Medimmune, LLC v. PDL Biopharma, Inc. Doc. 395

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IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF CALIFORNIA

SAN JOSE DIVISION

MEDIMMUNE, LLC, Plaintiff, v. PDL BIOPHARMA, INC., Defendant.	Case Number C 08-05590 JF (HRL) ORDER CONSTRUING THE CONTESTED TERMS OF CLAIM 28 OF U.S. PATENT NO. 6,180,370

The parties dispute the proper construction of the terms, "humanized immunoglobulin," "having CDRs from a donor immunoglobulin," and "human acceptor immunoglobulin," as used in United States Patent No. 6,180,370 ("the '370 patent").

I. BACKGROUND

The '370 patent involves the engineering of immunoglobulins that are capable of binding to particular antigens. An immunoglobulin, also known as an antibody, is a protein that protects the human body by binding to and neutralizing antigens. An immunoglobulin is comprised of four amino acid chains – two identical light chains and two identical heavy chains. The sequence of the amino acids in these chains determines the physical structure and function of the immunoglobulin.

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Each heavy and each light chain has a constant and a variable region. There is some variance in constant regions among immunoglobulins, but the variable regions differ greatly. It is each antibody's variable region amino acid sequence and structure that determines an immunoglobulin's ability to recognize and bind to particular antigens.

The variable region is comprised of three complementarity determining regions ("CDRs") and four framework regions that are found between and flanking each CDR. The three CDRs of a light chain and the three CDRs of a heavy chain primarily form the immunoglobulin's binding site to the antigen. The strength with which an antibody binds to an antigen is termed "binding affinity." Binding affinity is very sensitive: a small change to the amino acid sequence of a CDR can change the structure and properties of a binding site and in turn change the CDR's shape and chemical properties, the interactions between CDRs, and the orientation of the CDRs, resulting in a loss of the immunoglobulin's ability to bind to an antigen.

The framework of the variable region positions and aligns the CDRs so that they have the correct orientation to interact with the other chain's CDRs, thereby forming the antigen binding site. For this reason, the replacement of even one amino acid in the framework portion of the variable region can destroy or create an antibody's ability to bind to a particular antigen.

The human immune system produces antibodies as a natural response to the presence of an antigen in the body. However, some persons, such as premature infants whose immune systems are compromised, are not able to produce antibodies naturally. Scientists attempted to respond to this human health need by genetically engineering antibodies that could be administered to humans to treat disease. Ethical barriers prohibited scientists from infecting humans with viruses or bacteria in order to trigger the generation of immunoglobulins for harvesting. Thus, scientists attempted to generate useful antibodies by infecting mice and rats with antigens. However, the immunoglobulins produced by mice and rats cannot be administered safely to humans because the human immune system recognizes them as antigens themselves and mounts a dangerous "human anti-mouse antibody" ("HAMA"). The challenge for scientists thus was to develop antibodies that would retain the binding affinity of the murine antibody while eliminating the human immunogenic response. Scientists responded to this

challenge by creating "humanized" antibodies.

A number of different means were used to create humanized antibodies. First, scientists combined the mouse antibody's variable region (the six CDRs and the framework regions) with the constant region of a human antibody. This combination, referred to as a "chimeric" antibody, still often triggered a HAMA response. Scientists then tried to humanize the antibody even further by substituting only the CDRs in a human immunoglobulin as they were primary in the binding process, while retaining the human framework. This technique, termed CDR grafting, produced a result superior to chimeric antibodies, but the binding affinity still was not as desired.

The '370 patent reflects the invention of Dr. Cary Queen. Dr. Queen realized that while the CDRs are primary in the binding process, the framework of the variable region also affects the ability of the CDR to bind to the antigen. As a result, Dr. Queen developed two different approaches to respond to the problem of immunogenicity, while retaining the antibody's binding strength: (1) to make one or more amino acid substitutions in the human variable region framework according to specific rules so that the variable region framework is more like the original mouse variable region framework; or (2) to use a human variable region framework that has a high degree of similarity or homology[1] to the mouse antibody.

Claim 28, the only claim in dispute, adopts the second strategy, requiring 70% sequence identity between the human framework and the non-human donor antibody framework. The patent proposes that the invention will yield humanized immunoglobulins that are non-immunogenic in humans, while retaining substantially the same binding affinity that the mouse antibody has to the targeted antigen. '370 Patent 3:33-44; 12:38-44.

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[1]Homology or sequence identity is the measure of the similarity between two amino acid sequences. To determine homology, the amino acid at each position in one sequence is compared to the amino acid found at the corresponding position in a second sequence. The total number of matches divided by the total length of the sequences being compared is deemed the percent identity. To determine which amino acids correspond, the sequence of the amino acids must be aligned first by a system developed by Kabat. Kabat assigns a number to each amino acid position in an antibody sequence.

II. LEGAL STANDARD

Claim construction is a question of law to be determined by the Court. *Markman v. Westview Instruments, Inc*., 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd* 517 U.S. 370 (1996). "Ultimately, the interpretation to be given a term can only be determined and confirmed with a full understanding of what the inventors actually invented and intended to envelop with the claim." *Phillips v. AWH Corp*., 415 F.3d 1303, 1316 (Fed. Cir. 2005), quoting *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). Accordingly, a claim should be construed in a manner that "most naturally aligns with the patent's description of the invention." *Id*.

The first step in claim construction is to look to the language of the claims themselves. "It is a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude.'" *Phillips*, 415 F.3d at 1312, quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc*., 381 F.3d 1111, 1115 (Fed. Cir. 2004). A disputed claim term should be construed in a manner consistent with its "ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Id.* at 1312-13. The ordinary and customary meaning of a claim term may be determined solely by viewing the term within the context of the claim's overall language. *See id*. at 1314 ("the use of a term within the claim provides a firm basis for construing the term."). Moreover, the use of the term in other claims may provide guidance regarding its proper construction. *Id*. ("Other claims of the patent in question, both asserted and unasserted, can also be valuable sources of enlightenment as to the meaning of a claim term.").

