirk Leister ("Leister Tr.") at 30:25-31:9,

[1] Citations to "Resp. Ex." refer to exhibits directly attached hereto.

Ex. 18 (Deposition of Steven Nadler, September 20, 2007 ("Nadler II") at 63:12-21, Ex. 5 [redacted] at BMS001290162; Kirkland Decl., Ex.10 (Linsley JBC 1995 ("Linsley I") at BMS003700202.

3. Disputed. Dr. Gascoigne stated that [redacted] Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 204:21-205:2. [redacted] *See* Andre Decl., Ex. 14 (Ostrov Tr.) at 262:24-264:1, 271:14-17; *see also* Resp. Ex. 12 (Ostrov Tr.) at 274:8-14; Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9, Ex. 18 (Nadler Tr.) at 63:12-21, Ex. 5 (BLA) at BMS001290162; Resp. Ex. 1 (Gascoigne Report) at ¶¶17-19, Ex. 2 (Ostrov Report) at ¶20, Ex. 3 (Dr. Linsley Deposition Testimony) at BMS004256417-418 (69:24-70:10), Ex. 4 [redacted] at BMS003504382-84, Ex. 5 [redacted] at BMS001596163-64, Ex. 6 [redacted] at BMS001463910, Ex. 7 (Hollenbaugh Reference) at BMS 003700192-198; Kirkland Decl., Ex.10 (Linsley I) at BMS003700202.

4. Disputed. This is a nonsensical statement of fact: either an immunoglobulin in its native form is a tetramer, or when part of the CTLA4-Ig fusion protein, is always a dimer. *See* Andre Decl., Ex. 5 [redacted] at BMS001290162; *see also,* Ex. 4 (Orencia® product insert) at 1. Moreover, a paper written by Bristol scientists states that the Ig portion of Bristol's CTLA4-Ig was mutated for the purpose of "reduc[ing] binding to Fc receptors". *See* Resp. Ex. 7 (Hollenbaugh Reference) at BMS003700193. Dr. Kirk Leister, [redacted] *See* Andre Decl., Ex. 6 (Leister Tr.) at 53:8-12; *see also* Resp. Ex. 8 (Deposition testimony from Dr. David Smolin, [redacted] ("Smolin Tr.") at 37:12-17; Andre Decl. Ex. 11 (Deposition testimony from Dr. Gary Nadler on August 3,

2007, [redacted] ("Nadler I") at 27:19-25.

5. Not disputed. [redacted] Kirkland Decl., Ex. 16 [redacted] at BMS001290349.

6. Disputed. Dr. Gascoigne never made any admission, but opined that [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 210:3-12. [redacted] *See e.g.* Andre Decl., Ex. 14 (Ostrov Tr.) at 262:24-264:1, 271:14-17; *see also* Resp. Ex. 12 (Ostrov Tr.) at 274:8-14, Ex. 2 (Ostrov Report) at ¶20, Ex. 3 (Dr. Linsley Deposition Testimony) at BMS004256417-418 (69:24-70:10), Ex. 4 [redacted] at BMS003504382-84, Ex. 5 [redacted] at BMS001596163-64, Ex. 6 [redacted] at BMS001463910; Kirkland Decl., Ex.10 (Linsley I) at BMS003700202; Andre Decl., Ex. 5 (BLA) at BMS001290162, Ex. 6 (Leister Tr.) at 30:25-31:9, Ex. 18 (Nadler II) at 63:12-21; Resp. Ex. 1 (Gascoigne Report) at ¶¶17-19, Ex. 7 (Hollenbaugh Reference) at BMS 003700192-198.

7. Disputed. Dr. Gascoigne never admitted that [redacted] Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 202:25-203:2; 203:21-23. As it turns out, experiments by both Bristol scientists as well as Dr. Ostrov, prove [redacted] Andre Decl., Ex. 14 (Ostrov Tr.) at 262:24-264:1, 271:14-17; Resp. Ex. 12 (Ostrov Tr.) at 274:8-14, Ex. 2 (Ostrov Report) at ¶20, Ex. 3 (Dr. Linsley Deposition Testimony) at BMS004256417-418 (69:24-70:10),

Ex. 4 [redacted] at BMS003504382-84, Ex. 5 [redacted] at BMS001596163-64, Ex. 6 [redacted] at BMS001463910; Kirkland Decl., Ex.10 (Linsley I) at BMS003700202; Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9, Ex. 18 (Nadler II) at 63:12-21; Resp. Ex. 7 (Hollenbaugh Reference) at BMS003700192-198; Andre Decl., Ex. 5 [redacted] at BMS001290162; Resp. Ex. 1 (Gascoigne Report) at ¶¶17-19.

