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. 1:06-cv-00500-SLR-MPT REDACTED PUBLIC VERSION

BRISTOL-MYERS SQUIBB COMPANY'S
OPENING CLAIM CONSTRUCTION BRIEF

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INTRODUCTION

Pursuant to the Stipulated Amended Scheduling Order entered December 13, 2007, Defendant Bristol-Myers Squibb Company ("Bristol") submits this Opening Claim Construction Brief addressing the disputed claim terms of U.S. Patent Nos. 6,018,026 ("the '026 Patent") (Exh. 1)[1] and 5,843,725 ("the '725 Patent") (Exh. 2) (collectively "the patents-in-suit").[2]

Bristol respectfully requests the Court to note that, despite the requirement in the Scheduling Order (D.I. 138) that the parties provide "proposed constructions" for disputed claim terms, ZymoGenetics refused to do so for several terms in dispute. ZymoGenetics takes the position that it is not required to provide Bristol or the Court with a proposed construction of a claim term so long as it identifies the terms as having "ordinary meanings within context of claims", without further explanation of what the "ordinary meaning" is.

ZymoGenetics' tactics are contrary to the purpose of the Scheduling Order -- which is to define the areas of dispute before briefing -- and therefore have prejudiced Bristol by not beginning the claim construction briefing on a level playing field and by not permitting Bristol to address ZymoGenetics' proposed constructions in its summary judgment briefs.

As a result, Bristol respectfully requests that the Court either (i) adopt Bristol's proposed construction of disputed terms for which ZymoGenetics has not provided a construction, or (ii) preclude ZymoGenetics from later taking positions as to what is meant by the alleged "ordinary meanings" of these claim terms.

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[1] All exhibits may be found attached to the Declaration of David Kelly In Support of Bristol-Myers Squibb Company's Opening Claim Construction Brief.

[2] Also pursuant to the above-referenced Order, the parties conferred and prepared a Joint Claim Construction Chart, attached as Exhibit 3.

BACKGROUND

I. The Subject Matter of the Patents in Suit

As explained in greater detail in the following sections, the subject matter described and claimed in the patents-in-suit is compounds composed of two distinct parts coupled together (*i.e.*, "fusion proteins") and methods for producing these fusion proteins.

The First Part ("**A**" in Figure 1):

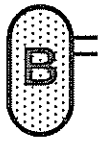
1. has a defined chemical structure -- *i.e.*, is a "non-immunoglobulin polypeptide",
2. displays biological activity only when joined to a second "**A**" (to form a "dimer"), and
3. does not form a dimer on its own.

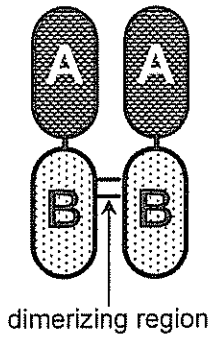
The Second Part ("**B**" in Figure 1):

1. is chemically different from the first part and
2. causes the formation of the dimer of "**AB**" that is required for biological activity -- *i.e.*, is a "dimerizing protein".

The construction of several of the claim terms set forth in this brief is required to conform to that description.

Figure 1

	"**A**" = "non-immunoglobulin polypeptide" "**A**" does not have biological activity when single (*i.e.*, a monomer). "**A**" does not form a dimer on its own.		"**B**" = "dimerizing protein" "**B**" causes the formation of the dimer of "**AB**" that is required for biological activity.



"**AB**" + "**AB**" = biologically active dimer

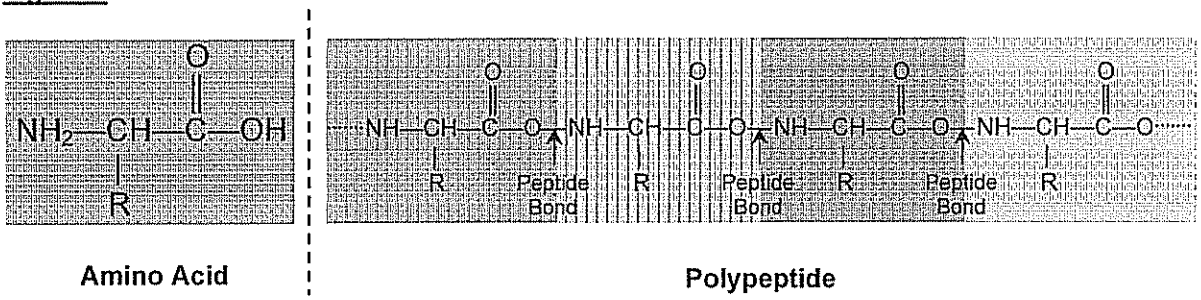
II. Technical Background

Bristol provided the Court with a technical tutorial on a CD-ROM on October 17, 2007. In addition to the technical tutorial, the following general background discussion has been provided to aid the Court in construing the claims at issue.

A. Proteins and Fusion Proteins

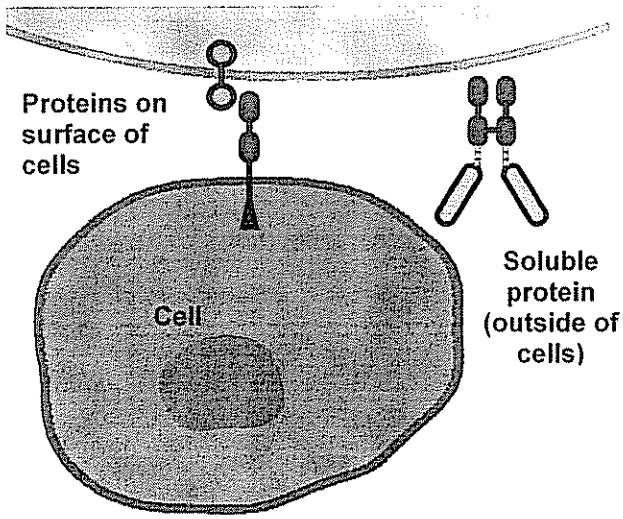
"Proteins", "polypeptides", and "peptides" are molecules comprised of amino acids held together by peptide bonds (see Figure 2).

Figure 2



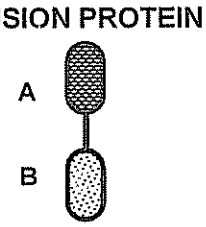
"Proteins" form essential parts of living organisms and participate in processes within an organism's cells. Proteins can interact with each other to affect various biological processes. For example, a protein present on the surface of a cell can communicate with the interior of a cell as a result of interacting with another protein, either one that is "soluble" (*i e* , is not attached to a cell) or one found on the surface of another cell, as shown below in Figure 3.

Figure 3



A "fusion" protein (also referred to as a "chimeric protein") is a term that generally refers to a compound consisting of two or more different proteins that have been artificially joined together. The following figure (Figure 4) depicts a fusion protein made up of two different proteins.

