IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

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

ZYMOGENETICS, INC.'S OPPOSITION TO BRISTOL-MYERS SQUIBB COMPANY'S MOTION FOR SUMMARY JUDGMENT OF NONINFRINGEMENT

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I. STATEMENT OF THE NATURE AND STAGE OF PROCEEDINGS

At this stage of the case, both fact and expert discovery have concluded. On May 16, 2008, the parties exchanged opening briefs in support of their motions for summary judgment along with short statements of material facts as to which there is no genuine issue to be tried. D.I. 161, 167, 173, 177. Parties also submitted their opening claim construction briefs. D.I. 156, 179. On June 2, 2008, the parties filed a disputed statement to the short statements submitted with the opening summary judgment motions. D.I. 205, 206, 207, 210. Rebuttal claim construction briefs were filed on June 23, 2008. Oral argument on the parties' claim construction and whether the summary judgment would be fully briefed was held at a hearing on June 27, 2008. According to the Court's order dated August 4, 2008, ZymoGenetics, Inc. ("ZymoGenetics") hereby submits the present brief in opposition to Bristol-Myers Squibb Co.'s ("Bristol") summary judgment motion of noninfringement. D.I. 239. A claim construction order has not yet issued. Also, the Court has not yet ruled on Bristol's motion for bifurcation of damages and willful infringement.

Various pretrial deadlines between late August and October of 2008 have been set by the Court. Mediation before Magistrate Judge Thynge is set for August 20, 2008. Trial is set to commence on October 20, 2008.

II. SUMMARY OF ARGUMENT

The entirety of Bristol's noninfringement motion rests on three positions Bristol takes regarding the nature of the CTLA4-Ig molecule contained in its Orencia® product. These positions, however, directly contradict representations Bristol made regarding the molecule before this litigation commenced. Specifically, Bristol characterized the CTLA4-Ig molecule found in its Orencia® product in one way to the United States Food and Drug Administration

("FDA) to obtain approval to administer the drug to patients. Bristol made the same representations regarding its CTLA4-Ig molecule to the United States Patent and Trademark Office ("PTO") in order to obtain patent protection for its drug. Now, faced with a finding of infringement of ZymoGenetics' Patents, Bristol is making representations to this Court regarding its CTLA4-Ig molecule that directly contradict its statements to the FDA and PTO.

Bristol also is making the scientifically flawed arguments that: (1) the immunoglobulin portion of Orencia® is not a dimerizing protein, despite its statements to the contrary to the FDA and PTO that it is in fact a dimerizing protein, (2) the CTLA4 of Orencia® does not require dimerization for biological activity, even though it represented to the FDA that it exists and functions as a dimer and Bristol's own scientists have written in notable, peer-reviewed journals that CTLA4 must exist as a dimer in order to exhibit biological activity, and (3) CTLA4 is an immunoglobulin, a statement that is in direct contradiction to its representation to the PTO and a position that even Bristol's experts reject. Beyond the inconsistent positions that Bristol is taking today regarding Orencia®, Bristol has advocated for and relied upon a claim construction that is scientifically flawed. However, even under Bristol's improper and strained construction, the undisputed scientific evidence demonstrates that Bristol's Orencia® product infringes ZymoGenetics' Patents. Therefore, the Court should deny Bristol's motion for summary judgment of non-infringement.

III. STATEMENT OF FACTS

A. THE INVENTION OF THE ZYMOGENETICS PATENTS IS UNIQUE TECHNOLOGY

The ZymoGenetics Patents, U.S. Patent No. 5,843,725 ("the '725 Patent") and U.S. Patent No. 6,018,026 ("the '026 Patent"), relate to fusion proteins and methods for producing fusion proteins. *See* D.I. 169, Exs. 1, 2. Fusion proteins are non-naturally occurring proteins

that are synthesized from two different proteins. The ZymoGenetics Patents describe, for example, a fusion protein called PDGFR-Ig that is made by fusing a portion of Platelet Derived Growth Factor Receptor (PDGFR) to a portion of an immunoglobulin (Ig). *See* id. PDGFR and other membrane-bound receptors were found by scientists to have properties that could be exploited to treat diseases. *See* D.I. 156 at 4-5. However, membrane-bound protein receptors cannot be easily isolated from the cell because they are trapped in the cell membrane. *See* id. ZymoGenetics' scientists cleverly solved the problem of how to obtain secreted forms of these membrane-bound proteins, such as PDGFR, in a biologically active form. The inventors of the ZymoGenetics Patents discovered that by fusing PDGFR to a dimerizing protein, such as immunoglobulin, a cell would secrete a biologically active dimerized fusion protein that can be isolated, such as PDGFR-Ig.

B. ORENCIA®, THE INFRINGING PRODUCT, IS A CTLA4-IG FUSION PROTEIN

Orencia®, also known as abatacept or CTLA4-Ig, is a fusion protein comprised of (1) the extracellular portion of CTLA4 (the Y-shaped arms in Figure 1 below) fused to (2) a portion of immunoglobulin G1 ("IgG1") (the legs or bottom portion of Figure 1 below).[1] Shown below are pictures taken from Bristol's materials, where A is CTLA4, B is Orencia®, and C is an immunoglobulin. Declaration of Lisa Kobialka In Support of ZymoGenetics' Opposition to Bristol's Motion for Summary Judgment of Noninfringement ("Kobialka Decl"), Ex. 7 at BMS004295554 (arrows in original); Ex. 8 at BMS004294488 (arrows in original).

[1] The term "Ig" or "IgG1" refers to the immunoglobulin that is used as the dimerizing protein in Orencia® throughout this brief.

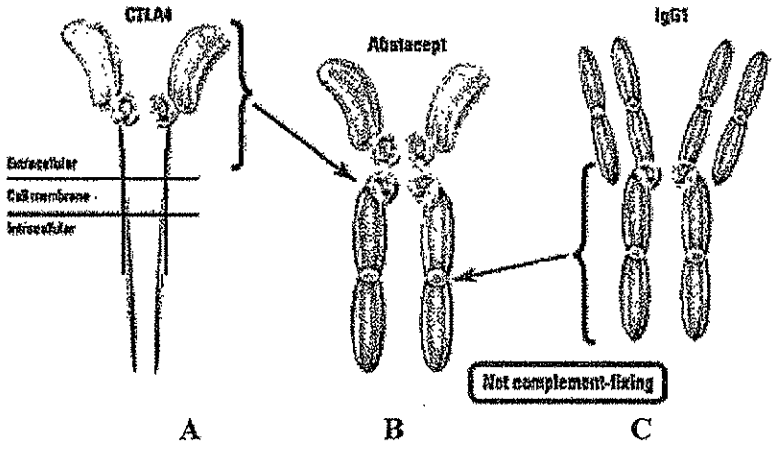

Figure 1.

1. The CTLA4 Portion of Orencia® Is Not An Immunoglobulin

CTLA4, the upper portion of CTLA4-Ig in Figure 1, is not considered to be an immunoglobulin or an antibody to a person of ordinary skill in the art. *See* D.I. 156, 227, 237; *see also* Declaration of Nicholas A. Gascoigne, Ph.D. in Support of ZymoGenetics' Opposition to Bristol's Motion for Summary Judgment of Noninfringement ("Gascoigne Decl."), ¶¶ 5-12; Declaration of David A. Ostrov, Ph.D. In Support Of ZymoGenetics' Opposition to Bristol's Motion for Summary Judgment of Noninfringement Decl. ("Ostrov Decl."), ¶¶ 9-11. It is, however, a member of the immunoglobulin superfamily ("IgSF") because it has some structural similarities to the immunoglobulins. *See* D.I. 171, Ex. 12 at BMS003504391; D.I. 178, Ex. 13; D.I. 174, Ex.9 at 270; Gascoigne Decl., ¶¶ 7-12. The immunoglobulin superfamily is a large classification of proteins that has in common the Ig fold, a structural feature of immunoglobulins. D.I. 227 at 14-15. CTLA4, however, does not have significant sequence homology with immunoglobulins other than sequence homology

with respect to "a few conserved residues" of the characteristic Ig fold. *See* D.I. 171, Ex. 12 at BMS003504391; Gascoigne Decl., ¶ 7.