8. Disputed. This statement is nonsensical because there is no [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 202:20; Resp. Ex. 13 (Gascoigne Tr.) at 16:20-17:1. [redacted] *See* Resp. Ex. 1 (Gascoigne Report) at ¶3. In fact, experiments prove that [redacted] *See e.g.* Andre Decl., Ex. 14 (Ostrov Tr.) at 262:24-264:1, 271:14-17; Resp. Ex. 12 (Ostrov Tr.) at 274:8-14, Ex. 2 (Ostrov Report) at ¶20, Ex. 3 (Dr. Linsley Deposition Testimony) at BMS004256417-418 (69:24-70:10), Ex. 4 [redacted] at BMS003504382-84, Ex. 5 [redacted] at BMS001596163-64, Ex. 6 [redacted] at BMS001463910; Kirkland Decl., Ex.10 (Linsley I) at BMS003700202; Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9, Ex. 18 (Nadler II) at 63:12-21; Resp. Ex. 7 (Hollenbaugh Reference) at BMS003700192-198; Andre Decl., Ex. 5 [redacted] at BMS001290162; Resp. Ex. 1 (Gascoigne Report) at ¶¶17-19.

9. Disputed. Mr. Gary Parker never admitted that [redacted]

[redacted] *See* Resp. Ex. 14 (Deposition of Gary Parker ("Parker Tr.) at 30:1-34:9.

10. Disputed. Dr. Wayne Kindsvogel never [redacted] Kirkland Decl., Ex. 27 (Deposition of Wayne Kindsvogel ("Kindsvogel Tr.") at 92:12-16 (emphasis added). Contrary to Bristol's misinterpretation, he specifically stated that [redacted] Id. at 91:17-25.

11. Disputed. Dr. Gascoigne never [redacted] Id. at 80:13-15. He also opined that the [redacted] *See* Resp. Ex. 13 (Gascoigne Tr.) at 81:20-24; 82:23-83:5; 85:24-86:4.

12. Disputed. The asserted claims of the Patents-in-Suit require that the "dimerizing protein" be "selected from the group consisting of yeast invertase, at least a portion of an immunoglobulin light chain comprising at least an immunoglobulin light chain constant region domain, and at least a portion of an immunoglobulin heavy chain comprising at least an immunoglobulin heavy chain constant region domain." Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844. Drs. Gascoigne and Ostrov opined [redacted]

[redacted] Resp. Ex. 1 (Gascoigne Report) at ¶14; Ex. 2 (Ostrov Report) at ¶6. [redacted] Kirkland Decl., Ex. 10 (Linsley I) at BMS003700202.

13. Not disputed.

14. Disputed. Dr. Ostrov testified that [redacted] Andre Decl., Ex. 14 (Ostrov Tr.) at 262:24-264:1; 271:14-17; Resp. Ex. 12 (Ostrov Tr.) at 274:8-14; Ex. 2 (Ostrov Report) at ¶20. [redacted] Id. [redacted] *See* Resp. Ex. 2 (Ostrov Report) at ¶3. In his deposition, Dr. Ostrov specifically pointed to an article published by a Nobel Prize winning scientist as evidence that the CH2 and CH3 domains of immunoglobulin heavy chain dimerize. Andre Decl., Ex. 14 (Ostrov Tr.) at 262:24-264:1; 271:14-17; Resp. Ex. 12 (Ostrov Tr.) at 274:8-14, Ex. 2 (Ostrov Report) at ¶20; Ex. 3 (Dr. Linsley Deposition Testimony) at BMS004256417-418 (69:24-70:10), Ex. 4 [redacted] at BMS003504382-84, Ex. 5 [redacted] at BMS001596163-64, Ex. 6 [redacted] at BMS001463910; Kirkland Decl., Ex.10 (Linsley I) at BMS003700202; Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9, Ex. 18 (Nadler II) at 63:12-21; Resp. Ex. 7 (Hollenbaugh Reference) at BMS003700192-198; Andre Decl., Ex. 5 [redacted] at BMS001290162; Resp. Ex. 1 (Gascoigne Report) at ¶¶17-19.