Figure 4



The fusion protein depicted above can exhibit properties of either one or both of the two different proteins that comprise the fusion protein. For example, fusion proteins made up of an "immunoglobulin" molecule (discussed *infra* Technical Background, Section D at 6-8) fused to another protein can take advantage of the long "half-life" that immunoglobulins provide and can allow the fusion protein to be purified more easily.[3]

B. Monomers and Dimers

The term "monomer" within the context of the technology at issue refers to either a single polypeptide (*e.g.*, Part "**A**" in Figure 4) or a single fusion protein (*e.g.*, the entire fusion protein depicted in Figure 4, consisting of "**A**" and "**B**"). The term "dimer" within the context of the technology at issue refers to a composition of two polypeptides or two fusion proteins bound to one another.[4] That is, two monomers bound to each other make a dimer. The following figure (Figure 5) depicts a dimer of a fusion protein, wherein the dimer is formed as a result of the interactions between "**B1**" and "**B2**".

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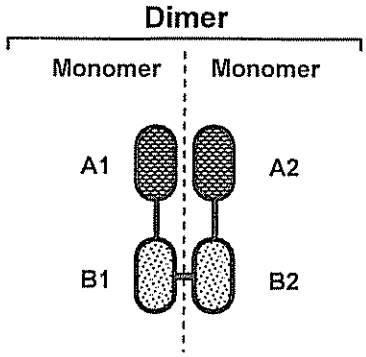
[3] "Half-life" is the time required for half the amount of a substance introduced into a living system to be eliminated or decomposed by natural processes. (*See* International Dictionary of Medicine and Biology, vol. 1, John Wiley & Sons (1986) at 1265) (Exh. 4).

[4] A "dimer" is "a compound formed by the union of two molecules of a simpler compound or a polymer formed by two molecules of a monomer." (*See* Webster's Third New International Dictionary, Merriam-Webster Inc. (1986) at 634) (Exh. 5)

Figure 5



C. Receptors And Ligands

"Receptors" and "ligands" are proteins that interact with each other. Receptors can exist on the surface of cells and can mediate (*e.g.*, promote or inhibit) biological responses within those cells. Such receptors are referred to as "membrane-bound" receptors because they are anchored in the membrane of the cell. The portion of the receptor that exists outside the cell is referred to as the "extracellular" portion. The term "ligand" refers to a protein that "binds" to the extracellular portion of a receptor. Ligands and receptors together form a matching pair, sometimes analogized to a lock and key. Ligands can be membrane-bound on the surface of another cell, or they can be "soluble" in the fluid of the body (*e.g.*, circulating in the blood). Receptors and ligands can exist as monomers or dimers.

There are various biological responses that receptor-ligand interactions can cause. For example, by binding to a receptor, a ligand can cause the receptor to transmit a "signal" to the interior of the cell, telling the cell to initiate some function, such as replication. Another example is, if one ligand ("L1") binds to a receptor, it can prevent another ligand ("L2") from binding to that same receptor by virtue of the fact that L1 is occupying the available binding site. In the foregoing circumstance, L1 would be functioning as an "antagonist" by blocking L2 from binding to the receptor.

Platelet derived growth factor receptor ("PDGF-R") is a membrane-bound receptor discussed in the patents-in-suit. It has various functions, including regulating cell growth and cell development. Under certain circumstances, PDGF-R can be activated by a ligand called platelet derived growth factor ("pdgf").[5] PDGF-R is found on the surface of the cell as a monomer **REDACTED**, whereas the soluble pdgf ligand is a dimer.

In the late 1980s, the named inventors were trying to create soluble (*i.e.*, not attached to the cell) PDGF-R that could function as an antagonist. That is, the scientists were trying to make soluble PDGF-R that could compete with naturally occurring (*i.e.*, membrane bound) PDGF-R for binding to pdgf. **REDACTED** The theory was that the soluble PDGF-R would occupy the pdgf binding sites, thereby preventing membrane-bound PDGF-R from binding to them. **REDACTED**

REDACTED As ZymoGenetics would learn, for soluble PDGF-R to function as an antagonist, it had to be "dimerized", to create a molecule with two PDGF-R monomers connected together. **REDACTED** That is, according to ZymoGenetics, PDGF-R requires dimerization for "biological activity".

D. Immunoglobulins

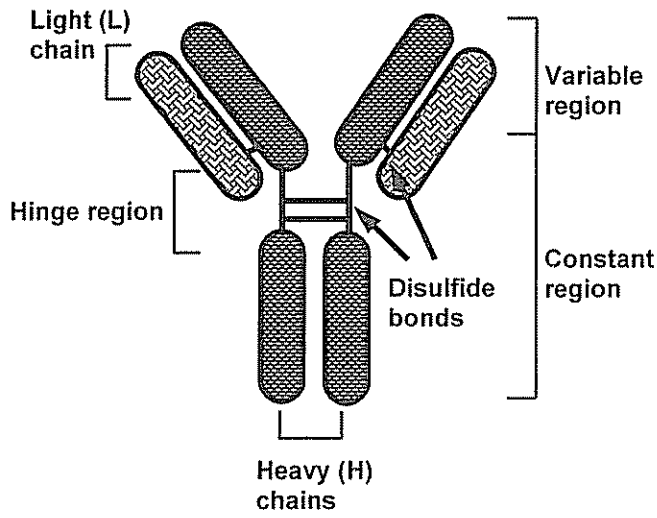
Immunoglobulins are proteins that are produced by the immune system to protect against foreign invaders, such as viruses. One of the most abundant types of human immunoglobulins are "antibodies", some of which are made up of four connected polypeptides (Figure 6). The bonds that hold the immunoglobulin units together are called "disulfide" bonds. Disulfide bonds occur frequently in proteins and function to create bridges between individual protein molecules.

[5] While platelet-derived growth factor ligands are typically referred to as "PDGF", it will be referred to herein as "pdgf" in an effort to avoid confusion between the ligand and its receptor.

They are formed when two amino acids called "cysteines" (with the thiol group "–SH") react with each other to give a disulfide bond ("–S–S–") between the two cysteines. The reaction can be written as: R–SH + R'–SH → R–S–S–R' (R and R' represent amino acid groups).

"Disulfide" bonds are a type of strong "covalent" bond. "Covalent" bonds are chemical bonds formed by the sharing of electrons. (*See*, Dorland's Illustrated Medical Dictionary, 27th Ed. (1988) at 223 (*See*, *e.g.*, "bond" at "covalent b." and "disulfide b.")) (Exh. 7). To the contrary, "non-covalent" bonds are weaker bonds that do not involve the sharing of electrons, but rather involve electromagnetic interactions. (*See* Exh. 7 at 223 (*See*, *e.g.*, "bond" at "hydrogen b." and "Van der Waals b.")). Disulfide bonds in the "hinge" region of an antibody hold the two "heavy" chain polypeptides together and a disulfide bond holds the heavy and "light" chains together, as shown in Figure 6.

Figure 6: Structure of an Immunoglobulin



Immunoglobulins are members of a family of proteins referred to as the "immunoglobulin superfamily" because they share certain features with each other.

