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 OPENING CLAIM CONSTRUCTION BRIEF

OF COUNSEL:

Paul J. Andre
Lisa Kobialka
KING & SPALDING LLP
1000 Bridge Parkway
Suite 1000
Redwood City, CA 94065
(650) 590-0700

Philip A. Rovner (#3215)
POTTER ANDERSON & CORROON LLP
Hercules Plaza
P. O. Box 951
Wilmington, DE 19899
(302) 984-6000
provner@potteranderson.com

Attorneys for Plaintiff ZymoGenetics, Inc.

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NATURE AND STAGE OF THE PROCEEDINGS

ZymoGenetics, Inc. ("ZymoGenetics") is the assignee of United States Patent Nos. 5,843,725 (the "'725 Patent") and 6,018,026 (the "'026 Patent") (collectively, "the ZymoGenetics Patents") relating to fusion proteins. On August 14, 2006, ZymoGenetics filed this patent infringement action against Bristol-Myers Squibb Co. ("Bristol"), claiming that Bristol's fusion protein product Orencia® infringes both of the ZymoGenetics Patents, and that such infringement is willful. *See* Declaration of Paul J. Andre in Support of Plaintiff ZymoGenetics, Inc.'s Opening Claim Construction Brief ("Andre Decl."), submitted concurrently herewith, at Exs. 1 (the '725 Patent) and 2 (the '026 Patent). The parties have completed fact discovery, and expert discovery has been nearly completed in this case.[1]

In accordance with the Scheduling Order entered by the Court, ZymoGenetics submits this Opening Claim Construction Brief seeking construction of certain claim terms and phrases in the ZymoGenetics Patents. This brief is filed concurrently with ZymoGenetics' motions for summary judgment relating to: (1) infringement of the ZymoGenetics Patents, and (2) validity of the ZymoGenetics Patents; along with ZymoGenetics' motion to exclude expert testimony under *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993).

SUMMARY OF THE ARGUMENT

The ZymoGenetics Patents cover "dimerized polypeptide fusion" and the methods of producing such fusion protein products.[2] *See* Andre Decl., Ex. 1 at col. 101, ll. 23-24; *see also id.*, Ex. 2 at col. 99, ll. 29-30. In particular, the fusion protein described in the ZymoGenetics Patents consists of two polypeptides (or proteins) joined together: (1) a "non-immunoglobulin

[1] One of ZymoGenetics' experts, Dr. Rick Meyers, and one of Bristol's experts, Jeffrey Ravetch, remain to be deposed. Though initially scheduled for April 24, 2008, Dr. Ravetch's deposition was postponed for reasons related to his health.

[2] For the purposes of this case, a "polypeptide" is also a "protein."

polypeptide requiring dimerization for biological activity" or a "ligand-binding domain of a receptor requiring dimerization for biological activity" and (2) a "dimerizing protein." *See id.*, Ex. 1 at col. 101, ll. 29-31, col. 103, ll. 57-58; *see also id.*, Ex. 2 at col. 99, ll. 32-34.

The parties agree that the following terms in the ZymoGenetics Patents require construction:

- "biological activity"
- "dimerizing protein"
- "receptor analog"
- "ligand-binding domain of a receptor"
- "ligand"

In addition, Bristol improperly contends that the terms " non-immunoglobulin polypeptide" and "requiring dimerization for biological activity," as well as the non-limiting terms "biologically active" (found in the preambles of the claims of the '026 Patent) and "active" (found in the preambles of the claims of the '725 Patent) require construction. *See generally* D.I. 153-2 [Joint Claim Chart].

Of these disputed terms, "biological activity," "dimerizing protein," "receptor analog," "ligand-binding domain of a receptor," and "ligand" are explicitly defined in the ZymoGenetics Patents. *See* Andre Decl., Ex. 1, col. 9, ll. 18-54; *see also id.*, Ex. 2, col. 9, l. 33 to col. 10, l. 6. When a patentee acts as his or her own lexicographer, the Court should adopt the definitions for these terms from the patents. *See K-2 Corp. v. Salomon S.A.*, 191 F.3d 1356, 1363 (Fed. Cir. 2003); *see also Honeywell Int'l, Inc. v. Universal Avionics Sys. Corp.*, 493 F.3d 1358, 1361 (Fed. Cir. 2007).

The remaining limiting terms -- i.e., "non-immunoglobulin polypeptide" and "requiring dimerization for biological activity" -- should be afforded their ordinary meaning to one of skill in the art in the context of the patents, including the definitions provided in the specifications.

See Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005). Indeed, the claim constructions proposed by ZymoGenetics for these terms are derived directly from the language and definitions used in the patents.

Bristol, on the other hand, urges the Court to adopt non-sensical constructions that are driven by its non-infringement position without regard to the actual claims and specifications of the ZymoGenetics Patents. In fact, Bristol even proposes that the Court construe the claims terms that are expressly defined in the ZymoGenetics Patents in a manner other than the definitions provided. This is improper. But, Bristol knows that if the claims are construed according to context of the patents, its Orencia® product must be found to infringe.

FACTUAL BACKGROUND

ZymoGenetics asserts that Bristol infringes claims 1-4, 7, and 30 of the '026 Patent and claims 1-3, 4, 5, 21, 22, 24, 25, 50, and 51 of the '725 Patent. Independent claim 1 of the '026 Patent and independent claims 1 and 21 of the '725 Patent have essentially identical limitations. The remaining asserted claims depend from these independent claims and therefore include all of the limitations of the claim from which they depend.

