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**

PLAINTIFF ZYMOGENETICS, INC.'S REPLY IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT OF INFRINGEMENT

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Dated: August 25, 2008
Public Version: September 2, 2008

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I. INTRODUCTION

Among the shortcomings of Bristol's infringement opposition is the utter void of actual facts to support its arguments. There are only two non-infringement arguments that Bristol advances in its opposition -- that CTLA4 does not require dimerization to perform its function in the body (i.e., its biological activity), and that the immunoglobulin ("Ig") portion of Orencia® is not a dimerizing protein.

Lurking beneath a veneer of "scientific" evidence is the astonishing realization that nowhere in any of Bristol's briefing does it ever state what the ***function*** of CTLA4 is ***in the body***. Its opposition is so well-disposed toward ignoring this central issue that it is impossible for Bristol to raise any relevant material facts to preclude a summary adjudication of infringement. The actual scientific facts are undisputed: (1) the function of CTLA4 in the body is to down regulate T-cell activation; (2) down regulation of T-cell activation by CTLA4 is accomplished via a multi-step process resulting in the formation and organization of multicomponent complexes in the cell required for signal transduction, leading to the activation of signaling pathways; and (3) dimerization of CTLA4 is required to perform this function in the body. Bristol never challenges these facts and completely ignores them. Instead, Bristol sets up a convenient strawman in the form of "ligand binding as biological activity." The Court should not reward such misdirection.

Bristol's only other infringement argument is the half-baked position that ZymoGenetics has not proven that the Ig portion of Orencia® is a dimerizing protein -- *i.e.*, that the two Ig portions associate under physiological conditions. To advance such a position, Bristol is magnificently indifferent to whether its own testing and representations to the FDA and PTO provide ZymoGenetics with ample and undisputed evidence that the Ig portion of Orencia® is a dimerizing protein.

Bristol has purposefully attempted to confuse the issues by misdirecting the focus onto scientific theories and testimony on such theories which do not address the issues of the case. These "might be" and "might not" theories are in direct contradiction to the overwhelming

scientific facts, including the scientific facts Bristol presented to the FDA and PTO, and what Bristol's own scientists and studies have stated. Each position put forward by Bristol is so clearly in contradiction to the scientific facts established in this case that a finding of infringement by Orencia® and its method of production is appropriate.

II. ARGUMENT

A. CTLA4 REQUIRES DIMERIZATION FOR BIOLOGICAL ACTIVITY

1. The Function of CTLA4 in the Body is to Down Regulate T-Cell Activation

The element "requiring dimerization for biological activity" of the asserted claims of ZymoGenetics' Patents is referring to the protein in Orencia®, CTLA4, which needs to be in a dimer form to perform its function in the body. The patent specifically states that the definition of "biological activity" *is the function performed by the protein in the body*, and the parties agree on at least this part of the construction. D.I. 169, Exs. 1-2. It is undisputed that the function of CTLA4 in the body is the down regulation or suppression of T-cell activation. Literally hundreds of scientific publications describe this as the function of CTLA4, for example:

- Schwartz *et al.* stating that CTLA4 regulates the adaptive immune response by creating an inhibitory signal that results in down regulation of T-cell activation. D.I. 174, Ex. 14 at 427.
- Stamper *et al.* stating that the "consequence" of CTLA4 signaling is the attenuation T-cell activation. D.I. 174, Ex. 13 at 608.
- Schwartz *et al.* stating that regulation of T cell activity is "dependent" on the engagement of CTLA4 leading to T cell suppression. D.I. 174, Ex. 12 at 604.
- Linsley *et al.* stating that CTLA4 negatively regulates T cell activation. Declaration of Amy Sun in Support of ZymoGenetics' Reply to Motion for Summary Judgment of Infringement ("Sun Decl."), Ex. 11 at BMS001122376 (Linsley *et al.*, Nature Struct. Biol., 4(7):527-531 (1997)).
- Greene *et al.* stating CTLA4 regulates the signal leading to T-cell suppression. Sun Decl., Ex. 14 at 26762 (Greene *et al.*, JBC, 271(43):26762 – 771 (1996)).
- Linsley *et al.* stating CTLA4 is a "key" negative signal in the T-cell response. D.I. 171, Ex. 12 at BMS003504385.
- Oosterwegel *et al.* stating that CTLA4 plays a "pivotal role" in downregulating the T-cell response. Sun Decl., Ex. 12 at 298 (Oosterwegel *et al.*, Curr. Opin. Immun. 11:294 – 300 (1999)).
- Ostrov *et al.* stating that CTLA4 play a dominant role in the modulation of T-cell activity, providing the inhibitory signal required for the downregulation of T-cell

activation. Sun Decl., Ex. 13 at BMS002569166 (Ostrov *et al.*, Science 290:816-819 (2000)).

Absent from Bristol's opposition is any description of this function of CTLA4 in the body. Instead, Bristol focuses its non-infringement argument on a scientifically untenable position that binding ligand in a laboratory is the function of CTLA4 in the body. By ignoring the fact that "biological activity" is defined as the function performed by the protein in the body, Bristol obviously hopes to confuse the Court. However, if the Court ascribes the correct function of CTLA4 in the body, then Bristol does not have any defense to infringement of this element.