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REDACTED

Portions of immunoglobulin molecules, such as portions of antibodies, have been used extensively in creating soluble fusion proteins.[6] In the patents-in-suit, ZymoGenetics' used portions of immunoglobulin antibodies to "dimerize" other polypeptides that are joined to the immunoglobulin antibodies that would not otherwise exist as dimers (and that were not biologically active as monomers) -- capitalizing on the fact that certain portions of native immunoglobulin antibodies can couple to each other and thereby "drive" dimerization of the resulting fusion protein.

E. Additional Technical Terms

There are several additional technical terms that appear throughout Bristol's brief. In defining the scope of the claim term "non-immunoglobulin peptide", ZymoGenetics took the position that "non-immunoglobulin polypeptides" do not include polypeptides encoded by immunoglobulin-like genes which encode discrete domains structurally similar to immunoglobulins. Further, ZymoGenetics took the position that "non-immunoglobulin peptides" do not include peptides that have significant sequence homology to immunoglobulin. The following discussion is intended to provide background and context to the terms underlined above.

The "sequence" (*i.e.*, order) of amino acids linked together to make a particular protein corresponds to a distinct sequence in an organism's genetic code. Organisms have many such "genes" (*i.e.*, specific sequences of what are referred to as "nucleotides"), each of which "encodes" (*i.e.*, specifies the genetic code for) a particular sequence of an amino acid that make

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[6] Immunoglobulin fusion proteins were made as early as 1984. (*See, e.g.*, Morrison, S.L., et al., *Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains*, Proc. Natl. Acad. Sci. USA, 81:6851-55 (1984)) (Exh. 9). Fusion proteins joining the T cell receptor (TCR) and immunoglobulin were made as early as 1986. (*See, e.g.*, Traunecker, A., et al., *A novel approach for preparing anti-T cell receptor constant region antibodies*, Eur. J. Immunol., 16:851-54 (1986)) (Exh. 10).

up the protein. Each protein can be considered to be composed of distinct three-dimensional subunits called "domains", and each domain of a protein can have a particular structural role (*e.g.*, to dimerize) or functional role (*e.g.*, to bind another protein). Proteins that have similar sequences of amino acids are referred to as being "homologous" or having "significant sequence homology." Proteins that have dissimilar sequences of amino acids are referred to as being "heterologous".

III. The Patents-In Suit

A. The '026 Patent

The '026 Patent was filed as U.S. Appl. No. 08/980,400 on November 26, 1997 and names Andrzej Z. Sledziewski, Lillian Anne Bell, and Wayne R. Kindsvogel as inventors. The '026 Patent issued on January 25, 2000. On March 16, 2004, ZymoGenetics filed a Request for Reexamination stating that prior art "raise[d] a substantial question of patentability for each of the 29 claims of the '026 patent . . . ." (ZymoGenetics' March 16, 2004 Request for Reexamination of U.S. Patent No. 6,018,026 at BMS004260620) (Exh. 11). A Reexamination Certificate was issued on July 4, 2006 after ZymoGenetics narrowed the claims.[7] Approximately 6 weeks later, on August 14, 2006, ZymoGenetics filed the present lawsuit alleging Bristol's Orencia® infringes the '026 Patent.

The asserted claims of the '026 Patent are related to fusion proteins that join (or fuse) a specific type of polypeptide ("**A**") to a specific type of protein ("**B**"). (See Figure 1). The polypeptide ("**A**") must (1) be "non-immunoglobulin", (2) "require dimerization for biological activity", and (3) not form dimers on its own. The protein ("**B**") that acts as a "dimerizing" protein must be selected from the group consisting of "yeast invertase, at least a portion of an

[7] When Bristol refers to the claims of the patents-in-suit, it is referring to the claims *post*-reexamination.

immunoglobulin light chain comprising at least an immunoglobulin light chain constant region domain, and at least a portion of an immunoglobulin heavy chain comprising at least an immunoglobulin heavy chain constant region domain." (*See, e.g.*, Exh. 1 at ZG000003, at col. 2, ll. 3-11). The polypeptide ("**A**") must not form a dimer on its own, otherwise the "dimerizing protein" ("**B**") would not be necessary -- that is, but for the presence and function of the "dimerizing protein" ("**B**"), the fusion protein ("**AB**") would not be a dimer.

B. The '725 Patent

The '725 Patent was filed as U.S. Appl. No. 08/475,458 on June 7, 1995 and names Andrzej Z. Sledziewski, Lillian Anne Bell, and Wayne R. Kindsvogel as inventors. The '725 Patent issued on December 1, 1998. On March 16, 2004, ZymoGenetics filed a Request for Reexamination stating that prior art "raise[d] a substantial question of patentability for each of the 49 claims of the '725 patent . . . ." (ZymoGenetics' March 16, 2004 Request for Reexamination of U.S. Patent No. 5,843,725 at BMS004261270) (Exh. 12). A Reexamination Certificate was issued on August 29, 2006 after ZymoGenetics narrowed its claims. Several weeks prior to issuance of the reexamination certificate, ZymoGenetics had already filed the present lawsuit alleging Bristol's process of making Orencia® infringes the '725 Patent.

The asserted claims of the '725 Patent are generally related to methods for producing the fusion proteins discussed above with respect to the '026 Patent, with the exception that some of the asserted claims refer to the fusion proteins as "receptor analogs", and rather than requiring "a non-immunoglobulin requiring dimerization for biological activity" they require "a ligand-binding domain of a receptor requiring dimerization for biological activity."

IV. Claims and Claim Terms At Issue

A. The '026 Patent

ZymoGenetics is asserting Claims 1-4, 7 and 30 of the '026 Patent against Bristol.

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The only independent claim of those asserted is Claim 1. '026 Patent Claim 1 is provided below, and the claim terms needing construction are underlined. The portions appearing in italics reflect changes made during reexamination of the '026 Patent.

> 1. 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, *wherein the dimerizing protein is selected from the group consisting of yeast invertase, at least a portion of an immunoglobulin light chain comprising at least an immunoglobulin light chain constant region domain, and at least a portion of an immunoglobulin heavy chain comprising at least an immunoglobulin heavy chain constant region domain.*

(Exh. 1 at ZG000003) (text in italics represents text added to the claim during reexamination).

B. The '725 Patent

ZymoGenetics is asserting Claims 1-3, 5, 6, 21, 22, 24, 25, 50 and 51 of the '725 Patent against Bristol. **REDACTED** The only independent claims of those asserted are Claims 1 and 21. '725 Patent Claims 1 and 21 are provided below. The claim terms needing construction are underlined. The portions appearing in italics reflects changes made during reexamination of the '725 Patent.

> 1. 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;

growing said host cell in an appropriate growth medium under physiological conditions to allow the secretion of a dimerized polypeptide fusion encoded by said DNA sequence; and

isolating said dimerized polypeptide fusion from said host cell,

wherein the dimerizing protein is selected from the group consisting of yeast invertase, at least a portion of an immunoglobulin light chain comprising at least an immunoglobulin light chain constant region domain, and at least a portion of an immunoglobulin heavy chain comprising at least an immunoglobulin heavy chain constant region domain.