15. Disputed. Dr. Purdue never made an "admission" that the [redacted] Bristol's question improperly asked a technical expert to answer a question that called for a legal conclusion. Dr. Purdue opined that [redacted] *See* Resp. Ex. 15 (Deposition of Paul E. Purdue ("Purdue Depo.") at 114:22-117:4. Indeed, [redacted]

[redacted] Kirkland Decl., Ex. 10 (Linsley I) at BMS003700202.

16. Disputed. This is a legal conclusion. The Patent Claims require that a non-immunoglobulin polypeptide requiring dimerization for biological activity be joined to a dimerizing protein selected from a group. *See e.g.* Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at 000844. Bristol is improperly attempting to read limitations into the claims. The claims state nothing about the whether or not the non-immunoglobulin need be or can be a dimerizing protein.

17. Disputed. Dr. Gascoigne never [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 32:17-23. Dr. Gascoigne was clear in his expert report that [redacted] Resp. Ex. 1 (Gascoigne Report) at ¶14. [redacted] Kirkland Decl., Ex. 10 (Linsley I) at BMS003700205. Indeed, [redacted] Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9; Ex. 18 (Nadler II) at 63:12-21. [redacted]

18. Disputed. Dr. Gascoigne stated [redacted] Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 36:10-17; Resp. Ex. 13 (Gascoigne Tr.) at 33:9-14. [redacted] *See* Kirkland Decl., Ex. 10 (Linsley I) at BMS 003700205. [redacted] Id. [redacted] Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9; Ex. 18 (Nadler II) at 63:12-21. Bristol fails to

distinguish between the extracellular domain of CTLA-4 in CTLA4-Ig, from the native form of CTLA-4 in its statements.

19. Disputed. This is a non-sensical statement because Bristol is using the extracellular domain of CTLA-4 and natural CTLA-4 interchangeably. [redacted] Kirkland Decl., Ex. 10 (Linsley I) at BMS003700205. [redacted] *See e.g.* Resp. Ex. 2 (Ostrov Report) at ¶6; Resp. Ex. 1 (Gascoigne Report) at ¶14; Kirkland Decl., Ex. 12 (Schwartz I) at 604 (CTLA-4 is a disulfide-linked homodimer); Kirkland Decl., Ex. 14 (Schwartz II) at 432. Bristol confuses these facts. Dr. Gascoigne stated [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 36:10-17; Resp. Ex. 13 (Gascoigne Tr.) at 33:9-14; *see also* Kirkland Decl., Ex. 10 (Linsley I) at BMS003700205. [redacted] Id. [redacted] Andre Decl., Ex. 6 (Leister Tr.) at 30:25-31:9; Ex. 18 (Nadler II) at 63:12-21. Thus, Bristol fails to distinguish the difference between the extracellular domain of CTLA-4 in CTLA4-Ig from the native form of CTLA-4.

20. Disputed. This is a legal conclusion based on claim interpretation, and is not fact. Dr. Gascoigne never [redacted] The question posed to Dr. Gascoigne at his deposition erroneously stated that [redacted] Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844. Moreover, even in the context of such an erroneous interpretation of the claim meanings, Dr. Gascoigne's response was that [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 217:14. Dr. Gascoigne

stated that he [redacted] Id. at 217:16; Resp. Ex. 13 (Gascoigne Tr.) at 218:4-5. The Patents-in-Suit only require that the non-Ig requiring dimerization for biological activity be joined to a dimerizing protein selected from a group. Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844. Bristol is improperly attempting to read into the claims a limitation that does not exist.

II. "requiring dimerization for biological activity"

21. Not disputed.

22. Disputed. ZymoGenetics stated that its claim construction position is that "requiring dimerization for biological activity" should be afforded its ordinary meaning within the context of the claims of the Patents-in-suit. Joint Claim Construction Chart (D.I. 153), Ex. A at 2. In addition, ZymoGenetics provided specific definitions for the terms contained in this statement: biological activity and dimerizing protein.

23. Disputed. Dr. Gascoigne opined that [redacted] Resp. Ex. 1 (Gascoigne Report) at ¶14 and ¶25. The testimony given in this instance is in response to a hypothetical question. When asked the following hypothetical question: [redacted] Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 106:16-18. Dr. Gascoigne replied [redacted] Id. at 106:19-20. The testimony given responds to hypothetical lines of questioning. In response to the questioning at 94:4-13, Dr. Gascoigne stated [redacted] and [redacted] Id. Such testimony is not fact, but speculation. [redacted] *See e.g.* Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199 and BMS003700205, Ex. 12 (Schwartz I) at 607, Ex. 14 (Schwartz II) at 429 and 432; Resp. Ex. 2 (Ostrov Report) at ¶18; Andre Decl., Ex. 11 (Nadler Tr.) at 85:17-20.

