IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ZYMOGENETICS, INC , a Washington Corporation,	)	
Plaintiff,	)	Civil Action 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
ANSWERING BRIEF OPPOSING ZYMOGENETICS'
MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT

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TABLE OF CONTENTS

TABLE OF AUTHORITIES iii

INTRODUCTION 1

BACKGROUND 3

I. Understanding of Technical Terms 3

II The Asserted Claims and the Claim Term Constructions Applied by ZymoGenetics in its Summary Judgment Brief 3

III The Accused Product -- Orencia® 4

A. Bristol's CTLA4-Ig 4

B. CTLA4-Ig – How It Works 5

C. The Invention of CTLA4-Ig 6

ARGUMENT 8

I SUMMARY JUDGMENT STANDARDS 8

II. CTLA4 DOES NOT "REQUIRE DIMERIZATION FOR BIOLOGICAL ACTIVITY" 9

A. CTLA4 has "Biological Activity" as a Monomer (*i e* , it does not need to be a dimer) 10

1. Binding is the Appropriate Measure of "Biological Activity" 10

2. Because Binding is an Appropriate Measure of "Biological Activity", CTLA4 has Biological Activity as a Monomer 14

3. Even if a Cellular Assay Is the Appropriate Measure of "Biological Activity", CTLA4 has Biological Activity as a Monomer 16

4. Redacted 17

B. ZymoGenetics Presents No Affirmative Evidence That CTLA4 19

1. Whether CTLA4 Exists as a Biologically Active Dimer is Irrelevant 20

2. Scientific Literature Exists Showing 20

3 CTLA4 Functions in Nature as *Both* 21

4. CTLA4 Exists in Cell Membranes as *Both* a Dimer and a Monomer 22

5. Redacted 24

III THE MUTATED "IG" IN BRISTOL'S CTLA4-IG IS NOT A "DIMERIZING PROTEIN" 25

A. ZymoGenetics' Arguments Ignore the Active Component of its Construction of "Dimerizing Protein" 27

B. ZymoGenetics has not Provided any Evidence that the Mutated Ig in Orencia is a Dimerizing Protein 28

1 Redacted 29

2 ZymoGenetics Improperly Relies on Data Concerning Wild-Type Ig 34

a) Small Mutations Can Affect Dimerization and Testing of Mutated Ig is Necessary to Ascertain the Effects of these Mutations 34

b) Bristol's Mutated Ig does not Behave like Wild-Type Ig 36

3. ZymoGenetics' Reliance on Experiments Performed Under Non-Physiological Conditions is Contradicted by Experiments Performed Under Physiological Conditions 37

IV. Non-Immunoglobulin Polypeptide 39

CONCLUSION 40

TABLE AUTHORITIES

Cases

Abbott Labs v Torpharm, Inc, 300 F.3d 1367 (Fed Cir 2002) 8

Advanced Med Optics, Inc v Alcon Inc., 2005 U S Dist LEXIS 5803 (D Del Apr 7 2005) 33

Anderson v Liberty Lobby, Inc, 477 U.S. 242 (1986) 8

Celotex Corp v Catrett, 477 U.S 317 (1986) 8

CheckpointSys, Inc v All-Tag Sec SA, 412 F.3d 1331 (Fed Cir 2005) 8

Eltech Sys Corp v PPG Indus, Inc., 710 F Supp 622 (W.D La 1988) 35

Inline Connection Corp v AOL Time Warner Inc, 472 F Supp 2d 604 (D Del 2007) 33

Judin v United States, 110 F.3d 780 (Fed Cir 1997) 35

Pell v E I DuPont de Nemours & Co., 231 F R D 186 (D Del 2005) 33

Praxair, Inc v ATMI, Inc, 445 F Supp 2d 460 (D Del 2006) 33

Other

35 U S C §285 35

Fed R Civ P 26(a)(2)(b) 33

Fed R Civ P 37(c)(1) 32, 33

Fed R Civ P 56(c) 8

Pursuant to the Court's Order dated August 4, 2008, Bristol-Myers Squibb Company ("Bristol") submits this answering brief in opposition to ZymoGenetics, Inc.'s ("ZymoGenetics") Brief in Support of its Motion for Summary Judgment of Infringement of the Patents-in-Suit (D.I. 167). Bristol previously submitted a Response to ZymoGenetics' Statement of Material Facts concerning ZymoGenetics' Motion for Summary Judgment of Infringement. (D.I. 210)

INTRODUCTION

ZymoGenetics is not entitled to summary judgment. To the contrary, on the undisputed facts, Bristol's Orencia®, and its active ingredient CTLA4-Ig, do not infringe U.S. Patent Nos. 5,843,725 ("the '725 patent") and 6,018,026 ("the '026 patent") (collectively "the patents-in-suit") even under ZymoGenetics' own constructions of the claims.

In asserting Bristol's CTLA4-Ig infringes the patents-in-suit, ZymoGenetics ignores peer-reviewed scientific publications, Redacted

For instance, for the claim limitation "requiring dimerization for biological activity", ZymoGenetics ignores scientific publications that indisputably show CTLA4 is biologically active as a monomer and, therefore, does not require dimerization to have biological activity. ZymoGenetics also ignores the admissions of its own fact and expert witnesses Redacted

Similarly, for the claim limitation "dimerizing protein", ZymoGenetics ignores its experts' testimony Redacted ZymoGenetics also ignores the fact that CTLA4 can form a dimer on its own. ZymoGenetics tries to rely on studies relating not to the mutated Ig in Bristol's CTLA4-Ig but an unmutated form of Ig -- the two are structurally and functionally different.

Redacted

The record evidence ignored by ZymoGenetics unquestionably supports Bristol's position that CTLA4-Ig does not infringe the patents-in-suit. Each of the scientific articles and admissions identified by Bristol refutes ZymoGenetics' assertion that the undisputed facts justify grant of its motion. ZymoGenetics' burden is to show the Court affirmative evidence establishing the absence of any genuine issue of material fact, leading to the conclusion of infringement. As discussed in detail below, the alleged "evidence" that ZymoGenetics does cite cannot withstand scrutiny.

In fact, ZymoGenetics fails to set forth even a *prima facie* case of infringement. For example, in asserting that the CTLA4 used in Bristol's CTLA4-Ig "requires dimerization for biological activity", ZymoGenetics sets forth no affirmative evidence, and instead argues the negative proposition that there is a lack of evidence showing that CTLA4 is biologically active when it is not a dimer. That assertion is contradicted by the many scientific publications establishing the exact opposite. But even if that negative argument were unrebutted, a jury could not find in ZymoGenetics' favor because it bears the burden of proving infringement by affirmative evidence of infringement.

In fact, ZymoGenetics cannot present any such affirmative evidence

Redacted

[1] Declaration of John W. Kirkland in Support of Bristol's Motion for Summary Judgment of Noninfringement (D.I. 174) Exh. 22 at 144:13-145:10; 202:13-15; Exh. 28 at 135:4-12; Declaration of Dana Lau in Support of Bristol's Response to ZymoGenetics' Statement of Facts

In order to prevail on its summary judgment motion under its proposed construction, ZymoGenetics must show there is no genuine issue of material fact that Bristol's CTLA4-Ig contains two limitations:

(1) a non-immunoglobulin polypeptide or ligand-binding domain of a receptor "requiring dimerization for biological activity"; and

(2) a "dimerizing protein"

Bristol's CTLA4-Ig does not contain either of those the limitations. Because ZymoGenetics fails to prove that there is no genuine issue of material fact that (1) CTLA4 requires dimerization for biological activity and (2) Bristol's mutated Ig is a dimerizing protein, ZymoGenetics fails to meet its burden on its Summary Judgment Motion of Infiingement Bristol respectfully requests that the Court deny ZymoGenetics' motion and grant Bristol's motion for summary judgment of noninfringement

BACKGROUND

I. Understanding of Technical Terms

In an effort to minimize duplication, Bristol respectfully refers to the "Technical Background" section of Bristol's Opening Claim Construction Brief for a brief discussion of the technical terms used herein. (D I 179 at 3-9)

II. The Asserted Claims and the Claim Term Constructions Applied by ZymoGenetics in its Summary Judgment Brief

The parties disagree as to the meaning of several claim terms. For purposes of ZymoGenetics' summary judgment brief concerning infringement, it assumed that its own constructions would prevail As such, Bristol has applied ZymoGenetics' constructions of the

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in Support of its Motion for Summary Judgment of Infringement (D I 211), Exh 15 at 276:11-15; 283:9-21; *see also infra* Section III B at 27-28 (objections omitted)

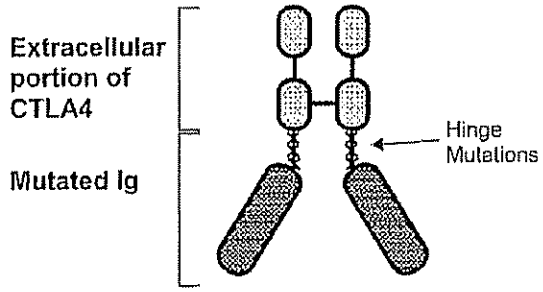
terms for purposes of opposing the present summary judgment motion In particular, ZymoGenetics' constructions of the relevant claim terms are as follows

Claim Term	ZymoGenetics' Proposed Construction Applied in its Summary Judgment Brief
non-immunoglobulin polypeptide:	Not an immunoglobulin (D I 167 at 6)
requiring dimerization for biological activity:	Must be in a dimer form (i.e., a pair) to exhibit biological activity (D I 156 at 23)[2]
biological activity:	A function or set of activities performed by a molecule in a biological context (D I 167 at 7)
dimerizing protein:	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 167 at 9)

III. The Accused Product -- Orencia®

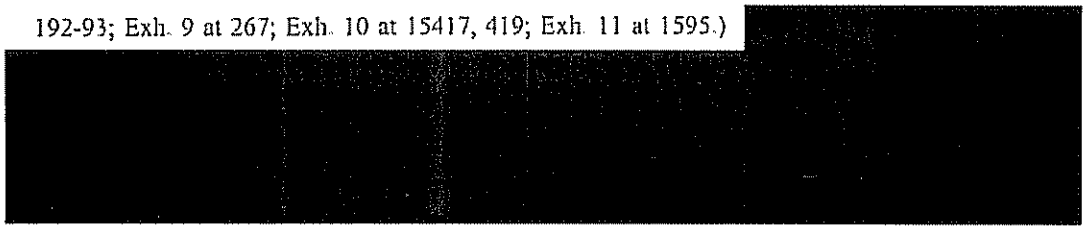
A. Bristol's CTLA4-Ig

Bristol's CTLA4-Ig is a fusion protein containing an extracellular portion of a CTLA4 joined to a portion of a mutated Ig [3] The following figure is a depiction of Bristol's CTLA4-Ig:



[2] While not explicitly spelled out in its summary judgment brief, this is presumably the construction applied by ZymoGenetics as it is the construction it proffered in its claim construction brief (ZymoGenetics' Opening Claim Construction Brief) (D.I 156 at 23).
[3] D I 174, Exh. 5 at 1.

CTLA4 naturally exists in humans as both a molecule attached to cells ("membrane-bound CTLA4") and a soluble molecule not attached to cells ("soluble CTLA4" or "sCTLA4") CTLA4, either attached to cells or as a soluble molecule, exists as a monomer and a dimer in nature. (D.I. 174, Exh. 6 at 3597-98 (Section 2.3); Exh. 7 at 151-52; Exh. 8 at 190 (Abstract), 192-93; Exh. 9 at 267; Exh. 10 at 15417, 419; Exh. 11 at 1595.)



The mutated "Ig" (immunoglobulin) 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. In wild-type Ig, the hinge region contains three "cysteines" capable of forming disulfide bonds (*i.e.*, covalent bonds). (D.I. 174, Exh. 15 at Figure 12.2(a).) These cysteines in the hinge are the only possible way that the natural hinge, CH2, and CH3 regions of a wild-type Ig can form a covalent bond with another natural hinge, CH2, and CH3 Ig molecule. And these cysteines act as dimerizing sites.