21. 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 at least one 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 *joined* to said dimerizing protein;

growing said host cell in an appropriate growth medium under physiological conditions to allow the secretion of a receptor analog encoded by said DNA sequence; and

isolating said receptor analog from said host cell,

wherein the dimerizing protein is selected from the group consisting of yeast invertase, at least a portion of an immunoglobulin light chain comprising at least an immunoglobulin light chain constant region domain, and at least a portion of an immunoglobulin heavy chain comprising at least an immunoglobulin heavy chain constant region domain.

(Exh. 2 at ZG000844) (text in italics represents text added to the claim during reexamination).

V. Bristol's Proposed Constructions

Bristol's proposed constructions were set forth in the Joint Claim Construction Chart filed on May 7, 2008 which is attached as Exhibit 3.

VI. The Immunex Litigation

In March of 2002, ZymoGenetics filed a lawsuit against Immunex Corporation ("Immunex Litigation") for infringement of six U.S. patents. (ZymoGenetics' March 7, 2002 Complaint for Patent Infringement Filed Against Immunex Corp.) (Exh. 14). The two patents-at-

issue in the present litigation were also at issue during the Immunex Litigation. While the Immunex Litigation ultimately settled, **REDACTED**

[8] The relevant positions taken by ZymoGenetics will be discussed in the appropriate sections below.

ARGUMENT

I. General Claim Construction Principles

Courts construe patent claims as a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). In the *en banc* decision in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), *cert. denied*, 546 U.S. 1170 (2006), the Federal Circuit provided a comprehensive restatement of the current law of claim construction. *Id* at 1312-17.

A. Claim Construction Begins With the Language of the Claim

The "claims . . . define or delimit the scope of the legal protection which the government grant gives the patent owner, the patent 'monopoly.'" *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1274 (Fed. Cir. 1992). The claim language sets the boundaries of the claim's scope via a series of limiting words or phrases known as "elements" or "limitations." *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1258 (Fed. Cir. 1989). Each claim element or limitation must be considered meaningful. *Unique Concepts, Inc. v. Brown*, 939 F.2d 1558, 1562 (Fed. Cir. 1991).

[8] While the patents-in-suit have been subject to a reexamination and the claims have been significantly narrowed since the Immunex Litigation, the claim terms at issue during the Immunex Litigation and discussed herein were not altered during reexamination.

B. The Patent Specification Must Be Considered When Construing The Claims

While the language of the claims defines the scope of the claims, the claims should not be read in a vacuum; instead, "claims must be read in view of the specification, of which they are a part." *Markman*, 52 F.3d at 979; *see also Toro Co. v. White Consol. Indus. Inc.*, 199 F.3d 1295, 1301 (Fed. Cir. 1999) (claims are "not construed in a lexicographic vacuum, but in the context of the specification and drawings."). The patent specification is important as it places the invention in its technological context. *Fromson v. Anitec Printing Plates, Inc.*, 132 F.3d 1437, 1442-43 (Fed. Cir. 1997).

The patent specification may limit the scope of a claim because claim scope cannot exceed the scope of the disclosure. *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001) ("neither do the claims enlarge what is patented beyond what the inventor has described [in the specification] as the invention."); *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998) ("the scope of the right to exclude may be limited by a narrow disclosure.").

C. The Prosecution History Is Significant In Determining The Meaning Of The Claims

The prosecution history of a patent contains a complete record of the proceedings before the Patent Office. *Jonsson v. Stanley Works*, 903 F.2d 812, 818 (Fed. Cir. 1990). "Prosecution history is an important source of intrinsic evidence in interpreting claims because it is a contemporaneous exchange between the applicant and the examiner." *Desper Prods., Inc. v. QSound Labs, Inc.*, 157 F.3d 1325, 1336-37 (Fed. Cir. 1998). Arguments made during prosecution shed light on what the patentee understood the claim terms to mean. *See Southwall Tech., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576-77 (Fed. Cir. 1995). The prosecution history,

therefore, "is often of critical significance in determining the meaning of the claims." *Vitronics, Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

"[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1317. Through statements made during prosecution, the patentee may commit to a particular meaning for a patent term, which is then binding. *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1159 (Fed. Cir. 1997). "Indeed, 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." *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000) (internal quotations and citation omitted). For instance, "[e]xplicit arguments made during prosecution to overcome prior art can lead to narrow claim interpretations." *Lampi Corp. v. American Power Prods., Inc.*, 228 F.3d 1365, 1374 (Fed. Cir. 2000) (*quoting Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372 (Fed. Cir. 1998)). Indeed, "[b]y distinguishing the claimed invention over the prior art, an applicant is indicating what the claims do not cover." *Id.*

D. Where Claims Are Equally Susceptible To Two Different Interpretations, the Narrower One Prevails

Whenever claim language is ambiguous and equally susceptible to two different interpretations, the narrower one controls. As stated by the Federal Circuit in *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1581 (Fed. Cir. 1996):

> Where there is an equal choice between a broader and a narrower meaning of a claim, and there is an enabling disclosure that indicates that the applicant is at least entitled to a claim having the narrower meaning, we consider the notice function of the claim [required under 35 U.S.C. § 112, ¶ 2] to be best served by adopting the narrower meaning.

E. Prosecution Of Related Applications Can Be Relevant To Claim Construction

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. *Jonsson* 903 F.2d at 818. In *Jonsson*, the patent-at-issue ("Patent B") was a continuation-in-part of another application ("Patent A"). Finding that the district court did not err in relying upon arguments and remarks made during prosecution of Patent A, the Federal Circuit concluded that the prosecution of Patent A with respect to the term "diffuse light" was relevant to construing the same term in Patent B. *Id.*; *see also Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004) ("[a]ny statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction . . ."), *cert. denied*, 543 U.S. 821 (2004); *Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999) ("[w]hen multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation"); *Genzyme Corp. v. Atrium Med. Corp.*, 212 F. Supp. 2d 292, 316 (D. Del. 2002) ("[a]s statements made during the prosecution of this related application may impact the claim construction of the limitations of the '531 patent, the court will review the prosecution history of this application as well").

Prosecution of foreign counterparts can also be relevant to the scope of claims. For example, in *Tanabe Seiyaku Co., Ltd. v. United States Int'l Trade Comm'n*, 109 F.3d 726, 730 (Fed. Cir. 1997), the Federal Circuit approved the International Trade Commission's consideration of foreign prosecution of counterpart applications in determining the scope of the claims. 109 F.3d 726, 730 (Fed. Cir. 1997).

> Because Tanabe represented that its "specific base-solvent combinations" distinguish its process from the prior art, Tanabe's statements to foreign patent offices suggest to a person skilled in the art that other solvents . . . may not be interchangeable with the claimed solvents.

Id. at 733.