24. Disputed. This is not a fact, but is rather a conclusion of law. The Patents-in-Suit cover fusion proteins, therefore it is unclear what Bristol means by [redacted] More precisely, the Patents-in-Suit cover fusion proteins that require dimerization for biological activity joined to a dimerizing protein selected from a group. Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844. [redacted] *See e.g.* Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199 and BMS003700205, Ex. 12 (Schwartz I) at 607-08, Ex. 14 (Schwartz II) at 429 and at 432 (dimer is an "obligate, preformed dimer"); Resp. Ex. 2 (Ostrov Report) at ¶18; Andre Decl., Ex. 11 (Nadler Tr.) at 85:17-20 and 56:15-21.

25. Disputed. Dr. Gascoigne was again responding to an incomplete hypothetical question. It is unclear what Bristol means by [redacted] The Patents-in-Suit cover polypeptides that require dimerization for biological activity joined to a dimerizing protein selected from a group. Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844. [redacted] *See e.g.* Kirkland Decl., Ex. 10 (Linsley I) at BMS 003700199 and BMS003700205; Ex. 12 (Schwartz I) at 607-08; Ex. 14 (Schwartz II) at 429 and at 432; Resp. Ex. 2 (Ostrov Report) at ¶18; Andre Decl., Ex. 11 (Nadler Tr.) at 85:17-20; 56:15-21; Ex. 9 (Expert Report of Jeffrey V. Ravetch ("Ravetch Report") at ¶108; Ex. 8 (Expert Report of John Kuriyan ("Kuriyan Report") at ¶112. [redacted] Andre Decl., Ex. 5[redacted] at BMS001290162; Andre Decl., Ex. 4 (Orencia® Product Insert) at 1. Such hypothetical questions, and the responsive testimony, are not relevant.

26. Disputed. Dr. Ostrov rendered his opinion that [redacted] Dr. Ostrov however also opined that [redacted] Kirkland Decl., Ex. 28 (Ostrov Tr.) at 153:4-10.

27. Disputed. Dr. Ostrov's testimony at the given cite does not support the claimed "admission". Kirkland Decl., Ex. 28 (Ostrov Tr.) at 54:13-15.

28. Disputed. The Interrogatory response in question was to an Interrogatory relating to U.S. Patent No. 6,291,646 B1, and is not a Patent-in-Suit.

29. Disputed. The Interrogatory response in question was to an Interrogatory relating to U.S. Patent No. 6,291,646 B1, and is not a Patent-in-Suit.

30. Disputed. The quote from the scientific article is taken out-of-context and is misleading, and should include the following text in order to understand that binding to a protein expressed from an artificial monomer construct is not representative of how the native dimeric CTLA-4 exists, nor how the native form binds ligand on the surface of the T cell:

> CD28 and CTLA-4 are homologous T cell receptors of the immunoglobulin (Ig) superfamily, which bind B7 molecules (CD80 and CD86) on antigen-presenting cells and transmit important costimulatory signals during T cell activation...We demonstrate CTLA-4 is a homodimer interconnected by one disulfide bond in the extracellular domain at cysteine residue 120...Thus, CTLA-4 and probably CD28 have a receptor structure consisting of preexisting covalent homodimers with two binding sites.
>
> * * *
>
> Some studies have suggested that CTLA-4 is also a disulfide-linked homodimer (10, 13, 15), but another suggested that it exists as a monomer (16)...We show that CTLA-4 is a disulfide-linked homodimer containing two binding sites for its ligands.
>
> * * *
>
> Our data show that although full-length CTLA-4 is predominantly homodimeric, removal of the transmembrane and cytoplasmic domains (CTLA4X) leads to predominantly monomeric protein. Thus, the presence of C120 does not ensure dimerization. This suggests that dimerization of CTLA-4 and formation of the disulfide bond at Cys120 requires the transmembrane and/or cytoplasmic domains of the two chains...Monomeric CTLA-4 had reduced binding activity when compared to dimeric CTLA-4...30 - 90-fold less active...

Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199, BMS003700205.

