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
REBUTTAL CLAIM CONSTRUCTION BRIEF

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Pursuant to the Stipulated Amended Scheduling Order entered December 13, 2007, Defendant Bristol-Myers Squibb Company ("Bristol") submits this Rebuttal to ZymoGenetics, Inc.'s ("ZymoGenetics'") Opening Claim Construction Brief

INTRODUCTION

The alleged invention of the patents-in-suit is methodology by which a first protein that requires dimerization in order to be biologically active is coupled to a second protein that causes it to dimerize.[1] ZymoGenetics accuses Bristol of urging claim constructions that avoid infringement, but it is, in fact, ZymoGenetics that seeks to construe the claims by reference to the accused product -- a tactic that is clearly impermissible *See, e.g., SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1118 (Fed. Cir. 1985) (en banc).[2]

ZymoGenetics seeks to interpret the claims much like the proverbial nose of wax -- one way to avoid prior art and another way in an attempt to capture Bristol's CTLA4-Ig. In doing so, ZymoGenetics repeatedly asks the Court to "look no further" than the specifications, to ignore established principles of claim construction that require consideration of the prosecution, and to ignore ZymoGenetics' admissions. ZymoGenetics' inconsistent arguments concerning the scope of the claim terms are summarized below.

Dimerizing Protein:

Faced with the fact that it has no evidence that the modified immunoglobulin portion of Bristol's CTLA4-Ig causes (*i.e.*, "drives") the dimerization of Bristol's fusion protein,

---

[1] The "patents-in-suit", whose specifications are substantively the same, are U.S. Patent Nos. 6,018,026 ("the '026 Patent") and 5,843,725 ("the '725 Patent"). Bristol notes that ZymoGenetics' Opening Claim Construction Brief states that it is asserting Claim 4 of the '725 Patent against Bristol. (D.I. 156 at 3). If true, this is contrary to ZymoGenetics' responses to interrogatories and expert reports.

[2] As Bristol's motion for summary judgment of non-infringement demonstrates, however, the accused CTLA4-Ig product does not correspond to any of three properly construed claim limitations.

ZymoGenetics argues that the "dimerizing protein" need not be "dimerizing" at all, and need not be involved in dimerization of the non-immunoglobulin polypeptide. This is despite the fact that:

- the specification states that portions of yeast invertase and portions of immunoglobulins (*i.e.*, the dimerizing proteins) ***drive*** the association of non-immunoglobulin polypeptides;
- to avoid prior art, during prosecution ZymoGenetics distinguished its alleged invention on the grounds that dimerization of the non-immunoglobulin is ***driven*** by the immunoglobulin portion of the molecule (*i.e.*, the dimerizing protein); and

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Biological Activity:

Because CTLA4 clearly does not "require[] dimerization" in order to bind to its natural ligand, ZymoGenetics argues that binding is not "biological activity", but instead such activities must be "multi-step" and do not include "indiscriminate chemical or physical interactions." This is despite the fact that:

- the only biological activity investigated in any of the dimerized fusion protein examples of the patents-in-suit is ***binding*** ligand; and

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Requiring Dimerization for Biological Activity:

ZymoGenetics now argues that a polypeptide that can dimerize on its own (and therefore, paradoxically does not need the "dimerizing protein" that is an essential claim element) can be a polypeptide "requiring dimerization for biological activity". This is despite the fact that:

- during prosecution of a related patent, ZymoGenetics distinguished its alleged invention to avoid prior art (wherein the non-immunoglobulin polypeptide could dictate dimerization) by stating that the prior art did not suggest ***the use of an immunoglobulin*** (*i.e.*, dimerizing protein) ***in the dimerization*** of non-immunoglobulin polypeptides;

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Non-Immunoglobulin Polypeptide:

ZymoGenetics now argues that a "non-immunoglobulin polypeptide" includes polypeptides encoded by immunoglobulin-like genes and includes polypeptides that have significant sequence homology to immunoglobulin. This is despite the fact that during prosecution of the priority application in an attempt to avoid prior art, ZymoGenetics represented and relied on the position that T-cell receptor was not a "non-immunoglobulin peptide" because it has immunoglobulin-like genes and has significant sequence homology to immunoglobulin.

