IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

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 MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT OF THE PATENTS-IN-SUIT

I. INTRODUCTION

In accordance with the Court's March 13, 2008 Order (**D.I. 148 at 1**), Defendant Bristol-Myers Squibb Co. ("Bristol") submits this Response ("Response") to Plaintiff ZymoGenetics, Inc.'s ("ZymoGenetics") Summary Statement in Support of Its Motion For Summary Judgment of Infringement of the Patents-in-Suit ("Statement").

II. BRISTOL'S RESPONSE TO ZYMOGENETICS' ALLEGED UNDISPUTED MATERIAL FACTS

ZymoGenetics alleges that there are 15 undisputed material facts. Bristol provides its responses below to each of ZymoGenetics' alleged undisputed material facts. Bristol's responses coordinate with the numbered paragraphs of ZymoGenetics' Statement. Because many of the terms used in ZymoGenetics' Statement have yet to be construed by the Court, in responding to ZymoGenetics' Statement, Bristol used its proposed constructions as in

the Final Joint Claim Construction Chart (**D.I. 153**) and its Claim Construction Opening Brief (**D.I. 156**).

ZymoGenetics' Statement did not cite to any record evidence which disputes the facts set forth in Bristol's Statement of Undisputed Facts in Support of its Motion for Summary Judgment of Noninfringement or as stated in Bristol's opening Noninfringement Summary Judgment brief and it did not identify any disputed facts which would preclude Summary Judgment.

1. Bristol does not dispute ZymoGenetics' allegation that ZymoGenetics is the assignee of United States Patent Nos. 5,843,725 ("the '725 Patent") and 6,018,026 ("the '026 Patent"), (collectively the "patents-in-suit").

2. ZymoGenetics' alleged "fact" that Bristol sells a pharmaceutical product known as Orencia®, which is indicated for the treatment of rheumatoid arthritis, is incomplete and in conflict with the undisputed record evidence which shows that Orencia® is "indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists" (**BMS Ex. 1, Orencia® Product Insert**).[1]

3. ZymoGenetics' alleged "fact" that Orencia® is a fusion protein that consists of a portion of CTLA4 joined to a portion of an immunoglobulin heavy chain is incorrect and in conflict with the undisputed record evidence, **REDACTED**

[1] 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 For Summary Judgment Of Infringement Of The Patents-In-Suit. ZymoGenetics exhibits ("**Ex.**") are attached to the Declaration of Paul J. Andre in Support of Plaintiff's Motion For Summary Judgment of Infringement of the Patents-In-Suit (**D.I. 169; 171; 184; 186**).

REDACTED

4. ZymoGenetics' alleged "fact" that this immunoglobulin heavy chain in Orencia® contains the constant region domain, including the hinge region, the C_H2 domain, and the C_H3 domain is incorrect and in conflict with the undisputed record evidence. *See* Response in Paragraph 3 above.

5. Bristol does not dispute ZymoGenetics' allegation that the CTLA4 portion and the modified immunoglobulin heavy chain in Orencia® are different molecules. *See* Response in Paragraph 3 above.

6. ZymoGenetics' alleged "fact" that CTLA4 is not an immunoglobulin is incorrect and in conflict with the undisputed record evidence, which demonstrates that CTLA4 is a member of the immunoglobulin superfamily (**BMS Ex. 3, Brunet 1987 at BMS001158437**). The undisputed record evidence demonstrates that ZymoGenetics defined the term "non-immunoglobulin polypeptide" to exclude members of the immunoglobulin superfamily (**BMS Ex. 4, EP 89100787.4 Application, Response to Office Action dated March 11, 1993 at BMS004261722-26**).

REDACTED

The Hood Immunology Textbook cited to by ZymoGenetics does not provide support that CTLA4 is not an immunoglobulin (**Ex. 7, Hood Immunology Textbook**), as it does not even mention CTLA4.

7. Bristol does not dispute ZymoGenetics' allegation that CTLA4 exists in nature bound together in pairs, forming what is known as a dimer. The undisputed record evidence demonstrates that CTLA4 on cells and in the blood also exists in nature as a monomer **(BMS Ex. 6, Walunas 1994 at BMS001043066-67; BMS Ex. 7, Lindsten 1993 at BMS001056768; BMS Ex. 8, June 1994 at BMS001043055-56, BMS Ex. 9, Magistrelli 1999 at BMS003334437; BMS Ex. 10, Oaks 2000 at BMS001147559; BMS Ex. 11, Saverino 2007 at 190)**.

