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
OPENING BRIEF IN SUPPORT OF ITS
MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

OF COUNSEL:

Robert L. Baechtold
Scott K. Reed
Colleen Tracy
Ha Kung Wong
Christopher P. Borello
FITZPATRICK CELLA HARPER & SCINTO
30 Rockefeller Plaza
New York, N.Y. 10112
Telephone: (212) 218-2100

Frederick L. Cottrell, III (#2555)
cottrell@rlf.com
Kelly E. Farnan (#4395)
farnan@rlf.com
Richards, Layton & Finger, P.A.
One Rodney Square, P.O. Box 551
Wilmington, DE 19899
(302) 651-7700

Attorneys for Defendant
Bristol-Myers Squibb Co.

Dated: May 16, 2008

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Defendant Bristol-Myers Squibb Company ("Bristol") moves, pursuant to Rule 56 of the Federal Rules of Civil Procedure, for summary judgment that its Orencia® product does not infringe the asserted claims of U.S. Patent No. 6,018,026 ("the '026 Patent") (Exh. 1)[1] and that the method for producing that product does not infringe the asserted claims of U.S. Patent No. 5,843,725 ("the '725 Patent") (Exh. 2) (collectively the "patents-in-suit"), either literally or under the doctrine of equivalents. In accordance with the Court's March 13, 2008 Order (D.I. 148 at 1), Bristol has concurrently filed "Bristol-Myers Squibb Company's Statement of Undisputed Facts in Support of Its Motion for Summary Judgment of Noninfringement" providing a short and concise statement of the material facts as to which there is no genuine issue to be tried, along with citations to the record supporting each contention and the legal issues upon which judgment is sought.

[1] All exhibits may be found attached to the Declaration of John W. Kirkland in Support of Bristol-Myers Squibb Company's Motion for Summary Judgment of Noninfringement being filed concurrently herewith.

INTRODUCTION

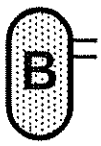
As explained in Bristol's Opening Claim Construction Brief,[2] the subject matter described and claimed in the patents-in-suit is compounds composed of two distinct parts coupled together (*i.e.*, a "fusion protein") and methods for producing these fusion proteins.[3]

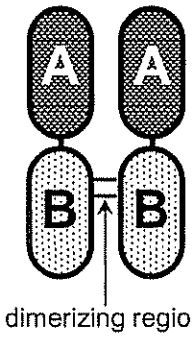
The first part (Part "**A**" in the diagram which follows):

1. has a defined chemical structure -- *i.e.*, is a "non-immunoglobulin polypeptide",
2. displays biological activity only when joined to a second "**A**" (to form a "dimer"), and
3. does not form a dimer on its own.

The second part (Part "**B**" in the diagram):

1. is chemically different from the first part and
2. causes the formation of the dimer of "**AB**" that is required for biological activity -- *i.e.*, is a "dimerizing protein".

	"**A**" = "non-immunoglobulin polypeptide" "**A**" does not have biological activity when single (*i.e.*, a monomer). "**A**" does not form a dimer on its own.		"**B**" = "dimerizing protein" "**B**" causes the formation of the dimer of "**AB**" that is required for biological activity.



"**AB**" + "**AB**" = biologically active dimer

[2] Bristol's Opening Claim Construction Brief, filed concurrently with this motion for summary judgment, will be referred to herein as "Bristol's Cl. Constr. Br."

[3] The '026 Patent is related to the fusion proteins themselves and the '725 Patent is related to the methods for producing the fusion proteins.

ZymoGenetics alleges that Bristol's Orencia® product -- which contains the active ingredient CTLA4-Ig -- and its method of producing CTLA4-Ig, infringe the patents-in-suit. ZymoGenetics alleges that the "CTLA4" portion of Bristol's CTLA4-Ig is "**A**" in the above figure, and that Bristol's mutated immunoglobulin ("Ig") is "**B**" in the above figure. But, Bristol's CTLA4-Ig and its method for producing CTLA4-Ig are missing every one of the key limitations required by each asserted claim of the patents-in-suit, because, *inter alia*: (1) the mutated Ig portion of Bristol's CTLA4-Ig is not a "dimerizing protein"; (2) CTLA4 is not a polypeptide "requiring dimerization for biological activity"; and (3) CTLA4 is not a "non-immunoglobulin polypeptide".

Both the chemical nature and function of the components of Bristol's CTLA4-Ig are diametrically opposite to the requirements of ZymoGenetics' claims, as summarized below:

ZymoGenetics' Claims	**Bristol's Product**
"**A**" is a non-immunoglobulin polypeptide	CTLA4 is not a non-immunoglobulin polypeptide
"**A**" is devoid of biological activity unless dimerized	CTLA4 has biological activity as a monomer (*i.e.*, when not dimerized)
"**A**" cannot dimerize on its own	CTLA4 dimerizes on its own
"**B**" is a "dimerizing protein"	Ig has been mutated to remove its dimerizing sites
The function of "**B**" is to drive dimerization; *i.e.*, cause a dimer of "**AB**" to form	The mutated Ig does not cause dimerization, its function is to improve the solubility and half-life of CTLA4

For at least the following reasons, Bristol's CTLA4-Ig and method for producing CTLA4-Ig cannot infringe. ZymoGenetics admits that it has no evidence to support its position that Bristol's mutated Ig forms a dimer. As such, ZymoGenetics cannot prove that Bristol's

mutated Ig is a "dimerizing protein" and Bristol is entitled to summary judgment as a matter of law. This is true irrespective of whether ZymoGenetics' or Bristol's proposed constructions are applied.

With respect to the "requiring dimerization for biological activity" and "non-immunoglobulin" claim terms, Bristol is entitled to summary judgment of noninfringement as a matter of law under Bristol's proposed constructions. It was not possible for Bristol to apply ZymoGenetics' proposed constructions of these terms in this brief, because ZymoGenetics refused to provide its proposed constructions in the Joint Claim Construction Chart filed on May 7, 2008, contrary to the Court's Scheduling Order.[4] (D.I. 22 at 6). Bristol respectfully submits that ZymoGenetics not be permitted to avoid summary judgment by belatedly proffering meanings of these disputed claim terms that are in conflict with Bristol's.