2. The Function of CTLA4 in the Body is Performed via a Multi-Step Process Resulting In the Formation and Organization of a Multicomponent Complex, and Signal Transduction Leading to T Cell Suppression

CTLA4 dimers exist on the surface of the T-cell. D.I. 174, Ex. 12 at 604; D.I. 211, Ex. 6 at 407. Engagement of CTLA4 by ***paired ligands*** begins the process of "cell signaling" – the process that leads to T-cell suppression. D.I. 174, Ex. 14 at 427; D.I. 174, Ex. 13 at 610 (CTLA4 must be dimeric to bind paired ligands and signal); D.I. 174, Ex. 12 at 604; D.I. 178, Ex. 13 at ZG054284; D.I. 171, Ex. 12 at BMS003504385. When CTLA4 dimers are bound by the paired ligands, recruitment of cellular proteins required for the formation of inhibitory signaling assemblies or complexes occurs in the cytoplasm. Sun Decl., Ex. 13 at BMS002569166; D.I. 174, Ex. 14 at 427. The cellular proteins that make up these signaling complexes are, for example, AP2, PP2A, PI3K, JAK2, and SHP2 -- each involved in the cellular processes that ultimately effectuates the T-cell suppressive biological activity of CTLA4. Id. Thus, CTLA4 dimers function to cause cell signaling, leading to T-cell suppression. It is this entire process which describes the function of CTLA4 in the body.

3. There is No Dispute that CTLA4 is Required to be a Dimer to Perform Its Function in the Body

It is an undisputed scientific fact that CTLA4 is a dimeric T cell surface receptor. D.I. 174, Ex. 12 at 604, 607 (CTLA4 is a preformed, obligate dimer); D.I. 174, Ex. 14 at 428, 432; D.I. 178, Ex. 13 at ZG054282; D.I. 211, Ex. 6 at 407; D.I. 244, ¶5; Sun Decl., Ex. 13 at BMS002569169. It is similarly undisputed that CTLA4 is required to be in dimeric form to

perform its biological function. D.I. 174, Ex. 14 at 429 (stating that an "essential functional feature" of CTLA4 is that is be a dimer); D.I. 171, Ex. 12 at BMS003504392; D.I. 174, Ex. 13 at 610 (stating that CTLA4-mediation suppression "requires the formation of unusually stable complexes" of the dimer); D.I. 178, Ex. 13 at ZG054281 and ZG054284 (stating CTLA4 is preexisting dimer, and signal transduction occurs); D.I. 244 at ¶¶ 6,7. Dimerization is critical for CTLA4 to function. D.I. 174, Ex. 14 at 432 (stating CTLA4 is an obligate, preformed dimer, and that cell signaling requires CTLA4 to be a dimer); D.I. 245, ¶¶ 24-25; D.I. 178, Ex. 13 at ZG054281 (stating that receptor dimerization is generally critical for signal transduction). CTLA4 is referred to as an "obligate dimer." D.I. 174, Ex. 12 at 607. Dr. Gascoigne, a ZymoGenetics' expert, stated that an obligate dimer meant "that the protein is ***only functional as a dimer***...." Sun Decl., Ex. 9 (Deposition of Dr. Nicholas Gascoigne ("Gascoigne Depo.") at 243:7-244:3) (emphasis added).

Beyond the wealth of scientific facts proving CTLA4 requires dimerization for biological activity, the FDA requires CTLA4 to be a dimer in Orencia®. D.I. 243, Ex. 13. When seeking FDA approval for Orencia®, Bristol admitted that functional CTLA4 is required to be in dimeric form in order to perform its function when it represented to the FDA that CTLA4 is required to be a dimer. D.I. 169, Ex. 5 at BMS001290162. Indeed, as Bristol informed the FDA, the source material that is used to produce Orencia® was obtained from cells expressing the dimeric 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.

Bristol also told the PTO that CTLA4 had to be in dimeric form in order to perform its function in the body when it attempted to obtain a patent for its infringing product. *See* D.I. 243, 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). Bristol's 30(b)(6) witness, Dr. Nadler, who is the Director of Immunology Drug Discovery, confirmed that CTLA4 requires dimerization for

biological activity, testifying that CTLA4 is required to be a dimer to be biologically active in humans. D.I. 171, Ex. 11 at 85:13-20. Indeed, other Bristol scientists agreed that CTLA4 is biologically active in the body only as a dimer. *See* D.I. 171, Ex. 12 at BMS003504385 and BMS003504391 (Bristol study stating that native CTLA4 exists as a homodimer); *see also* D.I. 174, Ex. 12 at 607 (Nature publication stating that CTLA4 exists as "an obligate dimer" and is a "dimeric cell-surface receptor"); D.I. 245, ¶¶ 24-28; D.I. 244, ¶¶ 14-17. Thus, the scientific facts and Bristol's' representations establish that there can be no dispute that CTLA4 is required to be a dimer to perform its function in the body.

4. The Biological Activity of CTLA4 is Not Only Ligand Binding

Both parties agree that biological activity at the very least, is "[a] function or set of activities performed by a molecule in a biological context (i.e., in an organism ...)" – *i.e.*, the function of the protein in the body. D.I. 153, Ex. A at 3. As explained above, the biological activity of CTLA4 is to down regulate T cell activation. This biological activity begins with dimers of CTLA4 binding paired ligands, followed by the recruitment of cellular proteins necessary for cell signaling, culminating in the transduction of the cell signal, the cellular response generated from that signal (including the down-regulation of CTLA4 expression) resulting in T cell suppression. *See* D.I. 171, Ex. 12 at BMS003504392; D.I. 178, Ex. 13 at ZG054281 and ZG054284 (CTLA4 is a preexisting dimer undergoing signal transduction); D.I. 244 at ¶ 4 (citing Nature Immunology that CTLA4 involved in T cell signaling), ¶ 6 (citing Immunity that CTLA4 causes cellular protein recruitment).

