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

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Pursuant to the Court's Order dated August 4, 2008 (D.I. 239), Bristol-Myers Squibb Company ("Bristol") submits this brief in reply to ZymoGenetics, Inc.'s ("ZymoGenetics'") Opposition to Bristol-Myers Squibb Company's Motion for Summary Judgment of Noninfringement. (D.I. 242).

INTRODUCTION

In simple but accurate terms, the invention (if there is one) described and claimed in the patent-in-suit is to take (i) a protein that *is* a non-immunoglobulin, is *required* to be in a dimer form in order to be biologically active, but which will *not* dimerize on its own, and couple it to (ii) a second protein that *does* dimerize on its own, and therefore *cause* the conjoined molecule to form a dimer. Bristol's CTLA4-Ig is the opposite in every respect. The CTLA4 portion is *not* a nonimmunoglobulin, it is *not* required to be in a dimer form to be biologically active (because it is biologically active in monomeric form), it *does* dimerize on its own, and the mutated Ig to which it is coupled was mutated intentionally to remove its dimerizing sites – it does *not* cause a dimer to form (CTLA4 is what causes the dimer to form). The function of Bristol's mutated Ig is to provide solubility and stability. No manipulation of the facts or the claim language can turn Bristol's CTLA4 Ig into an infringing product or its method of manufacture into an infringing method. The facts here provide the textbook example of the utility of the Court's summary judgment procedure and the absence of any material issues for trial.

I. Bristol's CTLA4-Ig Cannot Infringe Because The CTLA4 of Bristol's CTLA4-Ig Does *Not* "Require Dimerization For Biological Activity" Under Either Parties' Construction

All asserted claims contain the limitation "requiring dimerization for biological activity". The construction of this term as applied in Bristol's summary judgment motion is:

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

(D.I. 153, Exh. A at 2, 3); (Bristol's Claim Construction Br.) (D.I. 179 at 20-28).

Both parties agree with part (a) of the above construction.[1] As such, under either parties' construction, it is ZymoGenetics' burden to prove that the CTLA4 used in Bristol's CTLA4-Ig must be a dimer to exhibit biological activity – that is, it must prove that when a monomer, CTLA4 has no biological activity. Because ZymoGenetics has failed to set forth any evidence sufficient to create a genuine issue of material fact, Bristol is entitled to summary judgment.

A. ZymoGenetics Has Set Forth No Experiments or Data Showing CTLA4 Is Not Biologically Active As A Monomer

The briefs make it clear that the parties dispute: (1) what the appropriate biological activity of CTLA4 is and (2)what form of CTLA4 needs to be tested to determine whether CTLA4 is biologically active as a monomer. Bristol will discuss ZymoGenetics' unsupportable positions below. But even assuming ZymoGenetics' positions were correct, Bristol is entitled to summary judgment – because ZymoGenetics (which bears the burden of proof) has shown no evidence that CTLA4 lacks biological activity as a monomer.

ZymoGenetics now alleges that the "relevant" biological activity of CTLA4 is "signaling." It also argues that nothing but full-length or native CTLA4 is relevant to whether

[1] ZymoGenetics' construction is "must be a dimer (*i.e.*, in a pair) to exhibit biological activity." (D.I. 156 at 23). At the time that Bristol authored its opening brief, Bristol was unaware of ZymoGenetics' construction because ZymoGenetics did not provide its proposed construction until filing its opening claim construction brief (D.I. 170).

CTLA4 "requires dimerization for biological activity." As testing is required to ascertain whether the alleged "non-immunoglobulin polypeptide"[2] "requires dimerization for biological activity" (D.I. 174, Exh. 22 at 144:25-145:10), under ZymoGenetics' distorted interpretation, it must provide testing showing that full-length, monomeric CTLA4 does not signal – it has not done so.

ZymoGenetics states that "[a] monomer of *native* CTLA4 . . . would not be able to function in the biological context." (D.I. 242 at 20). In support, ZymoGenetics relies on opinions of its experts (discussed below) and an article indicating that "generally" dimerization is required for signal transduction. (D.I. 242 at 20). But this article does not state that CTLA4 requires dimerization for signal transduction.

Redacted This is an unsupported conclusion devoid of any support in the record and therefore is insufficient to defeat summary judgment:

> In the context of summary judgment motions, the Third Circuit has demanded that the factual predicate of an expert's opinion must find some support in the record, and has emphasized that mere "theoretical speculations" lacking a basis in the record will not create a genuine issue of fact. *Penn. Dental Ass'n. v. Med. Serv. Ass'n.*, 745 F.2d 248, 262 (3d Cir. 1984). Moreover, where an expert's opinion is predicated on factual assumptions, those assumptions must also find some support in the record. *Shaw v. Strackhouse*, 920 F.2d 1135, 1142 (3d Cir. 1990).

