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VIA CM/ECF AND HAND DELIVERY

The Honorable Sue L. Robinson
United States District Court
District of Delaware
844 King Street
Wilmington, Delaware 19801

Re: ZymoGenetics, Inc. v. Bristol-Myers Squibb Co.
C.A. No. 06-500 (SLR)

Dear Judge Robinson:

During the course of the June 27, 2008 claim construction hearing concerning the above-referenced litigation, the Court suggested that the parties review the *Syngenta Seeds, Inc. v. Monsanto Co.,* 2004 WL 2758673 (D. Del. Nov. 19, 2004) decision and provide claim construction of a particular phrase at issue so that it is more understandable and in context. In addition to the phrase specifically identified by the Court, Bristol believes it would be helpful to provide a similar construction with respect to similar language in Claim 21 of the '725 patent. Accordingly, Bristol provides constructions of the following phrases (*see* Attachment 1):

- "a non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein heterologous to said non-immunoglobulin polypeptide" (relevant to Claim 1 of the '026 Patent and Claim 1 of the '725 Patent); and

- "a ligand-binding domain of a receptor requiring dimerization for biological activity joined to a dimerizing protein heterologous to said ligand-binding domain" (relevant to Claim 21 of the '725 Patent).

Bristol also construed the three independent claims to provide context which it believes is further in line with the *Syngenta Seeds* decision. (*See* Attachment 1).[1] [2]

In an effort to (a) confirm that the parties had the same understanding regarding the Court's request, (b) exchange constructions to see if there could be some agreement reached with respect to language that the parties could agree upon, and (c) coordinate the filing (*i.e.,* either by filing jointly or by coordinating the format of the parties' respective filings), Bristol contacted ZymoGenetics and provided it with Bristol's proposed format for today's submission. ZymoGenetics indicated it did not agree with Bristol's approach, refused to exchange proposed constructions of the phrases at issue and would not provide Bristol with its proposed format.

If Your Honor has any questions concerning Bristol's submission or its constructions, counsel is available at the Court's convenience.

Respectfully,

Kelly E. Farnan

Kelly E. Farnan (#4395)

KEF/jmk
cc: Philip A. Rovner, Esq. (via CM/ECF)

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[1] Bristol believes its constructions provided in its opening claim construction brief were correct, and has incorporated these constructions into the full claims, while attempting to make the language more understandable in accordance with the Court's instructions.

[2] ZymoGenetics stated that it did not plan to submit constructions of the entire claims and indicated it would reserve its rights with respect to the Court's direction to the parties.

'026 Patent Claim 1	**BRISTOL'S Original Proposed Constructions of the Claim Terms**	**BRISTOL'S construction of the phrase "a non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein heterologous to said non-immunoglobulin polypeptide"**	**Entire '026 Patent Claim 1 Construed by BRISTOL**
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.	biologically active: exhibits one or more biological activities of its native counterpart non-immunoglobulin polypeptide: a polypeptide that: (a) is not encoded by immunoglobulin-like genes which encode discreted domains structurally similar to immunoglobulin; and (b) does not have significant sequence homology to immunoglobulin requiring dimerization for biological activity: 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 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) dimerizing protein: 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	a chain made up of two protein segments (Parts A and B) joined to each other, where: (1) Part A is a protein that: (a) is not immunoglobulin-like (that is, is not encoded by immunoglobulin-like genes and does not have significant sequence homology to immunoglobulin); (b) does not have biological activity (that is, does not perform a function or set of activities in a biological context either in an organism or in a simulation of what occurs in an organism) unless it is a dimer; and (c) will not become a dimer with another Part A on its own; (2) Part B is a protein that: (a) has an affinity for Part B of another chain, such that: (i) the Parts B of the two chains associate with each other under physiological conditions thereby causing the two chains to become a dimer; and (ii) the Parts B of the two chains cause Part A (which would not form a dimer with another Part A on its own) to become a dimer with another Part A; and (b) is different from Part A	A biologically active compound made up of two chains connected to each other (that is, a compound that is a dimer), where each chain contains two protein segments (Parts A and B) joined to each other, and where: (1) Part A is a protein that: (a) is not immunoglobulin-like (that is, is not encoded by immunoglobulin-like genes and does not have significant sequence homology to immunoglobulin); (b) does not have biological activity (that is, does not perform a function or set of activities in a biological context either in an organism or in a simulation of what occurs in an organism) unless it is a dimer; and (c) will not become a dimer with another Part A on its own; (2) Part B is a protein that: (a) has an affinity for Part B of another chain, such that: (i) the Parts B of the two chains associate with each other under physiological conditions thereby causing the two chains to become a dimer; and (ii) the Parts B of the two chains cause Part A (which would not form a dimer with another Part A on its own) to become a dimer with another Part A; (b) is different from Part A; and (c) is yeast invertase, or at least a portion of an immunoglobulin light chain with at least an immunoglobulin light chain constant region domain, or at least a portion of an immunoglobulin heavy chain with at least an immunoglobulin heavy chain constant region domain; (3) the resulting compound is biologically active (that is, it performs the function or set of activities of Part A that can not be performed by Part A unless it is a dimer).