BACKGROUND

Bristol provided the Court with a technical tutorial on October 17, 2007 in the form of a CD-ROM (D.I. 122), and also provided technical background on much of the technology described in this motion in Bristol's Cl. Constr. Br. Bristol respectfully invites the Court's attention to the technical background provided on pages 4 through 9 in Bristol's Cl. Constr. Br., as context for the present motion for summary judgment.

[4] In the Joint Claim Construction Chart, ZymoGenetics merely stated that these terms have their "ordinary meaning in the context of the claims". (D.I. 153, Exh. A). Such a characterization is not a proposed construction of a term.

I. The Asserted Claims and Construction

ZymoGenetics is asserting Claims 1-4, 7 and 30 of the '026 Patent against Bristol.[5] (Plaintiff ZymoGenetics' Responses to Bristol-Myers Squibb Company's First Set of Interrogatories (12/18/2006) at 6, 7) (Exh. No. 3). The only independent claim of those asserted is Claim 1. If Bristol is found not to infringe Claim 1, it cannot infringe the remaining asserted claims of the '026 Patent as they depend on Claim 1. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). '026 Patent Claim 1 is excerpted below. The portion in italics reflects changes made during reexamination of the '026 Patent.

> 1. A biologically active, dimerized polypeptide fusion, comprising:
>
> first and second polypeptide chains, wherein each of said polypeptide chains comprises a non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein heterologous to said non-immunoglobulin polypeptide, *wherein the dimerizing protein is 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.*

(Exh. 1 at ZG 000003).

ZymoGenetics is asserting Claims 1-3, 5, 6, 21, 22, 24, 25, 50 and 51 of the '725 Patent against Bristol. (Exh. 3 at 6); (Plaintiff ZymoGenetics' Third Supplemental Response to Bristol-Myers Squibb Company's First Set of Interrogatories (9/25/2007) at 4-8) (Exh. 4). The only independent claims asserted are Claims 1 and 21. If Bristol is found not to infringe Claims 1 and 21, it cannot infringe the remaining asserted claims of the '725 Patent as they depend on

[5] When Bristol refers to the claims of the patents-in-suit, it is referring to those claims as amended during reexamination.

Claims 1 and 21. '725 Patent Claims 1 and 21 are excerpted below. The portions in italics reflect changes made during reexamination of the '725 Patent.

> 1. A method for producing a secreted active dimerized polypeptide fusion, comprising:
>
> introducing into a eukaryotic host cell a DNA construct comprising a transcriptional promoter operatively linked to a secretory signal sequence followed downstream by and in proper reading frame with a DNA sequence encoding a non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein heterologous to said non-immunoglobulin polypeptide;
>
> growing said host cell in an appropriate growth medium under physiological conditions to allow the secretion of a dimerized polypeptide fusion encoded by said DNA sequence; and
>
> isolating said dimerized polypeptide fusion from said host cell, *wherein the dimerizing protein is 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.*

(Exh. 2 at ZG 000844).

> 21. A method for producing a secreted receptor analog, comprising:
>
> introducing into a eukaryotic host cell a DNA construct comprising a transcriptional promoter operatively linked to at least one secretory signal sequence followed downstream by and in proper reading frame with a DNA sequence encoding a ligand-binding domain of a receptor requiring dimerization for biological activity joined to a dimerizing protein heterologous to said ligand-binding domain, and optionally an immunoglobulin hinge or variable region *joined* to said dimerizing protein;
>
> growing said host cell in an appropriate growth medium under physiological conditions to allow the secretion of a receptor analog encoded by said DNA sequence; and isolating said receptor analog from said host cell,
>
> *wherein the dimerizing protein is 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.*

(*Id.*)

A. Each Asserted Claim Requires a "Dimerizing Protein"

Each asserted claim requires a "dimerizing protein". As addressed in Bristol's Cl. Constr. Br., the term "dimerizing protein" should be construed to mean:

> a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associate under physiological conditions to form a dimer, wherein the dimerizing protein causes or drives the dimerization of non-immunoglobulin polypeptide that is joined to it that would not otherwise form a stable dimer but for the action of said dimerizing protein

(D.I. 153, Exh. A at 3, 4) (Bristol's Cl. Constr. Br. at 28-31). ZymoGenetics alleges that this claim should be construed to mean:

> a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associate under physiological conditions to form a dimer. The second polypeptide chain may be the same or a different chain.

(D.I. 153, Exh. A at 3, 4). Under either proposed construction, the claims 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.*

(Exh. 1, '026 Patent Claim 1 at ZG000003) (Exh. 2, '725 Patent Claim 1 at ZG000844).

As discussed further below, under either Bristol's or ZymoGenetics' proposed construction of the claim term "dimerizing protein", neither Bristol's CTLA4-Ig nor the method for producing it can infringe the asserted claims of the patents-in-suit because the "Ig" in

Bristol's compound is a mutated immunoglobulin whose dimerizing sites have been mutated to prevent dimerization through that moiety.[6]

B. Each Asserted Claim Requires a Non-Immunoglobulin Polypeptide or Ligand-Binding Domain of a Receptor "Requiring Dimerization for Biological Activity"

Each asserted claim requires either a non-immunoglobulin polypeptide or a ligand-binding domain of a receptor "requiring dimerization for biological activity". As addressed in Bristol's Cl. Constr. Br., the term "requiring dimerization for biological activity" should be construed to mean:

> needing to be dimerized to have biological activity, *i.e*, (a) unless a dimer, it has no biological activity; and (b) will not dimerize on its own.

(D.I. 153, Exh. A at 2, 3) (Bristol's Cl. Constr. Br. at 20-28).

Neither Bristol's CTLA4-Ig nor the method for producing it can infringe any of the asserted claims of the patents-in-suit because CTLA4 does not "require dimerization for biological activity".