II. Bristol's Proposed Construction Of The Limitations At Issue

A. "biologically active" / "active" and "biological activity"

1. "biologically active" / "active"

The asserted claims of the '026 Patent require that the resulting fusion proteins be "biologically active" as set forth in the preamble to Claim 1: "[a] ***biologically active***, dimerized polypeptide fusion, comprising . . .". (Exh. 1 at ZG000003) (emphasis added). Likewise, Claim 1 of the '725 Patent (and all claims which depend thereon) is a method capable of producing a "biologically active" fusion protein as set forth in the preamble: "[a] method for producing a secreted ***active*** dimerized polypeptide fusion, comprising . . .". (Exh. 2 at ZG000844) (emphasis added).

REDACTED

The patents-in-suit define "biologically active" in the context of recombinant proteins (*i.e.*, fusion proteins):

[9] Similarly, Claim 21 of the '725 Patent (and all claims which depend thereon) must be "active" in that they require the method be capable of producing a fusion protein that is capable of binding ligand. *See* construction of "receptor analog" *infra* at 36-38.

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> A recombinant protein or peptide is considered to be ***biologically active*** if it exhibits one or more biological activities of its native counterpart.

(Exh. 1 at col. 9, ll. 61-63; Exh. 2 at col. 9, ll. 43-46) (emphasis added). As the relevant asserted claims are directed towards recombinant proteins (*i.e.*, fusion proteins), "biologically active" should be construed to mean "exhibits one or more biological activities of its native counterpart."

The terms "biologically active" and "active" are part of the claim preamble. A patent claim typically contains three parts: the preamble, the transition, and the body. The preamble is often an introductory phrase that summarizes the invention, its relation to the prior art, or its intended use or properties. (3-8 Chisum on Patents §8.06[1][b] (2008)). The Federal Circuit has held 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) ("review 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). In *Computer Docking*, the Federal Circuit stated:

> In considering whether a preamble limits a claim, the preamble is analyzed to ascertain whether it states a necessary and defining aspect of the invention, or is simply an introduction to the general field of the claim. *On Demand Mach. Corp. v. Ingram Indus.*, 442 F.3d 1331, 1343 (Fed. Cir. 2006). The terms at issue here clearly recite a necessary and defining aspect of the invention, specifically its portability. The written description and applicants' statements during prosecution emphasize this feature of the invention, yet this limitation does not appear in the body of the claims. As a result, this court finds that the terms "portable computer" and "portable computer microprocessing system" limit the scope of the asserted claims.

Id. (internal quotations omitted); *see also*, *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 866 (Fed. Cir. 1985) ("Although it appears in the preambles of the '012 patent claims, 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) ("[t]he 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).

Similarly, the fusion proteins of the '026 Patent being "biologically active" is a necessary and defining aspect of the alleged inventions in the asserted claims of the '026 Patent, as dimerization is required "***for biological activity***." (Exh. 1 at ZG000003, col. 2, ll. 1-2) (emphasis added).

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". (Excerpts of Prosecution History of U.S. Pat. No. 6,018,026 at BMS004258871-876, 879) (Exh. 17). In response, ZymoGenetics amended the claims by adding "biologically active" to the preamble. (Exh. 17 at BMS004258878).

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".

2. "biological activity"

All asserted claims of the '026 and '725 Patent contain the claim term "biological activity". According to the patent specification, the definition of the term "biological activity" is: "[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)." (Exh. 1 at col. 9, ll. 54-56; Exh. 2 at col. 9, ll. 35-37). However, ZymoGenetics' proposed construction of the term

"biological activity" as only corresponding to particular in vivo examples provided in the specification is improper. Treating those non-limiting in vivo examples as essential distorts and unduly limits the meaning of the claim.

B. "requiring dimerization for biological activity"

All asserted claims of the patents-in-suit contain the limitation "requiring dimerization for biological activity". The dictionary definition of "require" is "to demand as necessary or essential . . . make indispensable . . ." (*See*, *e.g.*, Exh. 5 at 1929, 3.b).[10] "Dimerization" is "the process of dimerizing or the state of being dimerized." (*See*, *e.g.*, Exh. 5 at 634). *See Phillips*, 415 F.2d at 1314 (where ordinary meaning of a language is readily apparent to lay judges, general purpose dictionaries may be helpful). However, as discussed below the specifications and prosecution histories provide further clarification as to the meaning of "requiring dimerization for biological activity", such that the term should be construed to mean:

> 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.

1. unless a dimer, it has no biological activity

As discussed in the Technical Background, *see supra* at 6, some polypeptides are not biologically active unless they are dimers. **REDACTED** For example, soluble PDGF-R will not function as an antagonist unless it is a dimer. (*See supra* Technical Background, Section C). On the other hand, some polypeptides are biologically active as monomers (*e.g.*, they can act as antagonists even as monomers), regardless of whether or not their biological activity is "enhanced" by dimerization.

REDACTED

ZymoGenetics clearly distinguished between circumstances where dimerization is "required" from where dimerization "enhances" biological activity. For example, in the specifications of the patents-in-suit, ZymoGenetics discusses EGF-R and insulin receptor, which differ in this regard:

> Receptor analogs that may be used in the present invention include the ligand-binding domains of the epidermal growth factor receptor (EGF-R) and the insulin receptor. . . . ***EGF-R diners [sic] have been found to exhibit higher ligand-binding affinity than EGF-R monomers. The insulin receptor requires dimerization for biological activity.***

(Exh. 1 at col 10, l. 58 - col 11, l. 4) (emphasis added)(internal references omitted).[11] And, the specification states that the invention:

> . . . provide[s] dimerized non-immunoglobulin polypeptide fusions of therapeutic value that are ***biologically active only as dimers***.

(Exh. 2 at col. 9, l. 67 - col. 10, l. 3) (emphasis added).

Further, the specification states the process described could have been used to produce either kind of fusion protein:

> As noted above, the present invention provides methods for producing dimerized polypeptide fusions that ***require dimerization for biological activity or enhancement of biological activity***. Polypeptides requiring dimerization for biological activity include, in addition to certain receptors, nerve growth factor, colony-stimulating factor-1 (CSF-1), transforming growth factor ß (TGF-ß) , PDGF, and factor XIII.

(Exh. 1 at col 11, ll. 51-58) (emphasis added). However, ZymoGenetics clearly limited the claims at issue to "requiring dimerization for biological activity" and did not claim using dimerization to "enhance" biological activity. Subject matter disclosed in a patent that is not claimed is deemed dedicated to the public under the Federal Circuit's disclosure-dedication rule:

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[11] "Affinity" is the tendency of a molecule to associate with another or combine or interact. (*See, e.g.*, Exh. 4 at 56).

> [W]hen a patent drafter discloses but declines to claim subject matter . . . this action dedicates that unclaimed subject matter to the public.

Johnson & Johnston, 285 F.3d 1046, 1054 (Fed. Cir. 2002) (*en banc*).