A. The Technological Landscape And Development Of The ZymoGenetics Patents

The ZymoGenetics Patents claim recombinant[3] fusion proteins and certain methods of making such proteins. A fusion protein is simply a fusion between two different proteins or polypeptides. The ZymoGenetics scientists invented the novel fusion proteins claimed in the

[3] The term "recombinant," when used to describe a protein, indicates that the protein has been made from recombinant DNA. Put simply, DNA is like a blueprint for making proteins. Recombinant DNA is basically DNA that has been synthesized in a laboratory and which does not exist naturally. When the recombinant DNA is inserted into a host cell (usually in a Petri dish or similar *in vitro* system), the host cell's machinery acts on the recombinant DNA to build the protein or proteins that the DNA encodes. *See, e.g.*, Andre Decl., Ex. 2, col. 17, ll. 13-48. A more detailed explanation of this process is available in the Technology Tutorial submitted by ZymoGenetics on October 17, 2007. *See* D.I. 120.

ZymoGenetics Patents to address particular problems incurred in producing and isolating certain types of proteins that are found in cell membranes. *See generally*, Andre Decl., Ex. 1 at col. 2, ll. 13-30; *see also id.*, Ex. 2 at col. 2, ll. 16-33. As explained below, scientists believed that some of these membrane-bound receptors might have therapeutic uses -- but studies would be needed to confirm that belief and to make therapeutic use of such proteins. *See generally*, *id.*, Exs. 1 & 2, Background Of The Invention Sections at cols. 1-3. To conduct such studies, researchers had to be able to acquire the membrane-bound proteins of interest for reasonable costs and at sufficient volume for research. Thus, the ability to isolate and produce membrane-bound proteins in a cost-efficient manner is important. *See id.*

The particular membrane-bound proteins of relevance here are receptor proteins, which can be compared to a car's ignition switch. With the right key, the ignition switch is flipped, allowing the car's ignition system to fire. In a cell, the receptor protein (the ignition switch) crosses the cell membrane, so that a part of it is sticking out from the cell and part of it is still inside the cell. When the right molecular "key" (known as a "ligand") comes along, it chemically binds to the part of the receptor that sticks out from the cell. This binding "unlocks" the receptor, causing the receptor to engage in some biological function like activating (or deactivating) a certain chemical pathway in the cell -- like an ignition switch signaling the ignition system process to start. Importantly, many of these receptor proteins require "dimerization" (i.e., binding together in pairs or "dimers") for biological activity.

Scientists believe that certain membrane-bound receptors that are part of what are called "signaling pathways" might have therapeutic uses. For example, in humans, when the signaling pathway for a receptor known as "CD28" is over-stimulated, the body produces too many of a certain type of immune cell, which scientists believe can lead to auto-immune diseases. It is

possible that these type of receptors, however, could be exploited to treat such diseases. Thus, scientists became interested in studying them as potential drugs.

However, scientists encountered a problem when attempting to isolate these membrane-bound protein receptors for study and drug development. Although they knew how to synthesize these membrane-bound receptors on demand, it was difficult to recover active forms of these proteins from the host cells. Of particular relevance here, the techniques that researchers had used to try to isolate receptor proteins interfered with the dimerization of the protein into its native form. *See generally*, Andre Decl., Ex. 1 at col. 2, ll. 13-30; *id.*, Ex. 2 at col. 2, ll. 16-33.

Scientists at ZymoGenetics came up with a solution to this problem. They realized that if they could somehow make the host cell secrete (i.e., expel) the receptor protein of interest in such a way that it would dimerize to resemble its native form, it would be much easier to isolate and obtain therapeutically useful proteins. *See id.*, Ex. 1 at col. 3, ll. 1-10; *see also id.*, Ex. 2 at col. 3, ll. 4-13. Thus, ZymoGenetics' scientists invented fusion proteins made up of: (1) the ligand-binding portion of the membrane-bound protein receptor of interest, but without the membrane spanning region (to avoid trapping the protein in the cell membrane) and (2) a portion of a different protein – specifically, a protein that dimerizes. This fusion of the ligand-binding portion of the receptor with a dimerizing protein that would not get trapped in the cell membrane allowed for the isolation of an active dimerized (fusion) protein. *See* Figure 1, below.

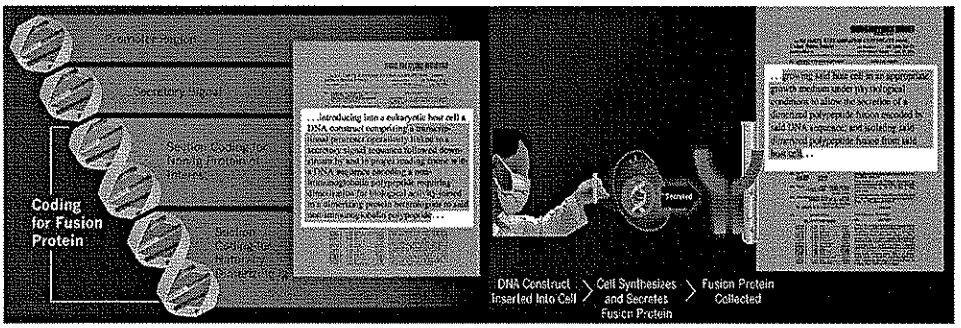

Figure 1. DNA Construct Introduced Into Cell and Fusion Protein Isolated

The '725 Patent is a method patent for the synthesis of secreted dimerized fusion proteins and receptor analogs. *See* Andre Decl., Ex. 1 at col. 101, ll. 23-24; *see also id.*, Ex. 2 at col. 103, l. 50. The fusion protein is created by inserting a DNA construct (i.e., recombinant DNA synthesized in a lab) into a host cell, which in turn translates the DNA into the protein and which the host cell secretes. *See, e.g., id.*, Ex. 1, claims 1 and 21. The DNA construct contains:

1) a "promoter region" (which is a segment of DNA that signals to the host cell's protein building machinery the beginning of a protein blue print);

2) a region encoding a protein that causes the fusion protein to be secreted from the cell;

3) a region coding for a "non-immunoglobulin polypeptide requiring dimerization for biological activity," or a "ligand-binding domain of a receptor requiring dimerization for biological activity"; and

4) and a region coding for a different protein (such as an immunoglobulin,) that is considered a dimerizing protein.