[2] In this case, extracellular CTLA4 is the alleged "non-immunoglobulin polypeptide," not "full-length" or "native".

Redacted

Novartis Corp. v. Ben Venue Labs., Inc., 271 F.3d 1043,1050-1055 (Fed Cir. 2001); *see also Phillips Petroleum Co. v. Huntsman Polymers Corp.*, 157 F.3d 866 (Fed. Cir. 1998) (expert's conclusory statements failed to raise a genuine issue of material fact).

Redacted

But according to ZymoGenetics, binding is not the relevant biological activity, and none of these experiments were using "full-length" CTLA4 as ZymoGenetics requires. But most important, none of the experiments showed the critical fact that ZymoGenetics must prove - that monomeric CTLA4 did not bind [5]

Redacted

Again, this is an unsupported, bare

[5] Increased binding affinity resulting from dimerization would be "enhancing" biological activity rather than "requiring dimerization for biological activity." ZymoGenetics' patents distinguished between circumstances where dimerization is "required" from where dimerization "enhances" biological activity. But the asserted claims only cover requiring dimerization for biological activity. Bristol discussed this fact at pages 20-24 of its opening claim construction brief – and it went uncontested by ZymoGenetics. (D.I. 179).

Redacted

See In re Safeguard Scientifics, No. Civ.A. 01-3208, 2004 WL 2644393, at *2 (E.D.Pa. Nov. 17, 2004). ("where [a] new affidavit offers so many new opinions that it dramatically changes the 'flavor and theory' of the case, it must be disregarded. . .")

conclusory statement, devoid of factual support in the record. *Penn Dental Assn. v. Medical Svc. Ass'n of Penn.*, 745 F.2d 248, 262 (3rd Cir. 1984) ("factual predicate of an experts' opinion must find some support in the record") *citing Merit Motors, Inc. v. Chrysler Corp.*, 569 F.2d 666 (D.C. Cir. 1977). As such, it does not raise a genuine issue of material fact, which is what is required to defeat summary judgment.

The only other affirmative allegations set forth by ZymoGenetics are irrelevant facts, mischaracterizations of the record, or misleading. These allegations are addressed below. None are sufficient to create a genuine issue of material fact.

- ZymoGenetics alleges that CTLA4 purportedly always exists as a dimer. Even if true (which it is not)[7], that is irrelevant to whether monomeric CTLA4 exhibits biological activity.
- ZymoGenetics alleges that Bristol purportedly told FDA that CTLA4 "must exist as a dimer." (D.I. 242 at 21). This is a mischaracterization – the document relied on states that the fusion protein, CTLA4-Ig, is a dimer. (Excerpts from Abatacept BMS-188667 Biologics Licensing Application) (Noninfringement Reply Brief "N.R.B." Exh. 1 at BMS001290162).[8]
- ZymoGenetics alleges that Bristol purportedly told the PTO that CTLA4 "had to be in dimeric form..." That is misleading – the patent states that "CTLA4 . . . occur[s] in nature as a dimer" and that "it is believed that successful ***expression*** of these proteins requires an expression system which permits these proteins to form as dimers." (D.I. 243, Ex. 9 at col. 12, ll. 49-52) (emphasis added). It says nothing about whether CTLA4 must be a dimer to be biologically active.
- ZymoGenetics states that CTLA4 is biologically active as a dimer. But that is irrelevant to whether CTLA4 *must be* a dimer to exhibit biological activity.
- ZymoGenetics also alleges that "[t]he scientific community and experts . . . agree that CTLA4 has to be a dimer ***to function*** in the biological context." (D.I. 242 at 21)(emphasis added). In support, it cites statements that CTLA4 exists as a dimer. The existence as a dimer says nothing about having to be a dimer ***to***

[7] While ZymoGenetics argues that CTLA4 only exists as a dimer in its native state, Redacted

[8] All N.R.B. Exhibits are attached to the accompanying Declaration of Dana Lau In Support Of Bristol's Reply Brief In Support Of Its Motion For Summary Judgment Of Noninfringement.

function.[9] [redacted]