2. The CTLA4 Portion of Orencia® Requires Dimerization For Biological Activity

CTLA4 is a homodimer on the surface of a T cell in the human body. D.I. 174, Ex. 12 at 604; Gascoigne Decl., ¶¶ 18, 24; Ostrov Decl., ¶¶ 5-6. CTLA4 is also called an "obligate dimer" by those of ordinary skill in the art, meaning that it is always found in a dimeric state. D.I. 174, Ex. 12 at 607. In other words, two full-length CTLA4 molecules come together to form the native CTLA4 dimer. Bristol acknowledges that CTLA4 is a dimer on the T cell. D.I. 173 at 10. Bristol cites to reports of mutant or truncated forms of CTLA4, but such forms do not exist in the human body. Ostrov Decl., ¶¶ 15, 17, 21-24. It is the dimeric native form of CTLA4 that exhibits biological activity. Gascoigne Decl., ¶¶ 26-28; Ostrov Decl., ¶ 16.

3. The Ig Portion of Orencia® Is A Dimer

The immunoglobulin portion of Orencia®, the lower portion of Orencia® in Figure 1, comes from the Fc domain of Ig which is composed of: the hinge, C_H2, and C_H3 domains. D.I. 169, Ex. 4. The immunoglobulin portion of Orencia® exists as a dimer, *i.e.*, two chains of immunoglobulin that are held together. Kobialka Decl., Exs. 4-6. The Ig portion of Bristol's Orencia® includes mutations in the hinge region, but not the C_H3 domain. D.I. 169, Ex. 4. In fact, the C_H3 domain of Ig, alone, forms a dimer. Gascoigne Decl., ¶19.

Dr. Peter Linsley, a former Bristol scientist who was one of the early investigators of CTLA4, has testified that mutations in the hinge region do not prevent dimerization. D.I. 205, Ex. 3 at BMS004256418. Dr. Ostrov, a ZymoGenetics expert, also testified that he found through testing that the Ig portion of Orencia® forms a dimer. D.I. 171, Ex. 14 at

263:7-264:1; Ostrov Decl., ¶ 18. Studies on CD28-Ig, a fusion protein containing the same modified Ig portion as that found in CTLA4-Ig, indicate that the Ig portion forms a dimer. D.I. 205, Ex. 4 at BMS003504382-383.

Bristol represented to the FDA that the Ig portion of Orencia® is a dimer when obtaining FDA approval for Orencia®. Kobialka Decl., Exs. 4, 6. In addition to claiming that the Ig portion of Orencia® is a dimer, Bristol also represented that the reason it mutated the hinge region of the Ig portion of Orencia® was to block complement fixation.[2] Id., Ex. 12. D.I. 171, Ex. 11 at 27:19-25; Kobialka Decl., Ex. 1 at 37:10-17; D. I. 169, Ex. 6 at 53:8-12. However, Bristol is now claiming that the hinge region of the Ig portion of Orencia® was mutated in order to block dimerization. D.I. 173 at 20. This unsupported claim fails to overcome the overwhelming scientific evidence to the contrary, which includes testimony of Bristol's scientists, Bristol's scientific studies, and independent scientific studies.

In addition to the FDA, Bristol also represented to the PTO that the Ig portion of CTLA4-Ig is a dimer when seeking patent protection for specific methods of use of the CTLA4-Ig that is found in Orencia®. The specification of U.S. Patent No. 5,770,197, one of the patents that covers the CTLA4-Ig found in Orencia®, states that the Ig portion of CTLA4-Ig "***enable[s] homodimer formation***." *See* Kobialka Decl., Ex. 9 at col. 13, ll. 10-19 (emphasis added); *see also id.*, col. 12, ll. 48-52.

[2] Complement fixation is the binding of complement proteins to immunoglobulins, and is part of immune response in the body (termed complement-dependent cytotoxicity (CDC)). Because Orencia® is a fusion protein of the extracellular domain of CTLA4 and an immunoglobulin, the FDA was concerned that complement fixation may occur when taking Orencia®. Complement fixation is not a desirable response with respect to Orencia® because it leads to inflammation and increased drug clearance. The FDA required Bristol to address this concern. Kobialka Decl., Ex. 16 at BMS001009188.

IV. ARGUMENT

A. SUMMARY JUDGMENT OF NONINFRINGEMENT IS NOT WARRANTED UNDER BRISTOL'S CLAIM CONSTRUCTION BECAUSE THERE ARE GENUINE ISSUES OF MATERIAL FACT

A court shall grant summary judgment only if "the pleadings, the discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c); *IMX, Inc. v. LendingTree, LLC*, 405 F. Supp. 2d 479, 483 (D. Del. 2005). On a motion for summary judgment of non-infringement, the movant "has the initial responsibility of identifying the legal basis of its motion, and of pointing to those portions of the record that it believes demonstrate the absence of a genuine issue of material fact." *Novartis Corp. v. Ben Venue Labs., Inc.*, 271 F.3d 1043, 1046 (Fed. Cir. 2001) (citation omitted). The moving party bears the burden of proving that no genuine issue of material fact exists. *IMX*, 405 F. Supp. 2d at 483 (citation omitted). As the moving party, Bristol must establish that no material facts are in dispute. *See Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH,* 139 F.3d 877, 881 (Fed. Cir. 1998). Bristol, however, fails to explain how its alleged evidence demonstrates the absence of the genuine issues of material fact.

The Court will "view the underlying facts and all reasonable inferences therefrom in the light most favorable to the party opposing the motion." *Karlin Tech., Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 970 (Fed. Cir. 1999); *P.N. v. Clementon Bd. of Education*, 442 F.3d 848, 852 (3d Cir. 2006) (citation omitted). The Court must draw all reasonable inferences and resolve all doubt over factual issues in ZymoGenetics favor. *See, e.g., Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986) (stating that "[t]he evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in his favor")

(citation omitted). Applying the legal standard for summary judgment, Bristol's motion for summary judgment of noninfringement should be denied.[3]

B. ORENCIA® INFRINGES THE ASSERTED CLAIMS OF THE ZYMOGENETICS PATENTS BECAUSE THE IG PORTION OF ORENCIA® IS A "DIMERIZING PROTEIN"

The Ig portion of Orencia® is a "dimerizing protein" as defined in the ZymoGenetics Patents. The explicit definition of "dimerizing protein" in the ZymoGenetics Patents is a "polypeptide chain having affinity for a second polypeptide chain, such that the two chains associate under physiological conditions to form a dimer." D.I. 169, Ex. 1 at col.9, ll. 30-34; Ex. 2 at col.9, ll. 45-51. Bristol infringes under the definition of "dimerizing protein" of the ZymoGenetics Patents for the reasons set forth in ZymoGenetics' briefing on summary judgment of infringement, hereby incorporated by reference. D.I. 167. Bristol's proposed claim construction, which is what it applied in its motion, adds the additional limitation that 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. 173 at 19. Even under Bristol's erroneous claim construction, Bristol infringes the "dimerizing protein" element of the asserted claims of the ZymoGenetics Patents.

[3] ZymoGenetics does not address its infringement positions under its own proposed claim construction to the extent that Bristol did not use ZymoGenetics' construction as a basis for its motion for summary judgment of noninfringement. Bristol's motion, however, should be precluded as a matter of law for its reliance on improper claim construction. At the very least, under Bristol's proposed claim construction, there are genuine issues of material fact that preclude summary judgment of noninfringement. Under ZymoGenetics' proposed claim construction, there are no genuine issues of material fact as to Bristol's infringement.