31. Disputed. The quote from the scientific article is taken out-of-context and is misleading, and should include the following text in order to understand that binding to a protein

expressed from an artificial monomer construct is not representative of how the native dimeric CTLA-4 form exists, nor how the native form binds ligand on the surface of the T cell:

> Antibodies (or immunoglobulin, Ig)…Receptor dimerization and/or oligomerization are generally critical for initiating signal transduction…CTLA-4 is a homodimer interconnected by one disulphide bond…Thus CTLA-4…have a receptor structure consisting of preexisting homodimers with two equivalent binding sites…The first of these is the availability of preexisting covalent dimers of…CTLA4 receptors…Since CD28/CTLA-4 are preexisting homodimers, signal transduction is most likely initiated by either allosteric changes in receptor structure…CD28 and CTLA-4 are coexpressed on T cells during the activation response…

Kirkland Decl., Ex. 30 (Linsley Research Immunol. 1995 ("Linsley II") at 131-137.

32. Disputed. The quote from the scientific article is taken out-of-context and is misleading, and should include the following text in order to understand that binding to a protein expressed from an artificial monomer construct is not representative of how the native dimeric CTLA-4 form exists, nor how the native form binds ligand on the surface of the T cell:

> CD28 and CTLA-4 are homologous T cell receptors of the immunoglobulin (Ig) superfamily, which bind B7 molecules (CD80 and CD86) on antigen-presenting cells and transmit important costimulatory signals during T cell activation…We demonstrate CTLA-4 is a homodimer interconnected by one disulfide bond in the extracellular domain at cysteine residue 120…Thus, CTLA-4 and probably CD28 have a receptor structure consisting of preexisting covalent homodimers with two binding sites.
>
> * * *
>
> Some studies have suggested that CTLA-4 is also a disulfide-liked homodimer (10, 13, 15), but another suggested that it exists as a monomer (16)…We show that CTLA-4 is a disulfide-linked homodimer containing two binding sites for its ligands.
>
> * * *
>
> Our data show that although full-length CTLA-4 is predominantly homodimeric, removal of the transmembrane and cytoplasmic domains (CTLA4X) leads to predominantly monomeric protein. Thus, the presence of C120 does not ensure dimerization. This suggests that dimerization of CTLA-4 and formation of the disulfide bond at Cys120 requires the transmembrane and/or cytoplasmic domains of the two chains…Monomeric CTLA-4 had reduced binding activity when compared to dimeric CTLA-4…30 - 90-fold less active…

Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199, BMS003700205.

33. Disputed. Dr. Gascoigne was responding to a hypothetical question. ZymoGenetics disputes that such opinion testimony regarding a hypothetical situation can constitute fact. Dr. Gascoigne opined that [redacted] Gascoigne Report at ¶¶14, 25. Dr. Gascoigne has opined that [redacted] Id. [redacted] *See e.g.* Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199; Ex. 12 (Schwartz I) at 607; Ex. 14 (Schwartz II) at 432; Resp. Ex. 2 at ¶¶8, 18.

34. Disputed. Dr. Ostrov was responding to a hypothetical question. ZymoGenetics disputes that such opinion testimony regarding a hypothetical situation can constitute fact.

35. Disputed. Bristol scientist Dr. Linsley stated in an article that "Some studies have suggested that CTLA-4 is also a disulfide-liked homodimer (citations omitted), but another suggested that it exists as a monomer (citation omitted)…We show that CTLA-4 is a disulfide-linked homodimer containing two binding sites for its ligands." Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199. Furthermore, an article cited by Bristol clearly states that CTLA-4 exists as a disulfide-linked homodimer in its native state:

> CTLA-4 is a homodimer interconnected by one disulphide bond…Thus CTLA-4…have a receptor structure consisting of preexisting homodimers with two equivalent binding sites…The first of these is the availability of preexisting covalent dimers of…CTLA4 receptors…Since CD28/CTLA-4 are preexisting homodimers, signal transduction is most likely initiated by either allosteric changes in receptor structure…CD28 and CTLA-4 are coexpressed on T cells during the activation response…