What is entirely clear from the scientific facts is that only binding of ligand (in a laboratory setting, no less) to CTLA4 is not CTLA4's biological activity, nor is CTLA4 monomeric binding sufficient to effectuate biological activity. A myriad of steps must occur before CTLA4 can exhibit its biological activity. *See* above. Mere binding ligand is not considered "biological activity" of CTLA4. *See id.*, ¶¶ 6, 14; *see also* D.I. 174, Ex. 14 at 427; D.I. 174, Ex. 12 at 604; D.I. 245, ¶28; D.I. 244, ¶¶ 4, 6-7, 14, 16-17; D.I. 171, Ex. 12 at BMS003504392 (Bristol paper stating CTLA4 exists as a preformed dimer and undergoes cell

signaling following ligand binding). Nonetheless, Bristol ignores the scientific facts, and asks the Court to find against the entire scientific community and determine that the function of CTLA4 is merely binding ligand.

5. ZymoGenetics' Representations in the Immunex Litigation are Not Relevant to this Case

Bristol misrepresents ZymoGenetics' position concerning the statements it made in the Immunex litigation regarding whether binding constitutes biological activity. D.I. 248 at 11. First, ZymoGenetics' statements in the Immunex litigation, even if somehow viewed as inconsistent with ZymoGenetics' current position (which they are not,) are not relevant. As the Federal Circuit explained in *Hybritech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1453-54 (Fed. Cir. 1988) (citation omitted):

> [A] patent holder [is] not precluded from taking a position in a subsequent action inconsistent with a position taken in a prior action if the opposing party in the subsequent action fails to demonstrate either (1) personal reliance on the decision granted in the prior suit, (2) prejudice to its litigation of the issues in the present suit by reason of the decision in the prior suit, or (3) the patent holder's apparent misuse of the court.

Bristol fails to address these factors and it has not shown that ZymoGenetics' statements made in the Immunex litigation are binding in the present action in any event.

Moreover, ZymoGenetics does not contest that the biological activity of a given protein "***can*** include" ligand binding. D.I. 248 at 11 (emphasis added). Such a position is entirely consistent with ZymoGenetics' position that "biological activity" is the function performed in the body by a protein. If a given non-immunoglobulin protein's sole function is to bind ligand, then ligand binding could be considered its biological activity. In other words, it is imperative to determine what the protein's function is in the body to determine what constitutes its biological activity. For some proteins this may be merely ligand binding, but for others, such as CTLA4, it is a much more complex set of activities. In the Immunex litigation, another protein, TNF, was at issue and its biological activity is different than that of CTLA4. Sun Decl., Ex. 15. Therefore, representations about the biological activity of TNF in the Immunex litigation are not relevant to the biological activity of CTLA4 in this litigation.

6. Bristol Claims CTLA4 Does Not Require Dimerization for Biological Activity

Bristol's sole argument disputing the plethora of scientific facts that CTLA4 requires dimerization for biological activity is that artificial constructs of CTLA4 binds ligand as a monomer. D.I. 248 at 20. Bristol defines biological activity as ***only*** ligand binding. *Id.* at 10. Thus, Bristol's ***theory*** is that if monomeric non-native or artificial forms of CTLA4 can bind ligand, then CTLA4 is not a non-immunoglobulin requiring dimerization for biological activity. *Id.*

Bristol attempts to prove that CTLA4 has biological activity in the monomeric form to dispute the overwhelming scientific evidence that CTLA needs to be in dimeric form to perform its function in the body.. D.I. 248 at 9. Bristol relies on three tenuous ***theories*** to make the leap-of-faith that monomeric non-native forms are biologically active: (1) a ***disproven theory*** that a monomeric form CTLA4 exists in the body, even though Bristol's own scientists proved that it did not exist; (2) a ***theory*** that ligand binding to monomeric non-native or artificial forms (recombinant fragments of CTLA4 made in the laboratory) some how relate to the native form, i.e., dimeric form found in the body; and (3) a ***theory*** that ***hypothetical*** monomeric non-native or artificial forms (truncated forms of CTLA4 made in the laboratory) exist, and somehow prove that the dimeric form found in the body does not require dimerization for biological activity.

None of Bristol's theoretical arguments can overcome the undisputed facts in this case -- ***functional*** CTLA4 exists only as a dimer in the body. To support its non-infringement theory, Bristol must show that a monomeric chain of CTLA4 actually exists and that it "can be" biologically active. In other words, the only relevant monomeric form which could support Bristol's ***theory*** that a monomeric form of CTLA4 may be biologically active is that monomeric CTLA4 functions the same way as the dimeric form of CTLA4. Studies on recombinant fragments or hypothetical truncated forms generated in the laboratory are not relevant because those monomeric forms are unable to exhibit the biological activity of native dimeric CTLA4. D.I. 244, ¶ 17 (monomeric forms of CTLA4 unlikely to be biologically active); D.I. 174, Ex. 14 at 432. Thus, Bristol's fanciful scientific theories are completely irrelevant to this motion.

a. Bristol's Theory that Monomeric Native CTLA4 is Biologically Active Is Not Supported Because Such a Form Does Not Exist

To support its noninfringement theories, Bristol must prove that (1) a monomeric form of native CTLA4 was present on the T cell surface and (2) that such a form was able to carry out cell signaling and result in the biological effects the dimeric form accomplished. Bristol cannot prove this theory because such a monomeric form of native CTLA4 does not exist, a scientific fact Bristol scientists proved.

Bristol's scientists conclusively determined that monomeric native CTLA4 does not exist. Bristol points to two papers to support its allegation that a monomeric form of native CTLA4 exists. *See* D.I. 248 at 22 (citing D.I. 211 Exs. 6 (Walnunas) and 7 (Lindsten)). This is a particularly disingenuous argument for Bristol to be making to the Court. The scientific literature cited by Bristol predates Dr. Linsley's 1995 article, which stated "[w]e demonstrate CTLA-4 is a homodimer...." D.I. 171, Ex. 12 at BMS003504385. What makes Bristol's representation to this Court more egregious is that Dr. Linsley, a Bristol scientist[1], made clear that he was refuting these earlier studies, as the paper states that "[s]ome studies have suggested that CTLA-4 is also a disulfide-linked homodimer (10, 13, 15), but another suggested that it exists as a monomer (16)[citing Lindsten]." *Id.* It is truly incredible that Bristol represents to the Court that the Lindsten study demonstrates that a monomeric form of native CTLA4 exists, despite Dr. Linsley's subsequent publication that such science is obsolete.