1. The Evidence Demonstrates that the Ig Portion of Orencia® 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 first part of Bristol's proposed construction of the term "dimerizing protein" is the same as ZymoGenetics' proposed construction. Both parties agree that a "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." D.I. 169., Ex. 1 at col. 9, ll. 30-35; Ex. 2 at col. 9, ll. 45-51. Under this construction, the Ig portion of Orencia® infringes this element because the two Ig chains in Orencia® associate to form a dimer, *i.e.*, the two immunoglobulin chains are held together. Contrary to Bristol's representation, the mutations that were made to the Ig portion of Orencia® do not change the fact that it exists as a dimer. In the numerous molecular models of Orencia®, like those Bristol submitted to the FDA, Bristol depicts the mutated Ig of Orencia® as a dimer.

a. Bristol Represented to the FDA that the Ig Portion of Orencia® Is a Dimer

Bristol's representation to the FDA that the Ig portion of Orencia® is a dimer is dispositive evidence proving Bristol's infringement. In all of the models in Figure 2, which come directly from materials that Bristol submitted to the FDA or which are from Bristol's internal documents, as well as Figure 1 above, the Ig portion or bottom portion of the molecule is shown associated together as a dimer, *i.e.*, the two chains of the immunoglobulin portion are held together.

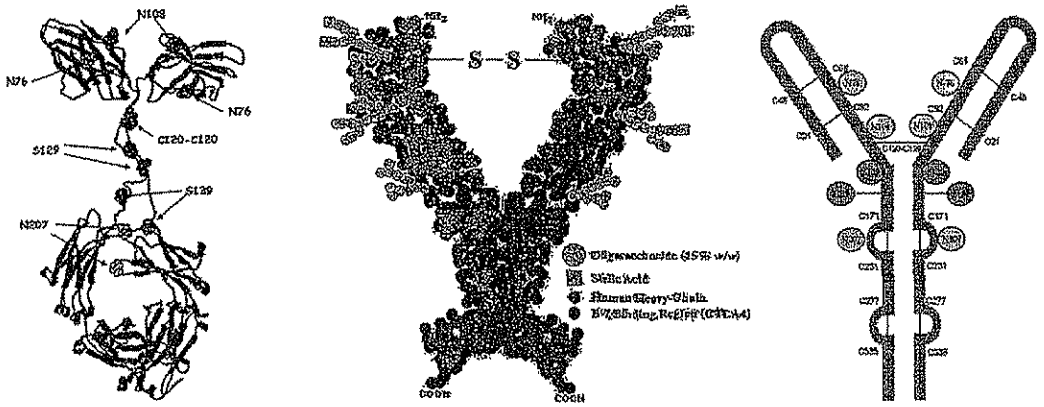

Figure 2.

Kobialka Decl., Ex. 4 (far left, submitted to FDA); Kobialka Decl., Ex. 5 (center, BMS internal document, "CTLA4-Ig Development History" at BMS 001011658); Kobialka Decl., Ex. 6 (far right, submitted to FDA).

Despite making representations to the FDA that the Ig portion of Orencia® is a dimer, Bristol, in this litigation, now conveniently argues that the Ig portion of Orencia® is ***not*** a dimer. D.I. 173 at 20-22. Bristol further argues that small changes in amino acid sequence can affect the ability of the Ig to dimerize and that it is impossible to know whether the Ig of Orencia® dimerizes in the absence of actual testing. *Id.* These arguments directly contradict its earlier representations to the FDA, which were made to obtain FDA approval for Orencia®. In fact, at that time, Bristol unequivocally represented to the FDA that the molecular models in Figure 2 above were an accurate depiction of the CTLA4-Ig that Bristol was seeking approval for, including the Ig portion. D.I. 169, Ex. 5 at BMS001290162. Those models given to the FDA unquestionably depict the Ig portion of Orencia® as a dimer. Thus, before the litigation, Bristol represented that the mutated Ig of Orencia®, like the

native form, dimerizes, a representation that Bristol cannot reasonably distance itself from now in order to avoid a finding of infringement.[4]

The first time Bristol ever alleged Orencia® to have free-floating, non-dimerized Ig tails is in their present summary judgment and claim construction briefing. Nowhere in the more than 4 million pages of documents produced to ZymoGenetics does the representation in Figure 3 ever appear:

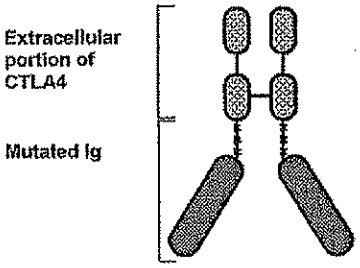

Figure 3. Bristol's Characterization of CTLA4-Ig to this Court

D.I. 173 at 10.[5] In fact, this representation takes on the complete opposite form of what Bristol represented to the FDA as the actual structure of Orencia® shown in Figure 4 below:

[4] Notably, to the extent that Bristol claims that its representations to the FDA regarding dimers is limited to CTLA4, *i.e.*, that Orencia® is only a dimer in the CTLA4 region of the fusion protein, such claims still do not address whether the Ig portion of Orencia® associates to form a dimer. That dimerization occurs in the CTLA4 portion of Orencia® does not mean that dimerization does not occur in the Ig portion, as described below.

[5] Bristol presented this depiction in its technical tutorial to the Court. D.I. 122. Though Bristol "invites" the Court to look at this tutorial, ZymoGenetics objects to this tutorial as expressly in violation of the Court's Scheduling Order as Bristol improperly injected argument on claim construction and noninfringement into the tutorial. *See* D.I. 128 (ZymoGenetics' letter objecting that Bristol's tutorial was in violation of Judge Thygne's express instructions).

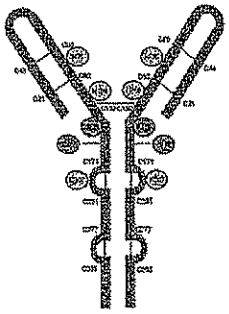

Figure 4. Bristol's Characterization of CTLA4-Ig to the FDA

Kobialka Decl., Ex. 6. Bristol's contradictory position that the Ig portion of Orencia® does not dimerize is a self-serving, litigation-derived noninfringement argument, lacking any basis in scientific fact.

b. Dr. Ostrov Personally Tested the Ig Portion of Orencia® and Discovered that It Dimerizes

Bristol took the deposition of ZymoGenetics' expert, Dr. David Ostrov, who testified that he had independently tested the Ig portion of Orencia® and "solved the structure of the C_H2 and C_H3 domains." D.I. 171, Ex. 14 at 263:7-264:1; *see also* Ostrov Decl., ¶ 18. He explained based on his "firsthand knowledge" that "those domains actually interact with each other," associating together to form a dimer. *Id.* Thus, there is evidence in the record from testing that an expert has performed which shows that the Ig portion of Orencia® forms a dimer.

c. Bristol Determined that the Ig Portion of Orencia® Dimerizes

Studies conducted by Bristol on "the same mutated Ig tail as CTLA4-Ig" demonstrate that the Ig portion forms a dimer. D.I. 205, Ex. 4 at BMS003504382-383. Notably, a former scientist who was an early investigator of CTLA4, Dr. Linsley, stated that mutating the hinge region cysteine residues had no effect on dimerization:

> As I recall, that was whether the immunoglobulins are put together with the hinge region which has disulfide bonds

> which hold the chains together. And as I recall, the hypothesis was if you left out the disulfide or mutated the disulfide or the cysteines that you would make a monomer because the chains wouldn't be held together. ***That turned out not to be true, it does not make a monomer.***

D.I. 205, Ex. 3 at BMS004256418 (emphasis added). Taken together, this scientific evidence and testimony overwhelmingly demonstrates that the Ig portion of Orencia® "associate[s] under physiological conditions to form a dimer." Thus, the Ig portion of Orencia® exists as a dimer and satisfies the definition of "dimerizing protein" in the ZymoGenetics Patents despite the fact that mutations were introduced.