A claim also should be construed in a manner that is consistent with the patent's specification. *See Markman*, 52 F.3d at 979 ("Claims must be read in view of the specification, of which they are a part."). Often the specification is the best guide for construing the claims. *See Phillips*, 415 F.3d at 1315 ("The specification is…the primary basis for construing the claims."). *See also Vitronics Corp. v. Conceptronic, Inc*., 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("the specification is always highly relevant to the claim construction analysis. Usually, it is

dispositive; it is the single best guide to the meaning of a disputed term."). Thus, the specification may be used to limit the meaning of a claim term that otherwise would appear to be susceptible to a broader reading. *SciMed Life Sys., Inc. v. Advanced Card. Sys., Inc.*, 242 F.3d 1337, 1341 (Fed. Cir. 2001). For example, the specification may provide a definition for a claim term that departs from the term's ordinary and customary meaning. *Phillips*, 415 F.3d at 1316. In addition, by distinguishing prior art the "the specification may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor." *Id.*

A final source of intrinsic evidence is the prosecution record and any statements made by the patentee to the United States Patent and Trademark Office ("USPTO") regarding the scope of the invention. *See Markman*, 52 F.3d at 980. "Like the specification, the prosecution history provides evidence of how the [US]PTO and the inventor understood the patent." *Phillips*, 415 F.3d at 1317. For example, statements that distinguish a claim from the prior art may narrow the scope of a disputed term. *See*, *e.g.*, *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003) ("The doctrine of prosecution disclaimer…preclud[es] patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution"). In addition, assertions made during the prosecution of related patent applications may prove relevant. *See Goldenberg v. Cytogen, Inc.*, 373 F.3d 1158, 1167 (Fed. Cir. 2004). For example, when multiple related patents descend from an initial "parent" application, any disclaimers made during the prosecution of the parent application will apply to any later-filed applications that contain the same claim limitation. *See Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999). However, because the prosecution history reflects an ongoing negotiation between the patentee and the USPTO, it often is difficult to determine with exact precision the scope or meaning of particular statements. *Phillips*, 415 F.3d at 1317. Thus, the prosecution history usually is accorded less weight than the claims and the specification. *Id*.

The Court also may consider extrinsic evidence, such as dictionaries or technical treatises, especially if such sources are "helpful in determining 'the true meaning of language used in the patent claims.'" *Phillips*, 415 F.3d at 1318, quoting *Markman*, 52 F.3d at 980. Ultimately, while extrinsic evidence may aid the claim construction analysis, it cannot be used to

contradict the plain and ordinary meaning of a claim term as defined within the intrinsic record. *Phillips*, 415 F.3d at 1322-23.

III. DISCUSSION

Each of the disputed terms addressed in this order is found in Claim 28 of the '370 patent. The claim is set forth in full as follows, with the disputed terms highlighted in bold:

> A **humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin,** and heavy and light chain variable region frameworks[2] **from human acceptor immunoglobulin** heavy and light chain frameworks which humanized immunoglobulin specifically binds to an antigen, wherein the sequence of the acceptor immunoglobulin heavy chain variable region framework is at least 70% identical to the sequence of the donor immunoglobulin heavy chain variable region framework, and the humanized immunoglobulin heavy chain variable region framework, comprises at least 70 amino acids identical to those in the acceptor human immunoglobulin heavy chain variable region framework, wherein percentage sequence identity is determined by aligning amino acids in said frameworks by Kabat numbering.
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> '370 Patent Col. 171:27-172:4.

A. "Humanized Immunoglobulin"

"Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity is one of clear and convincing evidence." *Young v. Lumenis, Inc.,* 492 F.3d 1336, 1345 (Fed. Cir. 2007). "[T]he specification may reveal a special definition given to a claim term," and "[i]n such cases, the inventor's lexicography governs.**"** *Phillips,* 415 F.3d at 1316. Here, the inventor provided a clear definition of humanized immunoglobulin in column 12 of the patent. That definition reads, "[A]n immunoglobulin comprising a human framework region and one or more CDRs from a non-human (usually a mouse or rat) immunoglobulin." '370 Patent, Col. 12:2-4. PDL's proposed construction is the exact language found in column 12, with the additional clarification that a "'human framework region' is a framework region that is substantially identical (i.e. at least about 85% identical) to

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[2] During the claim construction hearing on November 5, 2009, the parties clarified that the proper construction of the term, "heavy and light chain variable region frameworks," as that term appears in Claim 28, no longer is disputed. The parties agree that heavy and light chain variable region frameworks may deviate from those of the human acceptor immunoglobulin and only need be substantially identical (about 85% or more) to the framework region of a naturally occurring human immunoglobulin.

the framework region of a naturally occurring human immunoglobulin." '370 Patent, Col. 11:47-50. MedImmune concedes that PDL's proposed construction of "humanized immunoglobulin" is consistent with one definition of the term in the '370 patent, but it contends that the term is not amenable to construction because the patent also includes a second, irreconcilable definition of the same term in column 23.

This purported second definition reads, "As used herein, the term "humanized" immunoglobulin refers to an immunoglobulin comprising (1) a *human-like framework*, (2) at least one CDR from a non-human antibody, and (3) in which any constant region is substantially homologous to a human immunoglobulin constant region, i.e., at least about 85-90% identical, preferably at least 95% identical." '370 Patent Col. 23:52-58. "Human-like framework region" is defined as, "a framework region that in each existing chain comprises at least about 70-75 or more amino acid residues, typically 75 to 85 or more residues, identical to those in a human immunoglobulin." '370 Patent Col. 23:48-51. The singular difference between the two "definitions" is the use of the word "human" in column 12 and "human-like" in column 23. MedImmune contends that this difference makes the two definitions irreconcilable because the definition of "human" identifies a percentage homology and "human-like" identifies a specific number of amino acids, neither of which leads to a narrower construction than the other.[3]

The resolution of this dispute depends upon whether the language in column 23 in fact is a second, irreconcilable definition of "humanized immunoglobulin." The Court concludes that it is not. "In determining whether a statement by a patentee was intended to be lexicographic, it is important to determine whether the statement was designed to define the claim term or to

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[3] MedImmune contends that "human-like" requires that at least seventy amino acids in both the light and heavy chains be identical to a human immunoglobulin, as opposed to the sixty-eight and seventy-four amino acid identity required by the first definition for the light and heavy chains, respectively. Expert Report of Arthur M. Lesk ("Lesk Rep.") ¶¶ 62-63. To illustrate the conflict, MedImmune suggests that a humanized antibody with heavy and light chains having seventy-two amino acids identical to a human immunoglobulin would meet the second definition of "humanized immunoglobulin" but not the first, while a human antibody with seventy-five identical amino acids in the heavy chain and sixty-eight identical amino acids in the light chain would meet the first definition but not the second. MedImmune Opening Brief ("MOB") at 9-10.

describe a preferred embodiment." *E-Pass Tech., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369 (Fed. Cir. 2003) (emphasis added). The purported second definition of "humanized immunoglobulin" is found in a particular embodiment, that of the Anti-Il-2 Receptor Antibodies. The definition in column 12 appears in the detailed description of the invention and plainly is meant to apply throughout the patent. Moreover, this particular embodiment is not at issue in this case and the patent states explicitly that "[a]lthough the present invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims." '370 Patent Col. 70:20-26. PDL argues that no legal authority supports MedImmune's argument that language in a particular embodiment that may conflict with a clear definition in the detailed description of the invention renders that definition ambiguous or unamenable to construction.