Bristol removed those dimerizing sites -- it mutated all three of these cysteines to serines (which cannot form covalent bonds) -- thereby making it impossible for Bristol's Ig to form a covalent bond between the two Ig regions. (D.I. 174, Exh. 16 at BMS001290348-351.) The figure on page 5 depicts where these mutations in the hinge region are with three "X" marks on each mutated Ig. There is also a fourth mutation -- a proline to serine mutation -- in the CH2 region of Bristol's mutated Ig. (*Id.*) (not shown in p. 5 Figure)

B. **CTLA4-Ig -- How It Works**

Bristol's CTLA4-Ig treats rheumatoid arthritis by disrupting what is known as the "CD28-B7 pathway." (*See* D.I. 174, 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 "B-cells".[4] When CD28 binds to B7, it turns on an immune response

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

C. **The Invention of CTLA4-Ig**

In the late 1980's, scientists at Oncogen (a small biotechnology company that was later purchased by Bristol), were involved in characterizing and understanding CD28 and its role in the immune system (D I 174, Exh 17 at BMS004254740-742; Exh 18 at 1753) 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 involved in the immune response. (D I 174, Exh 18 at 1753-60) In early 1989, Dr Peter Linsley, an Oncogen scientist, joined an ongoing research effort with a specific goal in mind -- discovering what it was that bound to CD28 (*i e* , the "natural ligand" for CD28) (D I. 174, Exh 17 at BMS004254742-743)

By December 1989, Dr. Linsley discovered that B7 was a natural ligand to CD28 and that B7 could be used to turn the immune response "on" by binding to CD28 (*Id.*; D I 174, 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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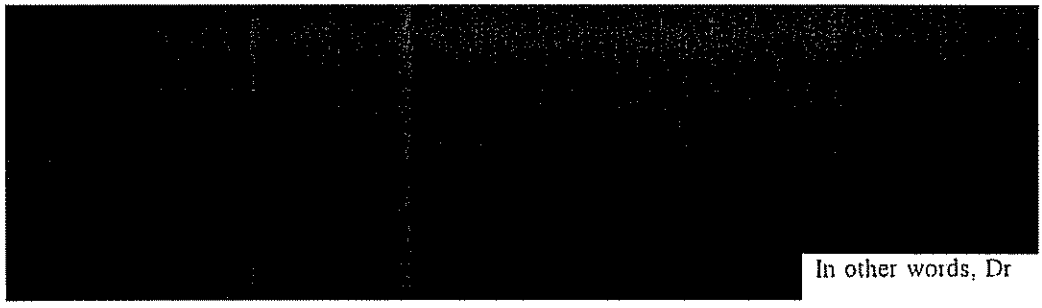
[4] Note that references cited in this brief also refer to B7 as B7-1 (or CD80) and B7-2 (or CD86) because at least two types of B7 exist and there is more than one nomenclature for B7 molecules

Soon after this initial discovery, Dr. Linsley hypothesized that CTLA4, which shared significant homology to CD28, may also bind B7. (D.I. 174, Exh. 17 at BMS004254745-746, 759-761.) It turned out that Dr. Linsley's hypothesis was correct -- CTLA4 was not only capable of binding to B7, but it was, unexpectedly, capable of binding "competitively". That is, CTLA4 was capable of disrupting the CD28-B7 pathway, essentially serving as an "off" switch.

In the process of investigating the role of CD28 and B7, Dr. Linsley collaborated with another scientist named Dr. Alejandro Aruffo. (*Id.* at BMS004254761-764.) Dr. Aruffo was working with Dr. Brian Seed, and both were affiliated with Massachusetts General Hospital and Harvard Medical School. Drs. Aruffo and Seed had invented a way of making membrane bound receptors and ligands -- such as CD28 and B7 -- into soluble molecules that could be purified easily, that is creating fusion proteins of those receptors and ligands with Ig molecules.[5] By joining Igs to a polypeptide that had a desired activity, the resulting fusion protein was also more soluble and stable in the patient's blood. (*Id.* at BMS004254769-770.)

Dr. Aruffo's laboratory had attempted to make CD28-Ig for Dr. Linsley. However, the CD28-Ig made by Dr. Aruffo's laboratory did not bind B7. (*Id.* at BMS004254761-764.) Dr. Linsley hypothesized that disulfide bonds in the Ig portion of the fusion protein dimerized and interfered with the CD28 portion of the molecule. (*Id.* at BMS004254772-774.)



In other words, Dr.

[5] This invention is the subject of some of Bristol's invalidity claims.

Linsley intentionally engineered out of his Ig the dimerizing sites that are essential to the natural Ig's function as the "dimerizing protein".

Dr. Linsley's CD28-Ig fusion protein using the monomeric Ig bound B7 (D.I. 174, Exh 17 at BMS004254835-837; Exh 20 at BMS 18955-957, 19104.) When Dr. Linsley decided to make CTLA4-Ig, he used the same monomeric Ig that he used to make CD28-Ig (D.I. 174, Exh. 17 at BMS004254783-788; Exh. 21 at BMS004254880-881.)

ARGUMENT

I. SUMMARY JUDGMENT STANDARDS

Summary judgment may be granted only if the record "show(s) that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." FED. R. CIV. P. 56(c). ZymoGenetics bears the initial burden of demonstrating the absence of a genuine issue of material fact. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). A dispute is "genuine" if a reasonable jury could find for the non-movant. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 251-52 (1986). As stated by the Supreme Court:

> [The inquiry is] whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law.

Id. Bristol's evidence must be believed, and all doubts must be resolved in Bristol's favor. *See CheckpointSys., Inc. v. All-Tag Sec. S.A.*, 412 F.3d 1331, 1336, 1338 (Fed. Cir. 2005); *Abbott Labs. v. Torpharm, Inc.*, 300 F.3d 1367, 1372-73 (Fed. Cir. 2002). In addition, the evidence must be viewed "through the prism of the substantive evidentiary burden." *Anderson*, 477 U.S. at 254. Thus, to prevail here, ZymoGenetics must show that no reasonable jury could find noninfringement.

II. CTLA4 DOES NOT "REQUIRE DIMERIZATION FOR BIOLOGICAL ACTIVITY"

In order for Bristol's CTLA4-Ig to infringe, the "CTLA4" portion of Bristol's CTLA4-Ig must be shown to be a polypeptide "requiring dimerization for biological activity."[6] Although ZymoGenetics never set forth a construction for the term "requiring dimerization for biological activity", it argued in its claim construction brief that it means "must be in a dimer form (*i.e.*, in a pair) to exhibit biological activity." (D.I. 156 at 23). Under this construction, the record evidence supports the exact opposite of what ZymoGenetics' argues in its infringement summary judgment brief, such that there is no genuine issue of material fact that the CTLA4 in Bristol's CTLA4-Ig is not a polypeptide "requiring dimerization for biological activity" because CTLA4 has biological activity as a monomer as well as a dimer. If CTLA4 performs a given biological activity as a single chain (*i.e.*, a monomer), it cannot "require dimerization for biological activity" under ZymoGenetics' proposed construction.

In fact, it is quite remarkable that in its summary judgment brief ZymoGenetics argues it is "indisputable" that CTLA4 "requires dimerization for biological activity" (D.I. 167 at 7). By doing so, ZymoGenetics must:

- ignore its own proposed construction of this term;
- ignore the testimony of its own experts -- [redacted]
- ignore contradictory peer-reviewed scientific literature that has been brought to its attention

[6] Noticeably absent from ZymoGenetics' summary judgment brief is what alleged "biological activity" CTLA4 does not exhibit unless a dimer. This absence is telling -- ZymoGenetics has no evidence.

A. **CTLA4 has "Biological Activity" as a Monomer (*i.e.*, it does not need to be a dimer)**

ZymoGenetics has no evidence that CTLA4 "requires dimerization for biological activity" -- because CTLA4 does not need to be a dimer to be biologically active. ZymoGenetics does not cite to any experimental data that indicate CTLA4 loses its biological activity when not a dimer, needs to be in dimer form to have biological activity, or does not have biological activity as a monomer. Despite having the burden of proof, rather than pointing to any evidence concerning such experiments, ZymoGenetics (incorrectly) argues that "unpaired CTLA4 molecules ***have not been found*** in the scientific literature to be biologically active . . ." (D.I. 167 at 7) (emphasis added). This is wrong -- to the contrary, Bristol has identified many peer-reviewed publications that prove CTLA4 has biological activity when not a dimer, *i.e.*, CTLA4 has biological activity as a monomer.

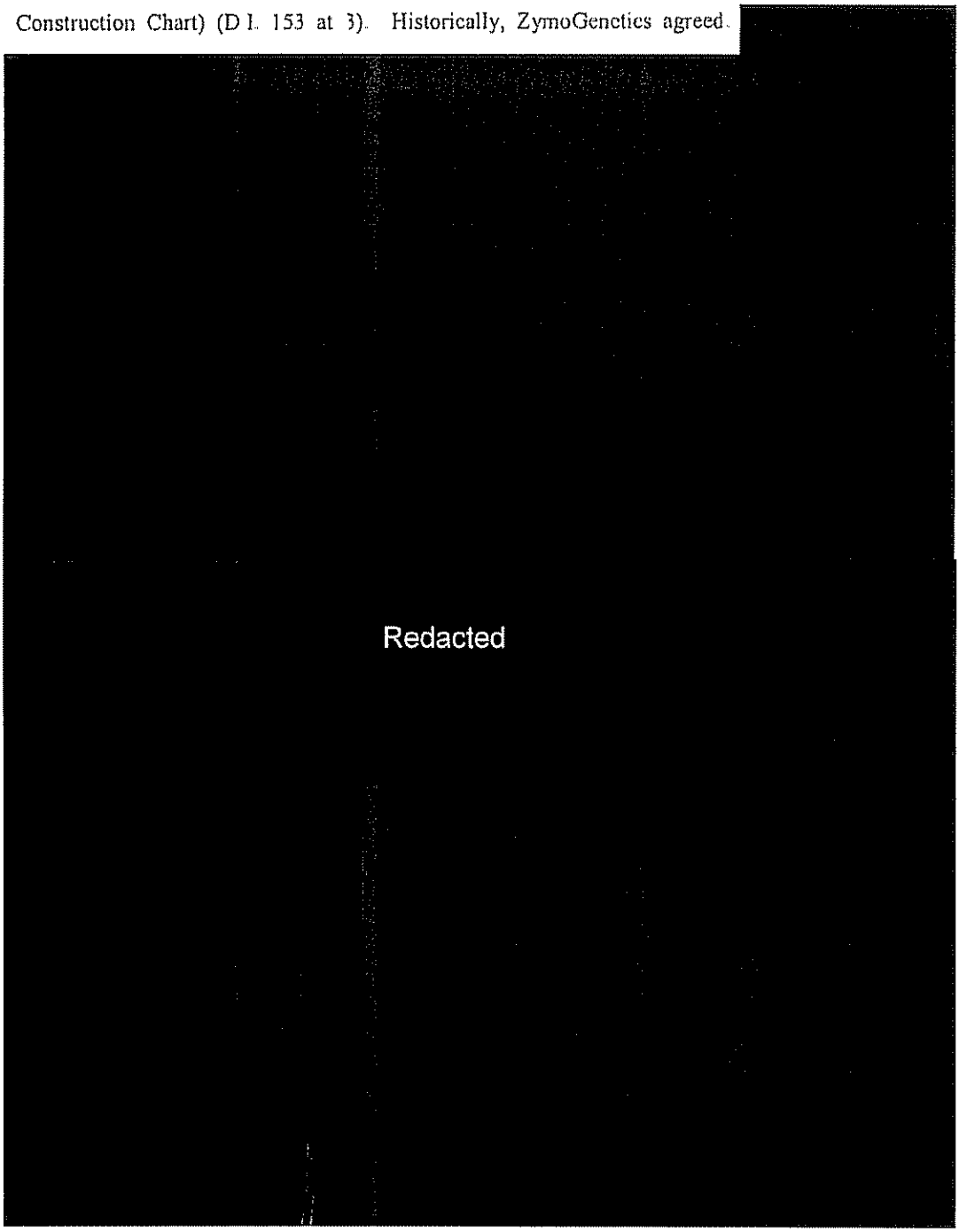
As discussed below, an appropriate measure of biological activity is "binding" (*i.e.*, "binding" and "competitive binding" of ligand). CTLA4 can bind ligand as a monomer and, therefore, is biologically active as a monomer.[7] However, even if binding is deemed insufficient and activity in a "cellular assay" is considered an appropriate measure of biological activity (that is, monomeric CTLA4 must be shown to have an effect on cells), CTLA4 monomer has biological activity in that sense as well. Peer reviewed publications have shown it to have biological activity by either measure.