REDACTED

8. ZymoGenetics' alleged "fact" that when CTLA4 is not in a dimerized state (i.e., bonded in a pair), it does not exhibit biological activity, is incorrect and in conflict with the undisputed record evidence which demonstrates that CTLA4 exists naturally in cells and in blood in both dimeric and monomeric forms **(BMS Ex. 6, Walunas 1994 at BMS001043066-67; BMS Ex. 7, Lindsten 1993 at BMS001056768; BMS Ex. 8, June 1994 at BMS001043055-56, BMS Ex. 9, Magistrelli 1999 at BMS003334437; BMS Ex. 10, Oaks 2000 at BMS001147559; BMS Ex. 11, Saverino 2007 at 190)**, and that CTLA4 monomer exhibits biological activity including inhibition of T cell proliferation **(BMS Ex. 10, Oaks 2000 at BMS001147559; BMS Ex. 11, Saverino 2007 at 190)**.

REDACTED

The undisputed record evidence also demonstrates that recombinant CTLA4 monomer exhibits biological activity by binding to its ligand B7 **(BMS Ex. 12, Linsley 1995 at ZG001830-31)** and by competitively inhibiting the binding of CD28 to B7 **(Id.)** which results in inhibition of the CD28-

B7 costimulation pathway (**BMS Ex. 1, Orencia® Product Insert at 1**).

REDACTED

Thus, the undisputed record evidence demonstrates that when CTLA4 is not in a dimerized state, (i.e., bonded in a pair), it does exhibit biological activity.

REDACTED

9. ZymoGenetics' alleged "fact" that the portion of the immunoglobulin heavy chain in Orencia® is a dimerizing protein is incorrect and in conflict with the undisputed record evidence, which demonstrates that the portion of the immunoglobulin heavy chain in Orencia® is a modified immunoglobulin heavy chain containing four amino acid changes, including three changes at the immunoglobulin hinge dimer interface (*See* paragraph 3 above).

REDACTED

The undisputed record evidence demonstrates that the immunoglobulin portion of CTLA4-Ig does not form a dimer (**BMS Ex. 12, Linsley 1995 at ZG001829**), and has unique properties consistent with it not being a dimer such as, for example, its not binding to low affinity Fc receptors (**BMS Ex. 13, Davis 2007 at 2204**) that bind exclusively to immunoglobulin dimers (**BMS Ex. 14, Sandor & Lynch at 238**).

Whereas Bristol has undisputed record evidence that the modified immunoglobulin in Orencia® does not form a dimer and is not a dimerizing protein,

ZymoGenetics does not provide any undisputed record evidence that the modified immunoglobulin in Orencia® does form a dimer and is a dimerizing protein.

REDACTED

The "Deisenhofer Reference" does not dispute these undisputed facts, because, REDACTED the Deisenhofer Reference tested unmodified wild-type immunoglobulin heavy chain, not the modified immunoglobulin heavy chain domain that is in Orencia® REDACTED

The Carter Paper[3] cited by ZymoGenetics does not dispute these undisputed facts, because it likewise did not test the modified immunoglobulin heavy chain domain that is in Orencia® REDACTED

10. Bristol does not dispute ZymoGenetics' allegation that the portion of CTLA4 in Orencia® naturally binds ligands as demonstrated by its binding to CD80 and CD86 thereby blocking interaction with CD28, which provides a costimulatory signal necessary for full activation of T lymphocytes (**BMS Ex. 1, Orencia® Product Insert**).

11.

12. REDACTED

13.

[3] The Carter Paper is referred to in as the Dall'Acqua paper. Scientific papers are usually referred to by the first author of the paper (in this case Dall'Acqua), but may also be referred to by the last author of the paper (in this case Carter).

14.

REDACTED

15.

REDACTED

Because there are no genuine issue of material facts in dispute, Bristol's Motion for Summary Judgment of Noninfringement should be granted for the reasons stated in its motion.

III. LEGAL ISSUES THAT DEPEND FROM THE DISPUTED MATERIAL FACTS

ZymoGenetics sought judgment on the following legal issues and Bristol responds as follows below:

1. Orencia® does not infringe, literally or under the doctrine of equivalents, any of the asserted claims of the '725 patent.

2. Orencia® does not infringe, literally or under the doctrine of equivalents, any of the asserted claims of the '026 patent.

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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:

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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:

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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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