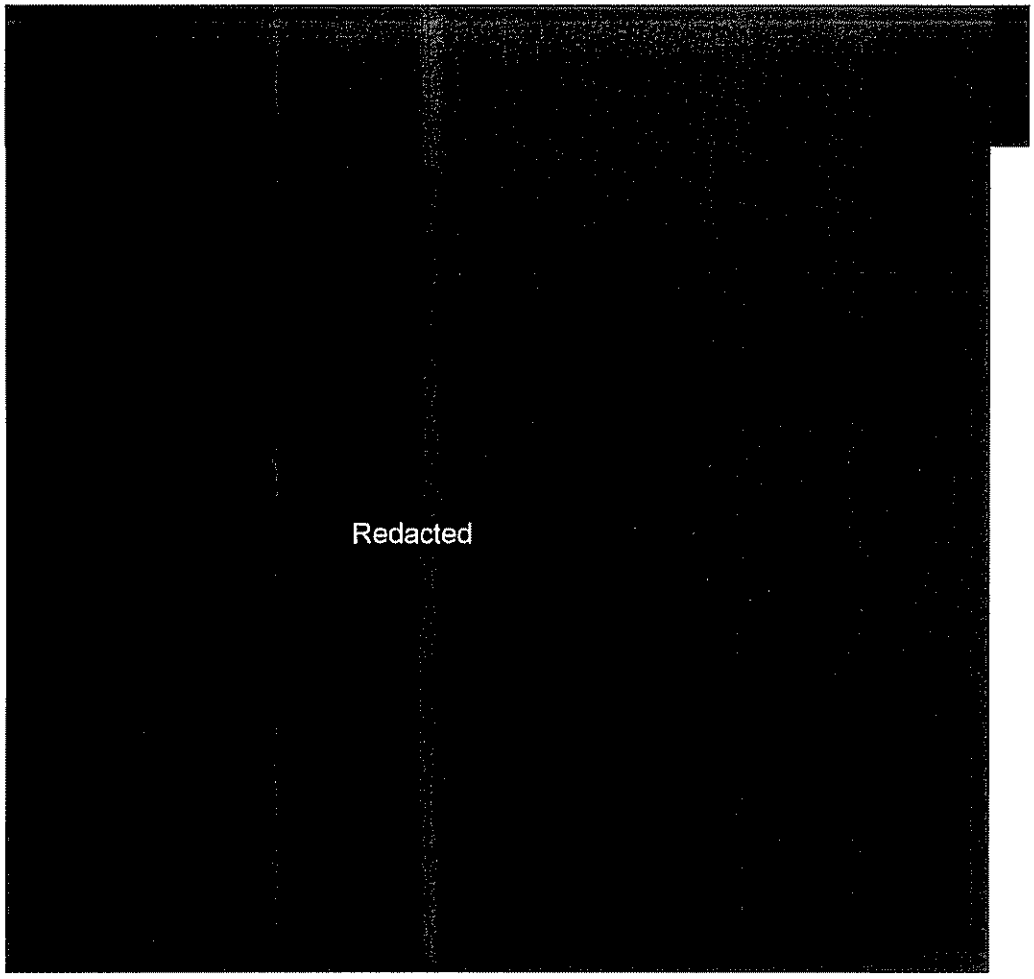
- ZymoGenetics alleges that "[w]ritten scientific publications . . . confirm that CTLA4 ***must be a dimer to function*** in the biological context" (D.I. 242 at 21). Following this statement are references to two scientific publications. The first reference purportedly states that native CTLA4 exists as a homodimer and the second article purportedly states that CTLA4 exists as an "obligate dimer" and is a "dimeric cell-surface receptor." Such statements, even if true, are not evidence of whether CTLA4 has to be a dimer to function.

The foregoing section sets forth ZymoGenetics' affirmative evidence concerning the first part of the construction of "requiring dimerization for biological activity" (*i.e.*, unless a dimer, it has no biological activity). Because ZymoGenetics has no evidence that monomeric CTLA4 is not biologically active, Bristol is entitled to summary judgment – under either party's construction is warranted.

B. ZymoGenetics' Experts Concede That CTLA4 Dimerizes On Its Own

As discussed in Bristol's opening brief, ZymoGenetics' alleged inventions do not cover circumstances where "Part A" of the molecule dimerizes on its own – this is the only construction that makes sense, because in that circumstance, there would be no need for a second "dimerizing protein". In an attempt to avoid the fact that the extracellular CTLA4 used in Bristol's CTLA4-Ig, ZymoGenetics cites to an experiment wherein CTLA4 was purified following expression, destroying its ability to be a dimer,[10] and calls this "overwhelming evidence" that CTLA4 does not dimerize on its own. [redacted]

[redacted] Moreover, when the same experiment was performed under physiological conditions, 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 CTLA4']". (D.I. 249, I.A.B. Exh. 7 at 107 (identifying pH 8) and 110) (excerpted quotation).



The remainder of ZymoGenetics' arguments are an attempt to disparage Bristol's evidence that CTLA4 is biologically active as a monomer. Because ZymoGenetics has not provided any evidence that CTLA4 is not biologically active as a monomer – and it is ZymoGenetics' burden to do so – it is not necessary to address ZymoGenetics' attacks



However, to clarify the record, Bristol addresses several glaring problems and inconsistencies with ZymoGenetics' positions below.