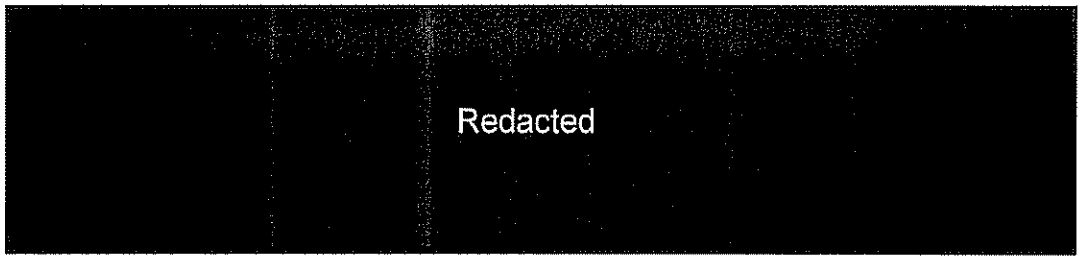
1. **Binding is the Appropriate Measure of "Biological Activity"**

As discussed in Bristol's Rebuttal Claim Construction Brief, "binding" is a "biological activity" within the meaning of the patents-in-suit. (D.I. 229 at 9-11). And nothing in

[7] ZymoGenetics' Statement of Undisputed Facts states "The portion of CTLA-4 in Orencia® binds ligands in nature." (D.I. 168, ¶ 10). That is correct as the CTLA-4 portion can bind ligand as both a monomer and dimer -- this is its biological activity.

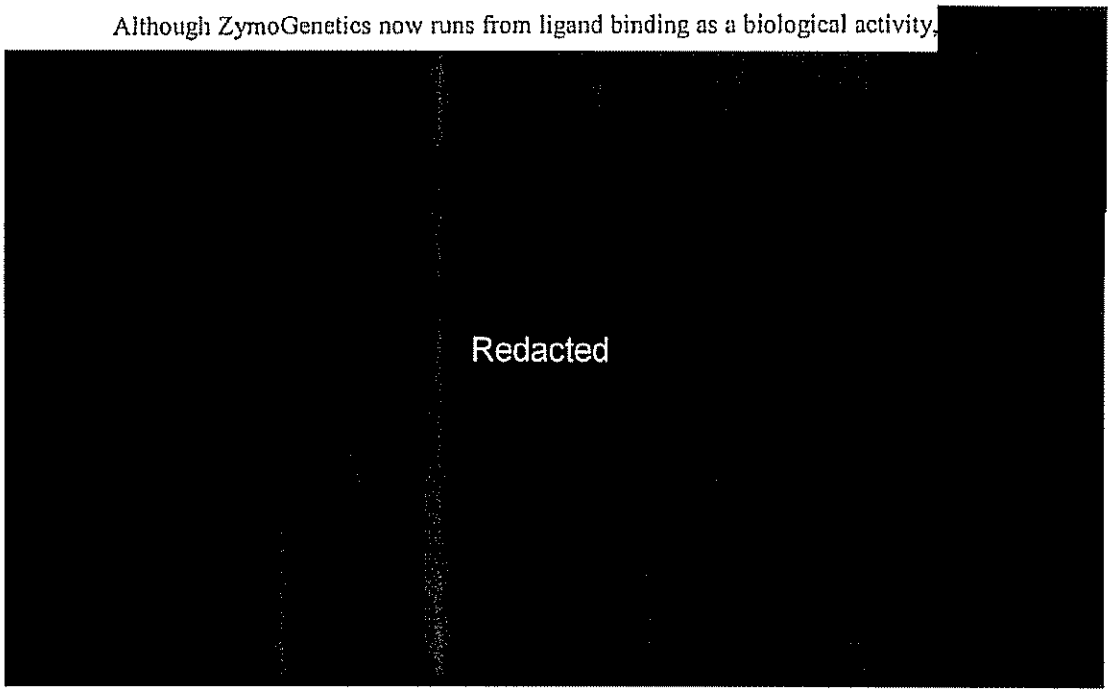
ZymoGenetics' claim construction of "biological activity" rules out binding. (Joint Claim Construction Chart) (D.I. 153 at 3). Historically, ZymoGenetics agreed.





ZymoGenetics now runs from binding being a biological activity -- because it knows it cannot dispute that CTLA4 does not need to be a dimer to bind ligand To attempt to capture Bristol's CTLA4-Ig, ZymoGenetics now argues in this litigation that biological activity must be "multi-step processes that have meaningful consequences for cells "[8] [9] (D I. 156 at 15)

Although ZymoGenetics now runs from ligand binding as a biological activity,



[8] While ZymoGenetics has not elaborated on what it means by "multi-step processes that have meaningful consequences for cells", presumably it means that a cellular assay (*e g* , showing inhibition of a cell's reaction to a foreign antigen) rather than a binding assay must be used As discussed *infra* Section II A.3 at 16-17, CTLA4 also shows biological activity by this measure.

[9] Bristol notes that ZymoGenetics did not ask for the term "biological activity" to be limited directly in its proposed construction. Rather, ZymoGenetics sought to include examples of biological activities in its construction in an attempt to limit the claim term

As noted *supra* at 6 in relation to the relative affinities of CTLA4 and CD28 to bind the B7 ligand, binding ligand can sometimes involve competitive binding (*e g* , the ability of CTLA4 to displace CD28 from B7)

Redacted

[10] ZymoGenetics cites only to two sections of the testimony of Bristol's witness Dr Nadler, but not relating to the meaning of "biological activity" (D.I. 167 at 7).

2. **Because Binding is an Appropriate Measure of "Biological Activity", CTLA4 has Biological Activity as a Monomer**

CTLA4 does not "require dimerization for biological activity" because as a monomer it retains the biological activity of binding ligand. Bristol's own scientists have demonstrated this and published their results in scientifically peer-reviewed publications, years before the patents-in-suit issued. These studies, discussed below, use what is called a high affinity ligand binding assay, which was recognized in the art to represent an *in vitro* (*i.e.*, in a "test tube") facsimile of what occurs *in vivo* (*i.e.*, in an animal). Such studies measure the binding ability of molecules, and Bristol scientists showed that CTLA4 monomer has biological activity because it can bind to the B7 ligand (also referred to as "CD80" and "CD86", the two forms of B7)

In their article in 1995 entitled "Binding Stoichiometry of the Cytotoxic T Lymphocyte-associated Molecule-4 (CTLA-4)", the Bristol scientists 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]

(D.I. 174, Exh. 10 at 15417, 15421) (emphasis added)

In another 1995 article entitled "CD28/CTLA4 Receptor Structure, Binding Stoichiometry and Aggregation During T-Cell Activation", Bristol scientists reported:

> 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.

(D.I. 174, Exh. 30 at 133) (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***

(D.I. 174, Exh. 10 at 15421-22) (internal citation omitted) (emphasis added).

As noted *supra* at 5, there is also a form of CTLA4 that exists in nature as a soluble monomer (sCTLA4). Scientists have confirmed that sCTLA4 binds natural ligands to CTLA4:

> ***sCTLA4*** ***demonstrated specific binding to each of the B7.1 and B7.2*** immunoglobulin fusion proteins

(D.I. 174, Exh. 7 at 150) (emphasis added).

> We showed that ***sCTLA4*** ***is able to bind its physiological ligands CD80/CD86*** [boths forms of B7]

(D.I. 174, Exh. 8 at Abstract) (emphasis added)

It is indisputable that the scientific record shows monomeric CTLA4 binds to B7 and that it does so competitively. Because monomeric CTLA4 binds ligand, CTLA4 has biological activity as a monomer and does not "require dimerization for biological activity" ZymoGenetics' recanting of its prior (and correct) position is litigation strategy, not science. Under a proper measure of biological activity, there can be no dispute that CTLA4 does not "require dimerization for biological activity" because it is indisputable that CTLA4 has biological activity as a monomer.

3. Even if a Cellular Assay Is the Appropriate Measure of "Biological Activity", CTLA4 has Biological Activity as a Monomer

ZymoGenetics now argues that biological activities are "multi-step processes that have meaningful consequences for cells" (D.I. 156 at 15), even though nothing in its claim construction requires this interpretation. (*See* D.I. 153 at 3). Even if that new and unsupported interpretation were correct, there is also undisputed evidence that monomeric CTLA4 has "meaningful consequences for cells" as shown in published experiments called "cellular assays". Cellular assays are *in vitro* experiments involving living cells (as opposed to binding assays which can test *in vitro* the biological activity of molecules in the absence of a cell). The cellular assays discussed below include "T cell proliferation" and "mixed-lymphocyte reaction" assays. These cellular assay studies demonstrate CTLA4 exhibits biological activity when not a dimer [11]

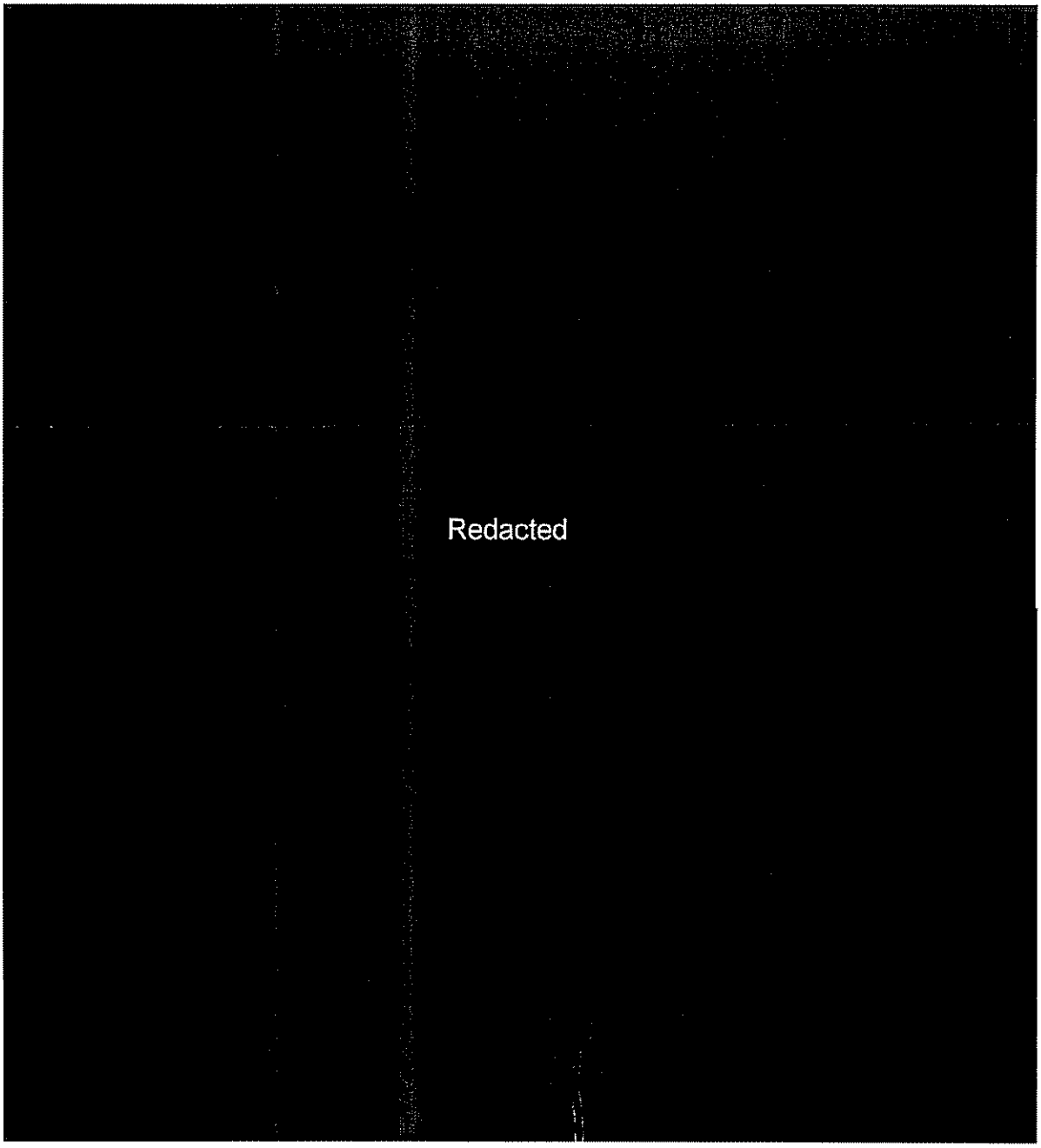
Published studies of cellular assays on soluble CTLA4, which exists naturally in the human body as an active monomer (*see supra* 5), show monomeric CTLA4 has the biological activity of inhibiting the immune response:

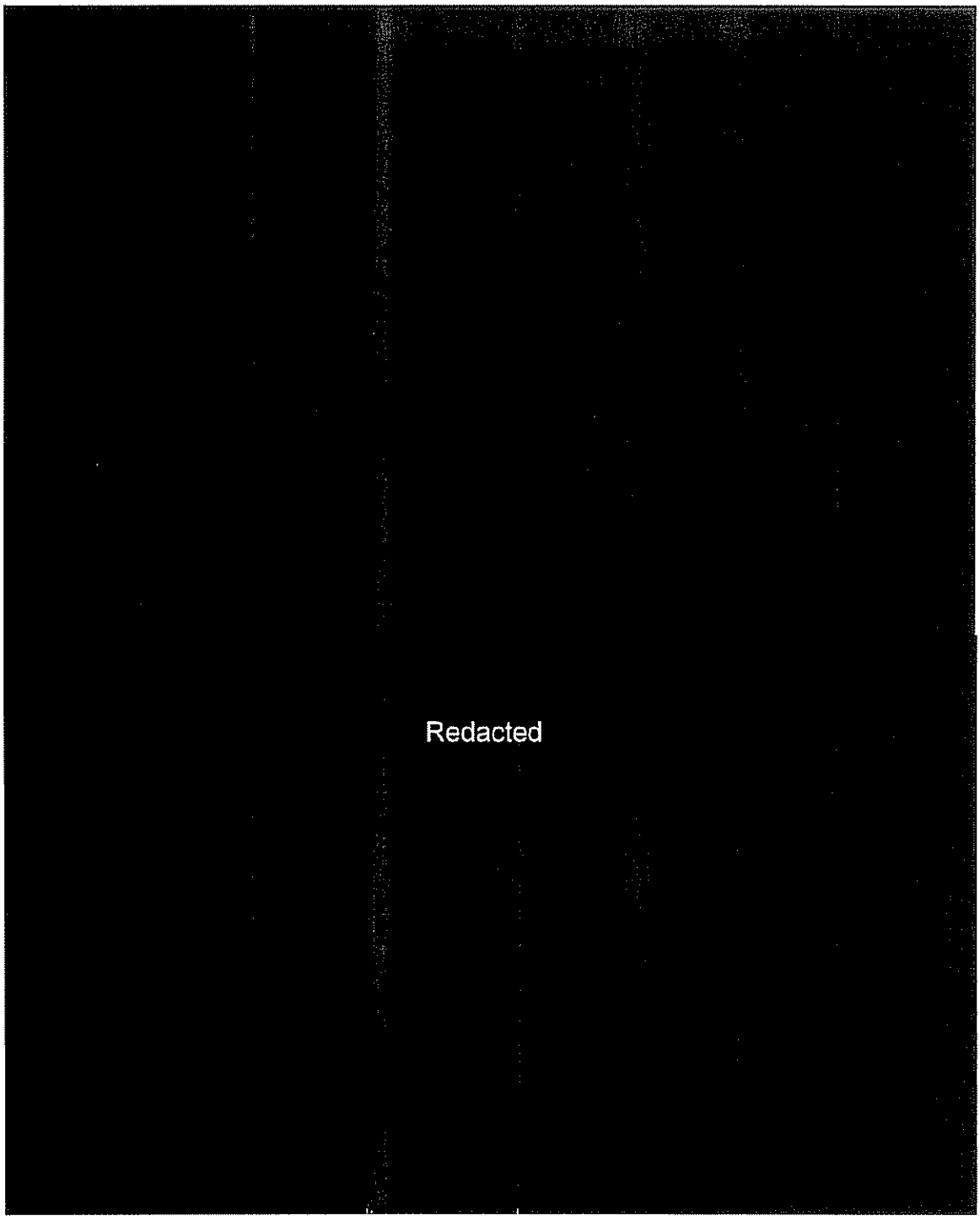
> We showed that ***sCTLA4*** . . . ***displays functional activities in different in vitro systems*** (T-cell proliferation induced by specific soluble antigens, bi-directional mixed-lymphocyte reaction)
>
> * * *
>
> ***sCTLA4*** . . . ***is able to inhibit both mixed lymphocyte reactions (MLR) and proliferation of antigen-specific T-cell clones*** in a dose dependent fashion

(D.I. 174, Exh. 8 at 190 (Abstract) and 194)(emphasis added). Therefore, even under ZymoGenetics' current, litigation driven, measure of biological activity, CTLA4 does not

[11] The specification defines 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***)" (D.I. 174, Exh. 2 at col. 9 ll. 35-37) (emphasis added). Therefore, *in vitro* assays can be used as a measure of biological activity.

"require dimerization for biological activity" and cannot infringe the asserted claims of the patents-in-suit because it is indisputable that CTLA4 is active as a monomer

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[redacted] and the record evidence discussed in Sections II.A.1-3 above, ZymoGenetics has failed to prove beyond any genuine issue of material fact that CTLA4 requires dimerization for biological activity.

There is a complete lack of affirmative evidence to support ZymoGenetics' infringement claim. As a result, no reasonable jury could find for ZymoGenetics and Bristol's Motion for Summary Judgment of Noninfringement should be granted.

B. **ZymoGenetics Presents No Affirmative Evidence That CTLA4 Requires Dimerization for Biological Activity**

ZymoGenetics proffers no evidence that CTLA4 needs to be a dimer to exhibit biological activity. Its brief merely sets forth the four assertions in the scant two paragraphs it devotes to this argument:

1. "The fact that CTLA4 exists as a dimer in its native state demonstrates that it is biologically active as a dimer." (D.I. 167 at 7).
2. "[U]npaired [*i.e.*, monomeric] CTLA4 molecules have not been found in the scientific literature to be biologically active as that term has been defined in the ZymoGenetics Patents." (D.I. 167 at 7).
3. "The biological context in which CTLA4 functions in nature is as a membrane-bound polypeptide." (D.I. 167 at 7).
4. "Bristol admits that CTLA4 is bound to cell membranes only in the dimerized, or paired, form." (D.I. 167 at 7).

None of these four assertions demonstrate that CTLA4 "requires dimerization for biological activity." In fact, these four assertions altogether avoid the relevant point -- because

CTLA4 has biological activity when not a dimer, *i e* , as a monomer, CTLA4-Ig cannot infringe Even if true, these assertions do not evidence that CTLA4 needs to be a dimer to exhibit biological activity -- the construction that ZymoGenetics itself argued for during the Markman hearing. At best, ZymoGenetics' allegations prove that CTLA4 exhibits biological activity when it is a dimer -- which is simply not germane to whether CTLA4 needs to be a dimer to exhibit biological activity In fact, ZymoGenetics' lack of evidence is not surprising,

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1. **Whether CTLA4 Exists as a Biologically Active Dimer is Irrelevant to Whether CTLA4 "Requires Dimerization for Biological Activity"**

In making its argument that CTLA4 requires dimerization for biological activity, ZymoGenetics states that "[t]he fact that CTLA4 exists as a dimer in its native state demonstrates that it is biologically active as a dimer." (D I. 167 at 7) ZymoGenetics' assertion is misleading because CTLA4 exists in native form as a biologically active monomer. Regardless, the fact of being biologically active as a dimer, while true, is not relevant to whether CTLA4 needs to be a dimer for biological activity. While it is true that some molecules are biologically active only as dimers, others are biologically active either as dimers or as monomer (or tetramers, etc.) The latter are not covered by the asserted claims CTLA4 is in this latter category because it has biological activity as a monomer, see *supra* Section II.A

2. **Scientific Literature Exists Showing CTLA4 is Biologically Active as a Monomer**

Rather than pointing to any evidence proving CTLA4 needs to be a dimer to be biologically active -- because it cannot -- ZymoGenetics states that monomeric CTLA4 "has not been found in the scientific literature to be biologically active" (D I 167 at 7) Even if it were

true that monomeric CTLA4 has not been reported in the literature to be biologically active, this is not affirmative evidence that CTLA4 "requires dimerization for biological activity". ZymoGenetics cannot meet its burden by merely stating that no evidence exists

However, as has been established, ZymoGenetics' assertion is false, as by any definition of "biological activity", the scientific literature does show monomeric CTLA4 has it *See supra* II.A. Noticeably absent from ZymoGenetics' summary judgment brief is what ZymoGenetics claims the "biological activity" of CTLA4 should be that it does not exhibit unless a dimer

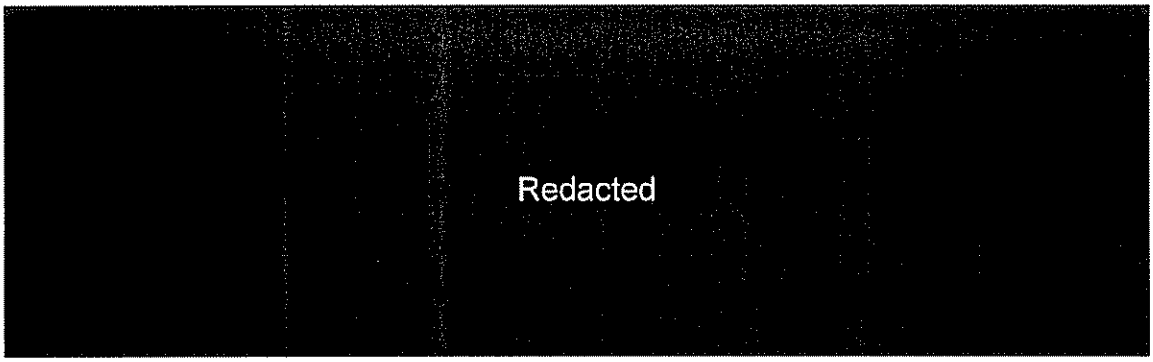
3. **CTLA4 Functions in Nature as *Both* a Membrane-Bound Molecule and a Soluble Molecule**

To support its position that CTLA4 requires dimerization for biological activity, ZymoGenetics also argues that "the biological context in which CTLA4 functions in nature is as a membrane-bound dimer." (D.I. 167 at 7). First, this statement is irrelevant to whether CTLA4 needs to be a dimer to exhibit biological activity because it would not preclude CTLA4 from having biological activity when not a dimer, *i.e.*, as a monomer

Second, to clarify the record, this statement is misleading because CTLA4 functions not solely in a membrane-bound form in nature, but also as a soluble molecule (referred to as "sCTLA4" or "CTLA-4delTM" in the literature). For example, the scientific literature states:

- "A ***soluble*** immunoreactive form of CTLA-4 was detected in the serum of . . . healthy subjects" (D.I. 174, Exh. 6 at 3596) (emphasis added);
- "Human serum contains immunoreactive material consistent with a native ***soluble*** form of CTLA-4" (D.I. 174, Exh. 7 at 144) (emphasis added); and
- "We demonstrate the presence of a ***soluble*** form of CTLA-4 in . . . sera from patients with autoimmune thyroid disease" (D.I. 174, Exh. 8 at 190) (emphasis added)

This soluble CTLA4 (which happens to be a monomer), binds to B7 (*i e*, a natural ligand to CTLA4) and inhibits a mixed lymphocyte reaction (*i e*, it prevents an immune response by a cell to a foreign antigen) (D.I. 174, Exh. 7 at 150; *see also* D.I. 174, Exh. 8 at 193-197).