ARGUMENT

I. Dimerizing Protein

ZymoGenetics' proposed construction of "dimerizing protein" (and indeed, its entire opening claim construction brief) is contrary to common sense, plain language, and ignores arguments made during prosecution. The parties' constructions, with the differences underlined, are as follows:

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

The salient difference between the parties' proposed constructions is whether the arguments made during prosecution to avoid prior art and the entire specification should be considered (as Bristol submits) or ignored (as ZymoGenetics desires).[3]

ZymoGenetics avoids addressing its own prosecution representations in its opening brief, stating instead that "[b]ecause ZymoGenetics acted as its own lexicographer" its construction "must be adopted."[4, 5] (D.I. 156 at 11). **Even if** the specification would otherwise permit the alleged invention to include circumstances wherein the "dimerizing protein" does not cause or drive the dimerization of the non-immunoglobulin (and it does not), the arguments made by ZymoGenetics during prosecution of related U.S. Patent No. 5,155,027 ("the '027 Patent") refute that interpretation and make clear that the first, "non-immunoglobulin polypeptide" portion of the fusion protein cannot be responsible for dimerization, and cannot be capable of forming a dimer on its own without the "dimerizing protein". A disclaimer of subject matter during prosecution trumps a broader disclosure in the specification:

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[3] ZymoGenetics also wishes the statement "[t]he second polypeptide chain may be the same or a different chain" to be included in the construction. Such information is unnecessary to a proper construction of "dimerizing protein".

[4] ZymoGenetics cites to page 1321 of *Phillips v. AWH*, stating that "where the patentee has provided such a dictionary, 'the patentee's definition[s] govern[].'" (D.I. 156 at 11). The words "the patentee's definition[s] govern[]" do not appear anywhere in *Phillips*. ZymoGenetics may have intended to refer to the following:

> . . . our cases recognize that the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs. *See CCS Fitness, Inc. v. Brunswick Corp.*, 288 F.3d 1359, 1366 (Fed. Cir. 2002).

Phillips v. AWH Corp., 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc). However, this statement in *Phillips* is related to altering the ordinary meaning of a claim term to a definition that appears in the specification -- not to whether a definition in the specification can be altered during prosecution. *Id.*; *see also CCS Fitness*, 288 F.3d at 1366 ("a court may constrict the ordinary meaning of a claim term . . . if the patentee acted as his own lexicographer").

[5] If ZymoGenetics' suggested approach were followed (*i.e.*, ignoring prosecution arguments whenever a patentee provides a definition in the specification), patentees could define terms broadly in the specification, rely on limiting constructions to avoid prior art during prosecution, and resuscitate the broader meaning in an infringement suit.

> The mere fact that a specific definition of a claim term is set forth in the specification does not mean that the prosecution history should be ignored . . . . The exchange between the patentee and the patent examiner often reveals representations made in obtaining the patent from the Patent and Trademark Office [] regarding the scope and meaning of claim terms, even those with definitions provided for in the specification. In other words, whether or not a specific definition of a term is present in the specification, "the prosecution history (or file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance."

Dunhall Pharms., Inc. v. Discus Dental, Inc., 2000 WL 1608803, at *4 (Fed. Cir. Oct. 26, 2000) (unpublished opinion) (internal citations omitted); *see also Jonsson v. Stanley Works*, 903 F.2d 812, 817-18 (Fed. Cir. 1990) (taking prosecution arguments into account in construing the term "diffuse" despite the fact that a definition was provided in an amended specification).

ZymoGenetics unequivocally represented during prosecution of the '027 Patent that the immunoglobulin portion (*i.e.*, the dimerizing protein) must drive the dimerization. As discussed in further detail in Bristol's Opening Claim Construction Brief, to avoid a rejection over prior art, ZymoGenetics distinguished their alleged invention, saying:

> The claimed dimerized polypeptide fusions are non-immunoglobulin polypeptides fused to at least an immunoglobulin constant region ***wherein the dimerization is driven by the immunoglobulin portion of the molecule. Boss et al. do not teach or suggest the use of the immunoglobulin constant region in the dimerization of non-immunoglobulin polypeptides.*** Applicants respectfully submit that on the basis of the above remarks, the Examiner's rejection under 35 U.S.C. § 102(e) has been overcome.

(D.I. 179, Exh. 20 at BMS004259290) (emphasis added).[6] It is clear and unambiguous that during prosecution, ZymoGenetics limited its alleged invention to circumstances where the "immunoglobulin portion" (*i.e.*, the "dimerizing protein") of the fusion dimerizes the non-

[6] In the claim at issue, an immunoglobulin constant region was being used as the "dimerizing protein".

immunoglobulin portion of the fusion protein.[7] *See, e.g.*, *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000) ("prosecution history limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance.") (internal quotations and citation omitted); *Jonsson*, 903 F.2d at 818 (it is proper to use the prosecution of one patent in construing the claims of another patent, where the two patents shared a common patent application).