'725 Patent Claim 1	BRISTOL'S Original Proposed Constructions of the Claim Terms	BRISTOL'S construction of the phrase "a non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein heterologous to said non-immunoglobulin polypeptide"	Entire '725 Patent Claim 1 Construed by BRISTOL
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 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.	active: exhibits one or more biological activities of its native counterpart non-immunoglobulin polypeptide: a polypeptide that: (a) is not encoded by immunoglobulin-like genes which encode discreted domains structurally similar to immunoglobulin; and (b) does not have significant sequence homology to immunoglobulin requiring dimerization for biological activity: 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 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) dimerizing protein: 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	a chain made up of two protein segments (Parts A and B) joined to each other, where: (1) Part A is a protein that: (a) is not immunoglobulin-like (that is, is not encoded by immunoglobulin-like genes and does not have significant sequence homology to immunoglobulin); (b) does not have biological activity (that is, does not perform a function or set of activities in a biological context either in an organism or in a simulation of what occurs in an organism) unless it is a dimer; and (c) will not become a dimer with another Part A on its own; (2) Part B is a protein that: (a) has an affinity for Part B of another chain, such that: (i) the Parts B of the two chains associate with each other under physiological conditions thereby causing the two chains to become a dimer; and (ii) the Parts B of the two chains cause Part A (which would not form a dimer with another Part A on its own) to become a dimer with another Part A; and (b) is different from Part A	A method for producing an active compound made up of two chains connected to each other (that is, a compound that is a dimer), containing the following steps: introducing into a eukaryotic host cell DNA sequences that include a transcriptional promoter, linked to a secretory signal sequence, followed by a DNA sequence for a chain made up of two protein segments (Parts A and B) joined to each other, growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of the compound and isolating the compound from the host cell, where: (1) Part A is a protein that: (a) is not immunoglobulin-like (that is, is not encoded by immunoglobulin-like genes and does not have significant sequence homology to immunoglobulin); (b) does not have biological activity (that is, does not perform a function or set of activities in a biological context either in an organism or in a simulation of what occurs in an organism) unless it is a dimer; and (c) will not become a dimer with another Part A on its own; (2) Part B is a protein that: (a) has an affinity for Part B of another chain, such that: (i) the Parts B of the two chains associate with each other under physiological conditions thereby causing the two chains to become a dimer; and (ii) the Parts B of the two chains cause Part A (which would not form a dimer with another Part A on its own) to become a dimer with another Part A; (b) is different from Part A; and (c) is yeast invertase, or at least a portion of an immunoglobulin light chain with at least an immunoglobulin light chain constant region domain, or at least a portion of an immunoglobulin heavy chain with at least an immunoglobulin heavy chain constant region domain; (3) the method produces a compound that is active (that is, it performs the function or set of activities of Part A that can not be performed by Part A unless it is a dimer).

'725 Patent Claim 21	BRISTOL'S Original Proposed Constructions of the Claim Terms	BRISTOL'S construction of the phrase "a ligand-binding domain of a receptor requiring dimerization for biological activity joined to a dimerizing protein heterologous to said ligand-binding domain"	Entire '725 Patent Claim 21 Construed by BRISTOL
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.	receptor analog: 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-binding domain of a receptor: 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 discreted domains structurally similar to immunoglobulin; and (b) does not have significant sequence homology to immunoglobulin ligand: a molecule capable of being bound by the ligand-binding domain of a receptor or by a receptor analog. requiring dimerization for biological activity: 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 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) dimerizing protein: 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	a chain made up of two protein segments (Parts A and B) joined to each other, where: (1) Part A is a protein that: (a) is a portion of a receptor that is involved with binding the natural ligand; (b) is not immunoglobulin-like (that is, is not encoded by immunoglobulin-like genes and does not have significant sequence homology to immunoglobulin); (c) does not bind to the natural ligand unless it is a dimer; and (d) will not become a dimer with another Part A on its own; (2) Part B is a protein that: (a) has an affinity for Part B of another chain, such that: (i) the Parts B of the two chains associate with each other under physiological conditions thereby causing the two chains to become a dimer; and (ii) the Parts B of the two chains cause Part A (which would not form a dimer with another Part A on its own) to become a dimer with another Part A; and (b) is different from Part A	A method for producing a secreted compound that contains a portion of a receptor (that is not immunoglobulin-like) which is capable of binding ligand, containing the following steps: introducing into a eukaryotic host cell DNA sequences that include a transcriptional promoter, linked to a secretory signal sequence, followed by and a DNA sequence for a chain made up of two protein segments (Parts A and B) joined to each other, growing the host cell in an appropriate growth medium under physiological conditions to allow the secretion of the compound and isolating the compound from the host cell, where: (1) Part A is a protein that: (a) is a portion of a receptor that is involved with binding the natural ligand; (b) is not immunoglobulin-like (that is, is not encoded by immunoglobulin-like genes and does not have significant sequence homology to immunoglobulin); (c) does not bind to the natural ligand unless it is a dimer; and (d) will not become a dimer with another Part A on its own; (2) Part B is a protein that: (a) has an affinity for Part B of another chain, such that: (i) the Parts B of the two chains associate with each other under physiological conditions thereby causing the two chains to become a dimer; and (ii) the Parts B of the two chains cause Part A (which would not form a dimer with another Part A on its own) to become a dimer with another Part A; (b) is different from Part A; and (c) is yeast invertase, or at least a portion of an immunoglobulin light chain with at least an immunoglobulin light chain constant region domain, or at least a portion of an immunoglobulin heavy chain with at least an immunoglobulin heavy chain constant region domain; (3) where an immunoglobulin hinge or variable region may be joined to Part B; (4) the method produces a compound that is a dimer where Part A binds to the natural ligand of Part A.