C. The Appropriate Biological Activity Cannot Be Signaling

ZymoGenetics now alleges that the relevant biological activity is the binding of ligand and signaling of the T-cell.[12] (D.I. 242 at 20 and 23) But this signaling cannot possibly be the relevant biological activity of CTLA4 in the context of the invention.

Claim 1 of the '026 Patent is, in part:

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

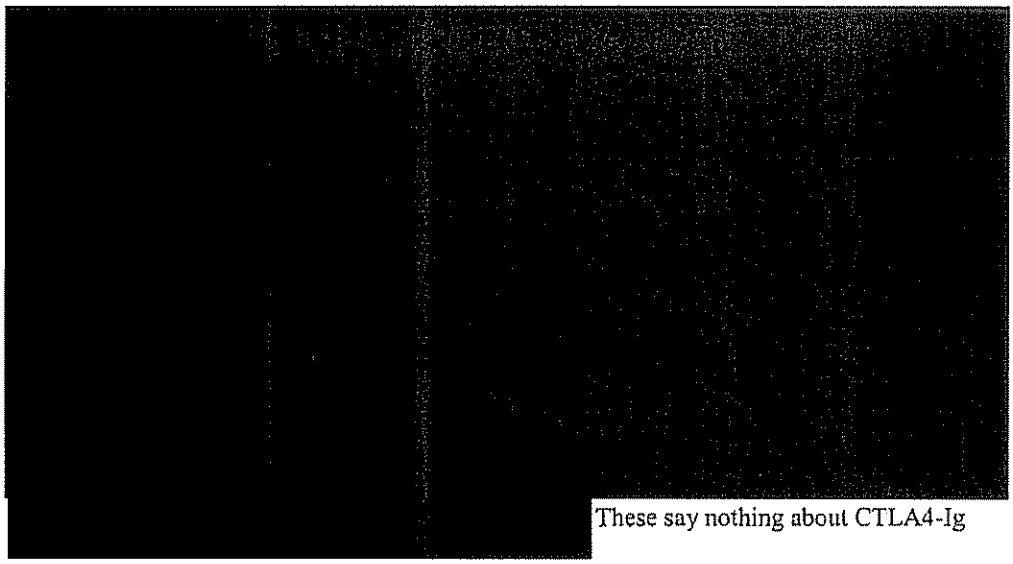
(D.I. 174, Exh. 1 at ZG000003) The biological activity of the resulting fusion has to be the same biological activity for which the non-immunoglobulin requires dimerization. Otherwise, the claim makes no sense.

And because they must be the same, the relevant biological activity cannot be signaling. CTLA4-Ig only contains extracellular CTLA4 and is therefore not attached to the T-cell. Once removed from the T-cell, there is no mechanism for CTLA4 to communicate (*i.e.*, signal) with the cell. Because CTLA4-Ig cannot signal, the relevant biological activity cannot be signaling.

Redacted

[12] Redacted (Bristol's Opening Brief In Support Of Its Motion For Summary Judgment) (D.I. 173 at 30-31). While ZymoGenetics alleges that Bristol "mischaracterized" their testimony (D.I. 242 at 24-25), Bristol included the excerpts in its opening brief. (D.I. 173 at 30-31). In fact, it is noteworthy that excluding "binding" from the definition of "biological activity" in the context of CTLA4 is so alien, that ZymoGenetics itself was unable to resist referring to binding as a biological activity in its opposition. ZymoGenetics' brief states "in this case, binding is not the ***only*** biological activity of native CTLA4." (D.I. 242 at 20) (emphasis added). Of course, this means binding ***is*** a biological activity.

The relevant biological activity must be an activity that the fusion protein is capable of accomplishing. For CTLA4, it is binding and interruption of the CD28-B7 pathway.



These say nothing about CTLA4-Ig "signaling" the T-cell because it does not and cannot signal.

ZymoGenetics' tortured analysis ignores the claim context and ignores the fact that the resulting fusion must be biologically active. It is simply an illogical attempt to avoid Bristol's evidence proving that monomeric CTLA4 binds, inhibits T-cell proliferation (through interruption of the CD28-B7 pathway), and inhibits an immune reaction (*See* D.I. 173 at 28-33).

D. The Relevant Form of CTLA4 For Consideration Cannot Be "Native" Or "Full-Length" CTLA4

ZymoGenetics contends that Orencia® infringes the asserted claims because Bristol failed to demonstrate that "native" or "full-length" CTLA4 exhibits biological activity as a monomer. (D.I. 242 at 23). As a preliminary matter, ZymoGenetics is mistaken – Bristol has no such burden. ZymoGenetics must prove that CTLA4 does not exhibit biological activity as a

[13] CD80 and CD86 are "B7" ligands.