Dr. Linsley co-authored the other study Bristol cited, the Walunas study. D.I. 211, Ex. 6 at BMS001043066. Not only is it clear from the passage cited from the Walunas study that Dr. Linsley was unsure if the form of CTLA4 observed was a dimer or monomer ("This nondisulfide-linked ***dimeric or monomeric*** form..."), but Dr. Linsley himself resolved this uncertainty in his later paper, demonstrating conclusively that CTLA4 is a disulfide-linked homodimer. D.I. 171, Ex. 12 at BMS003504385. Thus, despite its representations in this

[1] Notably, Bristol refers to Dr. Linsley as the alleged inventor of CTLA4-Ig. D.I. 248 at 8.

litigation, Bristol knows there is no native monomeric form of CTLA4, as such position is contrary to Bristol's own studies.[2]

b. Binding of Ligand to Monomeric Recombinant Fragments of CTLA4 is Not the Biological Activity of CTLA4

Bristol is grasping at straws in attempting to shift the focus from the biological activity of the native form of CTLA4 to mere binding of ligand to monomeric recombinant fragments of CTLA4 in an effort to mislead the Court that such binding proves that native CTLA4 does not require dimerization for biological activity. D.I. 248 at 14-17; D.I. 173 at 29-30. These studies have no bearing on whether CTLA4 requires dimerization for biological activity. No expert in this case stated that the binding of ligand to recombinant fragments constitutes the biological activity of CTLA4. Dr. Gascoigne made clear during his deposition that "biological activity" is defined differently depending upon the context. D.I. 174, Ex. 22 at 48:24-49:17. He also testified ligand binding is the ***first step*** in initiating biological activity, but it cannot be considered biological activity itself. *See* D.I. 243, Ex. 11 at 111:19-112:2, 116:11-117:11; *see also* D.I. 245, ¶ 28; D.I. 244, ¶¶ 14-15. Monomeric recombinant fragments of CTLA4 that only bind ligand ***cannot*** address the functional characteristics of the native form of CTLA4 because biological activity depends on more than just ligand binding. Sun Decl., Ex. 6 (Deposition of Dr. David Ostrov ("Ostrov Depo.") at 94:13 – 95:4; D.I. 244, ¶14.

Bristol is well aware that its theory that ligand binding to monomeric fragments of CTLA4 is not supported by the testimony it relies upon. It cites to testimony regarding the PDGF-R by Dr. Sledziewski in an attempt to confuse the issue. D.I. 248 at 12. It asked questions about the ***fusion proteins*** containing recombinant fragments of PDGF-R, not about the native forms. *Id.* at 13. Dr. Sledziewski was quite clear in indicating that binding would be

[2] Even if such a monomeric form of native CTLA4 actually existed, it would not be able to function in the biological context. D.I. 245, ¶¶ 26-28; D.I. 244, ¶¶ 15-17; *see* D.I. 178, Ex. 13 at ZG054281 (scientific article by Dr. Linsley stating dimerization is generally critical for signal transduction); D.I. 171, Ex. 12 at BMS003504392 (scientific article by Dr. Linlsey stating CTLA4 exists as a preformed dimer and undergoes cell signaling). Such a form of monomeric native CTLA4 would lack the required dimeric state needed to transduce signal from the cell surface. D.I. 245, ¶¶ 24, 28; D.I. 244, ¶¶ 15-16; D.I. 178, *see* Ex. 13 at ZG054281.

considered a biological activity of the fusion protein (the only function such a fusion protein could have), ***not*** native PDGF-R:

> Q. So then how would you characterize the role of the immunoglobulin fusion -- the immunoglobulin and these fusion proteins?
>
> A. Our hypothesis was that we can graft onto IgGs extracellular domain of PDGF-receptor. Our hypothesis was that since IgG existed as dimers that we would create an artificial analog of PDGF-receptor in a dimeric form and hopefully enable high affinity binding. So with those hypothesis in mind, the function of IgG and those fusions would be to provide a dimerization option or dimeric activity, if you will, for the – for the molecule.

Sun Decl., Ex. 10 (Deposition of Dr. Andrzej Sledziewski ("Sled. Depo.") at 94:14 – 95:25 (objections omitted). It is clear from this testimony that the goal was to create an "analog of PDGF-receptor" (PDGFR-Ig) in order to create a high-affinity binding fusion protein. *Id.* Like the CLTA4-Ig in Orencia®, such a fusion could be used as a biologic. But while binding to such a fusion could be therapeutically beneficial, it is the biological activity of the ***native PDGF-receptor***, the "non-immunoglobulin polypeptide," that the claims of the ZymoGenetics Patents refer to. D.I. 169, Exs. 1-2. Like in the case for native CTLA4, it is the ***native PDGF-receptor*** that requires dimerization for biological activity, thus making it a candidate for fusion to the immunoglobulin portion. Dr. Sledziewski did not state that binding of ligand was the biological activity of native PDGF-R.