The fact that ZymoGenetics understood the difference between "requiring" versus "enhanced" is evidenced by their other, related patents. For example, ZymoGenetics' U.S. Patent No. 6,323,323 B1 ("the '323 Patent"), which was a continuation of the '026 Patent and claims priority to the same Priority Application as the patents-in-suit claims:

> 1. A ligand-binding, dimerized polypeptide fusion comprising two polypeptide chains, each of said chains comprising:
> (a) a ligand-binding domain of either a growth factor receptor or a hormone receptor joined to
> (b) an immunoglobulin constant region polypeptide, wherein dimerization of the polypeptide fusion results in ***enhancement of biological activity***.

(U.S. Patent No. 6,323,323) (Exh. 18) (emphasis added).

The '323 Patent was at issue during the Immunex Litigation. **REDACTED**

REDACTED

(Exh. 15 at 9-10 (emphasis added); *see also* Exh. 16 83:9-23;143:11-144:2; 146:16-147:6).[12, 13] That is, for example, if the ligand binding of a non-immunoglobulin polypeptide or receptor

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analog was increased though dimerization, it would be considered an "enhancement" of biological activity through dimerization, rather than "requiring dimerization for biological activity".

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A polypeptide that, in monomeric form, possesses biological activity is not one "requiring dimerization".

REDACTED

(Exh. 15 at 17).

REDACTED

Therefore, "requiring dimerization for biological activity" means the polypeptide in question has biological activity only when it is a dimer, not when it is a monomer.

2. will not dimerize on its own

ZymoGenetics also intended the term "requiring dimerization for biological activity" to have a further meaning -- the polypeptide at issue will not dimerize on its own. As will be discussed in further detail below, the prosecution history of a related patent, U.S. Patent No. 5,155,027 ("the '027 Patent")(Exh. 19 at ZG051582-617), makes clear that ZymoGenetics disclaimed coverage of polypeptides (*i.e.*, Part "**A**" of Figure 1) which will dimerize on their own by adding the claim limitation "requiring dimerization for biological activity". *Jonsson*, 903 F.2d at 818.

The doctrine of prosecution disclaimer precludes patentees from recapturing meanings clearly and unmistakably disclaimed during prosecution under the guise of claim construction to protect the public's reliance on definitive statements made during prosecution. *See Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323-24 (Fed. Cir. 2003). Prosecution disclaimer can involve statements from prosecution of a related patent concerning the same subject matter as the claim language at issue. *See, e.g., Ormco Corp. v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007); *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 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" so long as the statement in the prosecution history is clear and unambiguous and constitutes a clear disavowal of scope) (*quoting Microsoft*, 357 F.3d at 1350); *Omega Eng'g, Inc.*, 334 F.3d at 1333 ("prosecution disclaimer may arise from disavowals made during the prosecution of ancestor patent applications"); *Wang Labs., Inc. v. Am. Online, Inc.*, 197 F.3d 1377, 1384 (Fed. Cir. 1999); *Jonsson*, 903 F.2d at 818.

Both patents-in-suit are continuations-in-part of U.S. application No. 07/347,291 filed on May 2, 1989, which resulted in the '027 Patent. (Exh. 1 at ZG000001; Exh. 2 at ZG000844). The '027 Patent prosecution history is relevant to the understanding of the meaning of "requiring dimerization for biological activity", as it was a claim term added during the prosecution of the '027 Patent to avoid prior art raised by the Examiner.

As of March 1992, there was a single claim pending for examination in the '027 Patent -- claim 22. Claim 22 was as follows:

> 22. A method for producing a secreted, biologically active peptide dimer, comprising:
>
> introducing into a eukaryotic host cell a first DNA construct comprising a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame with a first DNA sequence encoding a first polypeptide chain of a peptide dimer joined to a DNA sequence encoding an immunoglobulin light chain constant region;
>
> introducing into said host cell a second DNA construct comprising a transcriptional promoter operatively linked to a second secretory signal sequence followed downstream by and in proper reading frame with a second DNA sequence encoding a second polypeptide chain of a peptide dimer joined to a DNA sequence encoding at least one immunoglobulin heavy chain constant region domain selected from the group consisting of C_H1, C_H2, C_H3, and C_H4;
>
> growing said host cell in an appropriate growth medium under physiological conditions to allow the dimerization and secretion of said biologically active peptide dimer; and
>
> isolating said biologically active peptide dimer from said host cell.

(Excerpts of Prosecution History of U.S. Pat. No. 5,155,027 at BMS004259127-128) (Exh. 20).

In an office action dated March 2, 1990, the Examiner rejected the Claim 22 for being anticipated by two references referred to as Boss(A) and Boss(L). (Exh. 20 at BMS004259277-279).[14] Boss(A) describes immunoglobulin ("Ig") fusion proteins. (U.S. Patent No. 4,816,397 ("Boss (A)")) (Exh. 21). Boss(A) 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." (Exh. 21 at col. 5, ll. 18-20). That is, Boss (A) envisaged fusing Ig molecules (Part "**B**" of Figure 1) to polypeptides (Part "**A**" of Figure 1).

In response to this office action, ZymoGenetics amended Claim 22 and distinguished their alleged invention from Boss(A) and Boss(L) on the following grounds:

> Claim 22 was rejected under 35 U.S.C. § 102(e) as being anticipated by Boss et al. (U.S. Patent No. 4,816,397) and Boss et al. (EP 120,694).
>
> Applicants respectfully traverse this ground of rejection. Boss et al. do not teach or suggest the dimerized polypeptide fusions or methods of producing such fusions as claimed in the subject application. 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.

(Exh. 20 at BMS004259290) (emphasis added). In response, the Examiner pointed out the specific text of "Boss(L)":

> [ZymoGenetics] claim[s] that Boss et al. do not teach or suggest the use of the immunoglobulin constant region in the dimerization of non-immunoglobulin polypeptides. Boss(L) does teach that "it 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." This passage teaches the production of multichain fusion proteins in which one component is an immunoglobulin chain. ***Whether the peptide moiety becomes dimerized or not would be dictated by the moiety chosen.***

[14] A copy of the references referred to as "Boss(A)" and "Boss(L)" by the Examiner are attached as Exhibits 21 and 22, respectively.

(Exh. 20 at BMS004259315-316). That is, for example, if the peptide moiety[15] (Part "**A**" of Figure 1) chosen to be fused to the Ig (Part "**B**" of Figure 1) was 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. In response, ZymoGenetics amended the claim, as follows:

> 22. (Twice Amended) A method for producing a secreted, biologically active, dimerized polypeptide fusion, comprising:
>
> introducing into a eukaryotic host cell a first DNA construct comprising a transcriptional promoter operatively linked to a first secretory signal sequence followed downstream by and in proper reading frame with a first DNA sequence encoding a first polypeptide chain of a non-immunoglobulin polypeptide dimer requiring dimerization for biological activity joined to a DNA sequence encoding an immunoglobulin light chain constant region . . .

(Exh. 20 at BMS4259320). It is clear and unambiguous that ZymoGenetics disavowed circumstances where non-immunoglobulin polypeptides would form dimers on their own (without the aid of a "dimerizing protein") from the scope of the term "requiring dimerization for biological activity", as they amended their claim by adding this term to address the Examiner's rejection based on the fact that the "peptide moiety" (*i.e.*, Part "**A**" of Figure 1) in certain circumstances will dictate dimerization.