See generally id. (describing DNA construct); D.I. 120 (explaining process). After the fusion protein is secreted from the host cell, it is isolated. *See id.*

The '026 Patent is a product patent covering the "dimerized polypeptide fusion" produced using the method described above. *See* Andre Decl., Ex. 2 at col. 99, ll. 29-30. The fusion polypeptide is composed of:

1) a portion of a non-immunoglobulin polypeptide of interest that requires dimerization for biological activity; and which is

2) joined to a dimerizing protein different from the non-immunoglobulin polypeptide.

See id., Ex. 2, claim 1. The fusion protein forms a dimer and becomes appropriate for scientific and medical study and use. *See id.*

B. The Parties And Their Respective Claims

ZymoGenetics was founded in 1981 by professors Earl Davie and Benjamin Hall of the University of Washington, and Nobel laureate Michael Smith of the University of British Columbia. ZymoGenetics operated as an independent business for seven years prior to being acquired by Novo Nordisk in 1988. Acting as the United States research and development branch of Novo Nordisk for the following twelve years, ZymoGenetics was involved in the research and development process behind drugs such as Novolin® (recombinant human Insulin), NovoSeven® (Factor VIIa), Reagranex® (PDGF-BB), and Cleactor™ (TPA analog). ZymoGenetics became an independent company for the second time in 2000. ZymoGenetics currently has over five hundred employees and is actively engaged in the identification of new drug candidates through bioinformatics-focused research and development. The company's latest drug, RECOTHROM™, was granted FDA approval in January of 2008. Throughout its history, ZymoGenetics has been involved in the development of six recombinant protein products. *See generally* Andre Decl., Ex. 3 [ZymoGenetics website printout, *available at* http://www.zymogenetics.com/about/fact-sheet.html].

Defendant is in the business of making pharmaceutical products, including large biologic molecules such as proteins. *See id.*, Ex. 4 [Bristol website printout, *available at* http://www.bms.com/research/content/data/biologics.html]. In February 2006, Bristol launched a new fusion protein product with the brand name Orencia®. *See id.*, Ex. 5 [Bristol website printout, *available at* http://newsroom.bms.com/article_display.cfm?article_id=5063]. Orencia® is prescribed for the treatment of rheumatoid arthritis. *See id.*, Ex. 6 [Orencia® Package Insert]). In its product insert, Bristol describes Orencia® as follows: "Orencia® is a soluble ***fusion protein*** that consists of the ***extracellular domain of human CTLA-4*** [i.e., a non-Immunoglobulin polypeptide requiring dimerization for biological activity,] joined to the

modified Fc (hinge, CH2 and CH3 domains) portion of human IgG1 [i.e., a dimerizing protein]." *See id.* [Orencia® Package Insert]). The fusion protein is produced by recombinant DNA technology in a mammalian cell expression system. *Id.*

ZymoGenetics claims that Bristol has willfully infringed the ZymoGenetics Patents. Bristol has counterclaimed for a declaratory judgment of non-infringement and invalidity.

ARGUMENT

I. LEGAL STANDARDS FOR CLAIM CONSTRUCION

Claim construction begins and remains focused on the claims themselves. *See Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004) "claim construction analysis must begin and remain centered on the claim language itself . . . ."). At the same time, the claims should not be read "in a vacuum." *Medrad, Inc. v. MRI Devices Corp.*, 401 F.3d 1313, 1319 (Fed. Cir. 2005). Rather, the meaning of a claim term should be understood "in the context of the written description." *Id.*; *see also Vitronincs Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history…is the most significant source of the legally operative meaning of disputed claim language"). Indeed, the inventor's "intention, as expressed in the specification, is regarded as dispositive." *Phillips*, 415 F.3d at 1316.

It is well settled that a patentee may act as his or her own lexicographer and "[i]n such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316; *see also Medrad*, 401 F.3d at 1318 ("A patentee may define a particular term in a particular way, and in that event the term will be defined in that fashion for purposes of that particular patent, no matter what its meaning in other contexts."). Thus, the definitions expressly provided in the ZymoGenetics patents' specifications must apply. *See, e.g., Johnson Worldwide Assocs., Inc. v. Zebco Corp.*,

175 F.3d 985, 990 (Fed. Cir. 1999) (affording the term the meaning chosen by the patentee when "the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term.").

Similarly, where a disputed claim term is not expressly defined in the specification, terms must be afforded their ordinary meaning to one of skill in the art at the time of the invention, as read in the context of the specifications. *See Phillips,* 415 F.3d at 1313. The Federal Circuit has observed that most of the time, the intrinsic evidence will resolve claim construction of the disputed terms. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1583 (Fed. Cir. 1996). Indeed, it is improper to consider extrinsic evidence -- i.e., evidence outside the public record of the patent itself and the prosecution history -- when the claims can be construed through analysis of the intrinsic evidence. S*ee id.* Nevertheless, both the intrinsic and extrinsic evidence support ZymoGenetics' proposed claim constructions and undermine Bristol's.

II. ZYMOGENETICS' PROPOSED CONSTRUCTIONS OF THE DISPUTED TERMS

Claim construction begins with the claims. *See Innova,* 381 F.3d at 1116. The independent claims asserted by ZymoGenetics against Bristol are as follows.

Claim 1 of the '026 Patent claims:

> 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*** heterologous to said non-immunoglobulin polypeptide.