MedImmune contends that in light of *Edwards Lifesciences LLC v. Cook Inc.*, 582 F.3d 1322, 1333-34 (Fed. Cir. 2009), the fact that a second definition appears in a specific embodiment does not mean that the definition is confined to that section or that particular embodiment. *Id.* (holding that a Court should not ignore a definition because it appeared "in the context of a preferred embodiment" and concluding that this "does not limit the definition of [the term] in all contexts in the specification.") However, the patent at issue in *Edward Lifesciences* did not contain an explicit general definition in the specification. The dispute in that case was between the "plain meaning" of the term and a definition in a preferred embodiment that was arguably divergent from the plain meaning.

A similar argument was considered in *BioPharma, Inc. v. Alexion Pharms., Inc.,* 568 F.Supp.2d 445 (D. Del. 2008). In that case, in addition to adopting PDL's construction of the term "humanized immunoglobulin,"[4] the court also addressed a dispute as to whether the Kabat methodology or the aggregate of the Kabat and Cothia methodologies defined the boundaries of

[4] This Court has not treated the construction of "humanized immunoglobulin" in *Alexion* as persuasive authority because neither party in that case raised the precise issue presented by MedImmune here..

the CDRs. There, as here, the specification's definitions section clearly defined the term, but as MedImmune does here, Alexion claimed that language in column 23 describing the same term in a particular embodiment – the Anti-IL-2 Receptor Antibodies – contained the proper definition of the boundaries of the CDRs. The court, adopting the general definition contained within the specification and rejecting the more specific one found in the embodiment, concluded that "Alexion offers no plausible explanation as to why the inventor would make the effort to explicitly and clearly define the term...in the 'definitions' section of the patent in Columns 10-11, if he actually intended that [the term] be defined as set forth in Column 23. Later references in the specification...do not alter the explicit definition set forth in the specification's definitions section." *Id.* at 454.

The definition of "humanized immunoglobulin" in column 12 of the '370 patent is explicit and represents the inventor's lexicography. MedImmune's argument that the phrase "as used herein," preceding the purported second definition found in column 23, somehow transforms this limited language into a second, inconsistent general definition is unpersuasive. Given the clear definition of "humanized immunoglobulin" found in column 12, it is more likely that the phrase "as used herein" in column 23 is meant to suggest that the following language is intended to apply to the particular embodiment described therein, i.e, the Anti-IL-2 Receptor Antibodies.

The Court acknowledges that MedImmune's expert, Dr. Lesk, has opined that a skilled artisan would understand both the definition in column 12 and the purported definition in column 23 to apply equally and generally. However, Dr. Lesk's opinion on this point is entitled little weight in light of his concession that "no precise definition for the term 'humanized immunoglobulin' was known or accepted by skilled artisans by February 13, 1989." Lesk Report ¶ 57. *Symantec Corp. v. Computer Associates Intern., Inc.,* 522 F.3d 1279, 1291 (Fed. Cir. 2008), citing *Sinorgchem Co., Shandog v. Int'l Trade Comm'n*, 511 F.3d 1132, 1137 n.3 (Fed. Cir. 2007) (according little or no weight to expert testimony about the meaning of specification terms where the expert failed to present evidence of the generally accepted meaning of those terms to persons of ordinary skill in the art).

MedImmune has failed to show by clear and convincing evidence that the term "humanized immunoglobulin" is unamenable to construction or that Claim 28 otherwise is indefinite. *Young*, 492 F.3d at 1345. Because issued claims have "the benefit of a statutory presumption of validity, 35 U.S.C. § 282...[c]lose questions of indefiniteness in litigation involving issued patents are properly resolved in favor of the patentee." *Exxon Research and Eng'g v. United States*, 265 F.3d 1371, 1380 (Fed. Cir. 2001). "[W]e have not held that a claim is indefinite merely because it poses a difficult issue of claim construction." *Id.* at 1375. In this case, the construction of the term "humanized immunoglobulin" is not a close question, as the patentee provided an explicit and obvious definition in column 12 of the specification. '370 Patent Col. 12:1-4.

B. "From Human Acceptor Immunoglobulin"

Where the specification provides an express definition for a claim term, "the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. It is undisputed that the specification expressly defines acceptor: "the[5] human immunoglobulin providing the framework is called the 'acceptor.'" '370 Patent Col. 12:6-7. The parties' dispute concerns whether a variety of different human framework regions may be used in combination as a basis for the humanized immunoglobulins of Claim 28, as asserted by PDL, or whether the human acceptor immunoglobulin must come from a single naturally occurring human immunoglobulin, as argued by MedImmune.

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[5] MedImmune contends that the presence of the article "the" before the word "human" in the specification's definition of acceptor indicates that only a single, naturally occurring human immunoglobulin can provide the framework. The Federal Circuit has rejected the argument that "the" necessarily implies singularity. *Free Motion Fitness v. Cybex, Inc.*, 423 F.3d 1343, 1350-51 (Fed. Cir. 2005) ("reject[ing the]...argument that use of the word 'the' in connection with the word 'cable' later in the claim shows that the earlier reference to 'a' denotes singularity. Like the words 'a' and 'an,' the word 'the' is afforded the same presumptive meaning of 'one or more' when used with the transitional phrase 'comprising'"). While in this case "comprising" is not used in conjunction with "the," "the" still does not necessarily imply singularity. Because it concludes that the use of "the" does not support either party's proposed construction, the Court relies upon other language within the specification in determining the meaning of the contested term.