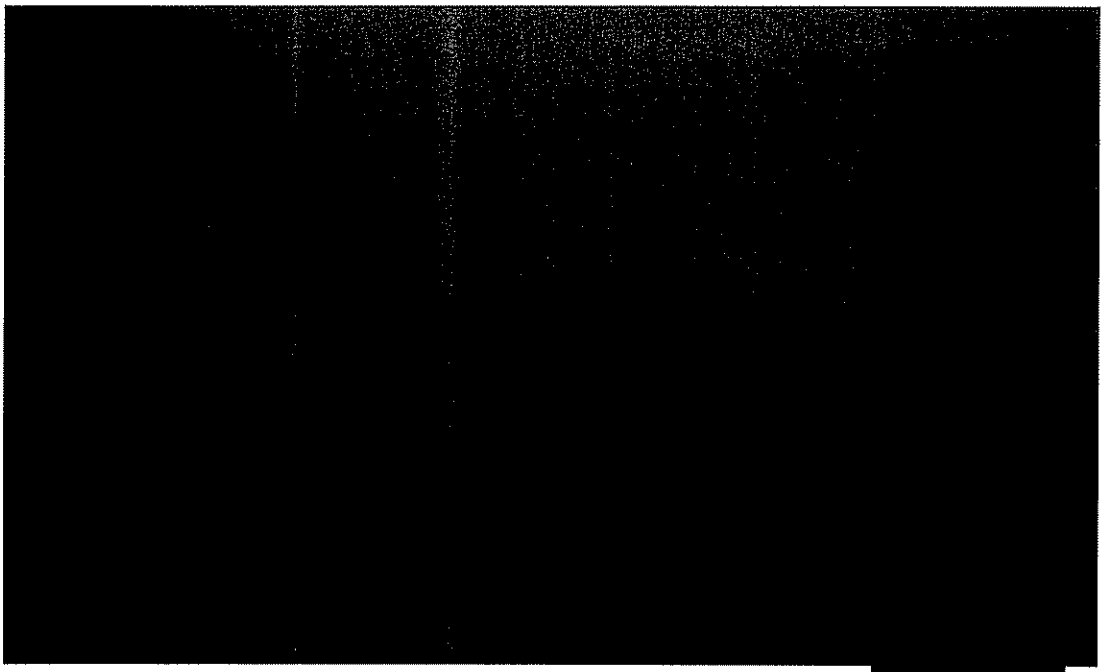
4. **CTLA4 Exists in Cell Membranes as *Both* a Dimer and a Monomer**

ZymoGenetics states "Bristol admits that CTLA4 is bound to cell membranes only in the dimerized, or paired, form". (D.I. 167 at 7) As with the other three statements, this one is also irrelevant as to whether CTLA4 needs to be a dimer to be biologically active -- it does not preclude its having biological activity when not a dimer, *i e*, as a monomer. Moreover, the scientific literature demonstrates that ZymoGenetics is wrong to state that "CTLA4 is bound to cell membranes only in the dimerized, or paired, form" And Bristol certainly made no such "admission"

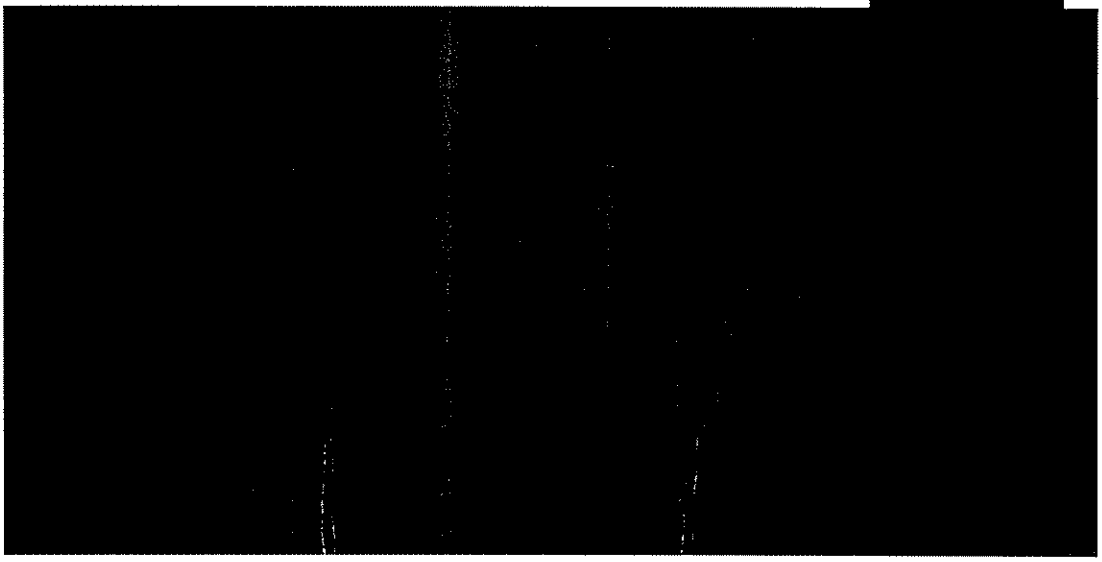
CTLA4 is present in cell membranes of T cells both as a dimer and as a monomer For example, scientific literature states:

- "CTLA-4 is expressed as a ***monomer on the surface of activated T cells***" (D.I. 211, Exh. 7 at 3495, Fig. 4) (emphasis added); and
- "A nondisulfide-linked form of CTLA-4 was observed . This nondisulfide-linked dimeric or ***monomeric form was observed on activated normal and CD28-deficient T cells***." (D.I. 211, Exh. 6 at 407) (emphasis added)

Therefore, ZymoGenetics' statement that CTLA4 only exists on the surface of cells as a dimer is simply not true because it is clear that a monomeric form is also present



It is true it is a dimer, but it is also true it is a monomer in our bodies



All four of ZymoGenetics' so called pieces of "evidence" fail to prove that CTLA4 "requires dimerization for biological activity." They are either irrelevant and/or flatly incorrect. Because these are the only assertions ZymoGenetics makes on the limitation "requiring dimerization for biological activity", ZymoGenetics cannot prove infringement and Bristol's motion for Summary Judgment should be granted.

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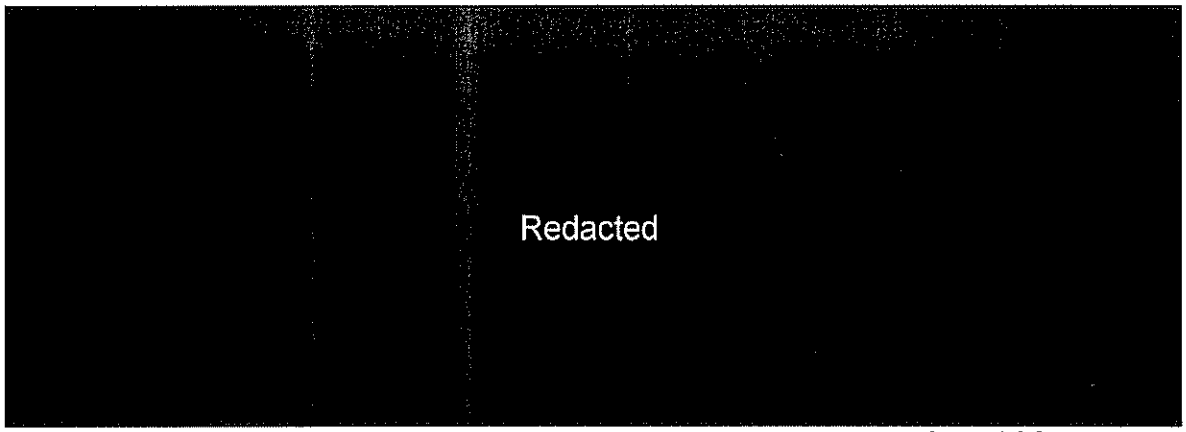


Not only has ZymoGenetics failed to prove that there is no genuine issue of material fact, but it failed to prove a *prima facie* case of infringement because it provides no evidence that CTLA4 "requires dimerization for biological activity" under its own construction of that term. Thus, on the limitation "requires dimerization for biological activity", ZymoGenetics' Motion for Summary Judgment of Infringement fails. In fact, no reasonable jury could find for ZymoGenetics, and Bristol's motion for Summary Judgment should be granted.[12]

III. THE MUTATED "IG" IN BRISTOL'S CTLA4-IG IS NOT A "DIMERIZING PROTEIN"

All asserted claims contain the limitation "dimerizing protein". In its summary judgment brief, ZymoGenetics argues that the mutated Ig portion of Bristol's CTLA4-Ig is a "dimerizing protein." But, by doing so, ZymoGenetics ignores its own proposed construction of this term and its own experts' testimony. In support of its argument, ZymoGenetics alleges:

- Orencia® is a dimer and therefore contains a dimerizing protein -- but this ignores the undisputed fact that the CTLA4 portion of CTLA4-Ig is itself a dimer (a fact

[12] Bristol was precluded from addressing ZymoGenetics' construction of "requiring dimerization for biological activity" in its opening summary judgment brief concerning noninfringement because ZymoGenetics repeatedly refused to provide its construction to Bristol until the deadline for filing briefs had passed. This was likely an attempt to avoid summary judgment, and Bristol hereby respectfully requests the Court find Bristol's CTLA4-Ig does not require dimerization for biological activity even under ZymoGenetics' construction.

admitted by its experts) and that ZymoGenetics must prove that it is the Ig portion of CTLA4-Ig that functions as the dimerizing protein

- Immunoglobulins are found in nature as dimers and can dimerize -- but this ignores the undisputed fact that Bristol's Ig is mutated and is not found in nature, and that Bristol's mutated Ig does not exhibit the characteristics of a natural dimeric Ig
- [redacted]
- That a particular study showed 80% of CTLA4 following a purification step was a monomer when not attached to an immunoglobulin -- despite that fact that this particular study was not performed under physiological conditions, and that when performed under physiological conditions, CTLA4, without being coupled to a second "dimerizing protein", was exclusively a dimer.

ZymoGenetics' proposed construction of "dimerizing protein" is:

> 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.

As admitted by ZymoGenetics during the Markman hearing, this is not a passive definition, it is a functional requirement:

> MR. ANDRE: The definition. The definition is a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associated -- they associate under physiological conditions.
>
> I think if a [chain] associates in the biological context, that's not passive. These chains associate each other. ***Association and polypeptide chains mean they are coming together through some type of interaction.*** They associate under physiological conditions to form a dimer.
>
> So with all due respect, I don't think they are necessarily passive to [one] skilled in the art. I think it does describe what's going on.

(Excerpts of the June 27, 2008 Markman Hearing Tr. at 62)(1 A.B. Exh. 3) (emphasis added).

Therefore, in order to infringe under ZymoGenetics' construction of "dimerizing protein", each of the two mutated immunoglobulin portions of Bristol's CTLA4-Ig must have an affinity for the other such that they associate under physiological conditions to form a dimer.

A. ZymoGenetics' Arguments Ignore the Active Component of its Construction of "Dimerizing Protein"

While ZymoGenetics admitted that its own definition of dimerizing protein is active, it ignores this fact through much of its summary judgment brief. For example, ZymoGenetics argues that Bristol's mutated Ig is a "dimerizing protein" because:

> [CTLA4-Ig] includes a portion of an immunoglobulin heavy chain containing the constant region domain. Thus, by definition, the immunoglobulin heavy chain Bristol uses in Orencia® is a dimerizing protein as that term is claimed

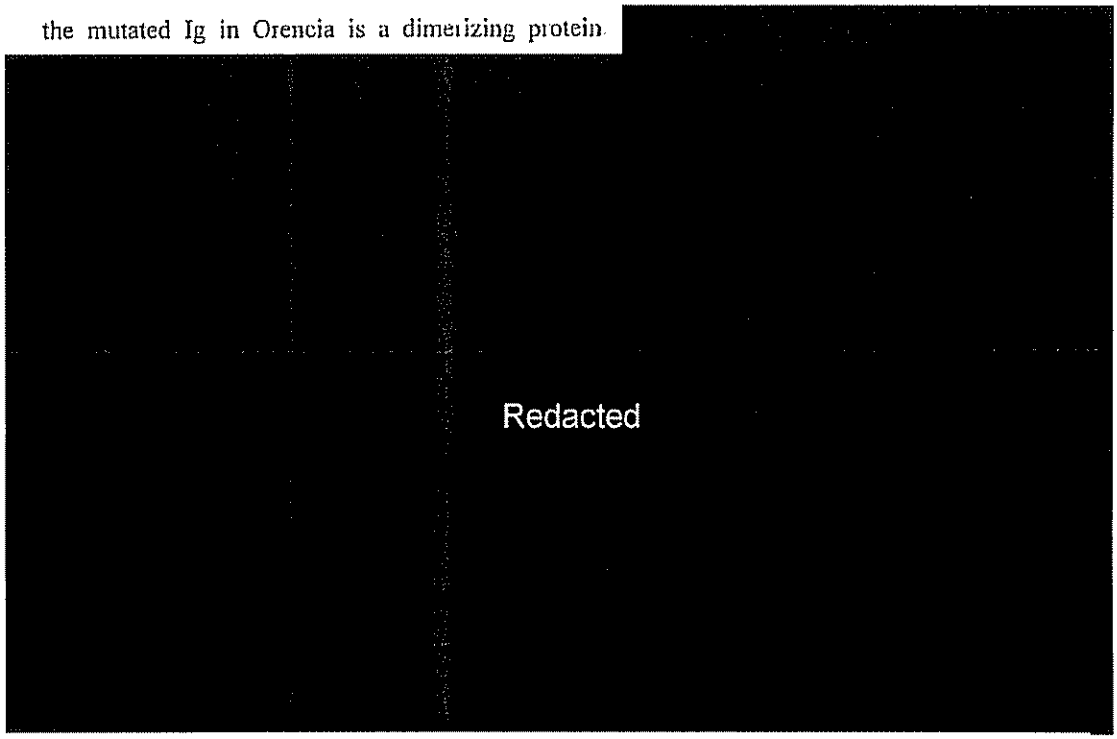
(D.I. 167 at 9). That totally ignores the functional requirement for a "dimerizing protein" and allows the Ig to be a passive passenger. Arguing that Bristol's CTLA4-Ig contains a dimerizing protein merely because it contains a portion of an immunoglobulin vitiates the active component of ZymoGenetics' own construction -- that is, ZymoGenetics also must show that the mutated Ig in Bristol's CTLA4-Ig is dimerizing the CTLA4 portion.