Nor does Dr. Ostrov's testimony support Bristol's ***theory*** that binding monomeric recombinant fragments of CTLA4 negates the scientific fact that the native CTLA4 requires dimerization for biological activity. *See* D.I. 245, ¶¶ 24, 28; D.I. 244, ¶¶ 14-16; Sun Decl., Ex. 6, Ostrov Depo. at 85:1-3 (stating that proteins referred to in the ZymoGenetics Patents "need to be dimeric, in order to achieve full biological activity"). Dr. Ostov explained why ligand binding to recombinant fragments of CTLA4 does not address the question of biological activity of the native CTLA4:

> Q. If the monomers of CTLA-4 was able to bind B7 in vivo with high affinity and displace CD28 in vivo, would that be a biological activity of the monomer as you understand biological activity in the patents?
>
> A. No, because ***biological activity depends on more than affinity*** between CTLA-4 and CD28 and the B7 molecules. It depends on the avidity as well as the off-rate. And on top of that, there are element -- there are portions of CTLA-4 and other molecules in the CTLA-4/CD28 family that play important roles in regulating T cell responsiveness that are not even in the extracelluar [sic] domains. So I would say no. I would be hesitant to answer that question so simplistically.

Id., Ex. 6, Ostrov Depo. at 94:13 – 95:4 (objection omitted) (emphasis added). Dr. Ostrov could not have been more clear – binding of ligand to the monomeric recombinant fragments is not sufficient. *See also* D.I. 244, ¶14. Thus, Bristol's ***theory*** that binding of ligand to monomeric recombinant fragments of CTLA4 means that native CTLA4 does not require dimerization for biological activity is not consistent with all that is known about the biological activity of native CTLA4.

Bristol is asking the Court to make a leap of faith that artificial, recombinant fragmented forms of CTLA4 are the same thing as native CTLA4. These recombinant fragments ***are not the same***. Bristol's statement that "[i]f CTLA4 performs a given biological activity as a single chain (*i.e.* a monomer), it cannot 'require dimerization for biological activity…'" is referring to fragments, not native CTLA4 . D.I. 248 at 9. Bristol is trying a slight-of-hand in an attempt to misdirect the Court.

c. Bristol's Hypothetical Monomeric Truncated Forms of CTLA4 Do Not Exist in Humans, and Are Dimeric

Just as monomeric recombinant fragments of CTLA4 generated in the laboratory do not bear upon the relevant issue of whether the native form of CTLA4 requires dimerization for biological activity, the hypothetical truncated forms of CTLA4 Bristol relies upon are similarly not capable of biological activity. *Id.* at 16, 21. Bristol relies upon three papers for this issue, for which it first disclosed its reliance upon when it improperly supplemented two expert reports

months after the deadline for such reports.[3] Dr. Gascoigne, who deposition occurred four days after the new opinions were served on ZymoGenetics, commented, "[n]one of these papers, as far as I can make out, show that the soluble CTLA4 [the hypothetical truncated form]…is active in vivo." Sun Decl., Ex. 9, Gascoigne Depo. at 166:16-18; D.I. 248 at 17. Thus, there was no evidence presented in the studies that such laboratory generated truncated forms had biologically active counterparts in the body. Dr. Gascoigne never agreed with the findings, but simply acknowledged what the reports stated. Sun Decl., Ex. 9, Gascoigne Depo. at 164:5-8; D.I. 248 at 18; *see also* Sun Decl., Ex. 9, Gascoigne Depo. at 165:9-15; D.I. 248 at 18. Like the monomeric recombinant fragmented forms, these hypothetical monomeric truncated forms would, at most, bind ligand, but would be incapable of exhibiting the biological activity of native CTLA4. D.I. 244, ¶17; D.I. 245, ¶28. Beyond the relevancy issue of how such hypothetical truncated forms could bear on the question of whether CTLA4 requires dimerization for biological activity, the scientific studies Bristol relies upon suffer from fatal flaws that devastate Bristol's ***theory***.

Each of the studies reports the ability to artificially generate truncated forms of CTLA4. D.I. 244, ¶¶ 22-24. However, the studies fail to demonstrate that such truncated forms exist in the human body. D.I. 244; ¶ 21. The truncated forms are ***never*** isolated from the human body – they are artificially generated in the laboratory. Id. Nor do the studies examine whether T cells in the body, the presumed source of such mutant forms, actually produces such mutants. Id.; Sun Decl., Ex. 9, Gascoigne Depo. at 155:9-15 (when asked if the forms described in the studies were present in humans, Dr. Gascoigne stated: "They may be presuming it. I think that's going a little far, frankly."). Dr. Ostrov confirmed that the reports failed to demonstrate the existence of these hypothetical forms in humans. D.I. 244, ¶ 21. Thus, Bristol cannot show that such hypothetical truncated forms exist in the body.

[3] The untimely and unexplained supplementation of Drs. Ravetch and Kuriyan's expert reports on issues relating to infringement was unduly prejudicial. It was just 4 days before the deposition of ZymoGenetics' expert, Dr. Gascoigne, who had not had an opportunity to opine on these surprise reports and studies and he had never read the papers which served as a basis for Drs. Ravetch and Kuriyan's new opinions.

Even more damaging to Bristol's theory that monomeric truncated forms somehow dispute the wealth of scientific evidence that CTLA4 requires dimerization for biological activity is that the hypothetical truncated forms is reported as a dimer in at least one of the studies. D.I. 244 , ¶ 24 (citing the Saverino study). This questionable evidence vitiates Bristol's theory because it appears that the mutant form generated in the laboratory is actually a dimer. *Id.* Also, none of the studies appear to examine whether the hypothetical truncated form of CTLA4 made in the laboratory exists as a monomer. Such information is critical to Bristol's theory that a monomeric form of truncated CTLA4 exists in humans. D.I. 248 at 16. Thus, it cannot rely on such studies to support its ***theory*** that native CTLA4 does not require dimerization for biological activity.