d. Articles published by Bristol Scientists and Others, as Well as the Testimony of Bristol Witnesses, Establish that the Ig Portion of Orencia® Forms a Dimer

The scientific facts also establish that the Ig portion of Orencia® forms a dimer. There is overwhelming scientific evidence in the form of expert testimony, independent peer reviewed journals, and Bristol scientists that the C_H3 domain of Ig associates together under physiological conditions to form a dimer. Gascoigne Decl., ¶19; Kobialka Decl., Exs. 14-15. Bristol claims in its motion that the mutations in the hinge of the Ig portion of Orencia® inhibit dimerization because they eliminated disulfide bonds and covalent forces between the two immunoglobulin chains. However, even with Bristol's mutations, as described above, the Ig portion of Orencia® forms a dimer. The mutations to the immunoglobulin portion of Orencia® which affect disulfide bond formation were located in the hinge region, not the C_H3 region where dimerization occurs. *See* D.I. 211, Ex. 2 at BMS001290350. The C_H3 domain of the Ig in Orencia® is therefore the exact same as the C_H3 domain of native Ig. Id. Bristol's Director of Immunology Drug Discovery and 30(b)(6) witness, Dr. Nadler, acknowledged that the C_H3 domain participates in dimerization of Ig. Kobialka Decl., Ex. 2

at 73:25-74:7 (stating [redacted]

Indeed, Bristol's own studies leave no doubt that the Ig portion of CTLA4-Ig (containing the unaltered C_H3 domain) is able to form a dimer because without the Ig portion, very little dimer of the extracellular domain of CTLA4 forms. D.I. 171, Ex. 12 at BMS003504388. With the Ig portion, CTLA4-Ig is only found in dimeric form. *Id.* at BMS003504387 (stating CTLA4-Ig was a homodimer).

Therefore, even in the absence of disulfide bonds as a result of Bristol's mutations, dimerization of Ig still occurs because of the noncovalent forces in the C_H3 domain. Bristol cannot distance itself from its representations to the FDA, the scientific facts, and its own scientists' testimony that prove the mutated Ig of Orencia® forms a dimer.

e. Bristol Did Not Mutate the Ig Portion of Orencia® to Prevent Dimer Formation

Despite Bristol's present claims, it did not "purposefully mutate[]" the Fc portion of Orencia® "to prevent dimer formation." D.I. 173 at 20. Bristol's argument is once again engineered to avoid infringement rather than based on what the evidence shows. The evidence overwhelmingly demonstrates that mutations were introduced into the Ig portion (also referred to as the "Fc portion") of Orencia® for a different purpose, namely, to prevent complement fixation and effector functions involved in the human body immune response.[6] Numerous Bristol witnesses testified that Bristol sought to eliminate effector functions caused by Orencia® by mutating the Fc portion. Dr. Steven Nadler, Bristol's Director of Immunology Drug Discovery, testified as follows:

[6] "Effector functions" refer to the effects mediated by the Fc domain, such as complement fixation.

Q: [redacted]

A: [redacted]

Q: [redacted]

A: [redacted]

D.I. 171, Ex. 11 at 27:19-25. In addition, Dr. David Smolin, Bristol's Vice President of Protein Therapeutics Development, testified as follows:

Q: [redacted]

A: [redacted]

Kobialka Decl., Ex. 1 at 37:12-17. Finally, Dr. Kirk Leister, Bristol's Director of Process Analytical Sciences, testified as follows:

Q: [redacted]

A: [redacted]

D. I. 169, Ex. 6 at 53:8-12. *See also* Kobialka Decl., Ex. 12 at BMS004257889 ("[A] series of directed, select mutations in the hinge region were introduced (three cysteine residues at amino acid positions 130, 136, and 139 were replaced with serines) ***to reduce Fc-mediated binding and effector function*** associated with human IgG_1 heavy chain.") (emphasis added). Therefore, the mutations to the Ig portion of Orencia® were introduced to eliminate effector functions, not to prevent dimerization in the Ig portion.

Consistent with this purpose, Bristol did not make ***any*** representations to the FDA that the mutations in the Ig portion of Orencia® had any effect on the dimerization of the molecule, despite Bristol's claim now it introduced the mutations to prevent dimer formation. Bristol also did not submit any test results to the FDA regarding whether mutated Ig still dimerized.[7] The only study performed by Bristol and submitted to the FDA on the Ig portion of Orencia® was in response to an FDA inquiry that Bristol assess the ability of the mutated Ig to mediate effector functions. *See* D.I. 211, Ex. 13. The study was conducted for the purpose of showing that Orencia® could not activate complement fixation, not to show the mutations prevented dimerization of the Ig portion. *See* id.

Bristol even represented in multiple published articles and presentations, such as the one shown in Figure 5 below, that Orencia® was "[n]ot complement fixing."

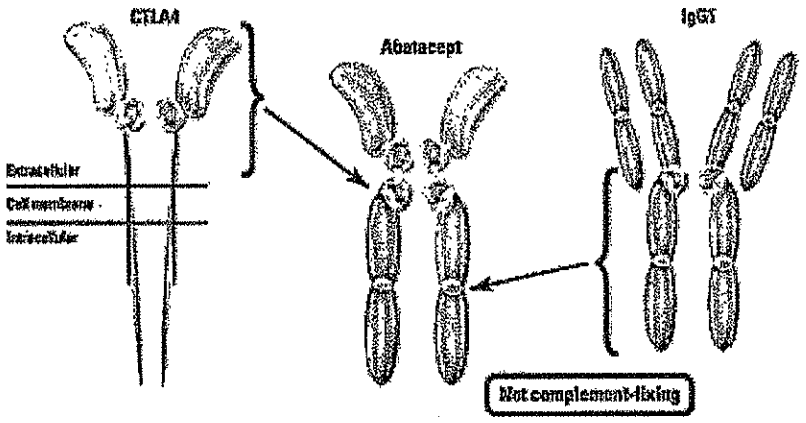

Figure 5.

See Kobialka Decl., Ex. 7 at BMS004295554 (arrows in original); *see also* id., Ex. 8 at BMS004294488 (arrows in original); Ex. 12 at BMS004257889. Thus, there can be no

[7] While Bristol incorrectly faults ZymoGenetics for failing to conduct testing on the Ig portion of Orencia® to determine whether the Ig portion dimerizes, Bristol, itself, cannot claim that it performed any such testing. Moreover, as discussed, ZymoGenetics' expert Dr. David Ostrov did perform independent experiments on the Ig portion of Orencia® and determined that it dimerized. Ostrov Decl., ¶¶ 18-20.

question from Bristol's documentation and representations to the FDA that Bristol mutated the Ig portion in order to avoid complement fixation, as opposed to its recent claim now that it was to prevent dimerization. Bristol's allegation that it purposely mutated the Ig portion of Orencia® to prevent dimer formation is therefore an unsupported hindsight justification contrived to manufacture a noninfringement argument.

2. The Ig Portion Of Orencia® Satisfies Bristol's Extraneous Claim Limitations

Bristol improperly adds an extraneous claim limitation to the term "dimerizing protein" by proposing the construction of the term include: "wherein said dimerizing protein causes or drives the dimerization of [sic] non-immunoglobulin polypeptide that is joined to it that would not otherwise form a stable dimer but for the action of said dimerizing protein." This limitation is not found in the explicit definition of "dimerizing protein" in the ZymoGenetics Patents, and is improper for the reasons articulated in ZymoGenetics' claim construction briefing. *See* D.I. 169, Ex. 1 at col.9, ll. 30-35; Ex. 2 at col.9, ll. 45-51; *see also* D.I. 227 at 8. However, even under Bristol's proposed claim construction, Orencia® still infringes the asserted claims of the ZymoGenetics Patents because it satisfies Bristol's improper proposed constructions that the Ig portion of Orencia® "causes or drives the dimerization of [sic] non-immunoglobulin polypeptide that is joined to it" and that the CTLA4 portion of Orencia® does not form a stable dimer without the action of the Ig portion of Orencia®.