See Andre Decl., Ex. 2 at col. 99, ll. 29-35 (emphasis added to indicate claim terms at issue).

Claim 1 of the '725 Patent claims:

> A method for producing a secreted active dimerized polypeptide fusion, comprising:
> introducing into a eukaryotic host cell a DNA construct comprising a transcriptional promoter operatively linked to a secretory signal sequence

> followed downstream by and in proper reading frame with a DNA sequence encoding a ***non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein*** heterologous to said non-immunoglobulin polypeptide…

See id., Ex. 2 at col. 101, ll. 23-32, emphasis added to indicate claim terms at issue). Claim 21 of the '725 Patent claims:

> A method for producing a secreted receptor analog, comprising: introducing into a eukaryotic host cell a DNA construct comprising a transcriptional promoter operatively linked to a secretory signal sequence followed downstream by and in proper reading frame with a DNA sequence encoding a ***ligand-binding domain of a receptor requiring dimerization for biological activity joined to a dimerizing protein*** heterologous to said ligand-binding domain, and optionally an immunoglobulin hinge or variable region to said dimerizing protein …

See id., at col. 103, ll. 50-61 (emphasis added to indicate claim terms requiring construction). In addition, ZymoGenetics claims that Bristol's Orencia® product infringes dependent claims 2, 3, 5, 6, 21, 22, 24, 25, 50, and 51 of the '725 patent and dependent claims 2-4, 7, and 30 of the '026 patent, all of which depend from, and are subject to the limitations of, the independent claims set forth above. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 1000 (Fed. Cir. 1995).

The evidence and authorities set forth below support ZymoGenetics' proposed claim constructions. For each disputed term, the definitions expressly provided in the specification and the ordinary meaning of the claim language to one of skill in the art in light of the specification provides the correct construction. Moreover "extrinsic evidence" also supports ZymoGenetics' proposed claim constructions.

A. "Dimerizing Protein," "Ligand-Binding Domain Of A Receptor," "Biological Activity," "Receptor Analog," And "Ligand" Must Each Be Afforded The Definitions Provided By The Inventors In The Specifications Of The Patents

As set forth above, it is well settled that a patentee may be his or her own lexicographer. *Phillips*, 415 F.3d at 1316. The ZymoGenetics Patents explicitly define "dimerizing protein," "ligand-binding domain of a receptor," "biological activity," "receptor analog," and "ligand" in

the specifications. *See generally,* Andre Decl. Ex. 1 at col. 8, l53- col. 10, l13; *see also id.*, Ex. 2 at col. 8, l. 61 to col. 10, l. 33. Specifically, the specifications state:

> Prior to setting forth the invention, it may be helpful to [*sic*] an understanding thereof to ***set forth definitions of certain terms*** to be used hereinafter.

Id., Ex. 1 at col. 8, ll. 53-55; *see also* Ex. 2 at col. 8, ll. 61-63(emphasis added). Immediately thereafter, the specification sets forth the explicit definitions of these terms. Therefore, the Court need look no further than the specifications to construe these disputed claim terms. *See Phillips*, 415 F.3d at 1321 (The specification "acts as a dictionary when it expressly defines terms used in the claims," and when the patentee has provided such a dictionary, "the patentee's definition[s] govern[].").

1. Dimerizing Protein

The parties' respective proposed constructions for "dimerizing protein" are:

ZymoGenetics' Construction	**Bristol's Construction**
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.

ZymoGenetics' proposed construction is taken directly from the definition expressly provided in the specifications of the patents. *See* Andre Decl., Ex. 1 at col. 9, ll. 30-34; *see also id.*, Ex. 2 at col. 9, ll. 46-50. Because ZymoGenetics acted as its own lexicographer when it defined the term "dimerizing protein," in the patents' specifications, ZymoGenetics' proposed construction must be adopted, and without the additional limitations desired by Bristol to avoid infringement.

Moreover, to the extent that the Court considers the extrinsic evidence upon which Bristol is likely to rely, the extrinsic evidence in fact further supports ZymoGenetics' construction of this term and undermines Bristol's.

a. The Term Is Expressly Defined In The Specifications

The claim term "dimerizing protein" is expressly defined in the specifications of the ZymoGenetics Patents as: "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." *See* Andre Decl., Ex. 1 at col. 9, ll. 30-34; *see also id.*, Ex. 2 at col. 9, ll. 46-50. This express definition provided in the intrinsic evidence is the best evidence of how this term should be construed. *See Vitronics*, 90 F.3d at 1582 (stating that intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language"). Thus, there is no ambiguity as to the meaning of this claim term because ZymoGenetics defined it in the specification.

b. Bristol's Proposed Construction Should Be Rejected

Instead of the express definition provided in the patents' specifications, Bristol urges the Court to adopt an unduly limiting construction of the term "dimerizing protein." Specifically, Bristol would have the Court construe "dimerizing protein" as the sole cause and driver for the polypeptides claimed in the patents to form dimers. This construction would add an additional limitation found nowhere in the patents, that the claimed polypeptides would not otherwise form a stable dimer without the action of the dimerizing protein. Once again, Bristol's position is driven by its non-infringement arguments instead of the actual language used in the patents, and should be rejected.

2. Ligand-Binding Domain Of A Receptor

The term "ligand-binding domain of a receptor" is found in independent claim 21 of the '725 method patent. The parties' respective proposed claim constructions for this term are as follows:

ZymoGenetics' Construction	Bristol's Construction
that portion of the receptor that is involved with binding the natural ligand	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

ZymoGenetics acted as its own lexicographer when it defined the term "ligand-binding domain of a receptor." *See Johnson Worldwide,* 175 F.3d at 990. The ZymoGenetics Patents' specifications state: "As used herein, the **ligand-binding domain of a receptor** is that portion of the receptor that is involved with binding the natural ligand." Andre Decl., Ex. 1 at col. 10, ll. 10-12; *id.*, Ex. 2. at col. 10, ll. 31-33 (emphasis added). Thus, there can be no doubt what ZymoGenetics intended "ligand-binding domain of a receptor" to mean. *See Phillips*, 415 F.3d at 1316 ("[the inventor's] intention, as expressed in the specification, is regarded as dispositive"). Accordingly, the Court should adopt the claim construction provided in the patent specifications and proposed by ZymoGenetics.