This construction is also consonant with what the specification requires when it explains the function of the yeast invertase and/or immunoglobulin (*i.e.*, the dimerizing proteins):

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

(D.I. 179, Exh. 1 at col. 13, ll. 42-44, 53-55; D.I. 179, Exh. 2 at col. 13, ll. 22-24, 32-34) (emphasis added). Indeed, any other construction would be illogical because the first peptide does not "require dimerization" if it inherently forms a dimer without help, and the second peptide is not a "dimerizing protein" if the dimer forms independently of it.

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(D.I. 179, Exh. 15 at 17-18).[8]

ZymoGenetics' arguments that Bristol's construction "would add an additional limitation found nowhere in the patents" and "is driven by its non-infringement arguments" (D.I. 156 at 12) are unfounded. Bristol's interpretation is soundly based on the specification's explanation that it is the dimerizing protein that drives the association of the non-immunoglobulin polypeptides -- therefore it is not a limitation "found nowhere in the patents". And, despite ZymoGenetics' protestation otherwise, Bristol's proposed construction is the one ZymoGenetics itself argued during prosecution.

II. Ligand-Binding Domain Of A Receptor and Ligand

ZymoGenetics' construction of the term "ligand-binding domain of a receptor" improperly ignores the context of the claims and the definition of non-immunoglobulin it provided during prosecution of the priority application. *See, e.g.*, *Phillips*, 415 F.3d at 1314 ("[T]he context in which a term is used in the asserted claim can be highly instructive."); *Hockerson-Halberstadt, Inc. v. Converse, Inc.*, 183 F.3d 1369, 1374 (Fed. Cir. 1999) ("proper claim construction . . . demands interpretation of the entire claim in context, not a single element in isolation").

In the context of Claim 21, the "ligand-binding domain of a receptor" must be part of a "receptor analog". And, as a "receptor analog" is a "non-immunoglobulin polypeptide", the

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"ligand-binding domain of a receptor" must also be a "non-immunoglobulin polypeptide".[9] Therefore, taking the fact that it must be a non-immunoglobulin polypeptide into account (*see infra* 12), "ligand-binding domain of a receptor" should be construed to mean:

> that portion of a receptor that is involved with binding the natural ligand, wherein said portion of receptor (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.

The term "ligand" is defined in the patents-in-suit as "[a] molecule capable of being bound by the ligand-binding domain of a receptor or by a receptor analog" (D.I. 179, Exh. 2 at col. 9, ll. 47-48). While Bristol disagrees that the term "ligand" needs construction, because it is not a limitation of the asserted claims (D.I. 179 at 38), ZymoGenetics' proposed construction contains superfluous definitions of agonists, antagonists and whether or not ligands can be chemically synthesized or occur in nature. As pointed out in Bristol's Opening Claim Construction Brief, such information is unnecessary to a proper construction of the term "ligand."

III. Biological Activity

ZymoGenetics' proposed construction for "biological activity" is an attempt to import limitations into the claim that are inconsistent with both the patents and ZymoGenetics' positions taken during a previous litigation.

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The patents-in-suit discuss three distinct concepts:

(1) the definition of "biological activity":

> "A function or set of activities performed by a molecule in a biological context (i.e., in an organism or an in vitro facsimile thereof)" (D.I. 179, Exh. 1 at col. 9, ll. 54-56; D.I. 179, Exh. 2 at col. 9, ll. 35-37);

(2) non-limiting examples of biological activities:

> "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" (D.I. 179, Exh. 1 at col. 9, ll. 56-61; D.I. 179, Exh. 2 at col. 9, ll. 37-42) (emphasis added); and

(3) when recombinant proteins (*e.g.*, fusion proteins) should be considered biologically active:

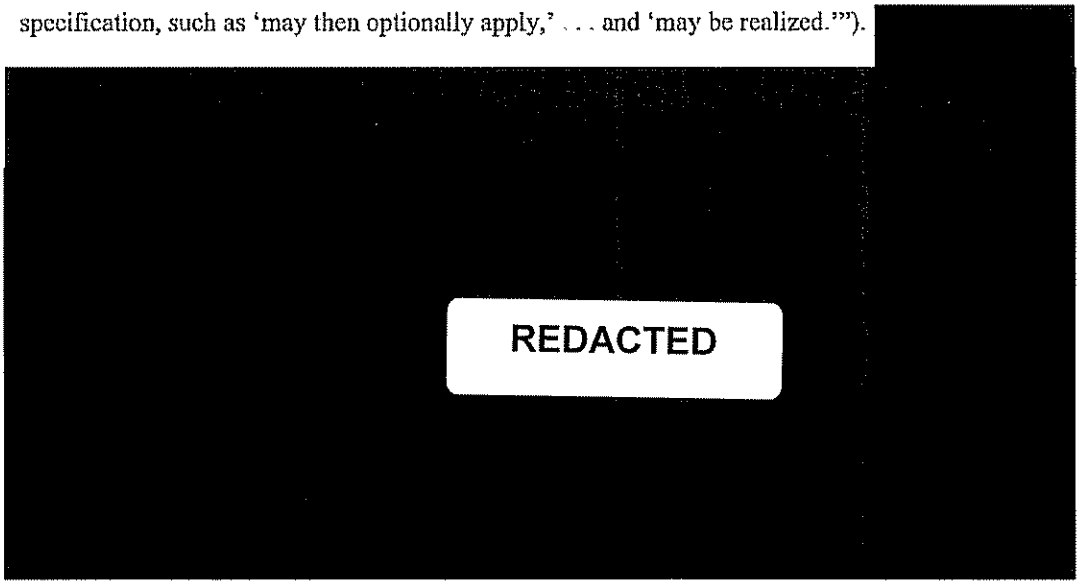
> "A recombinant protein or peptide is considered to be biologically active if it exhibits one or more biological activities of its native counterpart." (D.I. 179, Exh. 1 at col. 9, ll. 61-63; D.I. 179, Exh. 2 at col. 9, ll. 42-45).

Bristol's proposed construction consists of the definition (*i.e.*, part (1)). ZymoGenetics' proposed construction improperly includes parts (2) and (3) in addition to part (1).

The list of "may include" examples of biological activities provided in part (2) is exemplary, not exclusive, and does not limit the definition to those enumerated. ZymoGenetics argues that "all of these examples describe multi-step processes that have meaningful consequences for cells, and that Bristol's proposed definition leaves open the possibility that the term 'could encompass indiscriminate chemical or physical encounters between molecules that could happen in nature as a matter of chance, without regard to whether any biologically significant processes result.'" (D.I. 156 at 15).

It is unclear where ZymoGenetics finds basis for its argument that these are "multi-step processes" (it cites nothing for this proposition) and/or how many steps are required. The disparaging characterization "indiscriminate chemical or physical encounters" is inapposite and

misdirected. In making these arguments, what ZymoGenetics really seeks is to exclude binding and competitive binding from being "biological activities", despite the fact the specification clearly includes them.[10] There is no express disclaimer of binding or competitive binding from the meaning of biological activity. *See, e.g., In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004); *Michaels of Oregon, Co., v. Clean Gun, LLC*, 2002 WL 31496414, at *12 (D. Or. July 9, 2002) ("The need for an express disclaimer necessarily eliminates nonlimiting language in the specification, such as 'may then optionally apply,' . . . and 'may be realized.'").



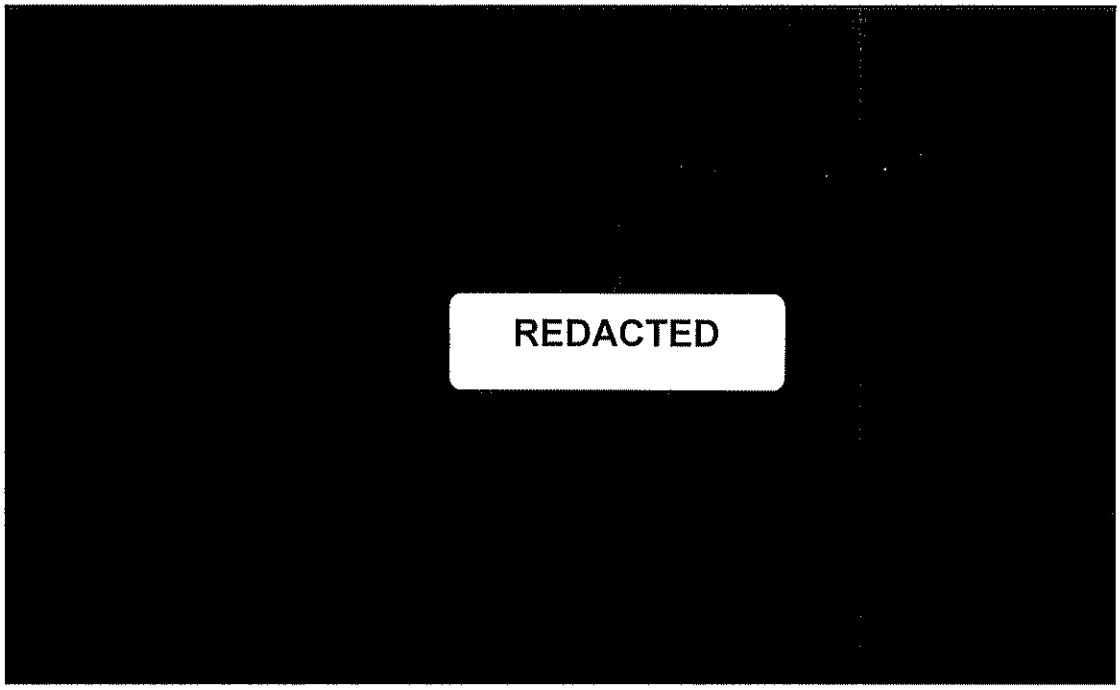
(D.I. 179, Exh. 15 at 7, 8). And, the examples provided in the patents-in-suit use binding studies and competitive binding studies as the measure of whether or not the resulting fusion proteins were biologically active. The patents state:

- "The results of the competition binding assay showed that the PDGFß-R-SUC2 fusion protein ***was able to competitively bind*** all three isoforms of PDGF." (D.I. 179, Exh. 2 at col. 35, ll. 47-50) (emphasis added).
- "Results of the assay showed that the PDGFß-R analog ***was able to bind*** PDGF-BB with high affinity." (D.I. 179, Exh. 2 at col. 41, ll. 41-42) (emphasis added).

[10] The purpose of course is to provide a bootstrapping argument that CTLA4, which in monomeric form indisputably binds its ligand and does so competitively, does not have "biological activity".

- "Unbound labeled PDGF-AA was removed, the wells were subsequently washed with binding media, and the bound, labeled PDGF-AA was harvested by the addition of 0.1M citrate, pH 2.5, as described for the saturation binding studies. PDGF-AB, PDGF-AA and PDGF-BB ***were found to compete for receptor binding*** with ^{125}I-PDGF-AA." (D.I. 179, Exh. 2 at col. 52, ll. 39-45) (emphasis added).

In fact, with respect to the dimerized fusion proteins, the only biological activity investigated in the examples of the patents-in-suit was binding.



To argue now that binding and competitive binding are not biological activities is inconsistent with the specification, and disingenuous based on ZymoGenetics' own earlier arguments.

Part (3), the discussion of when fusion proteins should be considered "biologically active", is not necessary for a construction of "biological activity". Rather, Part (3) is relevant to the construction of "biologically active" and "active". (*See infra* 19-20).

IV. Receptor Analog

The salient disputes concerning the construction of "receptor analog" are: (1) whether "non-immunoglobulin polypeptide" in the definition of "receptor analog" should have the same

meaning as that which ZymoGenetics set forth during prosecution of the priority application; and (2) whether in the context of the claims the focus of the "receptor analog" is on binding ligand rather than being recognized by anti-receptor antibodies.[11]

With respect to (1), the same interpretation that ZymoGenetics gave to "non-immunoglobulin polypeptide" during prosecution of the priority application should equally be applied to "receptor analog" as ZymoGenetics admits a "receptor analog" must be a "non-immunoglobulin polypeptide".

With respect to (2), "receptor analog" is described in the specifications as:

> A non-immunoglobulin polypeptide comprising a portion of a receptor which is ***capable of binding ligand and/or is recognized by anti-receptor antibodies***. . . .

(D.I. 179, Exh. 1 at col. 9, ll. 33-40; D.I. 179, Exh. 2 at col. 9, ll. 18-25) (emphasis added). The context in which the term is used in Claim 21 makes clear that rather than "being recognized by anti-receptor antibodies", the focus is on binding ligand:

> 21. A method for producing a secreted receptor analog, comprising:
> . . . a DNA sequence encoding a ligand-binding domain of a receptor requiring dimerization for biological activity . . . .

(D.I. 179, Exh. 2 at ZG000844, col. 2, ll. 13-25) (emphasis added).

V. Non-Immunoglobulin Polypeptide

ZymoGenetics argues "non-immunoglobulin polypeptide" "does not need to be construed by the Court" because -- according to ZymoGenetics – it should have an "ordinary meaning." (D.I. 156 at 16). In fact, it does not, as ZymoGenetics' experts agreed. In any event, proffering a purported ordinary meaning is not dispositive of whether construction is necessary. *See, e.g., O2*

[11] ZymoGenetics also wishes to include extraneous unnecessary language that is immaterial. For example, it wishes to include a discussion of amino acid sequences of the receptor analogs and PDGF-R analogs, none of which is necessary to the construction of "receptor analog".

Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd., 521 F.3d 1351, 1361 (Fed. Cir. 2008) ("A determination that a claim term . . . has the 'plain and ordinary meaning' may be inadequate . . . when reliance on a term's 'ordinary' meaning does not resolve the parties' dispute").

ZymoGenetics also argues that Bristol's construction is "inaccurate and nonsensical" and "unsupported by the evidence". (D.I. 156 at 16, 18 fn. 5). To the contrary, Bristol's construction is based on ZymoGenetics' own explicit definition of non-immunoglobulin peptide given during prosecution of the European priority application.[12] *See Liposome Co., v. Vestar, Inc.*, 1994 WL 738952, at *14 (D. Del. Dec. 20, 1994) (statements to European Patent Office relevant to how patentee understood the claim terms before filing a lawsuit and to how one of ordinary skill would understand the claim terms).

ZymoGenetics agrees that there is no explicit definition in the specification of a "non-immunoglobulin." It argues that the specification "implicitly" defines the term, referring to the discussion of immunoglobulins in the specifications.[13,14] But, the issue is not what are examples of immunoglobulins that are included within the claim element of a "dimerizing protein", but

[12] ZymoGenetics also incorrectly states that Bristol's position is "derived from the definition of 'immunoglobulin super family,' which is a loose classification of a set of molecules that share a structural component found in immunoglobulins." (D.I. 156 at 21). Rather, Bristol's construction is based on ZymoGenetics own arguments made during prosecution of the priority application.

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[14] Even assuming that the discussion of "immunoglobulins" in the specification is relevant to the construction of "non-immunoglobulin polypeptide", ZymoGenetics' argument is flawed. ZymoGenetics argues that an immunoglobulin is a molecule that fits into one of five classes (i.e., γ, α, ε, μ, and δ). (D.I. 156 at 18-23). In doing so, ZymoGenetics ignores the fact that the specification states that immunoglobulins include these five classes -- not that they are limited thereto. (See, e.g., D.I. 179, Exh. 2 at col. 14:16-19; D.I. 156 at 19).

rather what is excluded by the "non-immunoglobulin polypeptide" limitation. And ZymoGenetics defined that term during prosecution of the priority application.

ZymoGenetics states that the term "non-immunoglobulin polypeptide" was the "easiest, broadest, and perhaps only way to refer to [possible fusion partners for the dimerizing protein] in the claims". (D.I. 156 at 20). The broadest way to refer to these "possible fusion partners" would have been as a "peptide" requiring dimerization for biological activity. Indeed, this is what ZymoGenetics had done during prosecution of the priority application -- that is, until ZymoGenetics realized it had run afoul of prior art. ZymoGenetics also argues that the use of the term non-immunoglobulin polypeptide "stems from the disclosure of immunoglobulin for the other (dimerizing protein) half." (D.I. 156 at 20). But, this argument ignores the fact that the specification and claims also specify "yeast invertase" as a potential "dimerizing protein", and ZymoGenetics did not refer to the "possible fusion partners" as "non-yeast".

ZymoGenetics also argues that a "fundamental flaw" of Bristol's proposed construction is that the patent expressly identifies "PDGF" as "a subject of many of the working examples" and is a "preferred embodiment". Presumably ZymoGenetics meant to refer to PDGF-R, as PDGF (*i.e.*, the ligand to PDGF-R) was never made a fusion protein in any of the examples of the patents-in-suit. If that is the case, then the flaw is in ZymoGenetics' argument, as ZymoGenetics claimed PDGF-R fused to dimerizing proteins in other related patents, but when using the term "non-immunoglobulin polypeptide" in the patents-in-suit, it intended to claim something different. (*See*, *e.g.*, Exh. 3 at col. 99, ll. 57-63 (PDGF-R is known to be a growth factor receptor); Exh. 4 at col. 99, l. 20-col. 100, l. 43; D.I. 179, Exh. 18 at col. 99, l. 59-col. 102, l. 14). And, even assuming "PDGF-R" is a preferred embodiment, the *Vitronics* decision relied on by ZymoGenetics indicates that there are circumstances where it is proper to exclude a

preferred embodiment (D.I. 156 at 21); *see Vitronics Corp. v. Conceptronic Inc.*, 90 F.3d 1576, 1583-84 (Fed. Cir. 1996); *see, e.g., Elekta Instrument S.A. v. O.U.R. Scientific Int'l, Inc.*, 214 F.3d 1302, 1308 (Fed. Cir. 2000).