MedImmune contends that the use of the word "human" assumes that the "human acceptor immunoglobulin" occurs naturally in the human body and is not subject to engineering. MedImmune also contends that every time the patent uses the term "human acceptor," the term is synonymous with "naturally occurring human immunoglobulin." However, the specification teaches that "a variety of different human framework regions may be used *singly or in combination* as a basis for the *humanized immunoglobulins* of the present invention." '370 Patent Col. 17:17-19 (emphasis added). And, as PDL noted during the claim construction hearing, the specification also explains that "[a] principle is that as acceptor, a framework is used from a particular human immunoglobulin that is unusually homologous to the donor immunoglobulin to be humanized, *or use a consensus framework from many human antibodies*." '370 Patent 13:5-8.

MedImmune attempts to explain away this language in the specification, arguing that it refers only to the use of one human immunoglobulin to provide a light chain, and a different immunoglobulin to provide a heavy chain – not the engineering of one chain from different human immunoglobulins. MedImmune again relies upon the opinion of its expert, Dr. Lesk, as well as what it claims is the admission of PDL's expert, Dr. Strong, that "human" implies a single, naturally occurring human immunoglobulin. However, the law is clear that while extrinsic evidence such as expert opinion may aid the claim construction analysis, it cannot be used to contradict the plain and ordinary meaning of a claim term as defined within the intrinsic record. *Phillips*, 415 F.3d at 1322-23. In this case, the language in columns 13 and 17 of the specification recognizes that the state of the art was such that human framework regions could be combined and contradicts MedImmune's position that "human" necessarily means a single, naturally occurring human immunoglobulin.[6]

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[6] MedImmune also asserts that the language in column 17 cannot be relied upon in this context because it refers to "substantially homologous modified immunoglobulins," '370 patent 17:9-10, which are separate and distinct from the humanized immunoglobulins of Claim 28. However, language found only a few lines below expressly contradicts this assertion. The patent reads "[m]oreover, a variety of different human framework regions may be used singly or in combination as a basis for the *humanized immunoglobulins of the present invention.*" '370 Patent

PDL also contends that MedImmune's suggested construction would impose a method limitation on a non-method claim. "Courts must generally take care to avoid reading process limitations into an apparatus claim...because the process by which a product is made is irrelevant to the question of whether that product infringes a pure apparatus claims." *Baldwin Graphic Systems, Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1344 (Fed. Cir. 2008) (citations omitted). Claim 28 describes the invention of a humanized immunoglobulin and defines its characteristics, including the requisite degree of homology. Claim 28 does not define how that humanized immunoglobulin with those specified characteristics must be created. The language of the claim requires substantial homology, but it does not specify how that percent of identity must be achieved, whether by use of a single naturally occurring human immunoglobulin or an engineered combination.

MedImmune suggests that because all of the patent's preferred embodiments utilize a single naturally occurring human immunoglobulin, its proposed construction is more accurate. This argument lacks merit, for two reasons. First, the Federal Circuit has "expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment." *Phillips*, 415 F.3d at 1323 (holding that "persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments"). *See also Kara Tech., Inc. v. Stamps.com, Inc.*, 582 F.3d 1341, 1347 (Fed. Cir. 2009) (citations omitted) ("In the only detailed embodiments in the patent, the key is embedded in the preestablished data. This is not enough, however, to limit the patentee's clear, broader claims...The claims, not specification embodiments, define the scope of patent protection"). Second, the patent itself recognizes that other embodiments of the invention exist outside those exemplified. '370 Patent Col. 17:8-19 ("in addition to the humanized immunoglobulin specifically described herein...").

Finally, MedImmune contends that PDL should be estopped from disowning the construction it persuaded the *Alexion* Court to adopt. MOB at 16. "The doctrine of judicial

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Col. 17:17-19.

estoppel provides that '[w]here a party assumes a certain position in a legal proceeding, and succeeds in maintaining that position, he may not thereafter, simply because his interests have changed, assume a contrary position..." *Biomedical Patent Mgmt. Corp. v. Cal. Dep't of Health Servs.*, 505 F.3d 1328, 1341 (Fed. Cir. 2007). In *Alexion*, Judge Farnan concluded that "'Human acceptor immunoglobulin' and 'acceptor human immunoglobulin' are each construed to mean 'the human immunoglobulin providing the framework for the CDRs.'" *PDL BioPharma, Inc. v. Alexion Pharmaceuticals, Inc.*, 568 F.Supp.2d 445, 456 (D. Del. 2008). MedImmune insists that the use of the word "the" in the *Alexion* court's construction of acceptor human immunoglobulin implies the use of a single human immunoglobulin – its suggested construction in the instant dispute. Like MedImmune's other arguments, this contention is unpersuasive.

In *RF Delaware, Inc. v. Pacific Keystone Tech.*, 326 F.3d 1255 (Fed. Cir. 2003) the Federal Circuit held that

> The party seeking to invoke collateral estoppel bears the burden to prove all necessary elements: (1) the issue at stake must be identical to the one involved in the prior litigation; (2) the issue must have been actually litigated in the prior suit; (3) the determination of the issue in the prior litigation must have been a critical and necessary part of the judgment in that action; and (4) the party against whom the earlier decision is asserted must have had a full and fair opportunity to litigate the issue in the earlier proceeding.

Id., 326 F.3d at 1261.

None of these elements is present here. First, while Judge Farnan construed the term "human acceptor immunoglobulin," the issue disputed here–whether the human acceptor must be from a single human immunoglobulin–was not raised in *Alexion*. Second, there was no judgment in *Alexion* because the parties entered into a settlement agreement. Third as discussed above, this Court disagrees with MedImmune's assertion that the use of "the" in *Alexion's* construction of the term supports a conclusion in this case that only a single human immunoglobulin can be utilized.

For all of the foregoing reasons, this Court construes "from human acceptor immunoglobulin" to allow the use of a variety of different human framework regions in combination as a basis for the humanized immunoglobulins of Claim 28.

C. "Having CDRs from a Donor Immunoglobulin"

The remaining disputed claim terms concern the material supplied by the non-human "donor" immunoglobulin that is utilized to prepare humanized immunoglobulins.

1. "Having CDRs"

A. Numerosity

i. Specification v. Ordinary Meaning

PDL proposes a construction requiring that one or more CDRs in each chain be transferred; MedImmune asserts that Claim 28 requires that all three CDRs be transferred. A term's accepted meaning in the art is dispositive unless the specification or file history demonstrates a clear intent to deviate from this ordinary meaning. *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442 F.3d 1322, 1328 (Fed. Cir. 2006). MedImmune contends that to persons having ordinary skill in the art in 1989, "CDRs" had an agreed-upon, accepted meaning of "all three CDRs in an immunoglobulin chain (six in two chains)." MOB at 20, citing Lesk Rep. ¶¶ 96-107; Lesk Rebuttal Report ("Lesk Reb.") ¶¶ 14-15; 27-38; Lesk Transcript ("Tr."). 89:6-11.