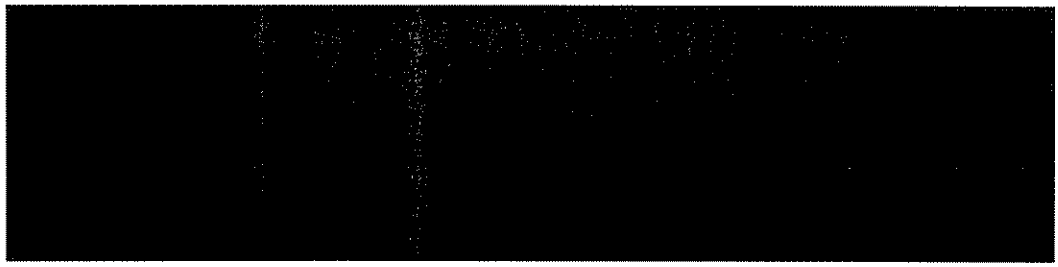
monomer. Nevertheless, alleging that "native" or "full-length" is the relevant molecule is contrary to the patents-in-suit, and contrary to ZymoGenetics' tutorial.

The relevant portions of the independent claims are as follows:

> . . . ***a non-immunoglobulin polypeptide*** requiring dimerization for biological activity joined to a dimerizing protein . . .
>
> * * *
>
> . . . ***a ligand-binding domain*** of a receptor requiring dimerization for biological activity joined to a dimerizing protein . . .

(Claim 1 of the '026 Patent and Claims 1 and 21 of the '725 Patent) (D.I. 174, Exh. 1 at ZG000003; Exh. 2 at ZG000844) (emphasis added). The claims are instructive – it is either the "non-immunoglobulin polypeptide" or the "ligand-binding domain of a receptor" that comprises "Part A" of the fusion protein (*see* the figure at page 2 of Bristol's opening brief) (D.I. 173 at 2) that requires dimerization for biological activity – not a "full-length" or "native" protein from which the non-immunoglobulin polypeptide is truncated. ZymoGenetics' position is nonsensical, and is an improper attempt to distort the claims.

The illogicality of ZymoGenetics' argument is highlighted in its brief, where it states "[t]he non-immunoglobulin polypeptide requiring dimerization for biological activity is *native* CTLA4" (emphasis added) (D.I. 242 at 23). If that is the case, then the lawsuit can go no further – because Bristol's CTLA4-Ig only contains the *extracellular* portion of CTLA4, not what ZymoGenetics calls "native" or "full-length" CTLA4, and therefore CTLA4-Ig could not possibly infringe.



[redacted]

Once again, ZymoGenetics' distortion of the claims is an unsupportable attempt to avoid the evidence demonstrating the extracellular portion of CTLA4 binds as a monomer, inhibits T-cell proliferation, and inhibits an immune reaction (*See* D.I. 173 at 28-33).

E. ZymoGenetics' Continued Mischaracterization of the Immunex Litigation

Apparently ZymoGenetics has finally dropped its allegation that the Immunex Litigation did not involve the patents-in-suit. (ZymoGenetics' Response Statement of Material Facts Concerning Bristol's Motion For Summary Judgment of Noninfringement) (D.I. 205 at ¶ 28-29). Instead, it now argues that the Immunex Litigation concerned an "entirely different product" with "different properties." (D.I. 242 at 24). [redacted] Moreover, the scope of the claims should not differ depending on the accused product [14]

II. ZymoGenetics Has Not Set Forth Evidence That Bristol's Mutated Ig Is A Dimerizing Protein In CTLA4-Ig

In order to defeat Bristol's summary judgment motion concerning "dimerizing protein", ZymoGenetics must set forth evidence that the mutated Ig in Bristol's CTLA4-Ig is:

> a polypeptide chain having affinity for a second polypeptide chain, such that the two chains associate under physiological conditions to form a dimer, wherein said dimerizing protein causes or drives the dimerization of non-immunoglobulin polypeptide that is joined

[redacted]

Redacted

> to it that would not otherwise form a stable dimer but for the action of said dimerizing protein

(D.I. 153, Exh. A at 3, 4).