B. THE IG PORTION OF ORENCIA® IS A DIMERIZING PROTEIN

1. There Is An Abundance of Evidence Relating to the Mutated Ig in Orencia® that Proves that the Ig Portion of Orencia® is a "Dimerizing Protein"

The Ig portion of Orencia® is the dimerizing protein. Bristol's theory that the Ig portion of Orencia® is unable to form a dimer is disproven by all the scientific evidence to the contrary. For its hypothesis, Bristol states that Dr. Linsley, the Bristol scientist who modified the Ig portion of Orencia®, made two forms of the Ig – an unmodified Ig and an "Ig mono." D.I. 248 at 7. The "Ig mono" form of the Ig contains mutations that Bristol believes might prevent the Ig from forming a dimer. *Id.* But Dr. Linsley himself disavowed that this was the case, as the "Ig mono" ***failed to prevent 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). Bristol cannot now for the first time advocate its debunked theory that the modified Ig portion of Orencia® now magically prevents dimerization. Bristol also represented to the FDA that the Ig in Orencia® formed a dimer, a position diametrically opposed to what it is representing to the Court today. *See* Fig. 1.

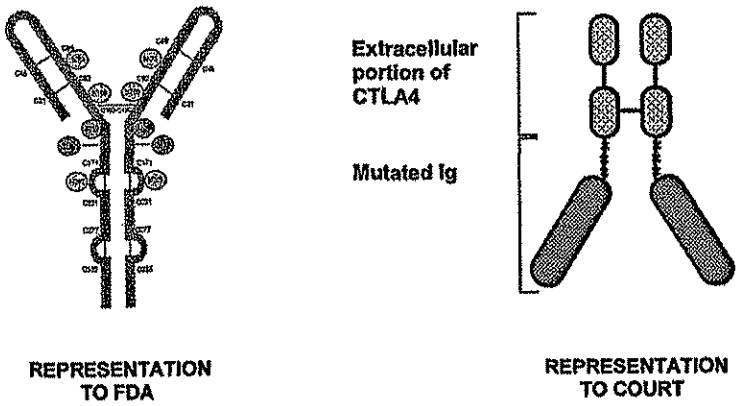


Figure 1. Bristol's Changing Theories: What It Told the FDA, and What It is Telling the Court

Such a change in position calls Bristol's credibility into question, as its deliberately manufactured arguments are not grounded in science.

a. The Ig of Orencia® Contains an Unmutated Domain Identical to the Native Form, Which Has Been Shown to Dimerize Based on Noncovalent Interactions

Bristol's statement that the "cysteines in the hinge are the only possible way [to] . . . form a covalent bond" and dimerize the Ig misleadingly suggests that its mutation of the cysteines completely eliminated the ability of the Ig to dimerize. D.I. 248 at 5. Bristol's statement, however, carefully avoids the issue of dimerization through noncovalent forces. It is well aware that ZymoGenetics' Patents explicitly provide that dimerization can occur in either a "covalent or noncovalent manner." D.I. 169, Ex. 1 at col. 13, l. 27; D.I. Ex. 169, Ex. 2 at col. 13, l. 47. *See also* D.I. 169, Ex. 1 at col. 10, ll. 3-6; Ex. 2 at col. 10, ll. 24-27 ("[T]he present invention provides methods of producing polypeptide dimers that are biologically active only as noncovalently associated dimers."); D.I. 245, ¶ 17 ("dimerizing protein does NOT require covalent linkage to form a dimer. . . [as] invertase, a dimerizing protein . . . is not a disulfide bonded dimer.").

Bristol is also well aware that such noncovalent forces are present in the Ig of its Orencia® molecule. The Ig portion of Orencia® comprises what is known as the Fc portion of an immunoglobulin molecule. The Fc portion is made up of a hinge, C_H2, and C_H3 domain.

While Orencia® contains a mutated form of Ig, all of the mutations relating to covalent binding are localized to the hinge domain. *See* D.I. 211, Ex. 2 at BMS001290350. The C_H3 domain remains identical to the native form, which both the scientific community and Bristol's own scientists recognize as associating into a dimer through noncovalent interactions. *See* id. Bristol Director, Dr. Steven Nadler, testified in deposition that [redacted] Sun Decl., Ex. 8 (Deposition of Steven Nadler at 72:25-73:7). Scientific publications also refer to the "homodimer of the C_H3 domain" as a "compulsory complex," *i.e.*, one "in which free monomers are not readily detected." *Id.*, Ex. 1 at ZG054363; *see also* D.I. 243, Ex. 15 (scientific publication describing the "naturally occurring . . . non-covalent homodimer formed by the C-terminal domains (C_H3) of the heavy chains of IgG"). Finally, Dr. Gascoigne explained the results of numerous scientific experiments demonstrating that the C_H3 domain "alone is sufficient to form a non-covalently bound homodimer, and the dimerization is of remarkably high affinity." D.I. 245, ¶ 19. Thus, even in the absence of disulfide bonds, the Ig portion of Orencia® forms a dimer through the noncovalent forces acting in the C_H3 domain, which is unmutated and identical to the native form.

b. Bristol's Own Scientists' Experiments Confirmed that the Ig Portion of Orencia® Dimerizes

Studies by Bristol scientists on the Ig portion of Orencia® demonstrated that it forms a dimer -- *i.e.*, associates under physiological conditions. In one study involving the same Ig portion that is found in Orencia®, Bristol discovered that the Ig portion of Orencia® forms a dimer, notwithstanding the mutations Bristol introduced. *See* D.I. 205, Ex. 4 at BMS003504382-83. In another Bristol study, Bristol cleaved off the Ig portion of a fusion protein into its individual constituents. D.I. 205, Ex. 7. The Ig used in this study was again identical to the mutated Ig of Orencia®. *Id.* at BMS003700194; Sun Decl., Ex. 2 at 4319. Bristol reported that the experiment produced a "dimeric hinge-CH2-CH3" of the Ig portion found in Orencia®. D.I. 205, Ex. 7 at BMS003700196. Finally, Bristol demonstrated that, in the absence of Ig, CTLA4 exists predominantly as a monomer, but that joining Ig to CTLA4 yields 100% dimeric CTLA4-