Despite the fact that the specifications provide a definition for the term, Bristol nevertheless again seeks to add unwarranted and unsupported limitations to the claims. Bristol should not be allowed to re-define terms that are so unmistakably defined.

3. Biological Activity

The parties' respective proposed claim constructions for this term are as follows:

ZymoGenetics' Construction	Bristol's Construction
A function or set of activities performed by a molecule in a biological context (i.e., in an organism or an in vitro facsimile thereof). Biological activity may include the induction of extracellular matrix secretion from responsive cell lines, the induction of hormone secretion, the induction of chemotaxis, the induction of mitogenesis, the induction of differentiation, or the inhibition of cell division of responsive cells. A recombinant protein or peptide is considered to be biologically active if it exhibits one or more biological activities of its native counterpart	a function or set of activities performed by a molecule in a biological context (i.e., in an organism or an in vitro facsimile thereof)

"Biological activity" is one of the explicitly defined terms in the definitions sections of the specifications of the '725 and '026 patents. The definition states:

> 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). Biological activity may include the induction of extracellular matrix secretion from responsive cell lines, the induction of hormone secretion, the induction of chemotaxis, the induction of mitogenesis, the induction of differentiation, or the inhibition of cell division of responsive cells. A recombinant protein or peptide is considered to be biologically active if it exhibits one or more biological activities of its native counterpart.

Andre Decl., Ex. 1 at col. 9, ll. 52-63; *id.*, Ex. 2 at col. 9, ll. 36-45. The '725 and '026 Patents could not be any clearer that the term "biological activity" is to be understood in the manner explicitly defined within the detailed description of the invention. And, the law could not be any clearer that in such a case, "the patentee's definition governs." *Honeywell*, 493 F.3d at 1361. Therefore, the claim term "biological activity" should be construed as the definition quoted above.

What is critical about ZymoGenetics' proposed construction is that it includes the entire definition provided in the patents, whereas Bristol's proposed construction leaves out most of the provided definition, including important limitations on the definition. Thus, for example, the full definition propounded by ZymoGenetics and set forth in the specifications includes specific examples of the types of "functions or set of activities" that may qualify as "biological activities." *See* Andre Decl., Ex. 1 at col. 9, ll.52-53; *see also id.*, Ex. 2 at col. 9, ll. 36-45. Importantly, all of these examples describe multi-step processes that have meaningful consequences for cells. In contrast, Bristol's definition leaves open the possibility that the term "biological activities" 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.

4. Receptor Analog And Ligand

The parties' respective proposed claim constructions for these terms are as follows:

ZymoGenetics' Construction	**Bristol's Construction**
Receptor Analog	
A non-immunoglobulin polypeptide comprising a portion of a receptor which is capable of binding ligand and/or is recognized by anti-receptor antibodies. The amino acid sequence of the receptor analog may contain additions, substitutions, or deletions as compared to the native receptor sequence. A receptor analog may be, for example, the ligand-binding domain of a receptor joined to another protein. Platelet-derived growth factor receptor (PDGF-R) analogs may, for example, comprise a portion of a PDGF receptor, capable of binding anti-PDGF receptor antibodies, PDGF, PDGF isoforms, PDGF analogs, or PDGF antagonists	A polypeptide comprising a portion of a receptor which is capable of binding ligand, wherein said polypeptide (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
Ligand	
A molecule capable of being bound by the	A molecule capable of being bound by the

ligand-binding domain of a receptor or by a receptor analog. The molecule may be chemically synthesized or may occur in nature. Ligands may be grouped into agonists and antagonists. Agonists are those molecules whose binding to a receptor induces the response pathway within a cell. Antagonists are those molecules whose binding to a receptor blocks the response pathway within a cell.	ligand-binding domain of a receptor or by a receptor analog.

Once again, the Court need look no further than the definitions sections in the specifications in each of the ZymoGenetics Patents for the proper claim constructions because the terms "receptor analog" and "ligand" are expressly defined therein. *See* Andre Decl., Ex. 1 at col. 9, ll. 18-29, ll. 47-54; *see also id.*, Ex. 2 at col. 9, ll. 31-45, l. 64 to col. 10, l. 6. And, again, Bristol's attempt to avoid the rules of patent construction and the plainly expressed definitions of "receptor analog" and "ligand" is simply further evidence that Bristol's claim constructions are improperly results-driven and should be rejected.

B. "Non-Immunoglobulin Polypeptide" Should Be Construed As A Polypeptide That Is Not An Immunoglobulin

It is ZymoGenetics' position that the term "non-immunoglobulin polypeptide" does not need to be construed by the Court, and that the ordinary meaning within the context of the claims should be applied to this term. Bristol, on the other hand, would have this Court construe this term in such as way to make it scientifically inaccurate and nonsensical. The parties' respective proposed constructions are as follows:

ZymoGenetics' Construction	**Bristol's Construction**
the ordinary meaning within the context of the claims (i.e., a polypeptide that is not an immunoglobulin)	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 (emphasis Bristol's)

The construction proposed by ZymoGenetics is based on the plain import and ordinary and customary meaning as viewed in the context in which the term is used within the claims. Furthermore, the written description of the '725 and '026 Patents fully support ZymoGenetics' construction. Moreover, extrinsic evidence also supports ZymoGenetics' proposed construction. Finally, the ZymoGenetics Patents implicitly define "non-immunoglobulin polypeptide" in a manner directly contrary to Bristol's proposed construction.