By way of another example, ZymoGenetics also argues that Bristol's mutated Ig is a dimerizing protein because CTLA4-Ig is a dimer and therefore "to argue that Orencia® does not contain a dimerizing protein is without merit." (D.I. 167 at 10-11). However, the fact that the entire CTLA4-Ig molecule is a dimer is irrelevant. CTLA4 dimerizes on its own. It needs no help to do that. ZymoGenetics must show that it is the two mutated immunoglobulins in Bristol's CTLA4-Ig that associate with each other to form a dimer under physiological conditions. But they do not. The dimer is formed by the two CTLA4 portions of Bristol's CTLA4-Ig that form dimerizing disulfide bonds with each other. ZymoGenetics is wrong in stating that Bristol claims there is no dimerizing protein in Orencia®. The CTLA4 portion is the

dimerizing protein in CTLA4-Ig, but the claims require a dimerizing protein that is different from the protein having biological activity [13]

B. **ZymoGenetics has not Provided any Evidence that the Mutated Ig in Orencia is a Dimerizing Protein**

ZymoGenetics has not met its burden of proving by a preponderance of the evidence that the mutated Ig in Orencia is a dimerizing protein.



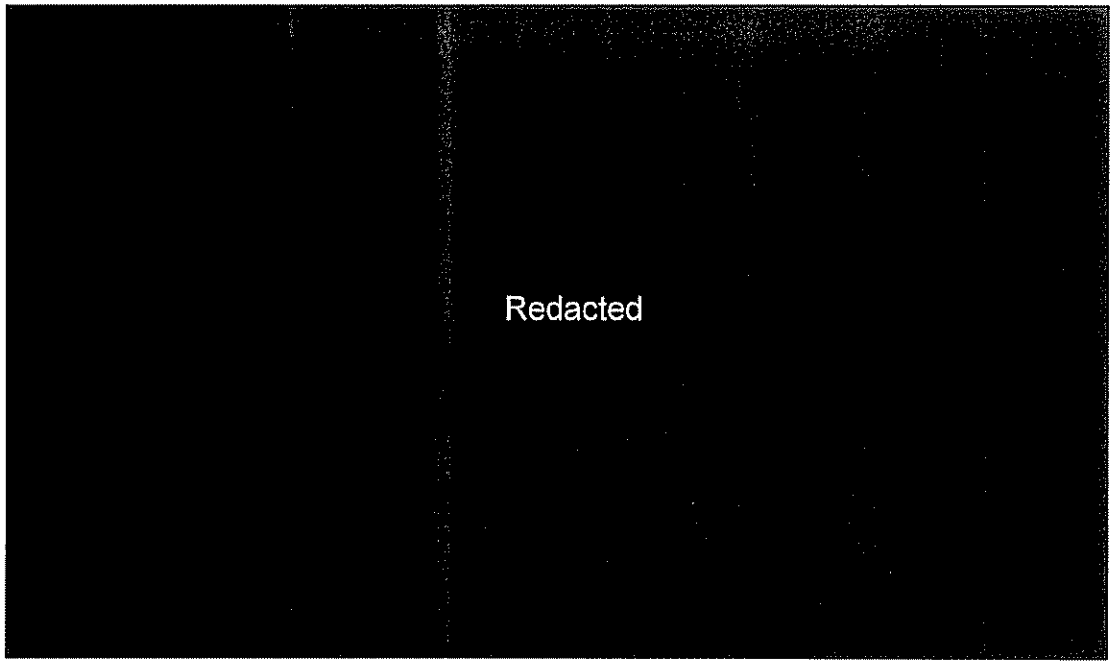
[13] The asserted claims require two things of a "dimerizing protein":

(a) the "dimerizing protein" must be heterologous (*i e*, different) from the "non-immunoglobulin polypeptide" (*i e*, allegedly CTLA4) and "ligand-binding domain" of a receptor (again, allegedly CTLA4) (so CTLA4 cannot both be the "non-immunoglobulin" / "ligand-binding domain" and the "dimerizing protein"), and

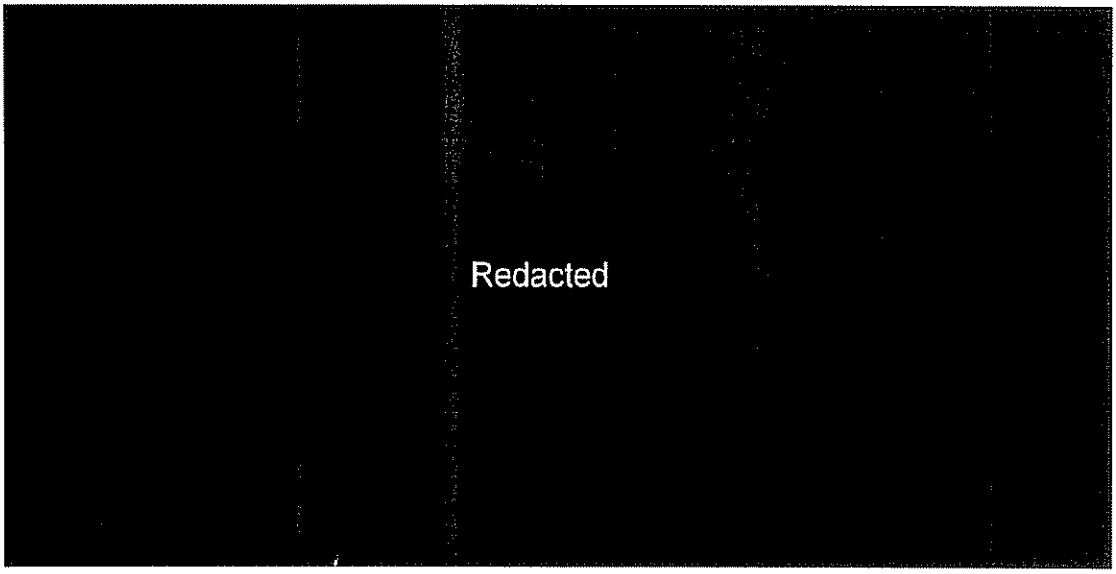
(b) the "dimerizing protein" is limited to one of the following: (1) yeast invertase, (2) a portion of an immunoglobulin light chain, or (3) a portion of an immunoglobulin heavy chain (there is no dispute that CTLA4 is none of these)

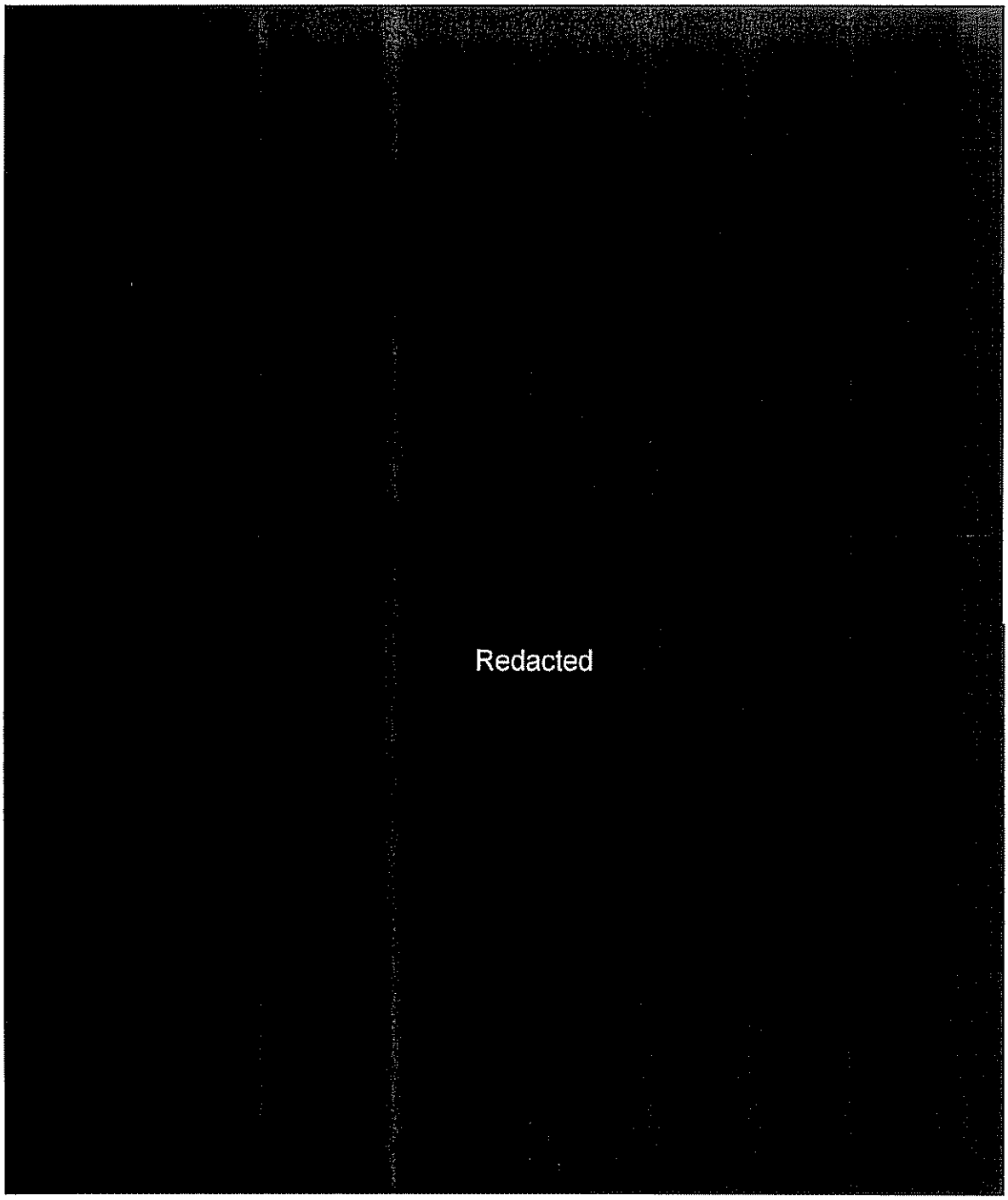
(*See* D I. 174, Exh. 2 at ZG000844, col. 1, ll. 27-50)

[14] 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)



Because ZymoGenetics does not have any proof that the mutated Ig in Orencia forms a dimer, that is, the mutated Ig in Orencia is a "dimerizing protein", ZymoGenetics is forced to rely on information obtained either from a different molecule entirely (portions of wild-type non-mutated Ig that is not part of any fusion protein) (discussed *infra* Section III.B.2 at 33-36) or,

