IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMGEN INC.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	Civ. No. 14-1317-SLR
	)	(Consolidated)
SANOFI; SANOFI-AVENTIS U.S. LLC; AVENTISUB LLC f/d/b/a AVENTIS PHARMACEUTICALS INC.; and REGENERON PHARMACEUTICALS, INC.,	)	
	)	
Defendants.	)	

MEMORANDUM ORDER

At Wilmington this 30th day of October, 2015, having heard argument on, and having reviewed the papers submitted in connection with, the parties' proposed claim construction;

IT IS ORDERED that the disputed claim language of U.S. Patent Nos. 8,829,165 ("the '165 patent"),[1] 8,859,741 ("the '741 patent"), and 8,871,914 ("the '914 patent") shall be construed consistent with the tenets of claim construction set forth by the United States Court of Appeals for the Federal Circuit in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005), as follows:

[1] As the patents share a specification, all citations are to the '165 patent unless otherwise indicated.

1. **"An isolated monoclonal antibody:"**[2] "Composition of intact immunoglobulins of any isotope (or fragments thereof that can compete with the intact immunoglobulin for specific binding to the target antigen) having identical amino acid sequences, i.e., essentially free of nonidentical amino acid sequences."

The specification explains that the "term 'antibody' refers to an intact immunoglobulin of any isotype, or a fragment thereof that can compete with the intact antibody for specific binding to the target antigen . . . ." (32:40-42) An intact antibody will generally comprise at least two full-length heavy chains and two full length light chains . . . ." (32:45-47) "The antigen binding proteins, antibodies, or binding fragments can be produced in hybridomas, by [various techniques]. Unless otherwise indicated, the term 'antibody' includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof . . . ." (32:52-60) "Furthermore, unless explicitly excluded, antibodies include monoclonal antibodies, bispecific antibodies, . . . humanized antibodies, human antibodies, . . . , and fragments thereof, respectively." (32:60-66)[3]

As to "isolated," the specification explains that:

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[2] Found in all asserted claims.

[3] The parties referenced related U.S. Patent Nos. 8,563,698 ("the '698 patent") having the same specification as the patents-in-suit. The prosecution history of the '698 patent reflects an independent claim reciting "[a]n isolated monoclonal antibody or fragment thereof . . . ." (D.I. 79, ex. 6 at AM-SA 4743-44) The issued claims recite "[a]n isolated monoclonal antibody" (independent claim 1); "[t]he isolated monoclonal antibody of claim 1, wherein the monoclonal antibody comprises a full length monoclonal antibody" (dependent claim 3); and, "[t]he isolated monoclonal antibody of claim 1, wherein the monoclonal antibody is an immunologically functional fragment" (dependent claim 6). (D.I. 79, ex. 4, '698 patent, 401:1-21) The court does not find such evidence dispositive of the claim construction dispute at bar, i.e., whether "an isolated monoclonal antibody" includes "fragments."

> The term "isolated protein" . . . means that a subject protein (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, e.g., from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature.

(25:37-55)

2. **"Binds [to]" residues:**[4] "Interacts with [residues] and contributes to the affinity of the PCSK9-antibody interaction."

The specification describes an "antigen binding region" as "that portion of an antigen binding protein [e.g. antibody] that contains the amino acid residues that interact with an antigen and confer on the antigen binding protein its specificity and affinity for the antigen." (32:6-13)

> The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antigen binding protein (including, e.g., an antibody or immunological functional fragment thereof). . . . An antigen can possess one or more epitopes that are capable of interacting with different antigen binding proteins, e.g., antibodies.