As discussed in further detail in Bristol's Opening Claim Construction Brief, ZymoGenetics amended a pending claim during prosecution of the priority application by adding the term "non-immunoglobulin peptide" to avoid art related to T-cell Receptor immunoglobulin fusion protein ("TCR-Ig") prior art. ZymoGenetics represented that the TCR in the distinguished prior art was not a "non-immunoglobulin peptide" because:

> The T cell receptor is a disulfide-bonded heterodimer encoded by immunoglobulin-like genes that have exon structures analogous to immunoglobulin genes and which encode discrete domains structurally similar to immunoglobulins. Moreover, characterization of T cell receptor cDNA clones has shown significant sequence homology between T cell receptors and immunoglobulins (see Hedrick et al. Nature 308: 153-158, 1984). Thus, the T cell receptor is not a non-immunoglobulin peptide.

(D.I. 179, Exh. 26 at BMS004261732) (emphasis in original). Those representations, distinguishing TCR in order to exclude the prior art TCR-Ig from its claims, mean that a "non-immunoglobulin polypeptide" cannot be:

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

(b) a polypeptide that has significant sequence homology to immunoglobulin.

When ZymoGenetics then included the "non-immunoglobulin polypeptide" limitation in the claims of the patents-in-suit, the applications for which were filed years later, it was well aware of the definition of that term it had previously adopted to avoid the prior art.

VI. Requiring Dimerization for Biological Activity

ZymoGenetics' belated proposed construction of "requiring dimerization for biological activity" ignores the prosecution history, inventor testimony and positions previously taken by ZymoGenetics. The parties' proposed claim constructions are:

ZymoGenetics	Bristol
the claimed polypeptides must be in a dimer form (i.e., in a pair) to exhibit biological activity[15]	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

The parties agree that unless a dimer, there is no biological activity (compare ZymoGenetics' construction with the non-underlined portion of Bristol's construction). The dispute is with respect to the underlined portion of Bristol's proposed construction, that is, whether a polypeptide that dimerizes on its own is a polypeptide requiring dimerization (by a "dimerizing protein") for biological activity.

It is simple common sense that, if the polypeptide in question can dimerize on its own, there is no need to join it to a "dimerizing protein". And, as discussed below, the history of how and why the claim term "requiring dimerization for biological activity" was added during prosecution shows that the claims-in-suit are invalid unless Bristol's construction is followed.

The prosecution history of the related '027 Patent (D.I. 179, Exh. 19), makes clear that avoidance of prior art was the reason ZymoGenetics disclaimed coverage of polypeptides that can dimerize on their own. *See, e.g., Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1306-07 (Fed. Cir. 2007) (finding a clear disavowal of scope where applicants, in a related application, restricted their invention while distinguishing prior art).

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[15] ZymoGenetics states that its construction is "requiring dimerization to exhibit biological activity", but then expands on that definition in the text of its brief. (D.I. 156 at 23).

As discussed above, the Examiner rejected the pending claim as anticipated by two references referred to as "Boss". (D.I. 179, Exh. 20 at BMS004259277-279). Boss states "[i]t is also envisaged that the Ig molecule may be synthesized by a host cell with another peptide moiety attached to one of its constant domains." (D.I. 179, Exh. 21 at col. 5, ll. 18-20). That is, Boss envisaged fusing Ig molecules to polypeptides. The Examiner pointed out in response to ZymoGenetics' attempt to argue around Boss: "[w]hether the peptide moiety [of Boss] becomes dimerized or not would be dictated by the moiety chosen" to be joined to the immunoglobulin. (D.I. 179, Exh. 20 at BMS004259315-316). That is, for example, if the peptide moiety chosen to be fused to the Ig were capable of forming a dimer on its own, it would do so with or without the Ig portion, and the Ig portion would not be driving the dimerization. To obtain allowance, ZymoGenetics amended the claim by adding "requiring dimerization for biological activity", as follows:

> 22. (Twice Amended) A method for producing a secreted, biologically active, dimerized polypeptide fusion, comprising:
> . . . a non-immunoglobulin polypeptide dimer requiring dimerization for biological activity joined to a DNA sequence encoding an immunoglobulin light chain constant region . . .