PDL does not dispute that in isolation, "CDRs" refers to the three CDRs in the heavy chain and the three CDRs in the light chain. It also recognizes that the glossary in the file history defined "CDRs" as such. Lesk Rep., Ex. 27 at 1 (defining CDRs as "the six short segments of an immunoglobulin, three in the light chain variable region and three in the heavy chain variable region, which fold up together in 3-dimensional space to form the binding site for the target antigen"). Nonetheless, PDL contends that in the context of the phrase "CDRs from a donor" in the '370 patent, "having CDRs" means that *one or more* CDRs in each chain need be transferred.

In *On Demand Machine Corp. v. Ingram Industries, Inc.*, 442 F.3d 1331 (Fed. Cir. 2006), the Federal Circuit held that "each term must be construed to implement the invention described in the specification....Care must be taken lest word-by-word definition, removed from the context of the invention, leads to an overall result that departs significantly from the patented invention." *Id.* at 1344. The Court has adopted PDL's construction of the term "humanized immunoglobulin" – that definition, which is found in column 12 of the specification, states that

"the term 'humanized' immunoglobulin refers to an immunoglobulin comprising a human framework region and *one or more CDR's* from a non-human (usually a mouse or rat) immunoglobulin." '370 Patent Col. 12:1-4 (emphasis added). In fact, the patent asserts repeatedly–in the abstract, the summary of the invention, the detailed description of the invention, and in many other places–that humanized immunoglobulins involve "one or more complementarity determining regions (CDR's)." '370 Patent Abstract (57) ("Novel methods for producing, and compositions of, humanized immunoglobulins having one or more complementarity determining regions (CDR's) and possible additional amino acids from a donor immunoglobulin"); Col. 2:35-39 ("Summary of the Invention: [t]he present invention provides novel methods for preparing humanized immunoglobulin chains having generally one or more complementarity determining regions (CDR's) from a donor immunoglobulin..."); Col. 10:63-67 (the detailed description of the invention states, "[t]he humanized immunoglobulins will have a human framework and have one or more complementary determining regions (CDR's)...from a donor immunoglobulin..."). The Court is not required to accept expert testimony that is inconsistent with the intrinsic evidence. Here, the intrinsic evidence consistently supports a construction of "CDRs" as "one or more CDRs from a non-human immunoglobulin." *Kara Tech., Inc. v. Stamps.com, Inc.*, 582 F.3d at 1348 (rejecting expert testimony inconsistent with the specification).

Despite this abundant intrinsic evidence, MedImmune claims that the specification always uses the unmodified term "CDRs" to mean each and every CDR. For example, column 11 of the patent explains that "an immunoglobulin light or heavy chain variable region consists of a "framework" region interrupted by three hypervariable regions, also called CDR's." '370 Patent Col. 11:38-40. However, other language in the patent refutes MedImmune's contention. The Abstract describes:

> Novel methods for producing, and compositions of, humanized immunoglobulins having **one or more complementarity determining regions** (CDR's) and possible additional amino acids from a donor immunoglobulin and a framework region from an accepting human immunoglobulin are provided. Each humanized immunoglobulin chain will usually comprise, in addition to the **CDR's,** amino acids from the donor immunoglobulin framework that are, e.g., capable of interacting with the **CDR's** to effect binding affinity, such as one or more amino

> acids which are immediately adjacent to a CDR in the donor immunoglobulin or those within about 3 A as predicted by molecular modeling.

'370 Patent at (57) Abstract. In fact, the '370 patent uses the unmodified term "CDR's," interchangeably with the phrase, "one or more complementarity determining regions." MedImmune's proposed construction of "CDRs" as always meaning "all three CDRs" would make the patent's other invocations of the phrase "three CDR's" redundant. '370 Patent Col. 3:67. 4:10, 4:20, 4:30; 4:40; 4:50 ("the *three CDR's* in each chain are underlined").

PDL also refers to a related patent, U.S. Patent No. 7,022,500 ("the '500 Patent"), which shares the same specification as the claim in dispute. Claims should be interpreted consistently across patents that originate from the same parent application. *NTP Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1293 (Fed. Cir. 2005). The '500 patent makes clear that the unmodified term "CDR's" does not mean "all CDRs." Although the '500 patent contains several dependent claims that add the limitation that each chain of the humanized immunoglobulin has three CDRs from the donor, the independent claim simply refers, as does Claim 28, to "CDRs from a donor immunoglobulin." Declaration of Peter Sandel ("Sandel Decl."), Ex. 13 ('500 Patent). PDL also calls attention to other relevant claims in the '500 patent. Independent Claim 67 describes "a humanized immunoglobulin having complementarity determining regions (CDRs) from a donor immunoglobulin..." '500 Patent Col. 153:1-3. Then, in the dependent Claim 69, the patent reads, "[a] humanized immunoglobulin according to claim 67 or 68 having three CDRs from the heavy chain of the donor immunoglobulin and three CDRs from the light chain of the donor immunoglobulin." '500 Patent Col. 153:18-21. Dependent Claims 25, 61, 78, and 87 share similar language. '500 Patent Col. 151:29-32; Col. 152:53-56; Col. 153:53-56; Col. 154:34-37.

"[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips*, 415 F.3d at 1315. If MedImmune's construction of "CDRs from a donor" were correct, there would be no need to specify the transfer of all three CDRs from each chain in dependent Claim 69 because the independent Claim 67 necessarily would have conveyed the same meaning. Moreover, as PDL argues, the doctrine of claim differentiation is "especially strong when [as

here] the limitation in dispute is the only meaningful difference between an independent and dependent claim." *Sunrace Roots Enter., Co. v. SRAM Corp.*, 336 F.3d 1298, 1303 (Fed. Cir. 2003).