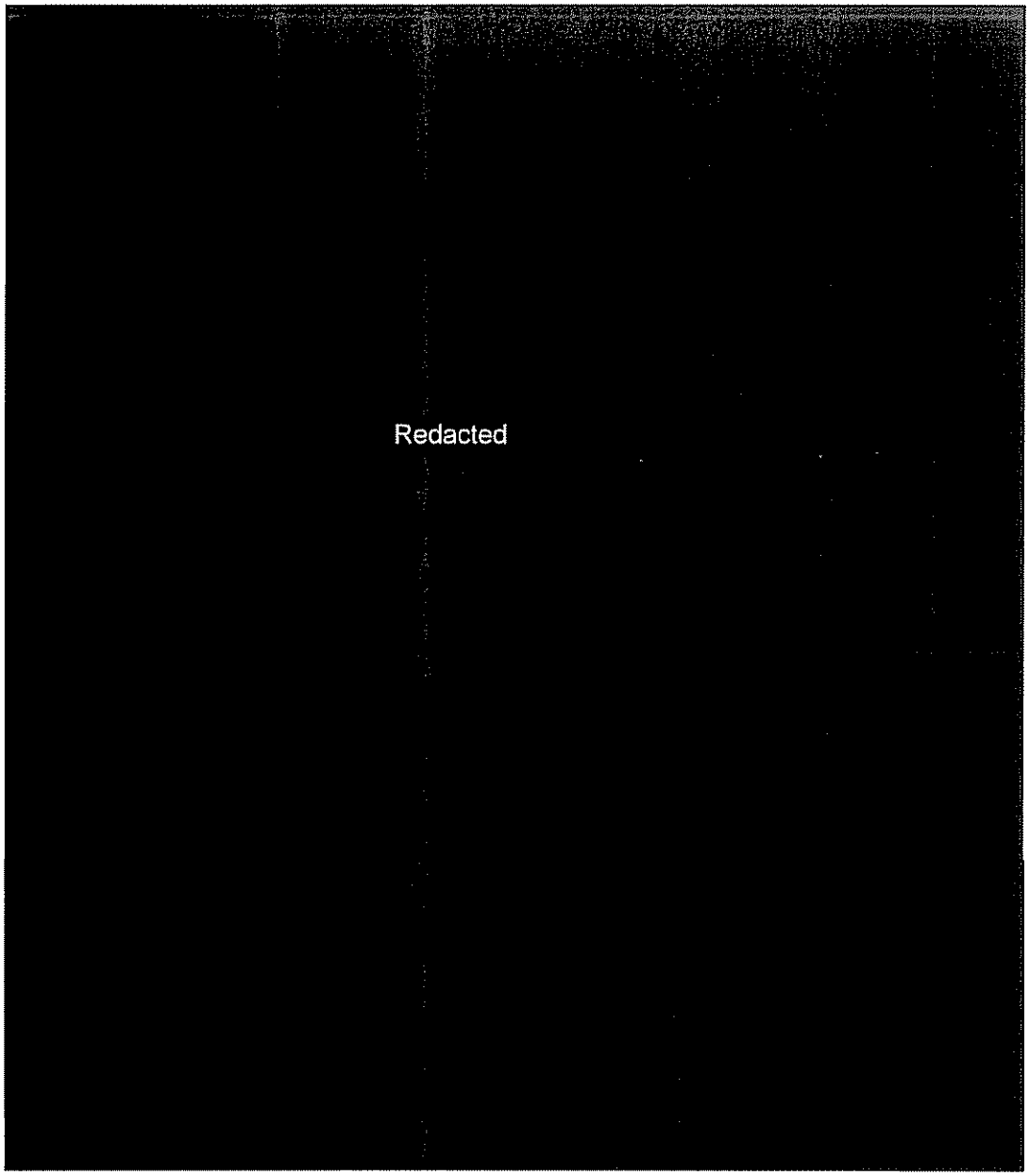
As a preliminary matter, there is no dispute that the "Ig" in Bristol's CTLA4-Ig has four mutations (three in the hinge) in its amino acid sequence. Redacted Therefore, ZymoGenetics must rely on an experiment performed with Bristol's CTLA4-Ig to determine if the mutated Ig, when a part of the fusion protein, fulfills the definition of dimerizing protein. ZymoGenetics has not done so. Instead, ZymoGenetics relies on the following alleged "evidence":

- Figures depicting CTLA4-Ig in Bristol's documents;
- Redacted
- A statement by a Bristol employee concerning B7-Ig;
- Scientific literature concerning unmutated Ig (when not attached to the extracellular portion of CTLA;
- The allegation that Bristol did not mutate its Ig to prevent dimer formation;
- An article concerning CTLA4 purified under non-physiological conditions; and
- Alleged representations made by Bristol to the PTO.

None of the foregoing is sufficient to create a genuine issue of material fact.