Ig. It demonstrated that the Ig dimerized the CTLA4-Ig. *See* D.I. 171, Ex. 12 at BMS003504388. Thus, its studies establish that the Ig portion of its Orencia® molecule associates into a dimer.

c. Dr. Ostrov's Sworn Testimony Regarding His Experiments on the Ig Portion of Orencia® Is Competent Evidence that It Forms a Dimer

Contrary to Bristol's claims, the Ostrov experiment was not untimely disclosed. Because Dr. Ostrov chose to emphasize published scientific data as a basis for his opinion, rather than his experiment, he was not required to disclose the latter when he submitted his expert report. It was Bristol that opened the door to Dr. Ostrov's experiment when it relentlessly examined him regarding his opinions and expert report and nuances thereof during deposition. *See* D.I. 171, Ex. 14 at 262:24-264:1. Bristol cannot selectively attempt to preclude the very evidence it uncovered on the grounds that it is unfavorable Bristol.[4]

Bristol grossly misrepresents Dr. Ostrov's deposition testimony regarding his CTLA4-Ig experiment. Dr. Ostrov did not "disavow[]" and "disparag[e]" his own experiment when he chose to rely on "high-caliber peer-reviewed journal articles" as a basis for his opinions. D.I. 248 at 30-31. His experiment "solved the structure of the C_H2 and C_H3 domains" of the mutated Ig portion of CTLA4-Ig, demonstrating these domains interact and associate into a dimer. D.I. 171, Ex. 14 at 262:24-264:1. However, he did not consider such findings to be relevant because (1) the goal of his own experiment was "to crystallize and solve the structure of CTLA4," not Ig, and (2) the structure of Ig was so well known in the scientific literature that such a finding was not worthy of scientific publication. Sun Decl., Ex. 6, Ostrov Depo. at 266:3-5. Moreover, even though evidence of dimerization in both native Ig (*i.e.*, the scientific publications) and mutated Ig

[4] What *is* both untimely and inappropriate is Bristol's motion *in limine* embedded in its answering brief to ZymoGenetics' motion. *See* D.I. 248 at 32-35. The Court has made clear that it "does not entertain motions *in limine*." D.I. 148, ¶ 5. To the extent that Bristol is attempting to exclude Dr. Ostrov under the *Daubert* standard, the time for filing a *Daubert* motion has long passed. *See* D.I. 148, ¶ 3(d).

(*i.e.*, Dr. Ostrov's experiment) are relevant to whether the Ig portion of Orencia® forms a dimer,[5] Dr. Ostrov's ultimate reliance on the former merely reflected his judgment that such evidence would be "better respected by individuals in the field." D.I. 171, Ex. 14 at 264:10-14. Dr. Ostrov in no way disavowed the results of his own experiment and it remains competent evidence that the Ig portion of Orencia® associates into a dimer.

d. Bristol's Alleged Evidence that the Ig Portion of Orencia® Does Not Dimerize Actually Shows That It Does in Fact Form a Dimer

Bristol cites to its study assessing the ability of the modified Ig in Orencia® and native Ig[6] to bind the Fc receptors CD16, CD32, and CD64. D.I. 248 at 36-37. This study showed that Orencia® was able to bind CD64, but not CD16 or CD32. D.I. 211, Ex. 13. Bristol's claim these functional differences between mutated and native Ig reflect structural differences between them, namely that the Ig portion of Orencia® does not form a dimer. However, such a conclusion is not supported by this study. It does not establish that binding Fc receptors depends on or has anything to do with Ig associating into a dimer. In fact, the study posits many "other possibilities" that may explain the loss of the mutated Ig to bind CD16 and CD32, such as "steric hindrance," "altered glycolyslation," and "conformational changes." *Id.* at 2210. Bristol's expert, Dr. Kuriyan, admitted tha[redacted] Sun Decl., Ex. 3 (Deposition of John Kuriyan at 118:9-119:6). Since the functional differences between mutated and native Ig cannot be attributed to any specific cause, including the failure of the mutated Ig to form a dimer, they cannot establish that the mutated Ig does not form a dimer.

Moreover, the results of the study are at best ambiguous and inconclusive. Even if the ability to bind Fc receptors depends solely on whether Ig forms a dimer, Bristol's study showed that the mutated Ig still retained the ability to bind CD64. These mixed results could just as

[5] Based on Bristol's representations to the FDA, evidence that the native form of Ig associates into a dimer is directly relevant to whether the mutated Ig of Orencia® forms a dimer and thus satisfies the "dimerizing protein" claim element. *See infra* Part II.B.2.

[6] Native Ig is the same thing as the "wild type" or unmodified form of Ig found in nature.

easily be interpreted to mean that the mutated Ig possesses similar structure to the native form, *i.e.*, that the mutated form, like the native, forms a dimer. In this way, this Bristol study is evidence that the Ig portion of Orencia® forms a dimer.

e. Bristol's Argument Regarding Experimentation Under "Physiological Conditions" Is Irrelevant

Further undermining its credibility, Bristol goes so far as to repudiate its own published study ("the JBC paper") to try and distance itself from the reality that the Ig portion of its Orencia® molecule forms a dimer. D.I. 171, Ex. 12. Bristol's witnesses, Dr. Linsley and Dr. Ravetch, attempt to undermine the findings of the JBC paper, reasoning that the findings were attributable to the "purification" process performed under "non-physiological" conditions. *See* D.I. 248 at 37-38. If the results of the study were due to the purification process instead of the actual cleavage of the CTLA4-Ig, then the study would be useless because it would teach nothing about the molecule of interest; the study would merely teach already known laboratory techniques and protocols about how to purify proteins. The after-the-fact, litigation-driven explanations of Bristol's witnesses and experts should not be credited over the objective and unequivocal findings reported in peer-reviewed articles regarding Ig published prior to the time of litigation.