In the Joint Claim Construction Chart, ZymoGenetics refused to provide any construction of this claim term and stated only that it has an "ordinary meaning within context of claims". (D.I. 153, Exh. A at 2). If, by that, ZymoGenetics means that the non-immunoglobulin polypeptide does not display biological activity unless it is dimerized, then there is no dispute. Bristol submits that the ordinary meaning of "require" is to be essential, necessary, indispensable. However, ZymoGenetics' refusal to make that simple, definitive

[6] A "moiety" is one of the portions into which something is divided. (Merriam-Webster's Online Dictionary, http://www.merriam-webster.com/dictionary/moiety, *last visited on 5/15/2008*) (Exh. 32).

acknowledgement, suggests it has some other (so far undisclosed) definition it intends to propound.

Bristol believes its own proposed construction is consistent with the ordinary meaning of these terms within the context of the claims, and also takes into account arguments that ZymoGenetics made to the United States Patent and Trademark Office ("USPTO"). ZymoGenetics should not be permitted now to assert a contrary, belated proposed construction of this claim term under the guise of an "ordinary meaning" because its tactics have prejudiced Bristol.[7]

C. Each Asserted Claim Requires a "Non-Immunoglobulin"

Independent Claim 1 of the '026 Patent and independent Claim 1 of the '725 Patent directly recite the claim term "non-immunoglobulin". And, as Bristol points out in Bristol's Cl. Constr. Br., both the "receptor analog" and "ligand-binding domain of a receptor" must be a non-immunoglobulin polypeptide. (Bristol's Cl. Constr. Br. at 36-40). In fact, ZymoGenetics admits that a "receptor analog" is a "non-immunoglobulin polypeptide". (D.I. 153, Exh. A at 4, 5). Therefore, there is no dispute that all asserted claims require a "non-immunoglobulin polypeptide".

As Bristol pointed out in Bristol's Cl. Constr. Br., "non-immunoglobulin polypeptide" should be construed to mean:

> a polypeptide that: (a) is not encoded by immunoglobulin-like genes which encode discrete domains structurally similar to immunoglobulin; and (b) does not have significant sequence homology to immunoglobulin

(D.I. 153, Exh. A at 2) (Bristol's Cl. Constr. Br at 31-36).

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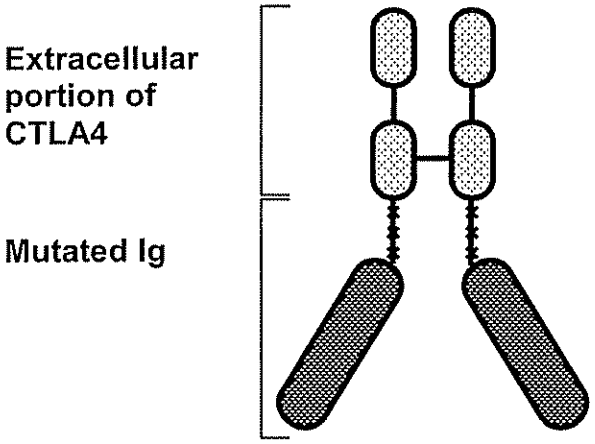
[7] Bristol's prejudice cannot be cured, as Bristol was not provided ZymoGenetics' proposed construction before the deadline for summary judgment motions.

Based on Bristol's proposed construction of "non-immunoglobulin polypeptide", neither Bristol's CTLA4-Ig nor the method for producing Bristol's CTLA4-Ig can infringe the asserted claims of the patents-in-suit. As with the term "requiring dimerization for biological activity", ZymoGenetics refused to provide its proposed construction of "non-immunoglobulin polypeptide" prior to the deadline for filing summary judgment motions, and should not now be permitted to argue one that is in conflict with Bristol's construction.

II. The Accused Product -- Orencia®

A. Bristol's CTLA4-Ig

Bristol's CTLA4-Ig is a fusion protein containing an extracellular portion of CTLA4 joined to a portion of a mutated Ig. (Orencia® Label at BMS004286461) (Exh. 5). The following figure is a depiction of Bristol's CTLA4-Ig:



The protein CTLA4 naturally exists in humans as both a soluble monomer not attached to a cell, and a cell membrane-bound dimer. (Magistrelli et al., *A soluble form of CTLA4 generated by alternative splicing is expressed by nonstimulated human T cells*, EUR. J. IMMUNOL. 29:3596 at 3597-98 (Section 2.3) (1999)) (Exh. 6); (Oaks et al., *A native soluble form of CTLA-4*, CELL. IMMUNOL. 201:144 at 151-52 (2000)) (Exh. 7); (Saverino et al., *Soluble CTLA-4 in autoimmune thyroid diseases: Relationships with clinical status and possible role in the*

immune response dysregulation, CLIN. IMMUNOL. 123:190 at 190 (Abstract), 192-93 (2007) (Exh. 8); (Brunet et al., *A new member of the immunoglobulin superfamily -- CTLA-4*, NATURE 328:267 at 267 (1987)) (Exh. 9); (Linsley et al., *Binding Stoichiometry of the Cytotoxic T lymphocyte-associated Molecule (CTLA-4)*, J. BIOL. CHEM. 270:15417 at 15417, 19 (1995)) (Exh. 10); (Linsley et al., *Coexpression and Functional Cooperation of CTLA-4 and CD28 on Activated T Lymphocytes*, J. EXP. MED. 176:1595 at 1595 (1992) (Exh. 11). In Bristol's CTLA4-Ig, the CTLA4 portion is a dimer. The dimer forms when two CTLA4 polypeptides couple together through the formation of covalent and non-covalent bonds. (Schwartz et al., *Structural basis for costimulation by the human CTLA-4/B7-2 complex*, NATURE, 410:604 at 605 (2001)) (Exh. 12); (Stamper et al., *Crystal structure of the B7-1/CTLA-4 complex that inhibits human immune responses*, NATURE 410:608 at 608-9 (2001)) (Exh. 13); (Schwartz et al., *Structural mechanisms of costimulation*, NATURE IMMUNOLOGY, 3:427 at 429-30 (2002)) (Exh. 14). Because CTLA4 is physically joined to Ig in the fusion protein, and because CTLA4 causes dimerization, Bristol's CTLA4-Ig fusion protein is a dimer.