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[15] A "moiety" is one of the portions into which something is divided. (Exh. 4 at 1791).

REDACTED

For the foregoing reasons, "requiring dimerization for biological activity" should be construed to mean:

> 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.

C. "dimerizing protein"

All asserted claims of the patents-in-suit contain the limitation "dimerizing protein". As stated above, a "dimer" is a compound formed by the union of two monomer molecules. (*See*, *e.g.*, Exh. 5 at 634). The term "dimerize" is a verb that means "to polymerize to a dimer." *Id.*

REDACTED

Adding the suffix "-ing" serves to form a present participle of the verb "dimerize". Therefore, the "dimerizing protein" must cause the formation of a dimer.

REDACTED

As discussed in the specifications of the patents-in-suit, dimerization is accomplished by one polypeptide having an "affinity" for a second polypeptide:

> 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.

(Exh. 1 at col. 9, ll. 47-50; Exh. 2 at col. 9, ll. 30-34) (emphasis added). The fusion protein becomes "dimerized" by the affinity that the "dimerizing protein" polypeptide chains have for each other.

According to the specifications of the patents-in-suit, the "affinity" of the dimerizing protein polypeptides chains for each other must "drive" the association of the non-immunoglobulin portion of the molecule:

> As shown herein, the present invention utilizes such an arrangement to ***drive*** the association of the polypeptide or receptor analog to form a biologically active molecule upon secretion.
>
> * * *
>
> 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.

(Exh. 1 at col. 13, ll. 28-31, 42-44, 53-55; Exh. 2 at col. 13, ll. 7-10, 22-24, 32-34) (emphasis added).

Moreover, ZymoGenetics made clear during prosecution of the '027 Patent that the immunoglobulin portion (*i.e.*, the dimerizing protein) must be the portion of the fusion protein

that drives the dimerization of the fusion protein. As discussed earlier, as of March 1990, there was a single claim, Claim 22, pending for examination, and the Examiner rejected it for being anticipated by the Boss(A) and Boss(L) references. (See *supra* at 25-27); (Exh. 20 at BMS004259277-79).

In response to this office action, ZymoGenetics amended claim 22 and distinguished their alleged invention from Boss on the following grounds:

> Claim 22 was rejected under 35 U.S.C. § 102(e) as being anticipated by Boss et al. (U.S. Patent No. 4,816,397) and Boss et al. (EP 120,694).
>
> Applicants respectfully traverse this ground of rejection. Boss et al. do not teach or suggest the dimerized polypeptide fusions of methods of producing such fusions as claimed in the subject application. 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.

(Exh. 20 at BMS004259290) (emphasis added).[17] Therefore, the "immunoglobulin portion" (*i.e.*, the "dimerizing protein") of the fusion protein must be what drives the dimerization of the "non-immunoglobulin" portion of the fusion protein. The "non-immunoglobulin" portion of the fusion protein must not be driving the dimerization.

REDACTED

[17] In the claim at issue, an immunoglobulin molecule was being used as the "dimerizing protein".

REDACTED

Therefore, the "dimerizing protein" is not the "non-immunoglobulin" portion of the fusion protein (*i.e.*, Part "**A**" of Figure 1). And, "dimerizing protein" should be construed as follows:

> 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

D. "non-immunoglobulin polypeptide"

The asserted claims of the '026 Patent and asserted claims 1, 2, 3, 5, 6 and 50 of the '725 Patent contain the term "non-immunoglobulin polypeptide".[18] "Non-immunoglobulin polypeptide" does not have an ordinary meaning in the scientific community, and the specifications of the patents-in-suit do not define it. However, ZymoGenetics made

[18] The remaining asserted claims of the '725 Patent -- claims 21, 22, 24, 25 and 51 -- are methods for producing "receptor analogs" which also must be "non-immunoglobulin polypeptides". *See infra* at 36-38. Therefore, all of the claims asserted against Bristol require a polypeptide that is a "non-immunoglobulin".

representations concerning the scope of the term "non-immunoglobulin peptide"[19] in an attempt to distinguish prior art during prosecution of the priority application for the patents-in-suit. As discussed further below, based on ZymoGenetics' representations, "non-immunoglobulin polypeptide" should be construed to exclude:[20]

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

(b) polypeptides that have significant sequence homology to immunoglobulin.

1. The Prosecution Of The Priority Application

The '725 Patent identifies European patent application 8910087 as "Foreign Application Priority Data" ("Priority Application")(Exh. 26) and identifies a January 18, 1989 date for this application. (Exh. 2 at cover page).[21] The Priority Application and the patents-in-suit share the same parent application -- U.S. Patent Appl. No. 07/146,877. (*See* Exh. 1; Exh. 2; Exh. 26).

As discussed above, related applications, including those prosecuted in foreign countries, can be relevant to the scope of claim terms. (*Supra* at 16). In the present instance, the related application at issue is the Priority Application itself.

The term "non-immunoglobulin" was used in the Priority Application, but it was not a limitation in the claims as originally filed. (Exh. 26 at BMS004261581-588). The limitation was added to modify the term "peptide" in an attempt to overcome prior art. (Exh. 26 at BMS004261732-741). On September 4, 1992, the Examiner rejected the pending claims of the

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[19] While the claim term added was non-immunoglobulin "peptide" rather than non-immunoglobulin "polypeptide", the terms "peptides" and "polypeptide" are used interchangeably.

REDACTED

[20] The terms "domains", genes", "sequence", and "homology" appearing in (a) and (b) are discussed *supra* Technical Background Section E at 8-9.

[21] While the '026 Patent does not identify the same Foreign Priority Application Data, ZymoGenetics alleges it is entitled to a priority date based on the same European patent application.

REDACTED

Priority Application on the basis that prior art described fusion proteins composed of (1) T-cell receptor ("TCR") and (2) immunoglobulin ("Ig").[22] (Exh. 26 at BMS004261718). The prior art at issue was Kuwana, Y., et al., *Expression of chimeric receptor composed of immunoglobulin-derived V regions and T-cell receptor-derived C regions*, Biochem. and Biophys. Res. Commun., vol. 149, issue 3, 960-68 (1987) ("Kuwana") (Exh. 27). In the communication rejecting the claims, the examiner stated that "[Kuwana] is novelty-destroying (Article 54(1)(2) EPC) for Claims 3, 6-8 and 16." (Exh. 26 at BMS004261718).[23] At the time the Examiner made the rejection, a representative claim pending during prosecution of the Priority Application was as follows:

> 3. A method for producing a secreted, biologically active peptide dimer, comprising:
> introducing into a host cell a DNA construct capable of directing the expression and secretion of a biologically active peptide dimer, said DNA construct containing a transcriptional promoter operatively linked to at least one secretory signal sequence followed downstream by and in proper reading frame with a DNA sequence encoding a peptide requiring dimerization for biological activity fused to a dimerizing protein;
> growing said host cell in an appropriate growth medium under conditions allowing the dimerization and secretion of the peptide dimer; and
> isolating said polypeptide dimer from said host cell.