ZymoGenetics' allegation that figures depicting CTLA4-Ig are somehow "dispositive evidence" proving infringement because they allegedly show the Ig portion as a dimer has no merit. ZymoGenetics provides three figures in its brief on page 10 in Figure 2. (D.I. 242 at 10). The three figures will be referred to as "Far Left", "Middle" and "Far Right" as ZymoGenetics did in its brief. As a preliminary matter, of course the fusion proteins are depicted as dimers, because CTLA4-Ig is a dimer by virtue of the disulfide bond formed between the two CTLA4

portions – but that does not mean that the Bristol's mutated Ig is the required dimerizing protein, which must be different from the "biologically active" peptide. And ZymoGenetics ignores the fact that neither the Far Left figure nor the Middle figure were depictions of Bristol's CTLA4-Ig containing the mutated Ig. With respect to the Far Left figure, Bristol told the FDA that it used native (*i.e.*, unmutated) Ig in preparation of the figure. [redacted] The reference provided makes it clear that the Ig that was used as the basis for the figure was not mutated. (Saphire et al., SCIENCE, 293:1155-59) (N.R.B , Exh 7 at BMS001288355-56 ("the hinge . . . region contains two adjacent pairs of cysteine residues . . .") [redacted] Regarding the Middle figure, Zymogenetics ignores the testimony it adduced from Bristol's employee. [redacted] With respect to the Far Right figure, the only bond depicted between the two chains is the disulfide bond in the CTLA4 region of the molecule. Therefore, these figures cannot be evidence that Bristol's mutated Ig is a dimerizing protein. ZymoGenetics also references a figure on Page 4 of its brief entitled Figure 1. (D.I. 242 at 4) This figure, taken from a guide (for nurses and written by a nurse) for administering CTLA4-Ig does not depict any bonds in the figure.


Redacted


Redacted

[redacted] And it turns out that B7 forms a dimer on its own, much like the CTLA4 used in Bristol's CTLA4-Ig. (Ikemizu et al., IMMUNITY, 12:51-60 (2000)) (N.R.B. Exh. 10 at BMS001598144) ("In the crystal lattice, sB7-1 unexpectedly forms parallel, 2-fold rotationally symmetric homodimers"). Therefore, the fact that a dimer of B7-Ig formed says nothing about whether the mutated Ig had anything to do with dimer formation.

ZymoGenetics also attempts to rely on information concerning wild-type unmutated Ig [16] [redacted] 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.

ZymoGenetics also takes issue with the reality that Dr. Linsley mutated the Ig to prevent dimerization. ZymoGenetics relies on statements made many years after the invention of CTLA4-Ig. The documents contemporaneous to the invention are unequivocal. [redacted] And, trial testimony by one of the inventors that occurred years before ZymoGenetics filed the present lawsuit confirms the meaning of the laboratory notebooks:

[redacted]

[17] *See Oddi v. Ford Motor Co.*, 234 F.3d 136, 158 (3d Cir. 2000) (finding no abuse of discretion in excluding expert testimony where expert failed to conduct tests or perform calculations, and he used little methodology beyond his own intuition in forming his opinion).

> A. There was one called dim, d-i-m, which basically coded the DNA region of the antibody, or gamma 1 chain. ***Then we had another one here, Ig 5' mono, which is the one where we mutated the hinge disulfide.***
>
> * * *
>
> Q. And with respect to the – Ig 5' mono, where you did the . . mutation, would doing that cysteine mutation, um, potentially affect the structure of the molecule and potentially the function of the molecule?
>
> A. Yes. What – what this – At this point in time, we had no idea of . . . what would work and what wouldn't . . . but ***we were concerned that the hinge disulfide might confer. What those do is actually make a very rigid part of the molecule, because they hold it together.*** And then ***we were concerned that all this engineering might not work if – if the molecules were held too tightly together, so we wanted to open them up a bit and let them have a little more breathing room. . . . We were making the native form, which is called dim. We were also making the mutated form, which we called mono.***

(D.I. 174, Exh. 17 at BMS4254773-74) (emphasis added).

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" and that this somehow supports the mutated Ig is a dimerizing protein (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 capable of damaging the dimerization state of molecules. (D.I. 169, Exh. 12 at BMS003504386) (*See also supra* FN10). The status of CTLA4 post-purification, unless the process was controlled, states nothing about the state of CTLA4 when expressed by the cell.

ZymoGenetics also argues that statements made to the PTO in a patent application support its position that Bristol's mutated Ig dimerizes CTLA4. But ZymoGenetics mischaracterizes what the patent says. It states that there are problems expressing proteins, and

the immunoglobulin was added to aid in the expression of a dimer. (D.I. 243, Ex. 9 at col. 12, ll. 49-52).