The "Ig" portion of Bristol's CTLA4-Ig contains what are referred to as a "hinge region", "CH2 domain", and "CH3 domain" of an "IgG1" Ig molecule -- with several very important differences from a natural (or "wild-type") Ig. A natural Ig IgG1 hinge region contains three "cysteines" per heavy chain polypeptide that are capable of forming disulfide bonds (*i.e.*, covalent bonds) with other cysteines. (Excerpt of Carl Branden & John Tooze, INTRODUCTION TO PROTEIN STRUCTURE 180 at Figure 12.2(a) (1991)) (Exh. 15). These cysteines are the only possible way that the natural hinge, CH2 and CH3 region of a wild-type Ig can form a covalent bond with another natural hinge, CH2 and CH3 Ig molecule.

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The figure on page 10 depicts where these mutations are with three "x" marks on each mutated Ig.

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B. CTLA4-Ig -- How It Works

Bristol's CTLA4-Ig treats rheumatoid arthritis by disrupting what is known as the "CD28-B7 pathway". (Exh. 5 at 1). CD28 is a receptor on the surface of cells called "T-cells". B7 is a natural ligand (*i.e.*, binding partner) to CD28, and exists on the surface of cells called "B-cells".[8]

When CD28 binds to B7, it turns on an immune response. In individuals with a normal immune system, this is beneficial, because the immune response is turned on in response to foreign pathogens, such as bacteria. For patients with autoimmune disorders, the immune response is misdirected against the individual's own, otherwise healthy, organs. For example, in the case of rheumatoid arthritis, the joints of the individual are attacked, resulting in inflammation and joint destruction.

CTLA4-Ig works by binding to B7 with a higher "affinity" than CD28. That is, the CTLA4 portion of CTLA4-Ig binds to B7 so strongly that it prevents CD28 from binding to B7. Such binding is often referred to as "competitive" binding. That is, CTLA4 can "compete" successfully with CD28 for the available B7 binding sites. Such "competitive" binding disrupts

[8] Note that references cited in this motion also refer to B7 as B7-1 (or CD80) and B7-2 (or CD86), because at least two types of B7 exist and there is more than one nomenclature for B7 molecules.

the CD28-B7 pathway, essentially serving as an "off" switch for an inappropriate, misdirected immune response in patients having autoimmune disease.

C. CTLA4-Ig -- Bristol's Invention Story

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; (Damle et al., *Differential regulatory signals delivered by antibody binding to the CD28 (Tp44) molecule during the activation of human T lymphocytes*, J. IMMUNOL. 140:1753 at 1753 (1988)) (Exh. 18). They had already learned that CD28 could be used to turn on an immune response using artificial means, but had not yet learned that B7 binding to CD28 was intimately involved in the immune response. (Exh. 18 at 1753-60).

REDACTED

(Exh. 11 at 1595). This was an important discovery, as it allowed a way to investigate methods to interrupt the CD28-B7 pathway to disrupt the misdirected immune response in patients with autoimmune disorders.

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REDACTED

[10] Cysteines are capable of forming covalent disulfide bonds. Serines are not.

REDACTED

ARGUMENT

I. Legal Standards

A. Summary Judgment Law, Generally

Summary judgment should be granted where the moving party shows that there is no genuine issue of material fact and that it is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). The Court of Appeals for the Federal Circuit has long held that: "[s]ummary judgment is as appropriate in a patent case as in any other." *Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd.*, 731 F.2d 831, 835 (Fed. Cir. 1984). In order to defeat a motion for summary judgment, Rule 56(c) demands that the non-moving party show there is more than "some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co. Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 586-87 (1986). Evidence which is "merely colorable, or is not significantly probative," is insufficient to defeat a motion for summary judgment. *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1571 (Fed. Cir. 1991) (citing *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 249 (1986)) (internal quotations omitted). Where there is no

"genuine issue of material fact" and the movant is entitled to judgment as a matter of law, the court should grant a motion for summary judgment in order to avoid unnecessary expense to the parties and the accompanying waste of judicial resources. *Id.* at 1570-71.

A fact is material if it is one that "might affect the outcome of the suit under the governing law . . . ." *Anderson*, 477 U.S. at 248. Therefore, disputes over facts that are irrelevant or unnecessary will not preclude summary judgment. *Id.* When the moving party has asserted facts showing that the non-movant's claims cannot be sustained, the opposing party must "set out specific facts showing a genuine issue for trial," and cannot rest "merely on allegations or denials in its own pleading[s]." Fed. R. Civ. P. 56(e). A dispute regarding a material fact is "genuine" so as to warrant the denial of summary judgment only "if the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson*, 477 U.S. at 248.

In deciding if summary judgment is appropriate, the Court should consider the evidentiary burden that will apply at trial. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 424 F.3d 1276, 1284 (Fed. Cir. 2005). It is the patentee who bears the burden of proof of infringement, by a preponderance of the evidence. *EnviroTech Corp. v. Al George, Inc.*, 730 F.2d 753, 758 (Fed. Cir. 1984).

Summary judgment is appropriate in this case because the undisputed facts establish that the manufacture, use, sale, offer for sale or importation of Bristol's Orencia® product will not infringe the asserted claims of the patents-in-suit.

B. Literal Infringement

The determination of infringement is a two-step inquiry. Step one requires the Court to construe the claims of the patent to determine their scope. Step two requires the Court to determine whether the properly construed claims of the patent encompass the accused product.

Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). The first step of construing the claims is a question of law, while the second step regarding the question of infringement is an issue of fact (to the extent there are genuine fact issues). *Markman*, 517 U.S. at 372; *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998).

When comparing the asserted claims to the accused product or method (*i.e.*, in performing the second step of the infringement analysis), each claim limitation is material and essential. Accordingly, literal infringement requires that every limitation of the patent claim must be specifically found in the accused product. *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 796 (Fed. Cir. 1990).