Studies published by Bristol's own scientists demonstrate that the extracellular domain of CTLA4 found in Orencia® is unable to dimerize effectively on its own. *See* D.I. 171, Ex. 12. When Bristol scientists synthesized the extracellular domain of CTLA4 and did

not attach it to an Ig portion, they discovered that 80% of the CTLA4 fragments existed in monomeric form as shown below in Figure 6. *Id.* at BMS003504388, Fig.2.

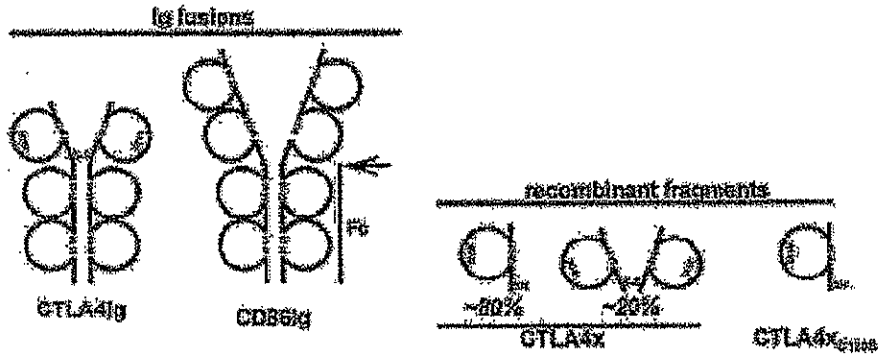

Figure 6.

When the Ig portion is attached to this same CTLA4 portion, all of the product recovered was found to form a CTLA4-Ig dimer. *Id.*, at BMS003504387 (published study finding that "as shown previously, CTLA4-Ig migrated . . . as a disulfide-linked homodimer . . . ."); D.I. 169, Ex.5 at BMS001290162 (statement from Orencia® Biologic License Application ("BLA") stating that "[CTLA4-Ig] exists as a covalent homodimer . . . ."). In other words, the overwhelming majority of the extracellular domain of CTLA4 that is found in Orencia® does not form a stable dimer on its own, and the extracellular domain of CTLA4 requires the Ig portion in order to form a stable dimer. Thus, there can be no reasonable dispute that CTLA4 does not form a stable dimer without the action of the Ig portion of Orencia®, and that the Ig portion of Orencia® "causes or drives the dimerization of the non-immunoglobulin polypeptide that is joined to it." In fact, the FDA requires that all of the CTLA4 be in a dimer form in order to permit sale of this drug for use in humans. Kobialka Decl., Ex. 13. This is precisely why Bristol added on the Ig fusion partner—to ensure that it enables and drives dimerization to the levels that Bristol represented to the FDA would occur.

Bristol also represented to the PTO, another government agency, that the Ig portion of CTLA4-Ig was a dimerizing protein. But this time, the goal was to obtain patent protection. In the specification of the '197 patent, which covers Orencia®, Bristol explicitly claimed that "successful expression" of CTLA4 meant that it had to be made as a dimer. Kobialka Decl., Ex. 9 at col. 12, ll. 48-52 ("Because CD28 and CTLA4 receptor proteins occur in nature as dimers, it is believed that successful expression of these proteins requires an expression system which permits these proteins to form dimers."). There can be no doubt that Bristol understood that the Ig portion of CTLA4-Ig facilitated the formation of the CTLA4-Ig dimer. Id. at col. 13, ll. 10-19 ("CTLA4 receptor genes are not readily expressed as mature proteins . . . . ***To enable homodimer formation*** [extracellular domain of CTLA4] . . . is fused . . . to the Fc domain of a naturally dimeric protein.") (emphasis added). Bristol represented these facts to the PTO to get patent protection, just as it represented facts to the FDA to procure approval to sell CTLA4-Ig (Orencia®) for human use.

Therefore, even under Bristol's proposed claim construction, Orencia® infringes the asserted claims of the '725 and '026 Patents because the CTLA4 portion of Orencia® does not form a stable dimer on its own, but for the action of the Ig portion -- the "dimerizing protein."

C. ORENCIA® INFRINGES THE ASSERTED CLAIMS OF THE ZYMOGENETICS PATENTS BECAUSE CTLA4 REQUIRES DIMERIZATION FOR BIOLOGICAL ACTIVITY

Because CTLA4 is a non-immunoglobulin that requires dimerization for biological activity in the body, Bristol infringes this claim element of the ZymoGenetics Patents. *See* D.I. 167. at 7-8. As mentioned, native CTLA4 is an obligate dimer. Ostrov Decl., ¶ 17. This means that it must exist as a dimer on the T cell surface where it interacts with B7, its

natural "ligand."[8] D.I. 174, Ex. 12 at 604. When the B7 ligand binds CTLA4, the process of cell signaling takes place. Gascoigne Decl., ¶ 28. Binding of the B7 ligand is the first step in this process, but is not considered to be the biological activity of CTLA4. Ostrov Decl., ¶ 14. It is the binding of ligand and cell-signaling process of CTLA4 that is the biological activity of CTLA4. For some native proteins that require dimerization for biological activity, binding of ligand may be its biological activity if binding is all the native protein does (say for example, a carrier protein of some type.) But in this case, binding is not the only biological activity of native CTLA4. Ostrov Decl., ¶ 16. The biological activity of native CTLA4 is far more complex than mere binding of B7. *Id.*

Bristol is attempting to shift the focus from the biological activity of the native form of CTLA4 to mere binding of artificial or mutant forms of CTLA4. D.I. 173 at 29-30. Contrary to Bristol's assertions, whether a truncated, artificial, monomeric form of the extracellular domain of CTLA4 can bind a molecule of ligand in the context of the ZymoGenetics Patents has no bearing on whether or not CTLA4 requires dimerization for biological activity. A monomer of *native* CTLA4 has never been detected or isolated, and would not be able to function in the biological context. Gascoigne Decl., ¶¶ 26-28; Ostrov Decl., ¶¶ 15-17; D.I. 178, Ex. 13 at ZG054281 (article by Dr. Linsley stating dimerization is generally critical for signal transduction).

1. CTLA4 In Its Native Form Is Always A Dimer

It is clear that dimerization is required for biological activity of CTLA4 because it is an obligate dimer. D.I. 157, Ex. 9 at ¶ 108; D.I. 169, Ex. 8 at ¶ 112; D.I. 174, Ex. 12 at 604, 607; D.I. 178, Ex. 13 at ZG054281. As discussed above, Bristol represented to the FDA that

[8] A ligand is a molecule that attaches to a membrane-bound receptor to activate a certain biological pathway in the cell. *See* D.I. 156 at 4.

CTLA4 must exist as a dimer when it sought and obtained FDA approval for Orencia®. D.I. 169, Ex. 5 at BMS001290162. Bristol also told the PTO that CTLA4 had to be in dimeric form in order to obtain a patent for its infringing product. *See* Kobialka Decl., Ex. 9 at col. 12, ll. 48-52 (CTLA4 receptor proteins occur in nature as dimers, and successful expression of these proteins requires dimer formation), col. 13, ll. 10-19 (fusion to Fc domain enables homodimer formation); *see also id.,* Ex. 10 at BMS001163849 and BMS001163851-852 (response to office action stating same positions). However, when faced with a finding of infringement, Bristol takes contrary positions. These representations to government agencies were made in order to receive FDA approval and patent protection for Orencia®.