(D.I. 179, Exh. 20 at BMS4259320). It is clear and unambiguous that, by inserting "requiring dimerization for biological activity", ZymoGenetics disavowed non-immunoglobulin polypeptides such as those described in the Boss fusion proteins that can form dimers on their own (without the aid of a "dimerizing protein"). *See, e.g., Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007); *Verizon*, 503 F.3d at 1306 (Fed. Cir. 2007) ("[A] statement made by the patentee during prosecution history of a patent in the same family as the patent-in-suit can operate as a disclaimer") (citing *Microsoft Corp. v. Multi-tech Sys., Inc.*, 357 F.3d 1340 1350 (Fed. Cir. 2004)). Therefore, unless "requiring dimerization for biological activity" is

construed to exclude circumstances where the polypeptide in question can dimerize on its own, all asserted claims are invalid based on the Boss references.[16,17]

Now that it is more convenient -- indeed critical -- for ZymoGenetics to disavow what it told the examiner [redacted] REDACTED [redacted], it proposes a new and inconsistent definition. It should not be permitted to run from its prior, and clearly correct, constructions of the meaning of that term.

VII. Biologically Active and Active

ZymoGenetics argues that "biologically active" and "active" do not need to be construed because they are part of the preamble. But, the decision ZymoGenetics relies on says only that "generally" preambles do not limit claims. *See Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002). ZymoGenetics does not explain why, on the facts here, the preamble should be deemed non-limiting.

ZymoGenetics' position that the preamble is not limiting is inconsistent with the patents and ZymoGenetics' prior statements. The title of the patents are "Methods of Producing . . . and ***Biologically Active*** Dimerized Polypeptide Fusions" and "***Biologically Active*** Dimerized . . . Polypeptide Fusions". (D.I. 179, Exh. 2 at ZG000842; D.I. 179, Exh. 1 at ZG000001) (emphasis

16 [redacted] REDACTED

added). Throughout the specifications, the resulting fusion proteins are referred to as "biologically active". (D.I. 179, Exh. 1, *passim*; D.I. 179, Exh. 2, *passim*).[18]

The Federal Circuit explained that "terms appearing in a preamble may be deemed limitations of a claim when they 'give meaning to the claim and properly define the limitation.'" *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994) (citation omitted) ("[R]eview of a patent in its entirety should be made to determine whether the inventors intended [preamble] language to represent an additional structural limitation . . . ."). Put another way, preambles can be limiting when they state "a necessary and defining aspect of the invention." *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008); *see also*, *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 866 (Fed. Cir. 1985) ("Although it appears in the preambles . . . the term 'anaerobic' breathes life and meaning into the claims and, hence, is a necessary limitation to them."); *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 896 (Fed. Cir. 1984) ("The system of claim 1 is one of unity magnification and is image forming. Those limitations appear in the preamble, but are necessary to give meaning to the claim and properly define the invention."), *cert. denied*, 469 U.S. 857 (1984).

Paradoxically, ZymoGenetics argues that it is necessary that the first polypeptide component of the claim be one that requires dimerization to display biological activity, yet the dimer that results from its association with the "dimerizing protein" need not have the activity that is the whole purpose of creating the molecule. Not only is that an incredible contradiction, it would mean that the claims include compounds that have no utility.

[18] [redacted]

REDACTED

Being "biologically active" is a necessary and defining aspect of the alleged inventions, as dimerization is required "***for biological activity.***"[19] Moreover, the Examiner rejected pending claims 29-58 (later renumbered claims 1-29) during prosecution of the '026 Patent under 35 U.S.C. § 112, second paragraph, as "failing to set forth the subject matter which applicant(s) regard as their invention" because the claim did not recite the limitation "biologically active". (D.I. 179, Exh. 17 at BMS004258864). In response, ZymoGenetics amended the claims by adding "biologically active" to the preamble. (*Id.* at BMS004258870-876, 879).

As a result, "biologically active" and "active" should serve to limit the claims and should be defined as "exhibits one or more biological activities of its native counterpart".

CONCLUSION

For the foregoing reasons, Bristol respectfully requests the Court adopt Bristol's proposed constructions of the disputed terms of the patents-in-suit.

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[19] Similarly, Claim 21 of the '725 Patent must be "active" in that it requires that the method be capable of producing a fusion protein that is capable of binding ligand. Consistent with this, ZymoGenetics took the position during the Immunex Litigation that receptor analogs such as '725 Patent claim 21 are considered to be "biologically active" in that they bind ligand. (D.I. 179, Exh. 16 at 75:21-22).

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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I hereby certify that on June 23, 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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