Kirkland Decl., Ex. 30 (Linsley II) at 131-137. In yet another article relied upon by Bristol, CTLA-4 is described as an "obligate dimer" and is a type of "dimeric cell-surface receptor" -- meaning is exists as a dimer in order to function. Id. Ex. 12 (Schwartz I) at 607. Bristol expert Jeffrey Ravetch testified that [redacted] Andre Decl., Ex. 9 (Ravetch Report) at ¶¶108, 144. Michael Kuriyan, another Bristol expert, also testified that [redacted] Id. Ex. 8 (Kuriyan Report) at ¶122. Steve Nadler, a 30(b)(6) witness for Bristol, stated that [redacted] Id. Ex. 11 (Nadler Tr.) at

85:13-16. In fact, Dr. Nadler stated that [redacted] Id. at 85:17-20. Dr. Nadler also stated [redacted] Id. at 56:15-21. In addition, the cited reference (Kirkland Decl., Ex. 6 (Magistrelli Reference)) refers to a mutant form of CTLA-4, not the native form. The data in the cited reference does not demonstrate monomeric CTLA-4, but is merely speculation by the authors.

36. Disputed. The reference, like that cited in ¶35, is referring to a mutant form of CTLA-4, not the native form. Such a mutant is not naturally occurring, and the only experiments on such a form are from an artificial system (COS cells expressing the mutant from a DNA construct.) Kirkland Decl., Ex. 7 (Oaks Reference) at BMS003334445. In addition, the Saverino reference does not demonstrate that the mutant form is actually present. *See* Kirkland Decl., Ex. 8 (Saverino Reference). Furthermore, figure 4 of this reference in fact indicates the purported mutant form of CTLA-4 under investigation is a dimer. *See* id. at 195; s*ee also* Resp. Ex. 13 (Gascoigne Tr.) at 246:4-7.

37. Disputed. Dr. Gascoigne opined that [redacted] Resp. Ex. 1 at ¶¶14 and 25. Such a question is ambiguous, as it seeks to prove a negative. What Dr. Gascoigne was aware of or was not aware of does not speak to the ultimate question of fact as to whether a [redacted] Such evidence has not been presented by Bristol, nor has Dr. Gascoigne reviewed such evidence. Dr. Nadler also agrees that [redacted] Andre Decl., Ex. 11 (Nadler Tr.) at 85:13-16.

38. Disputed. Dr. Gascoigne simply acknowledged that [redacted] Dr. Gascoigne stated in his expert report that [redacted] Resp. Ex 1 at ¶¶14, 25. Bristol is well aware that Dr. Gascoigne opined that [redacted]

[redacted] Resp. Ex. 13 (Gascoigne Tr.) at 103:15-22. In addition, studies done by Bristol confirm CTLA-4 is always a homodimer. Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199. Other independent studies confirm CLTA-4 is found as an "obligate dimer" -- indicating it is a dimer when it is biologically active. *See* Kirkland Decl., Ex. 12 (Schwartz I) at 607; *see also* Resp. Ex. 2 (Ostrov Report) at ¶¶8, 18. Dr. Nadler testified that [redacted] Andre Decl., Ex. 11 (Nadler Tr.) at 85:17-20.

39. Disputed. Dr. Gascoigne expressed his opinion, not fact. He testified:

[redacted]

Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 49:2-17.

40. Disputed. ZymoGenetics agrees that Dr. Gascoigne testified that [redacted] but disputes that such opinion is an "admission."

41. Disputed. Dr. Gascoigne actually stated:

[redacted]

Id. at 51:22-52:5.

42. Disputed. Dr. Linsley stated that high affinity binding of CTLA4 to B7 is a natural cell interaction itself, but rather that the high affinity binding transmits important costimulatory signals which results in inhibiting T-cell activation, a natural cell interaction. *See*

Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199. [redacted] Resp. Ex. 2 (Ostrov Report) at ¶¶8, 18.

43. Disputed. Dr. Gascoigne's response was to a hypothetical question: [redacted] Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 118:12-17. Such testimony is opinion in response to a hypothetical situation, not fact. Dr. Gascoigne repeatedly emphasized in his deposition that his opinion [redacted] *See* Resp. Ex. 13 (Gascoigne Tr.) at 111:24-112:2; 116:11-12.

44. Disputed. Dr. Gascoigne rendered opinion testimony in response to a question that sought a legal conclusion [redacted] Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 106:10-14. ZymoGenetics disputes that such opinion testimony on legal issues can be considered fact. Dr. Gascoigne stated that [redacted] *See* Resp. Ex. 13 (Gascoigne Tr.) at 108:11-12; 109:4-5. The claims of the Patents-in-Suit state that the polypeptides simply require dimerization for biological activity. Kirkland Decl., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844.