1. Construction Turns On The Meaning Of "Immunoglobulin"

The real issue to be decided with respect to this term is how broadly to construe "immunoglobulin," as there can be no meaningful dispute that "non" means "not" or "the opposite of." *See, e.g., Phillips,* 415 F.3d at 1314 ("In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words."). ZymoGenetics asserts, consistent with the ordinary meaning and the specification of the patents, that "immunoglobulin" is limited to that class of polypeptides commonly known among scientists as immunoglobulins.[4] In

[4] The term "immunoglobulin" is a very common term used by those skilled in art, and has a well defined construction. There is nothing in the patent that indicates a special meaning for the term.

contrast, Bristol contends that the term immunoglobulin should encompass not only immunoglobulins, but also immunoglobulin-like molecules.[5]

2. The Claim Language Defines Immunoglobulin As The Molecules Known As Immunoglobulins

In *Phillips*, the Federal Circuit held that "the claims themselves provide substantial guidance as to the meaning of particular claim terms" *Phillips*, 415 F.3d at 1314. The *Phillips* Court gave the following example of looking to the context to provide instruction as to the meaning of a disputed term: "To take a simple example, the claim in this case refers to 'steel baffles,' which strongly implies that the term 'baffles' does not inherently mean objects made of steel." *Id.* In addition, unasserted claims "can also be valuable sources of enlightenment as to the meaning of a claim term." *Id.*

Similarly, here, the word "immunoglobulin" is used throughout the claims of the '725 and '026 Patents, which provide a detailed description of the features of an immunoglobulin. Immunoglobulins, usually abbreviated "Ig," are molecules involved in the body's immune response. There are five classes of immunoglobulins, and the classifications are based on differences in the molecules' heavy chain constant region domains (a chemical feature found in all immunoglobulins): IgG (gamma (γ) heavy chain), IgA (alpha (α) heavy chain), IgE (epsilon (ε) heavy chain), IgM (mu (μ) heavy chain), and IgD (delta (δ) heavy chain).

Here, the claims of the '026 Patent teach that immunoglobulins have a "light chain constant region," a "heavy chain constant region," a "hinge region," and a "variable region." *See, e.g.,* Andre Decl., Ex. 2 at claims 3-8. The claims of the '725 Patent provide the same

[5] In fact, Bristol's proposed construction would conceivably encompass not only immunoglobulin-like polypeptides (however that might be further determined), but also any polypeptide that is encoded by DNA that is similar to DNA that encodes immunoglobulins, regardless of whether the final polypeptide is in any way immunoglobulin-like. Not only is Bristol's proposed construction nearly impossible to decipher logically, it is simply unsupported by the evidence.

definition of an immunoglobulin as the claims of the '026 Patent. *See, e.g.*, *id.*, Ex. 1 at claims 3-8, 21-27. Indeed, the claims of the ZymoGenetics Patents go into additional detail describing particular features of immunoglobulins. For example, claim 7 of the '026 Patent and claim 22 of the '725 Patent each refer to an "immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3, and C_H4 of a γ, α, ε, μ, or δ class immunoglobulin heavy chain." *See id.*, Ex. 1 at col. 103, ll. 67 to col. 104, ll. 3; *see also id.*, Ex. 2 at col. 99, ll. 52-55. In fact, the only molecules that have the described characteristics are immunoglobulins.

3. The Specification is Consistent with the Claims

The claims of a patent "do not stand alone" and "must be read in view of the specification, of which they are a part." *Phillips*, 415 F.3d at 1315 (citing *Markman*, 52 F.3d at 979). The specifications of the ZymoGenetics Patents define immunoglobulins in a manner fully consistent with the claims. They teach:

> Immunoglobulins comprise variable and constant regions, which in turn comprise discrete domains that show similarity in their three-dimensional conformations. These discrete domains correspond to immunoglobulin heavy chain constant region domain exons, immunoglobulin heavy chain variable region domain exons, immunoglobulin light chain variable region domain exons and immunoglobulin light chain constant region domain exons in immunoglobulin genes.
>
> . . .
>
> Immunoglobulin heavy chain constant region domains include C_H1, C_H2, C_H3, and C_H4 of any class of immunoglobulin heavy chain including γ, α, ε, μ, and δ classes.

See generally Andre Decl., Ex. 1, cols. 13-14; *see also id.*, Ex. 2, cols. 13-14.

The specifications, like the claims, describe immunoglobulins as molecules made up of light chains and heavy chains which comprise variable and constant region domains. It also specifies the exact same C_H1, C_H2, C_H3, and C_H4 constant region domains as the claims as well as variable region domains. Finally, the specification lists the exact same immunoglobulin classes as the claims, *i.e.*, γ, α, ε, μ, and δ. The definitions of immunoglobulin in the claims and

the written description are therefore uniform. As explained above, the only molecules which meet this definition are a group of molecules named *immunoglobulins*, of which there are five classes: IgG, IgA, IgE, IgM, and IgD. Therefore, the specification supports construing the term "non-immunoglobulin polypeptide" as "not an immunoglobulin polypeptide," and more precisely, "any polypeptide that is not IgG, IgA, IgM, IgE, or IgD, or any portion thereof."