The scientific community and experts from both ZymoGenetics and Bristol agree that CTLA4 has to be a dimer to function in the biological context. For example, Bristol's expert, Dr. Ravetch, stated that native CTLA4 exists as a dimer in its natural state. D.I. 157, Ex. 9 at ¶ 108. Bristol's expert, Dr. Kuriyan, also stated that CTLA4 is naturally a dimer. D.I. 169, Ex. 8 at ¶ 112. Bristol's 30(b)(6) witness, Dr. Nadler, further testified that CTLA4 is biologically active as a dimer in humans. D.I. 171, Ex. 11 at 85:13-20. Written scientific publications also confirm that CTLA4 must be a dimer to function in the biological context. *See* id., Ex. 12 at BMS 003504385 and BMS 003504391 (Bristol study by Dr. Linsley, inventor of CTLA4-Ig, stating that native CTLA4 exists as a homodimer); D.I. 174, Ex. 12 at 607 (Nature publication stating that CTLA4 exists as "an obligate dimer" and is a "dimeric cell-surface receptor"); Gascoigne Decl., ¶¶ 24-28; Ostrov Decl., ¶¶ 14-17. Nonetheless, in spite of all the evidence that CTLA4 must be a dimer to be biologically active, Bristol attempts to avoid infringement by pointing to truncated, artificial or mutated forms of CTLA4 to somehow prove that native CTLA4 can exist and be active as monomers in a biological context. D.I. 173 at 28. This is a red herring. Bristol is attempting a slight of

hand because the binding of ligand to an artificial monomer does not address the ultimate question of whether the native form of CTLA4 requires dimerization for biological activity. Indeed, nowhere does Bristol demonstrate that these forms of CTLA4 exhibit the biological activity of native or normal CTLA4. And for good reason – such mutant forms cannot exhibit the normal biological activity of CTLA4. Gascoigne Decl., ¶¶ 24, 28; Ostrov Decl., ¶¶ 15-16.

In any case, whether or not mutated, truncated, or artificial monomeric forms of CTLA4 can exhibit biological activity is irrelevant because the source material used to produce Orencia® was obtained from cells expressing the native form, and not the mutant, truncated, or artificial form of CTLA4. D.I. 171, Ex. 12 at BMS003504386 (DNA coding the full length, native form of CTLA4); D.I. 211, Ex. 2 at BMS001290340 (CTLA4 clone obtained from H38 cells (which express native, full-length CTLA4)). Bristol is asking the Court to make a leap of faith that artificial, truncated, mutated forms of CTLA4 are the same thing as native CTLA4. There is no evidence to support this theory. What is at issue with Orencia® is the native form. It was that form that Orencia® is made from, and it is that form of CTLA4 that requires dimerization for biological activity.

a. Binding Ligand Is Not Biological Activity For CTLA4 As Defined By The ZymoGenetics Patents

The claim term "biological activity" is explicitly defined in the ZymoGenetics Patents as follows:

> 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). Biological activities may include the induction of extracellular matrix secretion from responsive cell lines, the induction of hormone secretion, the induction of chemotaxis, the induction of mitogenesis, the induction of differentiation, or the inhibition of cell division of responsive cells. A recombinant protein or peptide is

> considered to be biologically active if it exhibits one or more biological activities of its native counterpart.

D.I. 169, Ex. 1 at col. 9, ll. 35-45; Ex. 2 at col. 9, ll. 52-63. Bristol agrees that the construction of the term should at least include the first sentence of the explicit definition, *i.e.*, "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)." The asserted claims recite a non-immunoglobulin polypeptide "requiring dimerization for biological activity." *See e.g.* D.I. 169, Ex. 1. The non-immunoglobulin polypeptide requiring dimerization for biological activity in this case is native CTLA4.

Bristol claims that Orencia® does not infringe because CTLA4 does not require dimerization for biological activity. But even under Bristol's abbreviated construction, Bristol's Orencia® nonetheless infringes the asserted claims of the ZymoGenetics Patents because Bristol has failed to demonstrate that native or full-length CTLA4 exhibits biological activity as a monomer in the biological context. Bristol cites to studies where the mutated or artificial monomeric form of CTLA4 binds ligand. However, these studies are not credible evidence of noninfringement for two primary reasons: (1) binding ligand is not biological activity for CTLA4 and (2) a native, monomeric form of CTLA4 does not exist. Ostrov Decl., ¶¶ 21-24.

It is undisputed that the function of CTLA4 in the "biological context" is to downregulate T cell signaling, and merely binding ligand is not considered "biological activity" of CTLA4 as defined by the ZymoGenetics Patents. *See* Ostrov Decl., ¶ 6. More specifically, CTLA4 on the cell surface recruits phosphotases which counteract the positive (stimulatory) signaling effects of the protein kinases. *See id.*, ¶ 7 (citing Egen *et al.*, "CTLA-4: new insights into its biological function and use in tumor immunotherapy," Nat. Immunol.

Jul. 3(7): 611-8 (2002)). If binding ligand was the only function a protein had, perhaps that might be considered its biological activity. But for CTLA4, while binding ligand is a first step, mere binding of ligand to CTLA4 does not constitute "biological activity." Gascoigne Decl., ¶28; Ostrov Decl., ¶¶ 4, 6, 7, 14, 16, and 17.

Nonetheless, Bristol attempts to twist the facts in this case to fit its legal theories. Bristol cites to statements made by ZymoGenetics in a former litigation matter from a different district court that does not bear at all on the issues presented in this case.[9] Moreover, any statements made in the former litigation regarding biological activity were ***not*** made with reference to the biological activity of CTLA4, as CTLA4 was not involved in that litigation. That litigation involved an entirely different accused product with different properties. Orencia® is an entirely new biologic with a novel mechanism of action. Bristol is merely attempting to inappropriately apply statements from a different proceeding without any proper context.

Bristol also mischaracterizes the testimony of ZymoGenetics' experts, Drs. Gascoigne and Ostrov. Neither expert stated that the binding of ligand, alone, constitutes the biological activity of CTLA4. Dr. Gascoigne made clear during his deposition that "biological activity" is a "very broad" term, and is defined differently depending upon the context. D.I. 174, Ex. 22 at 48:24-49:17. He repeatedly stated that ligand binding was a first step in initiating biological activity of some proteins, such as PDGFR disclosed in the ZymoGenetics Patents, but it could not be considered biological activity itself. *See* Kobialka

[9] *See Nat'l R.R. Passenger Corp. v. Penn. Pub. Utility Comm'n*, 288 F.3d 519, 525 (3d Cir. 2002) (holding that estoppel only applies when an issue was determined by a valid and final judgment in prior case). Because ZymoGenetics and Immunex settled, there was no final judgment issued in that former litigation. Also, the Immunex litigation occurred before reexamination of the ZymoGenetics Patents.

Decl., Ex. 11 at 111:19-112:2, 116:11-117:11; *see also* Gascoigne Decl., ¶ 28; Ostrov Decl., ¶¶ 14-15. With respect to CTLA4, upon the ligand binding to the receptor, the conformation of the native CTLA4 receptor is altered, and a signaling process from the cell surface to the nucleus of the cell begins, causing biological activity to occur, but the binding, in and of itself, is more of a "biochemical activity" rather the biological activity. *See* id.

ZymoGenetics' expert, Dr. Ostrov, similarly, clarified during his deposition that:

> if you're referring to the ***biological activity of the native protein***, then it's important to demonstrate biological activity by way of assays such as induction of extracellular matrix secretion, induction of hormone secretion, induction of chemotaxis, induction of mitogenesis, induction of differentiation, inhibition of cell division.

D.I. 174, Ex. 28 at 153:4-10 (emphasis added.) Thus, Dr. Ostrov was quite clear as to what biological activity was referring to – the native protein, not truncated or mutant forms of it.

Second, even if binding ligand were somehow considered a "biological activity," Bristol fails to provide any credible scientific evidence that native CTLA4 binds ligand as a monomer. Bristol attempts to mislead the Court by citing to studies where truncated or mutant forms of CTLA4 were examined to observe whether monomeric forms could bind ligand. D.I. 174, Ex. 12 at 604, 607. As discussed earlier, these forms are ***not*** the same as the native form.