45. Disputed. This is not a fact, but a conclusion of law. The testimony cited is based on hypothetical questioning. Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 106:10-15. The claims of the Patents-in-Suit state that the polypeptide simply requires dimerization for biological activity. Id., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844.

46. Disputed. This statement is confusing as written. ZymoGenetics, however, attempts to respond to the statement. The statement is nonsensical because CTLA-4 exists as a dimer in nature. Moreover, this is not fact, but opinion testimony in response to a hypothetical

situation. Dr. Gascoigne was answering a hypothetical question posed to him, and did not "admit" that a [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 129:23-130:3. Dr. Gascoigne was clearly responding to a hypothetical question, and stated his opinion and legal conclusion [redacted] Id. at 130:4-6. Furthermore, it is unclear what Bristol is referring to when it [redacted] The Patents-in-Suit cover fusion proteins. A "CTLA-4 monomer" does not appear to be a fusion protein.

47. Disputed. This statement is confusing as written. ZymoGenetics, however, attempts to respond to the statement. The statement is nonsensical because CTLA-4 exists as a dimer in nature. Moreover, Dr. Gascoigne was answering hypothetical questions that were posed to him, and did not "admit" that [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 129:23-130:9; 144:13-24. Dr. Gascoigne was responding to a hypothetical question, and stated his opinion and legal conclusion [redacted] Id. at 130:4-6. Furthermore, it is unclear what Bristol is referring to when it references a [redacted] The Patents-in-Suit cover fusion proteins. A "CTLA-4 monomer" does not appear to be a fusion protein.

48. Disputed. Dr. Gascoigne did not say that [redacted] Rather, Dr. Gascoigne said in his deposition that [redacted] *See* Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 144:25-145:10. Dr. Gascoigne never stated that [redacted]

[redacted] *See* Resp. Ex. 1 (Gascoigne Report) at ¶3. Dr. Gascoigne merely offered opinion testimony based on the hypothetical question posed. Kirkland Decl., Ex. 22 (Gascoigne Tr.) at 144:13-145:10. Dr. Gascoigne never posed any limitation that [redacted] Id. at 133:13-145:10. There is no data that monomeric CTLA-4 exists or can inhibit T cell activation. The reports Bristol refers to are of a possible mutant. *See* Kirkland Decl, Exs. 6 (Magistrelli Reference), 7 (Oaks Reference), and 8 (Saverino Reference). Native CTLA-4 is a dimer and is biologically active as such. Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199, BMS003700205; Resp. Ex. 1 (Gascoigne Report) at ¶¶14 and 25; Resp. Ex. 2 (Ostrov Report) at ¶¶6-7. Dr. Nadler, Bristol's 30(b)(6) witness testified that [redacted] Andre Decl., Ex. 11 (Nadler Tr.) at 85:17-20.

49. Disputed. There is no data that monomeric CTLA-4 exists – the studies referenced by Bristol are of a mutant, and do not prove such a mutant actually exists in humans, or if it does exist, that it is biologically active. Further, one reference indicates that even the mutant is a dimer. Kirkland Decl., Ex. 8 (Saverino Reference) at 195. Dr. Gascoigne responded to the following question: [redacted] Id. Ex. 22 (Gascoigne Tr.) at 166:2-6. Dr. Gascoigne appears only to be testifying that [redacted] Resp. Ex. 1 at ¶¶14, 25. Dr. Linsley also demonstrated that CTLA-4 existed naturally as a covalently-bonded homodimer. *See* Kirkland Decl., Ex. 10 (Linsley I) at BMS003700199. Other published articles support this finding. *See* Kirkland Decl., Ex. 12 (Schwartz I) at 604; Ex. 14 (Schwartz II) at 429. In addition, Dr. Steven Nadler, Bristol's 30(b)(6) witness, stated that [redacted] *See* Andre Decl., Ex. 11 (Nadler Tr.) at 85:13-20. He also stated that [redacted]

[redacted] Resp. Ex. 16 (Nadler Tr.) at 85:21-86:21.

50. Disputed. Dr. Ostrov never "admitted" that [redacted] Dr. Ostrov offered opinion testimony that [redacted] Kirkland Decl., Ex. 28 (Ostrov Tr.) at 79:6-15. Bristol mischaracterizes Dr. Ostrov's opinion as undisputed fact, when it is actually merely an opinion expressed by an unbiased scientific expert. In addition, the Claims of the Patents-in-Suit only state that the polypeptides require dimerization for biological activity. Id., Ex. 1 ('026 Patent) at ZG000003; Ex. 2 ('725 Patent) at ZG000844. The claims do not require that the protein, CTLA-4 in this case, be able to form a dimer on its own. Id.