Further, the specification demonstrates why the term "non-immunoglobulin polypeptide" is not itself a term of art having some independent meaning apart from being simply "not immunoglobulin" or the opposite of immunoglobulin. Essentially, the ZymoGenetics Patents disclose a fusion protein made up of a non-immunoglobulin polypeptide fused to a different protein -- a dimerizing protein. One of the claimed dimerizing proteins is an immunoglobulin. *See, e.g.,* Andre Decl., Ex. 1 at claims 3-5; *see also id.*, Ex. 2 at claims 3-5. Because the ZymoGenetics Patents disclose a diversity of possible fusion partners for the dimerizing protein (*e.g.*, EGF-R, insulin receptor, colony stimulating factor-1, transforming growth factor ß, PDGF, and factor XIII -- none of which is an immunoglobulin), the easiest, broadest, and perhaps only way to refer to these collectively in the claims was to use the term "non-immunoglobulin polypeptide." *See id.*, Ex. 1, col. 11, ll. 54-58; *see also id.*, Ex. 2, col. 11, ll. 33-36. Thus, use of the term "non-immunoglobulin polypeptide" to describe one half of the fusion protein stems from the disclosure of immunoglobulin for the other (dimerizing protein) half.

4. Bristol's Proposed Construction Finds No Support In The Claims Or Specifications Of The ZymoGenetics Patents

As set forth above, Bristol's proposed claim construction for "non-immunoglobulin polypeptide" depends on the Court interpreting immunoglobulin to mean "immunoglobulin-like." Pretermitting that, had the inventors of the ZymoGenetics Patents intended to claim a polypeptide that is not an immunoglobulin and not like an immunoglobulin, they could easily

have written the claims to say that, such an interpretation is plainly at odds with the express terms of the claims and the specification. Rather, Bristol's proposed claim construction is nothing more than a results-directed attempt to avoid infringement.

Specifically, Bristol's proposed claim construction 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. *See* Andre Decl., Ex. 7 at BMS001054677-701 [Alan F. Williams and A. Neil Barclay, *The immunoglobulin superfamily -- domains for cell surface recognition,* ANN. REV. IMMUNOLOGY 6:381-405]. Thus, under Bristol's proposed constructions, the claim limitation "non-immunoglobulin polypeptide" would be further limited to mean any polypeptide that is neither a true immunoglobulin nor a member of the "immunoglobulin super family." Bristol proposes this claim construction because the Orencia® fusion protein includes a section of a polypeptide known as CTLA-4, which is a member of the so-called "immunoglobulin super family" and thus, as Bristol argues, immunoglobulin-like. *See id.* at BMS00105469. Thus, under Bristol's proposed construction, CTLA-4 would not be a "non-immunoglobulin polypeptide" and therefore Orencia® would not infringe. The fundamental flaw in Bristol's position, however, is that the ZymoGenetics Patents expressly identify a polypeptide known as "PDGF," which is also a member of the immunoglobulin super family, as being a non-immunoglobulin polypeptide. *See* Andre Decl., Ex. 1 *passim.* PDGF is the subject of many of the working examples and preferred embodiments of the ZymoGenetics Patents. Thus, Bristol's proposed construction would write a preferred embodiment outside the scope of the claims. Such a construction is "rarely, if ever, correct." *Vitronics*, 90 F.3d at 1583.

5. Extrinsic Evidence Supports This Construction

Although extrinsic evidence need not be considered when the intrinsic evidence clearly provides the proper claim construction, extrinsic evidence may be "useful . . . to better

understand the underlying technology and the way in which one of skill in the art might use the claim terms." *Phillips*, 415 F.3d at 1318 (citations and internal quotations omitted).

The specifications of the ZymoGenetics Patents rely on extrinsic evidence to support their definition of an immunoglobulin. For example, cited in the specifications is the classic textbook entitled IMMUNOLOGY, authored by the highly regarded scientist, Leroy Hood. *See* Andre Decl., Ex. 1 at col. 13, ll. 44-45; *see also id.*, Ex. 2 at col. 13, ll. 64-66. According to this reference, "[t]he basic unit of immunoglobulin structure is a complex of four polypeptides, two identical 'light' (low molecular weight) chains and two identical 'heavy' (high molecular weight) chains, linked together by disulfide bonds." Andre Decl., Ex. 8 at 6 [L. HOOD ET AL., Immunology (Benjamin/Cummings Publishing Co. 1984)]. It goes on to describe "constant regions" and the "variable regions of the light and heavy chains." *Id.* at 6, 8. Further, it explains that immunoglobulins are "divided into five classes," i.e., IgM, IgG, IgA, IgD, and IgE, and describes some of the differences in structure and function between the different classes:

> The five immunoglobulin classes are distinguished structurally by differences in their heavy-chain constant regions. Comparisons of the C_H- region amino acid sequences show that there are five major heavy-chain classes, designated α, γ, ε, δ, and μ. These heavy-chain classes define the corresponding immunoglobulin classes IgA, IgG, IgD, IgE, and IgM, respectively.

Id. at 8, 36.

The extrinsic evidence characterizes immunoglobulins consistently with the claim language and written description of the patents-in-suit. Together, they reaffirm that at the time of invention, the word "immunoglobulin" was commonly understood by those of ordinary skill in the art to refer to a group of molecules termed *immunoglobulins* consisting of IgA, IgG, IgD, IgE, and IgM. Nothing in the claims, written description, or extrinsic evidence suggests that the word "immunoglobulin" was understood by persons of ordinary skill in the art at the time of the invention of the '725 and '026 Patents to encompass anything beyond *immunoglobulins*.

Therefore, the correct construction of the term "non-immunoglobulin polypeptide" is "a polypeptide that is not an immunoglobulin" or more specifically "any polypeptide that is not IgG, IgA, IgM, IgE, or IgD, or any portion thereof."