C. Doctrine of Equivalents and Prosecution History Estoppel

Occasionally, a claim not literally infringed may nonetheless be found infringed under the "doctrine of equivalents" if there is "equivalence" between features of the accused product and the limitations of the asserted claim. *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28-29 (1997); *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950); *Augustine Med., Inc. v. Gaymar Indus., Inc.*, 181 F.3d 1291, 1298 (Fed. Cir. 1999). This doctrine, which is premised upon language's inability to capture the essence of the invention, prevents someone from making unimportant and insubstantial changes in an attempt to take the copied matter outside of the scope of the claim. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 731-732 (2002).

Equivalency is determined in the context of the patent, the prior art and the particular circumstances of the case. *Graver Tank*, 339 U.S. at 609. An equivalent is present if there are only "insubstantial differences" between a particular claim limitation and a

corresponding feature of the accused product. *Sage Prods. Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1423 (Fed. Cir. 1997).

Even under the doctrine of equivalents, however, each limitation of a claim is deemed material to defining the scope of the patent, and special vigilance must be kept against allowing the doctrine to eliminate any claim limitation. *Warner-Jenkinson*, 520 U.S. at 29-30. Thus, the doctrine of equivalents must be applied to individual claim limitations, not the invention as a whole. *Id.* There can be no infringement under the doctrine of equivalents "if a claim limitation is totally missing from the accused device." *General Am. Transp. Corp. v. Cryo-Trans. Inc.*, 93 F.3d 766, 771 (Fed. Cir. 1996) (internal quotations omitted); *Warner-Jenkinson*, 520 U.S. at 39 n. 8 (noting that a theory of equivalence which would "entirely vitiate a particular claim element" may not be applied as a matter of law).

A patentee may be estopped from making a doctrine of equivalents argument if particular subject matter was disclaimed or disavowed either in the specification of the patent or by argument during prosecution. *See, e.g., L.B. Plastics, Inc. v. Amerimax Home Prods.*, 499 F.3d 1303, 1309 (Fed. Cir. 2007); *Texas Inst.'s Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1173 (Fed. Cir. 1993). If applicant makes an "unmistakable assertion" during prosecution in support of patentability, whether required for allowability of a claim or not, the patentee is precluded from later asserting equivalency between a particular claim limitation and a substituted structure. *Texas Inst.'s*, 988 F.2d at 1174.

To avoid application of prosecution history estoppel ("PHE"), the patentee bears the burden of establishing that a narrowing amendment was not made for purposes of patentability. *Warner-Jenkinson*, 520 U.S. at 33. In attempting to meet this burden, the patentee may not rely on extrinsic evidence, but is restricted to evidence in the prosecution history. *Festo*

Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co, 344 F.3d 1359, 1367 (Fed. Cir. 2003). If no explanation is established, the amendment is presumed to have been made for substantial reasons relating to patentability, and application of the doctrine of equivalents is barred. *Warner Jenkinson*, 520 U.S. at 33.

Likewise, when it is determined that a narrowing amendment was made for purposes of patentability, it is also presumed that all subject matter between the original claim limitation and the amended claim limitation has been surrendered and it is the patentee's burden to show that the amendment did not surrender the particular equivalent in question. *Festo*, 535 U.S. at 739-41. If the patentee fails to overcome this presumption and establish that the asserted equivalent is outside the scope of the surrender, PHE bars the patentee from relying on the doctrine of equivalents to demonstrate infringement by the accused element. *Id.* at 740-41.

The determination of whether PHE applies (*i.e.*, whether the doctrine of equivalents may be relied upon) for a particular claim limitation is a question of law, as is the question of the scope of the patentee's surrender. *Festo*, 344 F.3d at 1367-69.

II. Bristol's CTLA4-Ig Cannot Infringe Because It Does Not Contain a "Dimerizing Protein" As Required By The Claims

As discussed in Bristol's Cl. Constr. Br., and above, the proper construction of the term "dimerizing protein" should be:

> a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associate under physiological conditions to form a dimer, *wherein said dimerizing protein causes or drives the dimerization of non-immunoglobulin polypeptide that is joined to it that would not otherwise form a stable dimer but for the action of said dimerizing protein*

(D.I. 153, Exh. A at 3, 4). ZymoGenetics disagrees with the italicized portion of Bristol's construction. Nonetheless, the mutated Ig portion of Bristol's CTLA4-Ig does not meet either

the unitalicized portion of the definition (with which ZymoGenetics agrees) or the italicized portion of the definition.

A. ZymoGenetics has not proven that Bristol's mutated Ig is "a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associate under physiological conditions to form a dimer"

As discussed above, Bristol's Ig is purposefully mutated to prevent dimer formation. *See supra* Background Section II.A. That is, the "amino acid sequence" of Bristol's Ig has been modified to remove the cysteine dimerizing groups and replace them with non-dimerizing serines. It is undisputed that small changes in an amino acid sequence of Ig can affect the ability of that Ig to form a dimer.

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ZymoGenetics never performed any experiments on Bristol's CTLA4-Ig despite the fact that "some relatively simple tests" could have been done to determine whether or not the mutated Ig in Bristol's product formed a dimer.[11]

REDACTED

[11] Courts have found that, when necessary, patentees must perform experiments to determine whether a claim limitation is present. *See, e.g., Judin v. United States*, 110 F.3d 780, 783-85 (Fed. Cir. 1997) (patentee failed to obtain an accused device and test it). Courts have also found cases exceptional pursuant to 35 U.S.C. § 285 under similar circumstances. *See, e.g., Eltech Sys. Corp. v. PPG Indus., Inc.*, 710 F. Supp. 622, 636-38 (W.D. La. 1988) (finding a case exceptional when despite the fact that the accused product was available before filing of the lawsuit the patentee did not attempt to evaluate the product's diaphragms under operating conditions either before or during the litigation).

[12] This is despite the fact that ZymoGenetics own proposed construction of "dimerizing protein" requires Bristol's mutated Ig to "associate under physiological conditions to form a dimer." (D.I. 153, Exh. A at 3, 4).