ZymoGenetics also has no proof that Bristol's mutated Ig causes or drives the dimerization of CTLA4 (*See* Bristol's construction of "dimerizing protein") (D.I. 153, Exh. A at 3, 4) Redacted ZymoGenetics states Bristol "experiments" demonstrate CTLA4 cannot dimerize on its own. This is the same experiment performed in non-physiological conditions discussed on page 16. ZymoGenetics also cites to the same PTO document discussed on page 16, and says nothing about the Ig causing or driving dimer formation. Redacted

III. CTLA4 Is Not A Non-Immunoglobulin Polypeptide Under Bristol's Construction

All claims require a "non-immunoglobulin polypeptide". (D.I. 173 at 9). Bristol's summary judgment motion concerning this claim element is predicated on Bristol's construction being applied.

Bristol was quite surprised that ZymoGenetics is now contesting the fact that CTLA4 falls outside the scope of a "non-immunoglobulin polypeptide" under Bristol's construction, because ZymoGenetics previously admitted that this was the case. In fact, ZymoGenetics made this very representation to the Court in its briefs and during oral argument:

> Bristol's results-driven attempt to exclude the entire immunoglobulin superfamily from the meaning of "non-immunoglobulin polypeptide" ***reads*** not only ***the accused product (Orencia®) outside the scope of the claims***, but also the preferred embodiment of the ZymoGenetics' Patents.

(D.I. 227 at 21) (emphasis added)

> Bristol's proposed definition . . . would extend to the entire superfamily of immunoglobulins.

(Transcript of Markman Oral Argument June 27, 2008 at 24:3-5).[18]

Nevertheless, ZymoGenetics has not raised a genuine issue of material fact for purposes of Bristol's motion. "Non-immunoglobulin polypeptide" was construed as follows:

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

(D.I. 153, Exh. A at 2)

ZymoGenetics states that CTLA4 is covered by Bristol's construction purportedly because it does not share "significant" sequence homology to immunoglobulin.[19]

Redacted But 30% sequence homology must be significant based on the positions taken by ZymoGenetics. During prosecution of the priority application, ZymoGenetics argued that TCR shared "significant" sequence homology with immunoglobulin. (D.I. 179 at 32-34) Thus, the homology of TCR is an appropriate measure for the term "significant."

Redaction

Therefore, 30% sequence homology of CTLA4 must be considered "significant."

Redaction

[18] It is undisputed that CTLA4 is part of the superfamily of immunoglobulins (D.I. 245 at ¶10 10-12)(D.I. 174, Exh. 28 at 43:11-13)

[19] It does not contest that CTLA4 is encoded by immunoglobulin-like genes which encode discrete domains structurally similar to immunoglobulin.

The "sham affidavit doctrine"[20] also prevents ZymoGenetics' experts from creating a material issue of fact to defeat this summary judgment motion by filing a declaration that disputes their own sworn testimony "without demonstrating a plausible explanation for the conflict." *Jiminez v. All American Rathskeller, Inc.*, 503 F.3d 247, 251-254 (3d Cir. 2007) (*citing Baer v. Chase*, 392 F.3d 609, 624 (3d Cir. 2004)). *Adelman-Tremblay v. Jewel Cos.*, 859 F.2d 517, 519-521 (7th Cir. 1988) (finding no reason to not to apply the sham affidavit doctrine to the testimony and affidavit of an expert witness).

[redacted] Redacted [redacted] Now, they state that it is not significant. This is a direct contradiction for which no explanation was provided. Therefore, ZymoGenetics should not be permitted to rely on these portions of its experts' opinions.

Because ZymoGenetics represented to the Court that Bristol's construction excludes CTLA4, and because there can be no genuine dispute that a 30% sequence homology is "significant", Bristol is entitled to summary judgment of noninfringement under Bristol's construction of "non-immunoglobulin polypeptide".

[20] A sham affidavit is: a contradictory affidavit that indicates only that the affiant cannot maintain a consistent story or is willing to offer a statement solely for the purpose of defeating summary judgment. . . .A sham affidavit cannot raise a genuine issue of material fact because it is offered solely for the purpose of defeating summary judgment, it is proper for the trial judge to conclude that no reasonable jury could accord the affidavit evidentiary weight and that summary judgment is appropriate. The main practical reason supporting the sham affidavit is that prior depositions are more reliable than affidavits. *Jiminez*, 503 F.3d at 253.

CONCLUSION

For all the reasons set forth in Bristol's opening and reply briefs, and because ZymoGenetics has failed to raise a genuine issue of material fact, Bristol respectfully requests that the Court enter judgment of noninfringement of all the asserted claims as a matter of law.

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on August 25, 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 25, 2008, the foregoing document was sent to the following non-registered participants in the manner indicted:

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on August 28, 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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