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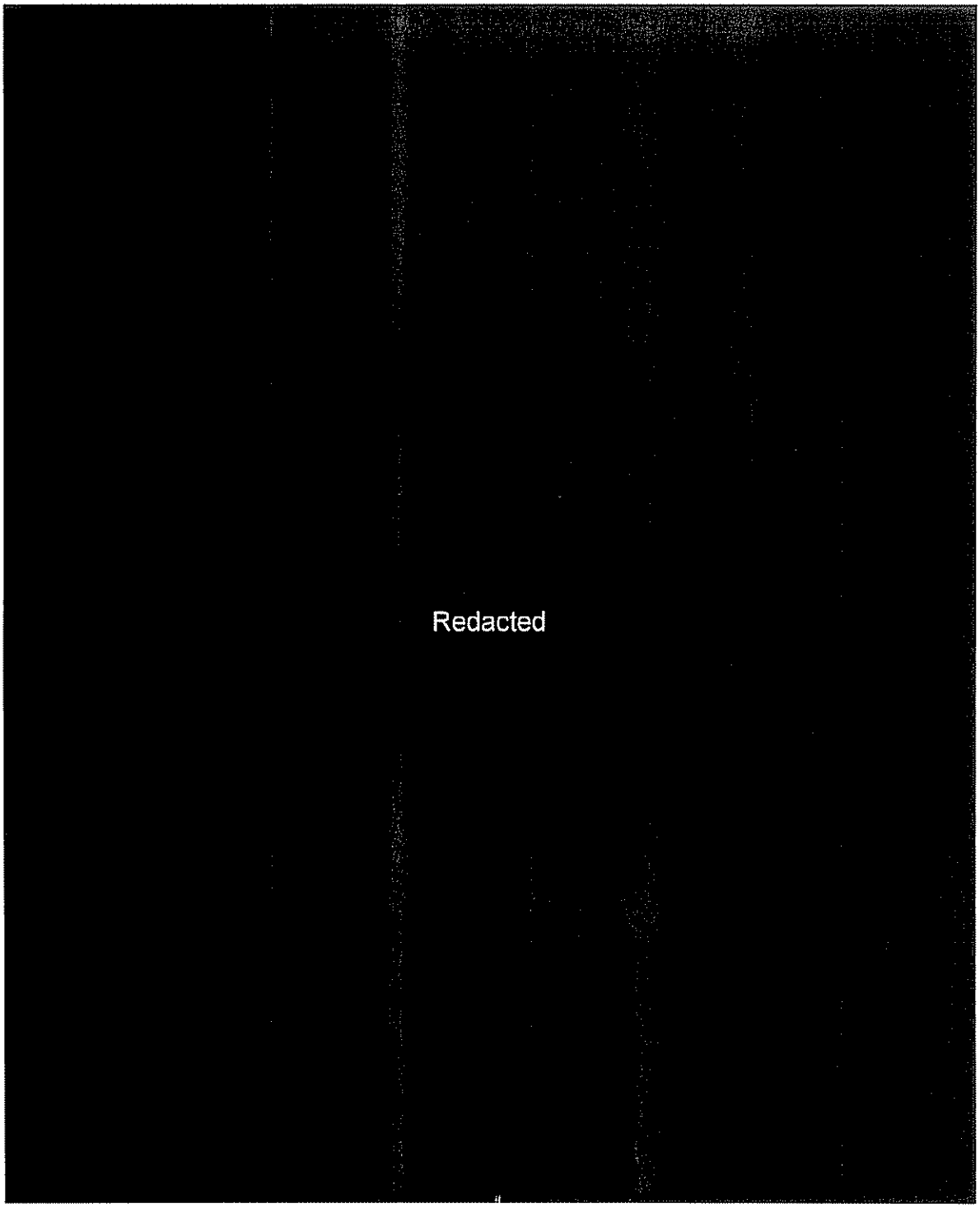
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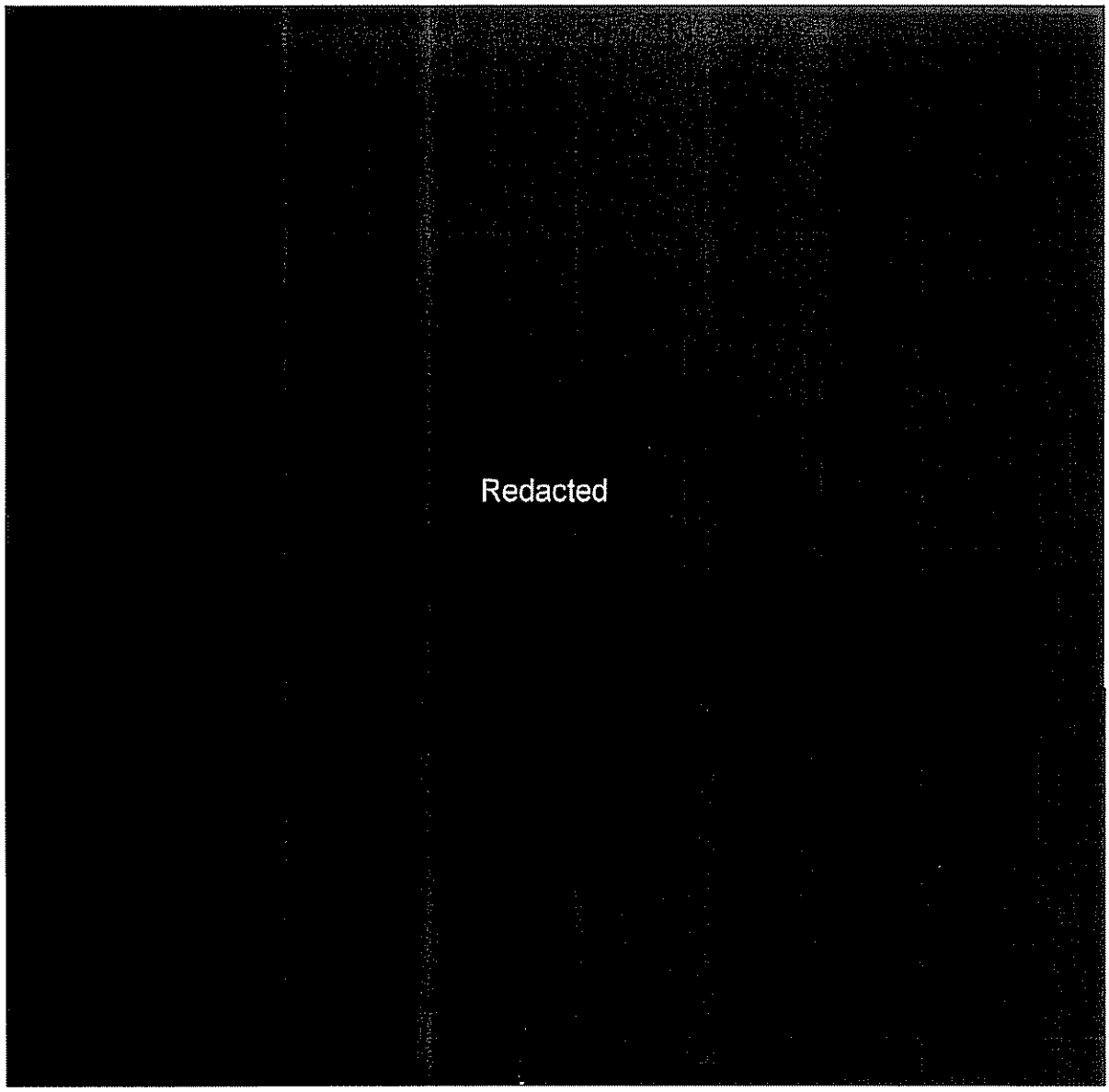
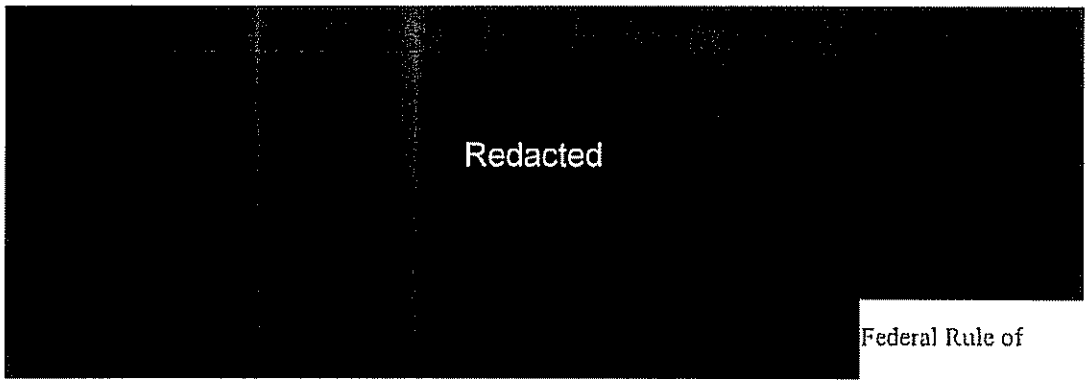


First, Federal Rule of Civil Procedure 37(c)(1) provides that if "a party fails to provide information as required by Rule 26(a) or (e), the party is not allowed to use that information or witness to supply evidence on a motion . . unless the failure was substantially justified or is harmless." The advisory committee notes to FED. R. CIV. P. 37 make clear that ZymoGenetics'

failure to disclose alleged testing evidence in response to BMS' infringement contention interrogatory requires the exclusion of that evidence. "If the party required to make the disclosure would need the material to support its own contentions, the more effective enforcement of the disclosure requirement will be to exclude the evidence not disclosed, as provided in subdivision (c)(1) of this revised rule." FED. R. CIV. P. 37, Advisory Committee Notes on 1993 Amendments

In this case, ZymoGenetics has no evidence that the Ig in Bristol's CTLA4-Ig forms a dimer. *See Praxair, Inc. v. ATMI, Inc.*, 445 F. Supp. 2d 460, 469-471 (D. Del. 2006)(excluding defendant from relying on belatedly identified prior art in proving invalidity of the patent in suit).



Federal Rule of Civil Procedure 26(a)(2)(b) requires that an expert's written report "must contain a complete statement of all opinions the witness will express and the basis and reasons for them." FED. R. CIV. P. 26(a)(2)(b); *see Pell v. E.I. DuPont de Nemours & Co.*, 231 F.R.D. 186, 191-192 (D. Del. 2005); *see also Inline Connection Corp. v. AOL Time Warner Inc.*, 472 F. Supp. 2d 604, 613-614 (D. Del. 2007) (excluding expert testimony on doctrine of equivalents when Plaintiff failed to address the doctrine in his expert report). When an expert fails to disclose the bases of his opinion as required by FED. R. CIV. P. 26(a)(2)(B), the proper remedy is exclusion and preclusion of reliance on that basis. *See Advanced Med. Optics, Inc. v. Alcon Inc.*, 2005 U.S.

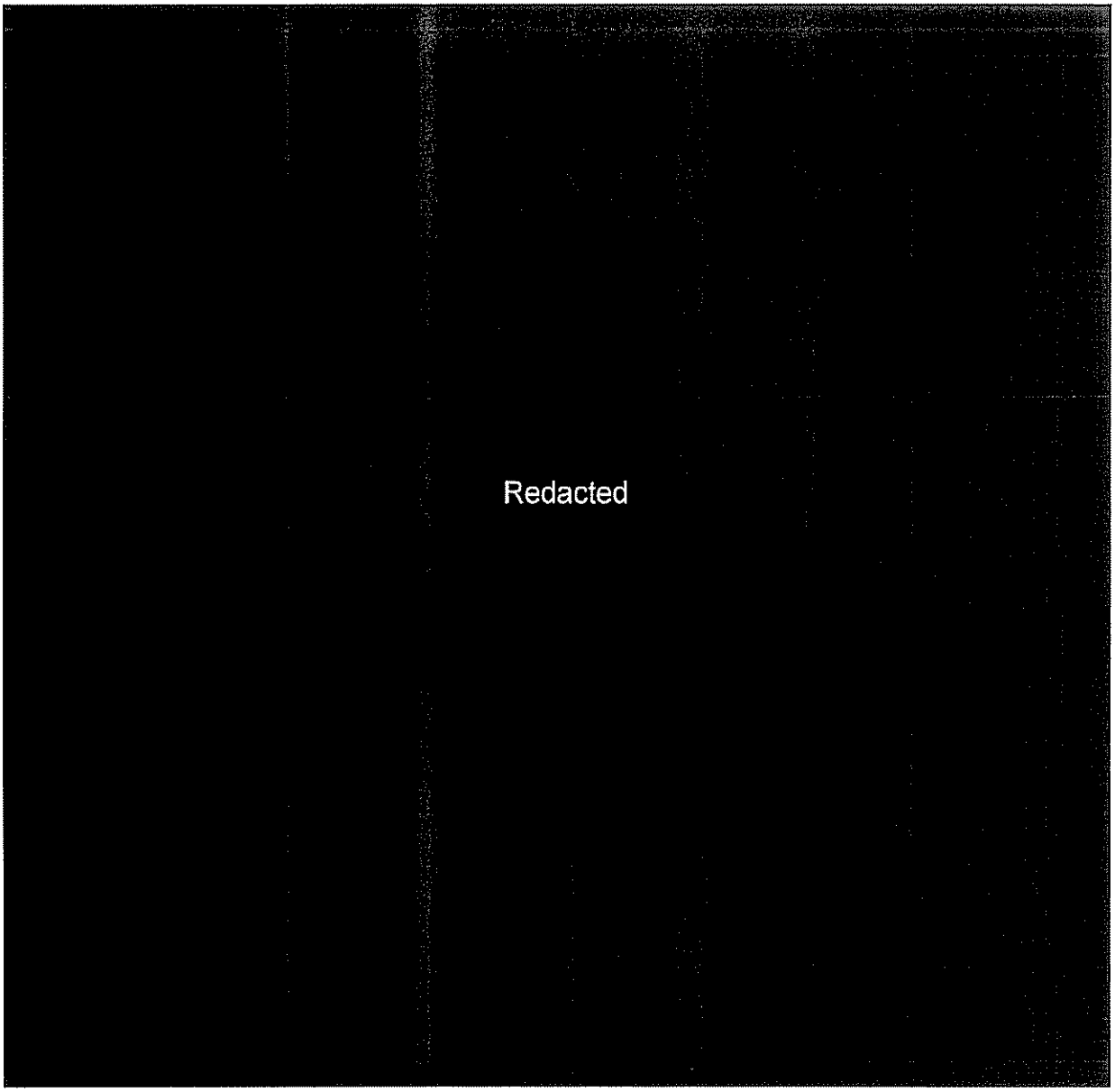
Dist LEXIS 5803, at *32-33 (D. Del Apr. 7, 2005) (holding expert was precluded from testifying regarding infringement because the bases of this opinion were not disclosed in his expert report)

2. **ZymoGenetics Improperly Relies on Data Concerning Wild-Type Ig**

[redacted] ZymoGenetics is forced to rely instead on data obtained using a fragment of wild-type unmutated Ig. But that is a completely different protein from the Ig in Bristol's CTLA4-Ig. [redacted] Further, scientific publications demonstrate that wild-type unmutated Ig and Bristol's mutated Ig do not behave the same way. (*See infra* Section III B.2.b). Therefore, the data on wild-type unmutated Ig that ZymoGenetics relies on is irrelevant to whether the mutated Ig in Bristol's CTLA4-Ig forms a dimer

a) **Small Mutations Can Affect Dimerization and Testing of Mutated Ig is Necessary to Ascertain the Effects of these Mutations**

Exhibits 15 and 16 referenced in ZymoGenetics' infringement brief are related to unmutated immunoglobulins. (D.I. 167 at 10). [redacted]



[16] 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).