REDACTED

In sum, both ZymoGenetics' and Bristol's proposed constructions state that a dimerizing protein must be "a polypeptide chain having affinity for a second polypeptide chain, ***such that the two chains associate under physiological conditions to form a dimer***". (emphasis added). And, for the following reasons ZymoGenetics' allegations of infringement fail as a matter of law:

REDACTED

- Small changes in amino acid sequence can affect the ability of Ig to form a dimer;
- It is impossible to know whether Bristol's mutated Ig forms a dimer without performing an experiment;
- ZymoGenetics could have performed a simple experiment to determine whether Bristol's mutated Ig forms a dimer;
- ZymoGenetics has not performed any experiments to determine whether Bristol's mutated Ig forms a dimer; and
- ZymoGenetics has no evidence that Bristol's mutated Ig forms a dimer.

B. ZymoGenetics has not proven that Bristol's Ig "causes or drives the dimerization of the non-immunoglobulin polypeptide that is joined to it that would not otherwise form a stable dimer but for the action of said dimerizing protein"

ZymoGenetics has also failed to set forth any evidence that Bristol's Ig "causes or drives the dimerization of non-immunoglobulin polypeptide that is joined to it that would not otherwise form a stable dimer but for the action of said dimerizing protein". In fact, the evidence

indicates otherwise -- CTLA4 forms a stable dimer without the aid of a dimerizing protein,[13] and it is CTLA4, not the Ig that is driving the dimerization of Bristol's CTLA4-Ig.[14]

Prior to discussing Bristol's evidence, Bristol will summarize why the "dimerizing protein" of the patents-in-suit must drive the dimerization of the non-immunoglobulin polypeptide (alleged here to be CTLA4).[15] First, the participle "dimerizing" means that which causes a dimer to form. Second, during prosecution of the United States Patent No. 5,155,027 Patent ("the '027 Patent"), a related patent to the patents-in-suit, ZymoGenetics disavowed circumstances under which the biologically active polypeptide (*i.e.*, Part "A" of the fusion protein depicted in the Figure on page 2) drives the dimerization of the resulting fusion protein.

In that prosecution of the '027 Patent, the Examiner rejected a claim for being anticipated by prior art references. (5,155,027 Prosecution History ("'027 Pros. Hist."), Office

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REDACTED

[14] Of course, CTLA4 cannot be both the "non-immunoglobulin polypeptide" that requires dimerization and the "dimerizing protein" that is an immunoglobulin.

[15] The specifications of the patents-in-suit are consistent with the notion that Ig is "driving" dimerization:

> In a preferred embodiment, *S. cerevisiae* invertase is used to ***drive*** the association of polypeptides into dimers.
>
> * * *
>
> Portions of immunoglobulin gene sequences may be used to ***drive*** the association of non-immunoglobulin polypeptides.

(*See, e.g.*, Exh. 1 at col. 13, lns. 42-44; lns. 53-55 at ZG 000033) (emphasis added).

Action (3/2/1990) at BMS004259274-279) (Exh. 23).[16] In response to this office action, ZymoGenetics amended the claim and distinguished their alleged invention from the prior art on the following grounds:

> Claim 22 was rejected under 35 U.S.C. § 102(e) as being anticipated by Boss et al. (U.S. Patent No. 4,816,397) and Boss et al. (EP 120,694).
>
> Applicants respectfully traverse this ground of rejection. Boss et al. do not teach or suggest the dimerized polypeptide fusions or methods of producing such fusions as claimed in the subject application. The claimed dimerized polypeptide fusions are non-immunoglobulin polypeptides fused to at least an immunoglobulin constant region ***wherein the dimerization is driven by the immunoglobulin portion of the molecule.*** Boss et al. do not teach or suggest the use of the immunoglobulin constant region in the dimerization of non-immunoglobulin polypeptides. Applicants respectfully submit that on the basis of the above remarks, the Examiner's rejection under 35 U.S.C. § 102(e) has been overcome.

('027 Pros. Hist., Amendment (6/29/1990) at BMS4259290) (Exh. 26) (emphasis added).[17]

As discussed above, PHE can result from arguments made to secure the allowance of claims that are rejected on the basis of prior art, even though no amendment to the claim language has been made (*i.e.*, "argument-based estoppel"). *See supra* Argument Section I.C. As ZymoGenetics made the above argument to attempt to secure allowance of claims that were rejected on the basis of prior art, the "dimerizing protein", or immunoglobulin being discussed during the prosecution of the '027 patent, must be what drives the dimerization of the portion of the fusion protein.

REDACTED

[16] A copy of the references referred to as "Boss(A)" and "Boss(L)" by the Examiner are attached. (U.S. Patent No. 4,816,397) ("Boss(A)") (Exh. 24); (EP 0 120 694) ("Boss(L)") (Exh. 25).

[17] In the claims of the patents-in-suit, the "immunoglobulin portion of the molecule" is referred to as the "dimerizing protein".

REDACTED

ZymoGenetics should not be permitted to capture subject matter that they clearly disavowed during prosecution. That is, ZymoGenetics should not be permitted to capture the circumstance where dimerization is not driven by Part "B" of the molecule depicted in the Figure on page 2.

And, as discussed in the previous section, ZymoGenetics has not shown that Bristol's mutated Ig forms a dimer, or that it is capable of driving the dimerization of Bristol's CTLA4. To the contrary, the CTLA4 portion of Bristol's CTLA4-Ig is driving the dimerization of CTLA4-Ig -- as it is capable of forming a strong covalent dimer by itself, and there is no evidence that Bristol's mutated Ig is contributing in the formation of the resulting dimer.

REDACTED

REDACTED

The "dimerizing protein" cannot be CTLA4 according to the claims. The claims require the dimerizing protein be selected from "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." (Exh. 1 at ZG 000003).

REDACTED

REDACTED

If ZymoGenetics cannot prove that Bristol's mutated Ig is a dimerizing protein under its own definition of "dimerizing protein", then ZymoGenetics also cannot prove Bristol's Ig is "driving" the dimerization of CTLA4, especially when CTLA4 itself is capable of forming a strong covalent dimer, and is itself a "dimerizing protein" under ZymoGenetics' definition of that term.