(Exh. 26 at BMS004261581-582).

On March 11, 1993, in response to the Examiner's rejection, ZymoGenetics amended the claim by adding the term "non-immunoglobulin" in the following phrase of pending claim 3: ". . . a DNA sequence encoding a non-immunoglobulin peptide requiring dimerization for biological

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[22] The fusion protein containing both TCR and Ig is referred to as "TCR-Ig".

[23] Article 54 of the European Patent Convention (entitled "Novelty") sections (1) and (2) are:
(1) An invention shall be considered to be new if it does not form part of the state of the art.
(2) The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.
European Patent Convention, art. 54, Oct. 5, 1973, 13 I.L.M. 268.

activity . . . ." Then, ZymoGenetics distinguished the T cell receptor ("TCR") from "non-immunoglobulin" peptides:

> With regard to paragraphs 2 and 2.1 of the [September 4, 1992] Communication, Claim 3 has been amended to recite a DNA constant region containing "DNA sequence encoding a non-immunoglobulin peptide requiring dimerization for biological activity.". This amendment has been made to claim more distinctly particular aspects which the Applicant regard as their invention.
>
> * * *
>
> 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.

(Exh. 26 at BMS004261732) (emphasis in original).[24] In making the above representations to the Examiner to distinguish TCR-Ig, ZymoGenetics excluded the following subject matter from the scope of the term "non-immunoglobulin":

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

(b) polypeptides that have significant sequence homology to immunoglobulin.

ZymoGenetics included the term "non-immunoglobulin" in the claims of the patents-in-suit, the applications for which were filed years later. ZymoGenetics should not be permitted to capture subject matter that was disavowed in an attempt to avoid prior art. *See, e.g.*, *Microsoft*, 357 F.3d at 1350 ("[a]ny statement of the patentee in the prosecution of a related application as to the scope of the invention would be relevant to claim construction . . .").

[24] The Examiner still rejected the claims in the EPO (Exh. 26 at BMS004261744), and ZymoGenetics made further amendments (Exh. 26 at BMS004261767-768, retaining the limitation "non-immunoglobulin").

2. Relevant 30(b)(6) And Inventor Testimony

REDACTED

[25] *See Phillips*, 415 F.3d at 1317 (stating inventor testimony may be considered by courts); *Wyeth v. Impax Labs, Inc.*, 526 F. Supp. 2d 474, 477 (D. Del. 2007) ("[a] court may consider . . . inventor testimony . . . in order to assist it in understanding the underlying technology, the meaning of terms to one skilled in the art and how the invention works.").

REDACTED

For the foregoing reasons, the term "non-immunoglobulin polypeptide" should be construed as follows:

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

E. "receptor analog"

Claim 21 of the '725 Patent (and therefore claims 22, 24, 25 and 51, which depend on claim 21) contains the following preamble: "[a] method for producing a secreted ***receptor analog*** . . .". (Exh. 2 at ZG000844, col. 2, ll. 13-14) (emphasis added). The term "receptor analog" appears elsewhere throughout Claim 21 as a limitation as well. (*See* Exh. 2 at ZG000844, col. 2, ll. 13-37).

In the field of cellular biology, a "receptor" generally refers to a structure on the surface of a cell or inside a cell that selectively binds to a specific substance.[26] An "analog" generally refers to a substance that is similar, but not identical, to another.[27] "Receptor analog" is described in the specifications as a "non-immunoglobulin":

> A ***non-immunoglobulin polypeptide*** comprising a portion of a receptor which is ***capable of binding ligand and/or is recognized by anti-receptor antibodies***. . . . A receptor analog may be, for example, the ligand-binding domain of a receptor . . .

(Exh. 2 at col. 9, ll. 18-25; Exh. 1 at col. 9, ll. 33-40]) (emphasis added). Therefore, the "receptor analog" of Claim 21 of the '725 Patent must be a "non-immunoglobulin polypeptide."

While the definition in the specification allows for a receptor analog that is "capable of binding ligand and/or is recognized by anti-receptor antibodies", 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 "capable of binding ligand":

> 21. 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 at least one 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 *joined* to said dimerizing protein . . .

(Exh. 2 at ZG000844, col. 2, ll. 13-25) (emphasis added, italics in original). Therefore, the receptor analog must be capable of binding ligand.

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[26] A "receptor" is a structure, often on a cell membrane, with binding affinity for a particular ligand. (*See supra* Technical Background, Section C at 5).

[27] An "analog", or analogue, is defined as a "substance that is similar in molecular structure and chemical properties to another." (Exh. 4 at 107 (*See, e.g.*, "analogue")).

Thus, the term "receptor analog" within the context of Claim 21 should be construed to mean: a non-immunoglobulin polypeptide comprising a portion of a receptor which is capable of binding ligand. Taking the definition of "receptor analog" in the patent specification and replacing the term "non-immunoglobulin" therein with Bristol's proposed construction (*supra* at 36), and applying the context of Claim 21, the construction of "receptor analog" becomes:

> 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.

F. "ligand-binding domain of a receptor" and "ligand"

Claim 21 of the '725 Patent (and therefore Claims 22, 24, 25 and 51, which depend on Claim 21) contains the claim term "ligand-binding domain of a receptor". (Exh. 2 at ZG000844, col. 2, ll. 20-21). It is unclear why ZymoGenetics wishes to construe the term "ligand". Other than within the phrase "ligand-binding domain of a receptor", it appears nowhere else within the asserted claims, and the specification defines "ligand-binding domain of a receptor". Nevertheless, ZymoGenetics' proposed construction contains superfluous information.

1. "ligand-binding domain of a receptor"

The specification indicates that the term "ligand-binding domain of a receptor"[28] is intended to mean "that portion of a receptor that is involved in binding the natural ligand":

> As used herein, ***the ligand-binding domain of a receptor is that portion of the receptor that is involved with binding the natural ligand***.

REDACTED

(Exh. 2 at col. 10, ll. 10-50) (emphasis added).

However, looking at how this term is used in Claim 21, it is clear that the "ligand-binding domain of a receptor" must be part of the "receptor analog". And, as the "receptor analog" must be a "non-immunoglobulin polypeptide", so must the "ligand-binding domain of a receptor".

REDACTED

Therefore, "ligand-binding domain of a receptor", when taking the description in the specification into account as well as the fact that it must be a "non-immunoglobulin polypeptide", 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.

2. "ligand"

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." (Exh. 2 at col. 9, ll. 47-48). ZymoGenetics' proposed construction contains definitions of agonists, antagonists and whether or not ligands can be chemically synthesized or occur in nature. Such information is unnecessary and superfluous to a proper construction of the term "ligand."

CONCLUSION

For the foregoing reasons, Bristol requests its construction of the claim terms be adopted by the Court.

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Dated: May 16, 2008

UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on May 16, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF and caused the same to be served on the plaintiff at the address and in the manner indicated below:

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