C. "Requiring Dimerization For Biological Activity" Should Be Construed In Accordance With Its Ordinary Meaning

The term "requiring dimerization for biological activity" is found in each of the asserted independent claims, and does not need construction from the Court. Rather, the ordinary meaning within the context of the claims should be applied to this term. The parties' respective proposed claim constructions for this term are as follows:

ZymoGenetics' Construction	Bristol's Construction
the ordinary meaning within the context of the claims (i.e., requiring dimerization to exhibit biological activity)	needing to be dimerized to have biological activity, i.e., (a) unless a dimer, it has no biological activity; and (b) it will not dimerize on its own

As fully set forth below, the construction proposed by ZymoGenetics is based on the plain and ordinary meaning of the claims as viewed by one of ordinary skill in the art and is fully supported by the specifications of the patents. In contrast, Bristol seeks to import limitations on this term that are not only unwarranted by the patent itself, but are plainly results-driven.

1. "Requiring Dimerization For Biological Activity" Is Self-Explanatory

As set forth above, the ZymoGenetics Patents provide an express definition for the term "biological activity." *See supra,* Section II.A.3. The term "dimerization" simply refers to the process through which two molecules (in this case, proteins) form a bonded-pair, also known as a dimer. Applying the ordinary meaning of "requiring dimerization" within the context of the ZymoGenetics Patents, this term can only mean that the claimed polypeptides must be in a dimer form (i.e., in a pair) to exhibit biological activity.

2. The Specifications Of The ZymoGenetics Patents Support ZymoGenetics' Proposed Construction

The specifications of the ZymoGenetics Patents support ZymoGenetics' proposed claim construction that "requiring dimerization for biological activity" means exactly what it says. Indeed, the specifications of the ZymoGenetics Patents provide examples of polypeptides requiring dimerization to exhibit biological activity. For example, the ZymoGenetics Patents identify "nerve growth factor," "colony-stimulating factor-1," "insulin receptor" and other polypeptides that do not exhibit biological activity unless in a dimer. *See* Andre Decl., Ex. 1 at col. 11, ll. 33-48; *see also id.,* Ex. 2 at col. 11, l. 53 to col. 12, l. 2; *id.*, Ex. 1 at col. 10, ll. 48-50 (explaining, for example, that "[t]he insulin receptor requires dimerization for biological activity."). And, the specifications teach that all of the above examples may be "used within the present invention." *Id.*, Ex. 1, col. 1, l. 60; *id.*, Ex. 2 at col. 12, l. 39.

3. Bristol Seeks To Import Unwarranted Limitations Into The Claims

In contrast to ZymoGenetics' proposed construction, Bristol takes a convoluted, multi-step approach to construing the straightforward term "requiring dimerization for biological activity." Importantly, Bristol contends that the term should be construed to limit the claimed polypeptides to only polypeptides that will not dimerize on their own (i.e., without a dimerzing protein). Bristol cannot import this limitation that it has essentially made up out of whole cloth. Such a narrowing of the scope of the claim term, presumably with extrinsic evidence, is improper in light of the unambiguous nature of the claim term meaning. *See Vitronics*, 90 F.3d at 1584 (extrinsic evidence may be used to "help the court come to the proper understanding of the claims, it may not be used to vary or contradict the claim language.")

Bristol's real strategy is clear, however, in light of its non-infringement position. Bristol contends that the relevant portion of the Orencia® molecule will dimerize on its own. *See, e.g.*,

Andre Decl., Ex. 9 at ¶¶ 103-04 [Expert Rebuttal Report of Jeffrey V. Ravetch, M.D., Ph.D. Regarding Non-Infringement of U.S. Patent Nos. 5,842,725 and 6,018,026]. While ZymoGenetics disagrees with Bristol's contention as to the Orencia® molecule's behavior, it is plain that Bristol is propounding this absurd claim construction to avoid a later infringement determination.

D. The Non-Limiting Preamble Terms "Active" and "Biologically Active" Do Not Require Construction

In addition to the claims described above, Bristol contends that the term "active," which is found only in the preamble of claim 1 of the '725 Patent and "biologically active," which is found in the preambles of the asserted claims of the '026 Patent, should both be construed to mean "exhibits one or more biological activities of its native counterpart." However, because these terms are non-limiting, they need not be construed. *See Allen Eng'g Corp. v. Bartell Indus., Inc.*, 299 F.3d 1336, 1346 (Fed. Cir. 2002) (explaining that "[g]enerally, the preamble does not limit the claims").

CONCLUSION

For the reasons provided above, ZymoGenetics respectfully requests that the Court construe the disputed claim terms as set forth herein.

POTTER ANDERSON & CORROON LLP

OF COUNSEL:

Paul J. André
Lisa Kobialka
King & Spalding LLP
1000 Bridge Parkway
Suite 100
Redwood City, CA 94065
(650) 590-0700

By: /s/ Philip A. Rovner
Philip A. Rovner (#3215)
Hercules Plaza
P. O. Box 951
Wilmington, DE 19899
(302) 984-6000
provner@potteranderson.com

Attorneys for Plaintiff
ZymoGenetics, Inc.

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

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BY HAND DELIVERY AND E-MAIL

Frederick L. Cottrell, III, Esq.
Kelly E. Farnan, Esq.
Richard Layton & Finger, P.A.
One Rodney Square
P. O. Box 551
Wilmington, DE 19899
cottrell@rlf.com
farnan@rlf.com

I hereby certify that on May 22, 2008 I have sent by E-mail the foregoing document to the following non-registered participant:

Christopher P. Borello, Esq.
Colleen Tracy, Esq.
Fitzpatrick Cella Harper & Scinto
30 Rockefeller Plaza
New York, NY 10112
cborello@fchs.com
ctracy@fchs.com

/s/ Philip A. Rovner
Philip A. Rovner (#3215)
Potter Anderson & Corroon LLP
Hercules Plaza
P. O. Box 951
Wilmington, DE 19899
(302) 984-6000
provner@potteranderson.com

748348