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Therefore, reliance on materials related to unmutated immunoglobulins is improper and does not provide evidence that Bristol's mutated Ig is a dimerizing protein, particularly in light of the fact that there are not just random mutations in the Ig portion of Bristol's CTLA4-Ig -- but rather ones specifically designed to avoid dimerization (*See supra* at 5, 8).

b) **Bristol's Mutated Ig does not Behave like Wild-Type Ig**

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Bristol's mutated Ig does not behave like dimeric wild-type Ig. This is seen in the way that wild-type Ig and Bristol's mutated Ig bind differently to Ig receptors.

Wild-type Ig dimers will bind to "Ig receptors" known as CD16, CD32, and CD64. But while monomeric Ig will bind to CD64, it will not bind to CD16 or CD32.[17] Published studies report that Bristol's CTLA4-Ig containing the mutated Ig only binds to CD64 -- the high affinity receptor -- and not to CD16 or CD32:

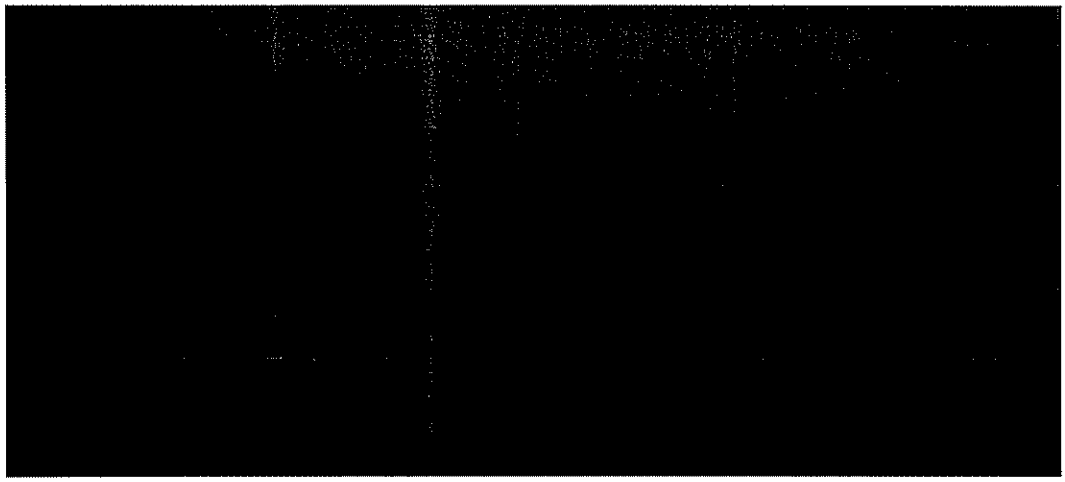
> The results from these studies demonstrate that abatacept [*i.e.*, CTLA4-Ig] containing a modified Fc domain was determined to have no cytotoxicity associated with either CDC or ADCC mechanisms . . . In contrast, CTLA4-Fc, which differs from abatacept by containing a non-engineered Fc domain, was fully functional for both CDC and ADCC.
>
> * * *
>
> As expected, CTLA4-Fc bound to all three immobilized Fc IgG receptors studied (CD16, CD32 and CD64)
>
> * * *
>
> These studies demonstrate that abatacept retains some level of Fc binding to the high affinity Fc IgG1 receptor (CD64), but not the lower affinity Fc IgG receptors CD32 and CD16

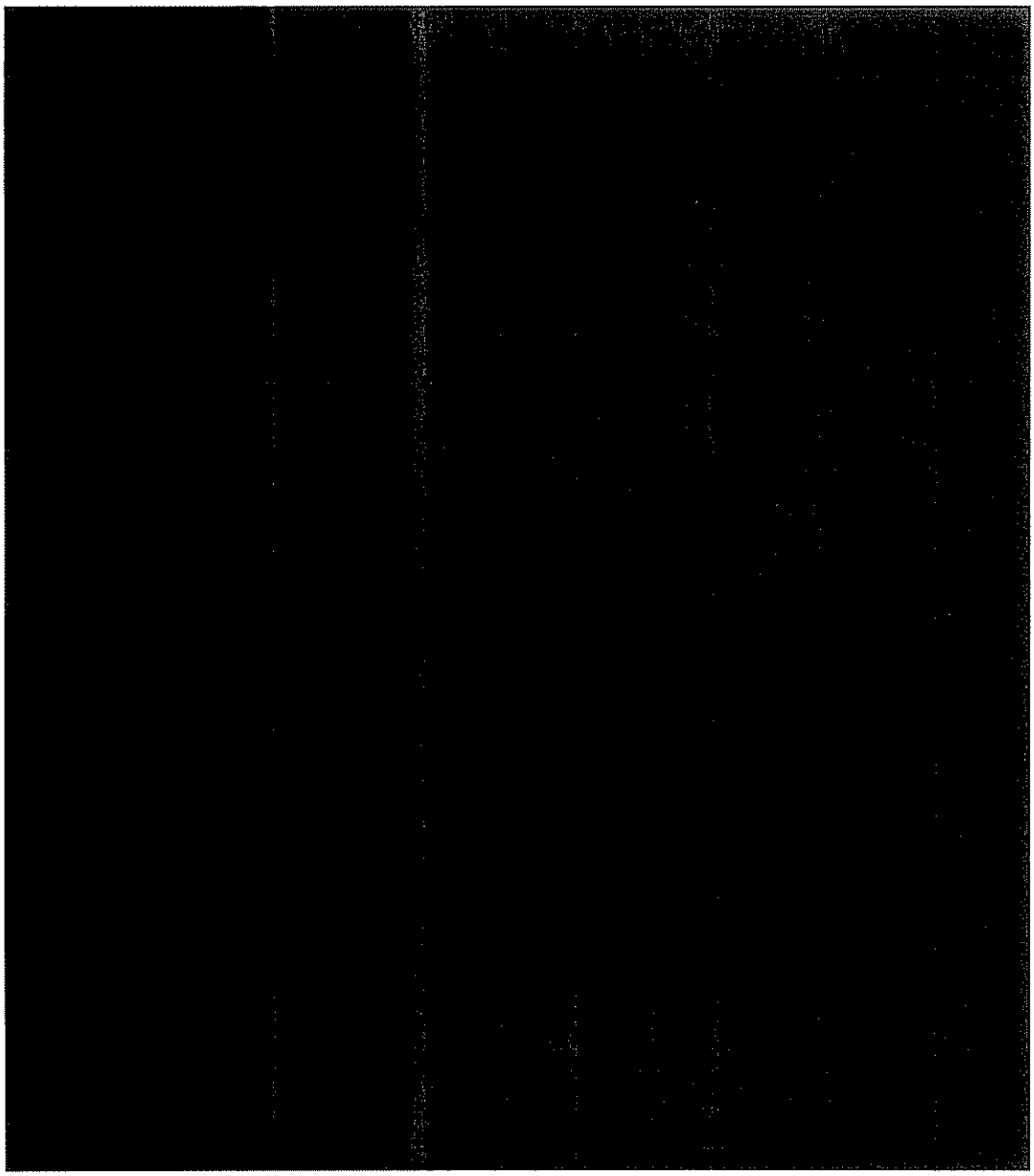
[17] D.I. 211, Exh. 13 at 2205 ("The CD64 proteins are high affinity receptors capable of binding monomeric IgG, whereas the CD16 and CD32 proteins bind IgG with lower affinities, usually restricted to recognizing IgG aggregates . . . ")

(D.I. 211, Exh. 13 at 2208-2210). Because the Ig portion of Bristol's CTLA4-Ig binds only to CD64 and not CD16 and CD32, these studies indicate that Bristol's mutated Ig does not behave the same as wild-type dimeric Ig and that the mutated Ig portion of Bristol's CTLA4-Ig has been affected by its mutations. Therefore, it cannot be genuinely disputed that Bristol's mutated Ig is structurally and functionally different from wild-type Ig. ZymoGenetics has identified no testing or publications indicating that wild-type Ig and Bristol's mutated Ig should be treated as identical. This further indicates that it is improper for ZymoGenetics to rely on studies of wild-type Ig to make claims about Bristol's mutated Ig.

3. **ZymoGenetics' Reliance on Experiments Performed Under Non-Physiological Conditions is Contradicted by Experiments Performed Under Physiological Conditions**

ZymoGenetics argues that "Bristol's scientists demonstrated that when the Orencia® molecule lacked the immunoglobulin heavy chain portion of Orencia®, at least 80% of the product failed to dimerize." (D.I. 167 at 10). But, the experiment referred to by ZymoGenetics was not reporting the status of CTLA4 following expression from a cell. It was concerning the status of CTLA4 following a harsh non-physiological (*e.g.*, pH of 11.5) purification process that can damage the dimerization state of molecules. (D.I. 168, Exh. 12 at 15418).





Moreover, when a similar experiment was performed under a physiological pH of 8 during purification, the resulting CTLA4 was a dimer:

> The . . expressed . CTLA4 homodimer runs as a monodisperse peak . . . On native PAGE, CTLA-4 runs as one sharp band (Fig 3B, lane 1) [identified in Figure 3 as a "Covalent CTLA-4 Dimer"]

(Zhang, X. et al , Protein Expression and Purification, 25:105-113 (2002) at 107 (identifying pH 8) and 110 (excerpted quotation)) (I.A.B. Exh 7)

Therefore, it is improper for ZymoGenetics to rely on experiments performed under non-physiological conditions to make claims about Bristol's mutated Ig when these claims are contrary to what is disclosed in scientific publications describing experiments performed under physiological conditions.

As the foregoing shows, even under its own construction of the term "dimerizing protein", ZymoGenetics has failed to prove that there is no genuine issue of material fact that Bristol's mutated Ig functions as a "dimerizing protein". Thus, on the limitation "dimerizing protein", ZymoGenetics' Motion for Summary Judgment of Infringement fails In fact, no reasonable jury could find for ZymoGenetics, and Bristol's motion for Summary Judgment should be granted

IV. Non-Immunoglobulin Polypeptide

ZymoGenetics applied its proposed construction of the claim term "non-immunoglobulin " While Bristol disagrees with ZymoGenetics' proposed construction and maintains that under a proper construction of "non-immunoglobulin" Bristol's CTLA4-Ig is not covered, Bristol does not dispute that, if the Court were to adopt ZymoGenetics' construction, that construction would not exclude CTLA4 from that term (but that would not change the fact that CTLA4 does not require dimerization to have biological activity).

CONCLUSION

For the foregoing reasons, ZymoGenetics' summary judgment motion should be denied.

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Dated: August 18, 2008

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on August 18, 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 August 18, 2008, the foregoing document was sent to the following non-registered participants in the manner indicted:

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/s/ Kelly E. Farnan
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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

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