REDACTED

III. Bristol's CTLA4-Ig Cannot Infringe Because CTLA4 Does Not "Require Dimerization for Biological Activity"

All claims of the asserted patents either require a "non-immunoglobulin *requiring dimerization for biological activity*" or a "ligand-binding domain of a receptor *requiring dimerization for biological activity*". As discussed in Bristol's Cl. Constr. Br., the proper construction for "requiring dimerization for biological activity" is

> needing to be dimerized to have biological activity, *i.e.*, (a) unless a dimer, it has no biological activity; and (b) will not dimerize on its own

(D.I. 153, Exh. A at 2, 3) (Bristol's Cl. Constr. Br., at 20-28).[18, 19] Because the CTLA4 -- the alleged "non-immunoglobulin" or "ligand-binding domain of a receptor" -- used in Bristol's

[18] While ZymoGenetics alleges that "requiring dimerization for biological activity" should have its plain and ordinary meaning in the context of the claims, it failed to provide Bristol with what their alleged plain and ordinary meaning is prior to the filing of this summary judgment brief.

REDACTED

CTLA4-Ig meets neither of those requirements -- it has biological activity as a monomer and dimerizes on its own – Bristol's CTLA4-Ig cannot infringe the asserted claims of the patents-in-suit.

A. CTLA4 Has "Biological Activity" as a Monomer

As discussed above, if a polypeptide displays biological activity as a monomer, it cannot satisfy the claim limitation of "requiring dimerization." The patents-in-suit define "biological activity" as "a function or set of activities performed by a molecule in a biological context (i.e., in an organism or an in vitro facsimile thereof)".[20]

REDACTED

Alternatively, if a cellular assay is the appropriate biological activity, CTLA4 is biologically active as a monomer as well.

i. If Binding is the Appropriate Measure of "Biological Activity", CTLA4 has Biological Activity as a Monomer

REDACTED

[20] ZymoGenetics agrees that "biological activity" is defined as "a function or set of activities performed by a molecule in a biological context (*i.e.*, in an organism or an *in vitro* facsimile thereof", but they add additional language unnecessary to construe "biological activity". (Bristol's Cl. Constr. Br. at 17-20).

REDACTED

Bristol demonstrated in scientifically peer-reviewed publications -- years before the patents-in-suit issued, and beyond any genuine dispute -- that monomeric CTLA4 binds to B7 with high affinity in a ligand binding assay which was recognized in the art to represent an *in vitro* facsimile of what occurs *in vivo*. Because monomeric CTLA4 indisputably possesses ligand binding activity, it is not "requiring dimerization for biological activity". In an article authored by Bristol scientists entitled "Binding Stoichiometry of the Ctyotoxic T Lymphocyte-associated Molecule-4 (CTLA-4)" in 1995, the following was reported:

> ***Each monomeric polypeptide chain of CTLA-4 contains a high affinity binding site for B7 molecules.***
>
> * * *
>
> To determine if monomeric CTLA-4 contained an intact binding site for B7 molecules, we compared B7 binding properties of monomeric and dimeric forms of CTLA-4. . . . . Fractionization of CTLA4X preparations by gel permeation chromatography separated monomeric and dimeric forms of CTLA-4. Both forms were immunoprecipitated with CD80Ig and CD86Ig [two forms of B7]. Identical results were obtained when purified CTLA4X was used for analysis. Thus, both ***monomeric and dimeric forms of CTLA-4 bound CD80 and CD86*** [both forms of B7].

(Exh. 10 at 15417; 15421) (emphasis added). In another article authored by Bristol scientists entitled "CD28/CTLA4 Receptor Structure, Binding Stoichiometry and Aggregation During T-Cell Activation" in 1995, it was reported that:

> CTLA4 was stably expressed as a monomer when cysteine 120 was mutated to serine, and ***monomeric CTLA-4 contained a high affinity binding site for B7*** molecules.

(Linsley et al., *CD28/CTLA-4 receptor structure, binding stoichiometry and aggregation during T-cell activation*, RESEARCH IN IMMUNOL., 146:130 at 133 (1995)) (Exh. 30) (emphasis added).

Bristol also demonstrated in peer reviewed publications that monomeric CTLA4 "competitively" binds to B7. That is, monomeric CTLA4 is capable of competing with CD28 for available B7 binding sites:

> The relative avidities of monomeric and dimeric CTLA-4 were compared by competitive binding assay in the experiment . . . . ***Monomeric CTLA-4 was a more effective competitor than multimeric CD28-Ig*** . . . .

(Exh. 10 at 15421-22) (internal citation omitted) (emphasis added).

REDACTED

REDACTED

Therefore, there can be no genuine dispute that monomeric CTLA4 binds to B7 with high affinity and does so competitively -- and that these are biological activities. And, as monomeric CTLA4 binds to B7 with high affinity and/or competitively binds B7 in comparison with CD28, there can be no genuine dispute that CTLA4 is not a polypeptide "requiring dimerization for biological activity".[21] Therefore, Bristol's CTLA4-Ig cannot infringe the patents-in-suit.

ii. If a Cellular Assay Is the Appropriate Measure of "Biological Activity", CTLA4 has Biological Activity as a Monomer

While Bristol disagrees that a cellular assay is required to show "biological activity" -- because ZymoGenetics clearly took the position that binding and competitive binding assays were sufficient to show biological activity, and because the patents-in-suit would not be enabled if only cellular assays could be used to demonstrate "biological activity" -- it matters not. As discussed in the Background Section, CTLA4 exists naturally in the human body as an

[21] A naturally occurring form of CTLA4 in humans, which is a monomer, also binds to B7. (Exh. 6 at 3597-98); (Exh. 7 at 150-51); (Exh. 8 at 193-94).

active monomer (referred to as sCTLA4),[22] and is capable of inhibiting an immune response in a cellular assay (*i.e.*, a mixed-lymphocyte reaction):

> We next examined the immunoregulatory properties of sCTLA-4 by determining its effect on two-way MLR. The data presented... show that ***sCTLA-4 had significant inhibitory effect***, similarly to that one obtained by the addition of CTLA-4 Ig.