(36:39-47) The specification further explains that "[a]n epitope is a region of an antigen that is bound by an antigen binding protein that targets that antigen, and when the

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[4] The parties presented the following limitations for construction: "The monoclonal antibody binds to at least one [or two or four] of the" identified residues of SEQ ID NO: 3, found in claims 1, 17, 19, 20, 29 of the '165 patent; "binds to . . . at two or more of amino acid residues S123, E129, A311, D313, or D337 of SEQ ID NO: 1," found in claim 16 (at one or more) and claim 17 (at least two) of the '914 patent; and "wherein the isolated human monoclonal antibody further binds at least one of amino acid residues 132, 351, 390, or 413 of SEQ ID NO: 1," found in claim 24 of the '914 patent. (D.I. 61) The dispute between the parties and the proposed constructions focus on the term "bind."

antigen is a protein, includes specific amino acids that directly contact the antigen binding protein." (36:50-54)

> Epitopes can be further defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction (e.g. hydrogen bonds, ionic interactions). Structural epitopes can be thought of as the patch of the target which is covered by the antibody [meaning those residues in the antigen which contact or are buried by the antibody.]

(114:66-115:4, 114:4-5)

The specification uses the term "affinity" to describe the binding "strength" of an antibody to an antigen.[5] For example, the specification states that "[a]n antigen binding protein is said to 'specifically bind' its target antigen when the dissociation constant (K_d) is $\leqq 10{-}7$ M." (31:59-60) In defining "modulator," the specification explains that "[c]ertain exemplary activities and functions of a molecule include, but are not limited to, binding affinity, enzymatic activity, and signal transduction." (37:51, 59-61) The specification further explains that in certain embodiments, "modification of an antibody by methods known in the art is typically designed to achieve increased binding affinity for a target" and "amino acid substitutions can be used to identify important residues of antibodies to PCSK9, or to increase or decrease the affinity of the antibodies to PCSK9." (44:58-60; 56:38-42)

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[5] In describing protein interactions and binding, plaintiff's expert explained that,

> [w]hen the structural arrangement of the amino acids on each protein allow for the formation of multiple points of non-covalent interaction between proteins, scientists say that the proteins have affinity for each other. The greater the number of interactions and the stronger they are, the more likely they are to remain associated, which means the higher the affinity (tighter binding).

(D.I. 67 at ¶ 32)

3. **"An epitope on PCSK9 comprising at least one of residues 237 or 238:"**[6] "A region on PCSK9 that is recognized by an antibody, wherein the region includes at least one of residues 237 or 238."

The specification describes epitopes as "a region of an antigen that is bound by an antigen binding protein that targets that antigen, and when the antigen is a protein, includes specific amino acids that directly contact the antigen binding protein." (36:50-54) "Generally, antibodies specific for a particular target antigen will preferentially recognize an epitope on the target antigen in a complex mixture of proteins and/or macromolecules." (36:60-63) "Epitope determinants can include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and can have specific three dimensional structural characteristics, and/or specific charge characteristics."[7] (36:56-63) The specification identities 237 and 238 as one of several residues of PCSK9. (*See, e.g.*, 9:32-53)

4. **"Wherein the epitope is a functional epitope:"**[8] "Wherein the epitope has those residues that directly contribute to the affinity of the interaction (e.g., hydrogen bonds, ionic interactions)."

As discussed above, the specification explains that "[f]unctional epitopes are generally a subset of the structural epitopes and have those residues that directly

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[6] Found in claim 1 of the '741 patent. The parties submitted "wherein the isolated monoclonal antibody binds an epitope on PCSK9" for construction, however "isolated monoclonal antibody" and "bind" were separately construed. The parties separately submitted "comprising at least one of residues 237 or 238" for construction. (D.I. 61)
[7] The discussion above regarding "affinity" is not repeated.
[8] Found in claim 7 of the '741 patent, which recites: "The isolated monoclonal antibody of claim 2, wherein the epitope is a functional epitope."

contribute to the affinity of the interaction (e.g. hydrogen bonds, ionic interactions)." (114:65-115:4)

5. **"PCSK9:"**[9] "Polypeptide as set forth in SEQ ID NO: 1 and/or 3 or fragments thereof."