51. Disputed. Such an opinion to a hypothetical question is not a fact. The Claims state that the non-Ig polypeptides require dimerization for biological activity. Id.

III. "non-immunoglobulin polypeptide"

52. Disputed. Dr. Gascoigne clearly opined, in response to the question [redacted] Resp. Ex. 13 (Gascoigne Tr.) at 20:24-25:5. Thus, Dr. Gascoigne merely opined that [redacted] CTLA-4, like all Ig superfamily members, contains Ig-like domains. Resp. Ex. 9 (Barclay Reference) at BMS001054677-1054702. [redacted] Resp. Ex. 1 (Gascoigne Report) at ¶17. The classification system Bristol cites clearly demonstrates that Igs occupy there own family, and all other superfamily members are "non" Igs. Resp. Ex. 9 (Barclay Reference) at BMS001054680-1054681, Table 1 (describing the Ig Superfamily as comprised of a single "Immunoglobulin" category and 11 non-immunoglobulin categories). Bristol experts acknowledge that [redacted] Andre Decl., Ex. 9

(Ravetch Report) at ¶58 [redacted] Ex. 8 (Kuriyan Report) at ¶46 [redacted]

53. Disputed. The opinion testimony cited does not constitute "fact." ZymoGenetics disputes that any opinion testimony given by any of the experts in this case constitutes undisputed fact. In addition, it is unclear what [redacted] All members of the super Ig family have homology to certain Ig domain. Resp. Ex. 9 (Barclay Reference)at BMS001054683. Dr. Gascoigne has opined that [redacted] Resp. Ex. 10 (Disclosure of Rebuttal Testimony for Nicholas R. J. Gascoigne (Gascoigne Rebuttal Report)) at ¶25. [redacted] Resp. Ex. 1 (Gascoigne Report) at ¶17.

54. Disputed. Dr. Sledziewski is not a legal expert, and his opinions as to what the claims of the Patents-in-Suit cover can not be characterized as undisputed fact. In addition, Dr. Sledziewski was testifying in regard to the [redacted] Kirkland Decl., Ex. 34 (Sledziewski Tr.) at 251:1-12. Bristol, subject to ZymoGenetics' objections [redacted] and the Court's ultimate ruling on admissibility, may well present such testimony to the trier of fact if such testimony is helpful in deciding material issues of fact, but ZymoGenetics disputes such improper testimony is undisputed fact itself.

POTTER ANDERSON & CORROON LLP

OF COUNSEL:

Paul J. Andre
Lisa Kobialka
King & Spalding LLP
1000 Bridge Parkway
Ste 100
Redwood Shores, California
(650) 590-0700

Dated: June 2, 2008
Public Version: June 9, 2008

By: /s/ Philip A. Rovner

Philip A. Rovner (#3215)
Hercules Plaza
P. O. Box 951
Wilmington, DE 19899
(302) 984-6000
provner@potteranderson.com

Attorneys for Plaintiff
ZymoGenetics, Inc.

EXHIBIT 1

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 2

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 3

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 4

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 5

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 6

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 7

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 8

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 9

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 10

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 11

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 12

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 13

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 14

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 15

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

EXHIBIT 16

THIS EXHIBIT HAS BEEN
REDACTED IN ITS ENTIRETY

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Philip A. Rovner, hereby certify that on June 9, 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.

BY HAND DELIVERY AND E-MAIL

Frederick L. Cottrell, III, Esq.
Kelly E. Farnan, Esq.
Richard Layton & Finger, P.A.
One Rodney Square
P. O. Box 551
Wilmington, DE 19899
cottrell@rlf.com
farnan@rlf.com

I hereby certify that on June 9, 2008 I have sent by E-mail the foregoing document to the following non-registered participant:

Christopher P. Borello, Esq.
Colleen Tracy, Esq.
Fitzpatrick Cella Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112
cborello@fchs.com
ctracy@fchs.com

/s/ Philip A. Rovner
Philip A. Rovner (#3215)
Potter Anderson & Corroon LLP
Hercules Plaza
P. O. Box 951
Wilmington, DE 19899
(302) 984-6000
provner@potteranderson.com

748348