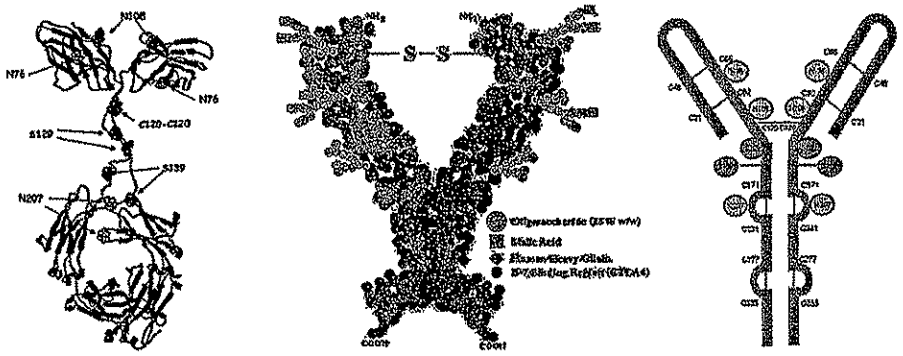
Recognizing the inadequacy of its witnesses' hindsight explanations, Bristol also attempts to counter the JBC paper with another published study (the "Zhang paper"). Bristol argues that this study was performed under "physiological" conditions and that, as such, its findings should be credited over the JBC paper. *See* D.I. 248 at 38-39. First, the Zhang paper has never previously been disclosed to ZymoGenetics. Production of a document for the first time in the middle of summary judgment briefing is wholly improper. FED. R. CIV. P. 37. Furthermore, this paper is not relevant because it does not address whether the Ig portion of Orencia® forms a dimer.[7] It discusses CTLA4, which cannot be a "dimerizing protein" under the explicit

[7] Contrary to Bristol's claim, this study did not directly synthesize a dimeric CTLA4 in the first instance. Rather, it synthesized what are known as inclusion bodies that had to be "***refolded*** [into a] covalent CTLA4-homodimer." D.I. 249, Ex. 7 at 110 (emphasis added).

limitations of the asserted claims. *See* D.I. 169, Exs. 1- 2 (limiting the "dimerizing protein" to either invertase or Ig). Whether CTLA4 dimerizes is immaterial to whether the Ig portion of Orencia® can or does dimerize, and thus whether it constitutes a "dimerizing protein." In contrast, the JBC paper directly determined the ability of the Ig portion of Orencia® to form a dimer. *See* D.I. 171, Ex. 12 at BMS003504388. Thus, the Zhang paper is not on point and does not refute the evidence of dimerization in the Ig portion of Orencia®.

2. Bristol Cannot Dispute ZymoGenetics' Evidence Relating to the Native Form of Ig Because It Itself Had Presented Such Data to the FDA to Obtain Approval for Orencia®

Bristol claims that ZymoGenetics' evidence regarding dimerization of the Ig portion of Orencia® is insufficient because it involves the native form of Ig, whereas Orencia® contains a mutated Ig. D.I. 248 at 34-36. It argues that data relating to the native form does not apply to mutated forms because even small mutations can affect the structure and function of a protein.[8] Id. Yet when Bristol sought to obtain FDA approval to market Orencia®, it submitted molecular models of the drug, which too were based on the native form of Ig. Bristol represented to the FDA that models such as the ones shown below in Figure 2 were accurate because the Ig in Orencia® was "***98% identical***" to the native form. D.I. 169, Ex. 5 at BMS001290162 (emphasis added).



[8] Bristol's argument that ZymoGenetics failed to perform tests on the Ig portion of Orencia® to determine whether it formed a dimer are incredible as such testing was unnecessary since Bristol's scientists had already performed such studies and ZymoGenetics relied upon Bristol's studies. *See supra* Part II.B.1.b.

Fig. 2 Bristol's Understanding of the Structure of CTLA4-Ig

Today, Bristol takes an entirely contradictory position, claiming that the two forms are "***completely different***" and "do not behave the same way." D.I. 248 at 34 (emphasis added). Bristol represents for the first time that the Ig portion does not form a dimer. The model Bristol submitted to the Court in its briefing (reproduced in Figure 1) does not appear to be from Bristol's document production of over 4 million documents. This cartoon, presumably generated for litigation, is the exact inverse of the models depicted in Figure 2, which were created before the litigation. *See* D.I. 173 at 10. Indeed, this figure was not included in the thousands of pages of documents submitted to the FDA in Bristol's Biologic License Application for Orencia® and the voluminous file histories of the eight United States Patents covering Orencia®. Sun Decl., Ex. 7 (response to Interrogatory No. 11).

ZymoGenetics can rely on the scientific facts regarding Orencia® that Bristol presented to the FDA. Specifically, ZymoGenetics should be able to use the data that Bristol used before the FDA regarding native Ig. Bristol has no credibility when it argues that data and evidence it affirmatively used to obtain FDA approval cannot be used to prove infringement. Unless Bristol chooses to inform the FDA that the structure and function of the Ig in Orencia® are "completely different" from that of the native form on which it relied to obtain FDA approval, Bristol is bound by its original statements to the FDA. *See, e.g., Syntex (U.S.A.), Inc. v. Paragon Optical Inc.*, 7 U.S.P.Q.2d 1001, 1006 (D. Ariz. 1987) (statements made in a submission to the FDA grounded a finding of infringement). Because of its reliance on data relating to native Ig before the FDA, it cannot now dispute that such evidence is directly relevant.

III. CONCLUSION

In light of the foregoing, ZymoGenetics respectfully requests the Court to grant its motion for summary judgment of infringement against Bristol.

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Dated: August 25, 2008
879910
Public Version: September 2, 2008

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, Philip A. Rovner, hereby certify that on September 2, 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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