In fact, the concept that a native, monomeric CTLA4 exists is a contradiction, as native CTLA4 does not exist in a biologically active form as a monomer. Ostrov Decl., ¶ 21. Native CTLA4 requires both chains of the dimer to function in the biological context. D.I. 157, Ex. 9 at ¶ 108; D.I. 169, Ex. 8 at ¶ 112; D.I. 174, Ex. 12 at 604; D.I. 178, Ex. 13 at ZG054281. CTLA4 is always found as a homodimer on T cell receptors, and mediates a negative signal to the T cell to suppress T cell activation. Ostrov Decl., ¶¶ 5-6; D.I. 178, Ex.

13 at ZG054281 (receptors must be dimeric form to facilitate signal transduction); D.I. 174, Ex. 13 at 608 (CTLA4 signaling attenuates activation); D.I. 174, Ex. 14 at 429 (indicating CTLA4 is a dimer that signals the T cell to suppress activity); and at 432 (dimer required for signaling, and is an "obligate, preformed dimer"); D.I. 178, Ex. 13 at ZG054281 (dimerization "generally critical" for signal transduction). Thus, the notion that a monomer chain of the CTLA4 dimer can mediate its biological activity is simply not proven. Ostrov Decl., ¶ 21. Building artificial constructs or studying mutant forms that allegedly are single chains does not mean that the native CTLA4 does not require dimerization for biological activity. *See* Gascoigne Decl., ¶¶ 24, 28; Ostrov Decl., ¶¶ 14-16. Indeed, Bristol should not be allowed to rely upon a position that is inconsistent with what it told the FDA and PTO about native CTLA4, and Bristol's summary judgment for non-infringement should be denied.

b. Cellular Assays Do Not Show That Native CTLA4 Is Biologically Active As A Monomer

The cellular assay that Bristol relies upon also does not show that CTLA4 is biologically active as a monomer, because it involves a soluble, mutant, monomeric form of CTLA4.[10] *See* Ostrov Decl., ¶¶ 21-24. As discussed above, the binding activity of mutant, altered forms of CTLA4 are irrelevant to whether native CTLA4 requires dimerization for biological activity. It is well-recognized in the scientific community that CTLA4 requires dimerization for biological activity, and experts from both Bristol and ZymoGenetics agree that CTLA4 must exist as a dimer in order to be biologically active. *See supra*. To avoid a finding of infringement, Bristol mischaracterizes Dr. Gascoigne's and Dr. Ostrov's statements by attempting to point out that each of the experts did not take the time to *personally* attempt

[10] Interestingly, this "soluble" form is depicted as a dimer. *See* D.I. 174, Ex. 8 at 195. Thus, Bristol's meritless argument is not even supported by the data it cites.

to disprove what is considered a widely accepted scientific truth, that CTLA4 must be a dimer in order to exhibit biological activity. However, as described above, there is overwhelming scientific evidence showing that CTLA4 must be a dimer in order to exhibit biological activity and experts from both ZymoGenetics and Bristol have confirmed this to be true. Thus, Bristol's hollow argument has no merit.

2. The CTLA4 of Orencia® Cannot Effectively Dimerize On Its Own

Despite the overwhelming evidence to the contrary, Bristol makes the unbelievable claim that the extracellular domain of CTLA4 found in Orencia® can dimerize on its own. As discussed above, the extracellular domain of CTLA4 found in Orencia® is unable to dimerize effectively on its own. Studies published by Bristol's own scientists confirm this to be true. *See* D.I. 169, Ex. 4; D.I. 171, Ex. 12 (showing that without the Ig portion, 80% of the extracellular domain of CTLA4 fails to dimerize.) As shown by these published studies, the overwhelming majority of the extracellular domain of CTLA4 that is found in Orencia® does not form a stable dimer on its own, and the extracellular domain of CTLA4 requires the Ig portion in order to form a stable dimer. *Id.* In fact, this Bristol publication of the studies explicitly stated that the extracellular domain of CTLA4 by itself "does not ensure dimerization." D.I. 171, Ex. 12 at BMS003504391. Thus, Bristol's arguments in this litigation contradict its own publications.

Bristol cites to U.S. Patent 5,155,027 in order to support its contention that "driving" dimerization is a required element of ZymoGenetics' asserted claims.[11] The prosecution history of this patent, however, is not relevant to the proper construction of the claims of the '725 and '026 Patents. As a preliminary matter, a prosecution disclaimer is pertinent to

[11] The '027 patent is a distantly related ancestor of the '725 and '026 Patents. *See* D.I. 227 at 10.

progeny continuation-in-part applications only "***where the same claim limitation is at issue***." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1335 (Fed. Cir. 2003) (emphasis added) (citations omitted). Different claim limitations were at issue in this case than those during the prosecution the '027 Patent.[12] During the prosecution of the '027 Patent, the claim limitation at issue was a "non-immunoglobulin polypeptide ***dimer*** requiring dimerization for biological activity." D.I. 180, Ex. 20 at BMS004259321 (emphasis added). The '725 and '026 Patents, in contrast, recite a "non-immunoglobulin polypeptide requiring dimerization for biological activity." D.I. 169, Exs. 1, 2. It is clear that different claim limitations are involved between the '027 Patent and the '725 and '026 Patents. There is simply no language in the single claim issued to the '027 Patent stating that the non-immunoglobulin portion be "driving" dimerization. In fact, the claim does not contain the term "dimerizing protein." Therefore, any alleged prosecution disclaimer from the '027 Patent does not apply to the '725 and '026 Patents. *See Omega*, 334 F.3d at 1335.

Furthermore, the "dimer" limitation in the '027 Patent renders Bristol's prosecution disclaimer argument nonsensical. Bristol's alleges that "ZymoGenetics disavowed circumstances where non-immunoglobulin polypeptides would form dimers on their own" based on the prosecution history of the '027 Patent. *See* D.I. 179 at 27, *see also* D.I. 173 at 33-34 (stating the same argument). However, the fact that the '027 Patent recites a "non-immunoglobulin polypeptide dimer" means that there could be no such instances where a "non-immunoglobulin polypeptide dimer" ***would not*** form a dimer on its own, because it would already exist, *a priori*. Therefore, it is nonsensical to argue that ZymoGenetics disavowed the very thing it was claiming in the single claim issued in the '027 Patent claims.

[12] By reference, ZymoGenetics incorporates its Claim Construction Rebuttal Brief which sets forth why the prosecution history of the '027 Patent is not relevant to the construction of the claims of the '725 and '026 Patents. *See* D.I. 227 at 10.

Moreover, Bristol mischaracterizes the statement of Dr. Gascoigne. He did not admit that the extracellular domain of CTLA4 in Orencia® could effectively form a dimer on its own. Rather, Dr. Gascoigne stated that "Orencia is a rather different beast" and expressed doubt that the extracellular domain of CTLA4 in Orencia®, rather than native CTLA4, could dimerize on its own. *See* Kobialka Decl., Ex. 11 at 36:10-37:7.

Thus, based on the overwhelming scientific evidence showing that CTLA4 does require dimerization for biological activity, the Court should deny Bristol's summary judgment of noninfringement.