(Exh. 8 at 194) (emphasis added). Therefore, there can be no dispute that monomeric CTLA4 inhibits an immune response in a cellular assay. As a result, CTLA4 is not a polypeptide "requiring dimerization for biological activity".

REDACTED

[22] As discussed in Section II.A., sCTLA4 is a monomer. (Exh. 6 at 3596-602).

REDACTED

Because CTLA4 does not require dimerization for biological activity, Bristol's CTLA4-Ig cannot infringe the asserted claims of the patents-in-suit.

B. Bristol's CTLA4 Dimerizes on its Own

Bristol's CTLA4-Ig and the methods for producing it also cannot infringe because CTLA4 is capable of dimerizing on its own, without any help from a second "dimerizing protein".

As discussed above, during prosecution of the '027 Patent, *ZymoGenetics took the position that the dimerizing protein must drive the dimerization of the molecule.* After ZymoGenetics made that argument, the Examiner rejected the claim again, pointing out the specific text of prior art at issue:

> [ZymoGenetics] claim[s] that Boss et al. do not teach or suggest the use of the immunoglobulin constant region in the dimerization of non-immunoglobulin polypeptides. Boss(L) does teach that "it is also envisaged that the ***Ig molecule may be synthesized by a host cell with another peptide moiety*** attached to one of its constant domains." This passage teaches the production of multichain fusion proteins in which one component is an immunoglobulin chain. ***Whether the peptide moiety becomes dimerized or not would be dictated by the moiety chosen.***

('027 Pros. Hist., Office Action (8/23/1990) at BMS004259315) (Exh. 31) (emphasis added). That is, for example, if the peptide moiety chosen to be fused to the immunoglobulin was capable of forming a dimer on its own, it would do so with or without the Ig portion, and the Ig portion would not be driving the dimerization. In response, ZymoGenetics amended the claim further, as follows:

> 22. (Twice Amended) A method for producing a secreted, biologically active, dimerized polypeptide fusion, comprising:
> introducing into a eukaryotic host cell a first DNA construct comprising a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame with a first DNA sequence encoding a first polypeptide chain of a non-immunoglobulin polypeptide dimer requiring dimerization for biological activity joined to a DNA sequence encoding an immunoglobulin light chain constant region
> ...

('027 Pros. Hist., Amendment (11/19/1990) at BMS004259320-21) (Exh. 33). It is clear and unambiguous that ZymoGenetics disavowed from the scope of the term "requiring dimerization for biological activity" circumstances where non-immunoglobulin polypeptides would form dimers on their own (without the aid of a "dimerizing protein"). And, as discussed above, a patentee is estopped from capturing subject matter that was disclaimed or disavowed during prosecution.

REDACTED

REDACTED

Because CTLA4 can dimerize on its own, CTLA4 is not a polypeptide "requiring dimerization for biological activity". And, therefore Bristol's CTLA4-Ig cannot infringe the asserted claims of the patents-in-suit.

IV. Bristol's CTLA4-Ig Cannot Infringe Because CTLA4 Is Not a "Non-Immunoglobulin Polypeptide"

As discussed in Bristol's Cl. Constr. Br., based on positions taken by ZymoGenetics during prosecution of the priority application to the patents-in-suit, the term "non-immunoglobulin polypeptide" should be construed to exclude:

(a) polypeptides that are encoded by immunoglobulin-like genes which encode discrete domains structurally similar to immunoglobulin; and

(b) polypeptides that have significant sequence homology to immunoglobulin.

It is undisputed that CTLA4 is structurally similar to immunoglobulin and has significant sequence homology to immunoglobulin. (Exh. 9 at Abstract)

REDACTED

REDACTED

REDACTED

Therefore, there can be no genuine issue of dispute that CTLA4 is a polypeptide that is encoded by an immunoglobulin-like gene which encodes a discrete domain structurally similar to immunoglobulin, and that CTLA4 has significant sequence homology to immunoglobulin. Under a construction that reflects ZymoGenetics' arguments concerning the meaning of the term "a non-immunoglobulin polypeptide", CTLA4 is not a "non-immunoglobulin polypeptide". And, therefore Bristol's CTLA4-Ig cannot infringe the asserted claims of the patents-in-suit.

CONCLUSION

For the foregoing reasons, Bristol respectfully requests that the Court enter judgment of noninfringement of all the asserted claims as a matter of law.

OF COUNSEL:

Robert L. Baechtold
Scott K. Reed
Colleen Tracy
Ha Kung Wong
Christopher P. Borello
FITZPATRICK CELLA HARPER & SCINTO
30 Rockefeller Plaza
New York, N.Y. 10112
Telephone: (212) 218-2100

Dated: May 16, 2008

Kelly E. Farnan
Frederick L. Cottrell, III (#2555)
cottrell@rlf.com
Kelly E. Farnan (#4395)
farnan@rlf.com
Richards, Layton & Finger, P.A.
One Rodney Square, P.O. Box 551
Wilmington, DE 19899
(302) 651-7700

Attorneys for Defendant
Bristol-Myers Squibb Co.

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on May 16, 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

Philip A. Rovner, Esquire
Potter, Anderson & Corroon
Hercules Plaza - 6th Floor
Wilmington, DE 19899

BY E-MAIL

Paul J. Andre
King & Spalding, LLP
1000 Bridge Parkway
Suite 100
Redwood Shores, CA 94065

Kelly E. Farnan (#4395)

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on May 23, 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

Philip A. Rovner, Esquire
Potter, Anderson & Corroon
Hercules Plaza - 6th Floor
Wilmington, DE 19899

BY FEDERAL EXPRESS

Paul J. Andre
King & Spalding, LLP
1000 Bridge Parkway
Suite 100
Redwood Shores, CA 94065

Kelly E. Farnan
Kelly E. Farnan (#4395)