MedImmune contends that the claim differentiation doctrine has no application in the context of the '370 patent because the use of claim differentiation in a later-issued patent to construe an earlier-issued patent has been rejected repeatedly by the Federal Circuit. MedImmune Reply Brief at 16, citing *ICU Med. Sys., Inc. v. Alaris Med. Sys., Inc.*, 558 F.3d 1368, 1376 (Fed. Cir. 2009). However, while the '500 patent issued more than five years later than the '370 patent, its filing date preceded the issuance of the '370 patent. *Compare* Sandel Decl., Ex. 6 ('370 Patent) *with* Sandel Decl., Ex. 13 ('500 Patent). Under these circumstances, the claim differentiation doctrine is at least instructive in construing the term "CDRs from a donor immunoglobulin."[7]

Finally, MedImmune contends that the claim differentiation doctrine should be rejected when it results in a construction inconsistent with the specification and file history. However, as should be clear from the foregoing discussion, the Court finds that differentiation among the claims of the '500 patent is consistent with the specification and file history of the '370 patent and supports PDL's proposed construction.

ii. Preferred Embodiments

MedImmune also points out that all of the preferred embodiments in the '370 patent utilize all three CDRs from each chain. While this is true, it does not support MedImmune's legal position. As discussed previously in connection with the construction of "human acceptor immunoglobulin," the Federal Circuit has "expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment." *Phillips*, 415 F.3d at 1323 (holding that "persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the

[7] PDL also draws the Court's attention to *Kara Tech., Inc.,* 582 F.3d at 1347, in which the Federal Circuit utilized a later-issued patent in applying the claim differentiation doctrine to determine the proper construction of a disputed term.

embodiments.") *See also Kara Tech.,* 582 F.3d at 1347 ("In the only detailed embodiments in the patent, the key is embedded in the preestablished data. This is not enough, however, to limit the patentee's clear, broader claims...The claims, not specification embodiments, define the scope of patent protection"). Moreover, the patent itself states that other embodiments of the invention exist beyond those exemplified. '370 Patent 17:8-19 ("in addition to the humanized immunoglobulin specifically described herein...").

iii. Prior Art

Finally, MedImmune argues that based on the prior art that existed when PDL filed its application for the '370 patent, persons having ordinary skill in the art always would have transferred all six CDRs. MOB at 20-22. However, this argument is refuted by prior art cited in the patent itself. The '370 patent, at column 1, line 65, to column 2, line 5, cites Winter's European Patent 0 239 400. The latter teaches in relevant part that "[t]hus, in order to transfer the antigen binding capacity of one variable domain to another, it may not be necessary to replace all the CDRs with complete CDRs from the donor variable region." Sandel Decl., Ex. 14 at 7. Another patent application from Winter's group describes, "[a]n antibody having at least one CDR (complementarity determining region) which is foreign with respect to the constant region of the antibody, said at least one foreign CDR being selected from CDRs substantially as identified in Figure 2..." Sandel Decl., Ex. 15 at 15 (Clark et al., EP 0 328 404).[8]

The parties also dispute whether the prior art cited by the '370 patent is properly incorporated by reference. MedImmune asserts that PDL's reference to Winter is improper because the '370 patent refers only to the general concept that Winter used recombinant DNA technology to produce "immunoglobulins which have human framework regions combined with

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[8] MedImmune points out that in 1999 opposition proceedings in the European Patent Office, PDL endorsed the statement that "substitutions of less than a complete set of CDRs (i.e. less than the three CDR sequences representing the Kabat-defined hypervariable regions) are not deemed to be encompassed by the [Winter] claims since...[s]uch modifications would require a significant amount of additional teachings not found in [Winter's] specification." Berl Ex. U at 33. MedImmune claims that PDL now seeks to rely upon Winter patent for exactly the opposite principle. However, even assuming that this claim has some historical significance, it does not undermine the overall strength of the intrinsic evidence in the '370 patent

complementarity determining regions (CDR's) from a donor mouse or rat immunoglobulin." '370 patent, Col. 1:67-2:2. MedImmune contends that this reference provides no identification "with particularity" of "what specific material" is incorporated or where that "material is found." However, in the present context the Court need not determine whether the prior art was incorporated properly, as it looks to the Winter patent not as intrinsic evidence but rather as extrinsic evidence of the fact that persons having skill in the art at the time of the '370 application contemplated the transfer of less than the complete set of three CDRs in creating humanized immunoglobulins.

Accordingly, the Court concludes that the '370 patent did not limit the invention of Claim 28 to the transfer of all three CDRs from each chain, and that it allows the transfer of one or more CDRs from a chain in creating a humanized immunoglobulin.

B. Sequence Identity

PDL next contends that "having complementarity determining from a donor immunoglobulin" should be construed to require that one or more CDRs per chain be substantially identical (at least about 85% identical) to those found in a non-human immunoglobulin. Based upon its proposed construction of "CDRs" and "Donor Immunoglobulin," MedImmune proposes a construction requiring 100% identity.

i. Language in the Specification

PDL contends that the '370 patent's specification teaches modification of CDRs and that MedImmune's construction would impose a limitation not found in Claim 28. PDL relies upon two passages in the '370 patent. The first reads:

> Regardless of how the acceptor immunoglobulin is chosen, higher affinity may be achieved by selecting a small number of amino acids in the framework of the humanized immunoglobulin chain to be the same as the amino acids at those positions in the donor rather than in the acceptor. A second principle is that the following categories define what amino acids **may** be selected from the donor. **Preferably, at many or all amino acid positions in one of these categories, the donor amino acid will in fact be selected.**
> Category 1: The **amino acid position is in a CDR** is defined by Kabat et al., op. cit.
> Category 2: If an amino acid in the framework of the human acceptor immunoglobulin...

'370 Patent Col. 13:55-65. PDL argues that use of the words "[p]referably" and "many or all"

indicates unambiguously that "it is preferred, but not required, that 'many or all' of the amino acids in a CDR come from a donor." PDL Opening Brief ("POB") at 19. PDL's characterization of this language is reasonable and persuasive.

MedImmune nonetheless argues that the following language is inconsistent with PDL's interpretation:

> To form the humanized variable region, amino acids in the human acceptor sequence **will be replaced** by the corresponding amino acids from the donor sequence if they are in the category.
> (1) **the amino acid is in a CDR.**

'370 Patent Col. 2:61-65. It is true that read together, these two passages appear to be contradictory. Citing the opinion of Dr. Lesk, MedImmune contends that a skilled artisan interested in the patent's rules for CDR substitution would rely upon the latter cited passage because it is more specific in its teaching. However, PDL suggests that the two passages can be read consistently because the language in column 2 is merely the specification's description of a method for making a humanized immunoglobulin, not a limitation on Claim 28. Claim 28 is not a method claim. Accordingly, PDL argues, the Court "must generally take care to avoid reading process limitations into an apparatus claim...because the process by which a product is made irrelevant to the question of whether that product infringes a pure apparatus claim." *Baldwin Graphic Systems, Inc.*, 512 F.3d at 1344. This argument also is persuasive, as it provides a consistent understanding of the patent's language without looking beyond the intrinsic evidence.