The specification explains that PCSK9 "refers to a polypeptide as set forth in SEQ ID NO: 1 and/or 3 or fragments thereof . . . ." (22:21-23) "An exemplary human PCSK9 amino acid sequence is presented as SEQ ID NOs: 1 and 3 [and a]n exemplary human PCSK9 coding sequence is presented as SEQ ID NO: 2 . . . . As described herein, PCSK9 proteins can also include fragments of the full length PCSK9 protein." (38:37-49) In one example, the specification explains that:

> For the purposes of the epitope sequences and the epitope based inventions involving changes in binding, the sequences are provided in reference to SEQ ID NO: 1 and/or SEQ ID NO: 303. . . . One of skill in the art will appreciate that the present results apply to other PCSK9 variants disclosed herein as well (e.g., SEQ ID NO: 1 and 3, as well as the other allelic variants).

(114:52-59)

6. **"Wherein the isolated monoclonal antibody is a human antibody:"**[10]

The specification explains that antibody "includes, for instance, chimeric, humanized, fully human, and bispecific antibodies." (32:40-44) More specifically, "an antigen binding protein that binds to PCSK9 can comprise a human (i.e., fully human)

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[9] Found in claims 1, 17, 20, 23, 29 of the '165 patent; claims 1 and 4 of the '741 patent; and claim 16 of the '914 patent. The parties requested construction of "PCSK9 . . . wherein the [isolated] monoclonal antibody binds to at least one of the following residues . . . of SEQ ID NO: 3, and … blocks binding of PCSK9 to LDLR," but submitted proposed constructions for "PCSK9." (D.I. 61 at 9) The court has separately construed "isolated monoclonal antibody" and "binds [to]."

[10] Found in claims 21 and 24 of the '165 patent.

antibody and/or part thereof." (45:45-47) The patent explains that mouse strains may be engineered to produce "high affinity fully human antibodies against any antigen of interest, including human antigens." (45:62-46:10; 52:43-57)

> Human antibodies avoid some of the problems associated with antibodies that possess murine or rat variable and/or constant regions. The presence of such murine or rat derived proteins can lead to the rapid clearance of the antibodies or can lead to the generation of an immune response against the antibody by a patient. In order to avoid the utilization of murine or rat derived antibodies, fully human antibodies can be generated through the introduction of functional human antibody loci into a rodent, other mammal or animal so that the rodent, other mammal or animal produces fully human antibodies.
> Humanized antibodies are those antibodies that, while initially starting off containing antibody amino acid sequences that are not human, have had at least some of these nonhuman antibody amino acid sequences replaced with human antibody sequences. This is in contrast with human antibodies, in which the antibody is encoded (or capable of being encoded) by genes possessed a human.

(46:25-42)

Plaintiff's expert states that the "specification discloses exemplary means by which the skilled artisan can generate human antibodies against PCSK9," which produces "antibody structures that 'look human' to the human immune system." (D.I. 67 at ¶ 112) Moreover, an antibody, no matter how it was made, would be understood as a "human" antibody "based solely on the sequence characteristics of the antibody itself (namely, if it is characteristic of an antibody that is produced by the human immune system)." (*Id.* at ¶ 112)

The description in the patent specification seems to indicate a source or process limitation.[11] Moreover, the examples from the specification cited by plaintiff's expert are

[11] The court's independent research also suggests a source limitation for "human antibody," as antibodies produced through various means from "human" starting material.

made with some type of "human" starting material – "naturally rearranged human V genes from peripheral blood lymphocytes" (52:39-40) and "human splenocytes (B or T cells)" (53:3-8). The explanation provided by plaintiff's expert seems to confuse "human" with "humanized" antibodies at least as described by the patent. As neither party has proffered helpful extrinsic evidence at this juncture, the court defers construction of this limitation until after expert discovery. Consistent with the scheduling order, the parties shall inform the court of such additional information during the in-person status conference following expert discovery.

7. The court has provided a construction in quotes for the claim limitations at issue. The parties are expected to present the claim construction consistently with any explanation or clarification herein provided by the court, even if such language is not included within the quotes.

United States District Judge