D. ORENCIA® INFRINGES THE ASSERTED CLAIMS OF THE ZYMOGENETICS PATENTS BECAUSE CTLA4 IS A "NON-IMMUNOGLOBULIN POLYPEPTIDE"

Contrary to Bristol's construction of the term "non-immunoglobulin polypeptide," the plain and ordinary meaning of the term is a protein that is not an antibody. *See* ZymoGenetics' Opening and Rebuttal Claim Construction Briefs and Supplemental Claim Construction Chart (D.I. 156, 227, 237); *see also* Gascoigne Decl., ¶ 5; Ostrov Decl., ¶¶ 9-11. There is overwhelming scientific evidence to support a finding of infringement of the claim term based on its plain and ordinary meaning. *See* ZymoGenetics' Opening Brief in Support of Summary Judgment of Infringement (D.I. 167). The simple fact is that Bristol's CTLA4-Ig is a fusion of a "non-immunoglobulin polypeptide" (CTLA4) and an immunoglobulin (Ig). *See* D.I. 169, Ex. 4 (Orencia® product insert); D.I. 178., Ex. 7 (BLA application naming Orencia® as CTLA4-Ig). The name of Bristol's product, itself, "CTLA4-Ig" is further evidence that Bristol infringes the ZymoGenetics Patents. *See* Kobialka Decl., Ex. 8 at BMS 004294488 (showing graphic of Orencia® as CTLA4-Ig, and not Ig-Ig). Under a proper construction of the term "non-immunoglobulin polypeptide," therefore, Bristol infringes.

Bristol proposes that the construction of the term "non-immunoglobulin polypeptide" 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***. D.I. 173 at 35 (emphasis added). Bristol's argument for non-infringement of the element "non-immunoglobulin polypeptide" is solely based upon **rejected** statements made by ZymoGenetics during the prosecution of a patent application in a **foreign** patent office. *See* ZymoGenetics' Rebuttal Claim Construction Brief (D.I. 227). Bristol's prosecution history-derived definition of "non-immunoglobulin polypeptide" is not even based on the actual prosecution history of the ZymoGenetics Patents, but rather on rejected arguments made in the prosecution history of a foreign patent application. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1317 (Fed. Cir. 2005) (defining the "prosecution history" as the "record of the proceedings before the [US]PTO") (citation omitted); *see also Tap Pharm. Prods., Inc. v. Owl Pharms., L.L.C.*, 419 F.3d 1346, 1350 (Fed. Cir. 2005) (affirming district court giving "little weight" to statements made during foreign prosecution of a related foreign patent that were rejected and not repeated during prosecution of U.S. patents); D.I. 227. However, even if the Court were to adopt Bristol's improper construction, a reasonable jury would have evidence to support a finding of infringement of the claim term "non-immunoglobulin polypeptide" because CTLA4 does ***not*** have ***significant*** sequence homology to immunoglobulin. Gascoigne Decl., ¶¶ 9-11.

In its opening summary judgment brief for noninfringement, Bristol cites to ZymoGenetics' experts' testimony stating that CTLA4 is "immunoglobulin-like" and a member of the immunoglobulin superfamily. *See* D.I. 173 at 35-37. However, ZymoGenetics' experts did not state that they believed CTLA4 is an immunoglobulin. In fact, the ZymoGenetics' experts were quite clear -- CTLA4 is not an immunoglobulin. Ostrov

Decl., ¶¶ 9-11; Gascoigne Decl., ¶¶ 5, 7, 10-12. ZymoGenetics' experts only commented that CTLA4 had minimal homology to the immunoglobulins, only sharing homology to the conserved portions that all members of the immunoglobulin superfamily must share. *See* D.I. 173 at 35-37; Gascgoine Decl. at ¶¶ 7, 10-12; Ostrov Decl. at ¶13. For example, Dr. Gascoigne, ZymoGenetics' expert, opines:

> There is some homology *in those conserved V-like domains* of CTLA-4 with the immunoglobulin V-like domain. But overall protein homology is extremely minimal. Thus it is incorrect to state that CTLA-4 shares a high or substantial degree of homology to the immunoglobulins--it does not. CTLA-4 is a non-immunoglobulin.

Gascoigne Decl., ¶11; *see also id.*, ¶¶ 7, 10, 12. Former Bristol scientist, Dr. Linsley, also stated in a scientific journal that CTLA4 has little else in common with other members of the immunoglobulin superfamily, apart from sharing a "few conserved residues characteristic of the Ig fold":

> The Ig domains of CD 28 and CTLA-4 display little sequence similarity with other members of the IgSF, limited to a few conserved residues characteristic of the Ig fold. Despite sharing a common structural scaffold, members of the IgSF have diverse structures, utilize different combinations of Ig domains to form binding sites, and have distinct binding stochiometries per molecule.

D.I. 171, Ex. 12 at BMS003504391.

In fact, the immunoglobulin superfamily is a large group of proteins consisting of members whose characteristics may greatly differ from each other, but only share in common the characteristic Ig fold. As opined by ZymoGenetics' expert, Dr. Ostrov:

> [t]he immunoglobulin 'superfamily' is one of the most prevalent families of protein domains in the animal kingdom. The functions of various members of this superfamily are disparate and provide a notable example of selection acting on a modular structure, the

> immunoglobulin domain fold…[h]emolin, an insect protein, DIM-1, in *C. elegans* (a roundworm), and CTLA-4 are members of this large superfamily of proteins.

See Ostrov Decl., ¶ 12; *see also* Gascoigne Decl., ¶¶ 7, 10, 12 (the immunoglobulin superfamily contains "numerous" proteins); D.I. 157, Ex. 7 at BMS001054689 ("The transmembrane sequences and cytoplasmic domains of Ig-related molecules show great diversity"). Bristol's own experts have admitted that the immunoglobulin superfamily is a large group of proteins including "many" members. *See* D.I. 171, Ex. 9 at ¶ 58; D.I. 171, Ex.10 at ¶ 61; *see also* D.I. 178, Ex. 13 (Dr. Linsley and Dr. Peach, another Bristol scientist, stated in another journal article: "Despite sharing a common structural scaffold, members of the IgSF show distinct structural properties, and engage in intermolecular interactions in many different ways."); *see also* D.I. 174, Ex. 9 at BMS001028736 (distinguishing CTLA4 from other members of the IgSF). CTLA4 has vastly different characteristics and functional properties from other members in the immunoglobulin superfamily, such as TCR, the protein referred in the statements made before the foreign patent office. *See* Gascoigne Decl., ¶ 12.

Bristol also attempts to make statements made by Dr. Sledziewski, an inventor of the ZymoGenetics Patents, as dispositive of its noninfringement of the claim term "non-immunoglobulin polypeptide." However, statements by an inventor do not determine the scope of a claim. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996) ("The subjective intent of the inventor when he used a particular term is of little or no probative weight in determining the scope of a claim.") (citation omitted); *see also Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379-80 (Fed. Cir. 2000) ("[I]t is not unusual for there to be a significant difference between what an inventor thinks his patented invention is and what the ultimate scope of the claims is after

allowance by the PTO.") (citation omitted). Thus, Bristol's reliance on Dr. Sledziewksi's statements to support its noninfringement argument is improper.

Moreover, the question posed to Dr. Sledziewski during his deposition only referred to "proteins that have significant sequence homology with immunoglobulins," in general, and not CTLA4 specifically. *See* D.I. 173 at 37; D.I. 180, Ex. 6 at 251:24-252:3. Because "[t]he functions of the various members of this superfamily are disparate," Dr. Sledziewski could not give an accurate response, and even he expressed hesitation with his response. *See* D.I. 180, Ex. 6 at 252:10 ("*I would guess* I agree with your statement.") (emphasis added). As the question posed to Dr. Sledziewski was ambiguous and extremely generalized, in addition to being improper, Dr. Sledziewski's statements do not have any reliable weight in construing the scope of the claim term "non-immunoglobulin polypeptide."

Based on the fact that there are material facts in dispute about whether CTLA4 is a "non-immunoglobulin polypeptide" under Bristol's improper construction of the term, the Court should deny Bristol's summary judgment motion for noninfringement.

V. CONCLUSION

For the foregoing reasons, ZymoGenetics respectfully requests that this Court deny Bristol's motion for summary judgment of noninfringement.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Philip A. Rovner, hereby certify that on August 25, 2008, the within document was filed with the Clerk of the Court using CM/ECF which will send notification of such filing(s) to the following; that the document was served on the following counsel as indicated; and that the document is available for viewing and downloading from CM/ECF.

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