PDL also points out that the specification includes language that expressly teaches the use of substantially homologous CDR sequences:

> In addition to the humanized immunoglobulins specifically described herein, **other "substantially homologous" modified immunoglobulins to the native sequences can be readily designed and manufactured utilizing various recombinant DNA techniques well known to those skilled in the art.** For example, the framework regions can vary specifically from the sequences in FIG.1A through FIG.6B at the primary structure level by several amino acid substitutions, terminal and intermediate additions and deletions, and the like. Moreover, a variety of different human framework regions may be used singly or in combination as a basis for the humanized immunoglobulins of the present invention. **In general, modifications of the genes may be readily accomplished by a variety of well-known techniques, such as site-directed mutagenesis (see, Gillman and Smith, *Gene*, 8, 81-97 (1979) and S. Roberts et al., *Nature*, 328, 731-34 (1987), both of which are incorporated herein by reference).**

> **Substantially homologous immunoglobulin sequences are those which exhibit at least about 85% homology, usually at least about 90%, and preferably at least about 95% homology with a reference immunoglobulin protein.**

'370 Patent Col. 17:8-28.

MedImmune argues that this language in column 17 refers only to the fact that framework regions may vary and in no way conveys any teaching about the modification of CDRs. MedImmune asserts that a skilled artisan would interpret the absence of any discussion of modifying donor CDR sequences as confirming that CDRs "must be transferred in complete sets with 100% identity to the donor's CDRs." MedImmune Responsive Brief at 10, citing Lesk. Reb. ¶ 64.

The Roberts paper, referenced specifically in the '370 patent's discussion of substantial homology, teaches that modifying CDR amino acid sequence can result in "a marked increase in affinity." Sandel Decl., Ex. 12 at 732 (S. Roberts et al., *Generation of an Antibody with Enhanced Affinity and Specificity*, 328 Nature 731, 731-34 (1987)). Indeed, it is undisputed that the Roberts paper teaches that a person of skill in the art can make changes in the amino acid sequence of the CDR in order to increase affinity of an antibody.[9] MedImmune's point is that the Roberts paper does not teach modification of CDRs in the context of engineering humanized

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[9] The Roberts paper reads in relevant part as follows:

> Our initial analysis of the computer model of the Gloop2-HEL complex, together with the results of binding studies of Gloop2 and a panel of variant avian lysozymes, strongly implicated the interaction of (1) Glu 28 (27A using the Kabat numbering system), in the light chain CDR1 (L1), with Arg 68 (HEL) and (2) Lys 56, in the heavy chain CDR2 (H2), with Asn 77 (HEL). In neither case are the residue pairs close enough to form hydrogen bonds (closest contact 4.7A), but it was suggested that they maybe important in the orientation of the two interacting protein surfaces. Based on these initial observations both Glu 28 (L1) and Lys 56 (H2) were chosen as candidates for mutagenesis. There were also a number of residues that appeared antigens, are shown in Gi. 3a and summarized in Table 1. The single mutant Glu 28 to Ser showed a moderate increase in affinity for both Pep1 and HEL (3-4 fold) whereas the mutant Lys 56 to Gln showed no significant change in binding. But combining the two single mutations within the same antibody gave a double mutant which showed a *marked increase in affinity* for HEL (8-9 fold), and a *moderate increase* for Pep1 (4-5-fold) (Fig. 3a). Sandel Decl., Ex. 12 (Roberts et al. At 732-33).

immunoglobulins. However, it clearly is relevant in construing the terms of the '370 patent that modifying CDR sequences to increase affinity was known to persons having skill in the art at the time of the '370 application. The most logical inference is that the '370 patent incorporated Roberts's teaching on modifying CDR sequences to increase affinity within the context of an invention on humanized immunoglobulins for this very reason. The Court concludes that the incorporation of Roberts's paper within the passage on modifying amino acid sequences supports PDL's position that the sequence identity of the CDRs only need be substantially homologous (i.e. at least about 85% identical).

ii. Prosecution History

MedImmune contends that the prosecution history of the '370 patent reveals that PDL disavowed the allowance of any CDR sequence variation, clearly admitting that the use of the term "CDRs from a donor immunoglobulin" intended the exact donor immunoglobulin sequences. PDL argues that the same prosecution history supports its own construction requiring that one or more CDRs per chain be substantially identical (at least about 85% identical) to those found in a non-human immunoglobulin.

During prosecution of the '370 patent, the phrase "CDRs *corresponding to CDRs* from a donor" was replaced with the disputed term "CDRs *from* a donor." This amendment was made in response to an inquiry from the Examiner. The Examiner asked the following questions:

> Is there sequence identity? Or are there certain amino acids which are the same as others leaving potential gaps in the overall sequence? If it is intended that the humanized immunoglobulin comprises CDRs from a donor and a framework region from an acceptor immunoglobulin, than it should be so stated.

Lesk Rep. ¶ 89.

PDL responded to the Examiner's inquiry as follows:

> The Examiner has alleged that claims 95, 103, 104, 105, and 115 are indefinite in their use of the language "corresponding" or "correspond" in that the Examiner finds "the nature of this correspondence is unclear." As explained previously, corresponding and similar terms mean "of" or "from," and are used as is common in the antibody engineering art. See, e.g., Claims 2, 4, and 5 of U.S. Patent No. 5,225,539, a copy of which is attached hereto. In order to expedite prosecution and obtain early allowance of claims, Applicants have amended the claims (without prejudice to subsequent renewal) to generally eliminate the word "correspond" and its variants. However, it is submitted that in line 10 of claims 104 and 105, the word "corresponding" clearly means "in the same position", and

thus has been retained.

Sandel Decl., Ex. 11 ('101 File History, October 4, 1993 Amendment) at 9. It is undisputed that the term "corresponding" generally permits deviation. MedImmune Responsive Brief at 11, n. 11 (indicating that MedImmune's expert, Dr. Lesk, agreed that "correspond" generally would be understood to permit deviation).

The parties' dispute with respect to the prosecution history stems in large part from MedImmune's insistence that "corresponding" and "from" have differing meanings, and that when PDL replaced "corresponding" with "from" it thereby limited Claim 28 to an invention requiring exact sequence identity. PDL contends that the amendment was a matter of clarification because the Examiner had indicated that "corresponding" was "unclear," and that it always intended that "corresponding" and "from" have the same meaning. PDL finds some support for its position in its response to the Examiner, which states explicitly that "corresponding and similar terms mean 'of' or 'from,' and are used as is common in the antibody engineering art." Sandel Decl., Ex. 11 at 9. However, in fairness to MedImmune, the prosecution history with respect to this amendment is not so obvious that is supports either party's construction completely.

That said, MedImmune has not provided sufficient evidence to meet the high bar of the "disavow" standard. The Federal Circuit has described this standard as follows, "we will find that the applicant disclaimed protection during prosecution only if the allegedly disclaiming statements constitute 'a clear and unmistakable surrender of subject matter.'" *Ecolab, Inc., v. FMC Corp.,* 569 F.3d 1335, 1342 (Fed. Cir. 2009), quoting *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1251 (Fed. Cir. 2000); *see also Paragon Solutions, LLC v. Timex Corp.*, 566 F.3d 1076, 1086 (Fed. Cir. 2009) (holding that "there [wa]s nothing in the amendment or the applicants' comments that clearly and unmistakably disavow[ed]" its proposed construction).

Finally, MedImmune points to a separate independent claim presented during the prosecution of the '370 patent that described CDRs "substantially homologous to" CDRs from a donor immunoglobulin. *See* Lesk Reb. ¶ 65. MedImmune argues that the phrase "substantially homologous" in this other claim would have been superfluous if "CDRs from a donor

immunoglobulin" already was intended to assume substantial homology, and that the term as used in Claim 28 thus must require 100% identity. However, the doctrine of claim differentiation doctrine does not apply to independent claims, and "patent drafters are free to, and commonly do, claim an invention using multiple linguistic variations in multiple independent claims." Patent Case Management Judicial Guide (Federal Judicial Center 2009) at 5-60, citing *Andersen Corp. v. Fiber Composites, LLC*, 474 F.3d 1361, 1370 (Fed. Cir. 2007). Indeed, "[i]t is not unusual that separate claims may define the invention using different terminology, especially where (as here) independent claims are involved." *Hormone Research Found v. Genentech, Inc.*, 904 F.2d 1558, 1567 n. 15 (Fed. Cir. 1990).

iii. Prior Art

PDL contends that prior art incorporated by reference into the '370 patent confirms that it is not necessary to use CDR sequences that are 100% identical to the donor. First, it cites a comment in the Clark EP that "[i]t is accordingly believed that some changes in the CDRs may similarly be made without necessarily having an adverse effect on antibody-antigen affinity." Sandel Decl. Ex. 15 at 3 (Clark EP). Second, it notes the Riechmann paper's contemplation of sequence variation in the CDRs, referred to here as the hypervariable regions: "[i]n principle, the idiotype of the reshaped CAMPATH-1 could be changed by altering the hypervariable region..." Sandel Decl. Ex. 5 at 327 (Riechmann Article). However, unlike the Roberts paper on mutagenesis, which also speaks to the modification of CDR sequences, the Clark and Riechmann articles are never incorporated specifically in the patent. Rather, at the end of column 70, the patent states: "All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference." '370 Patent Col. 70:17-20. As MedImmune argues, the law is clear that to incorporate a reference, the specification "must identify with *detailed particularity* what specific material it incorporates and *clearly indicate where* that material is found in the various documents." *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378-79 (Fed. Cir. 2007), quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). Accordingly, the Court concludes that the Clark EP

and Riechmann article were not incorporated by reference. However, despite the fact that their contents therefore cannot be considered as intrinsic evidence, this prior art still is relevant extrinsic evidence that persons having ordinary skill in the art in 1989 considered the modification of CDRs to increase antibody-antigen affinity.

iv. Consistent Construction of the Language within Claim 28

PDL contends that its proposed construction of the disputed terms of Claim 28 is internally consistent, and that MedImmune seeks to impose inconsistent constructions of the terms. Citing the parties' agreement that Claim 28 allows the variable region frameworks to deviate so that they need only be substantially identical (about 85% or more) to the framework of a naturally occurring human immunoglobulin, PDL argues that the undisputed construction of the term, "heavy and light chain variable region frameworks *from* human acceptor immunoglobulin heavy and light chain frameworks," reflects the fact that the patentee intended the word "from" to convey variance, both here and in the context of the phrase "CDRs from a donor immunoglobulin."

PDL claims that MedImmune's proposed constructions thus are inconsistent, in that they would include substantial homology in variable region frameworks but not CDRs. The Court agrees, consistent with its independent conclusions that Claim 28 does not limit the invention to a transfer of all six CDRs that are 100% identical in sequence to those found in a non-human immunoglobulin.

2. "Donor Immunoglobulin"

The parties agree that the patent defines "donor immunoglobulin" as "the nonhuman immunoglobulin providing the CDRs." '370 Patent 12:4-5. The parties' remaining dispute is dependent on the disputed construction of the term "CDRs." MedImmune contends that claim 28 necessitates that all CDRs must come from a single donor immunoglobulin, consistent with its position that all three CDRs from each chain must be transferred. PDL does not argue that the a combination of donor immunoglobulins may be utilized but rather that all the CDRs need not come from the donor.

Because it will adopt PDL's construction of "CDRs," permitting the transfer of less than

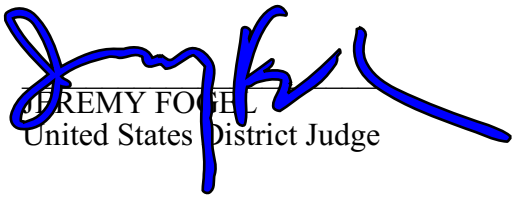
all three CDRs from each chain, the Court also will adopt PDL's construction of "donor immunoglobulin" – "the nonhuman immunoglobulin providing the CDRs." '370 Patent Col. 12:4-5.

IV. ORDER

The disputed terms of claim 28 are hereby construed as set forth above.

IT IS SO ORDERED.

DATED: February 22, 2010



JEREMY FOGEL
United States District Judge