United States District Court,
C.D. California.

SCANTIBODIES LABORATORY, INC,
Plaintiff.
v.
IMMUTOPICS, INC., and Immutopics International, LLC,
Defendants/Counterclaimants.

No. CV 04-8871 MRP (MANx)

May 1, 2008.

Brian W. Kasell, Marc Marmaro, Rod S. Berman, Jeffer Mangels Butler and Marmaro, Los Angeles, CA, for Plaintiff.

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CLAIM CONSTRUCTION ORDER

MARIANA R. PFAELZER**, District Judge.**

In this patent infringement action, Plaintiff Scantibodies Laboratory, Inc. ("Scantibodies") and Defendants Immutopics, Inc. and Immutopics Int'l, LLC (collectively, "Immutopics") seek construction of four terms in the post-reexamination claims of Scantibodies' U.S. Patent No. 6,689,566 ("The '566 Patent"), in accordance with Markman v. Westview Instruments, Inc., 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). These terms are: "specific for," "specifically binds to whole parathyroid hormone," "does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment," and "not detecting an interfering non-(1-84) parathyroid hormone fragment." This Court held a *Markman* hearing on March 24, 2008, at which both parties presented argument, and Scantibodies presented the testimony of its expert, Dr. Monica Ranes-Goldberg, Ph.D.

I. BACKGROUND

A. Technology

a. Parathyroid Hormone

Parathyroid hormone (PTH) is an amino acid peptide composed of a linear sequence of 84 amino acids. FN1 It is a naturally occurring hormone in humans and other animals that regulates the concentration of calcium ions in the blood. *See* '566 Patent at 1:19-21. This is accomplished through a feedback mechanism: when

calcium in the blood serum lowers, the parathyroid glands secrete PTH, which encourages the release of stored calcium. *Id*. at 1:25-28. Conversely, when serum calcium levels increase, the release of stored calcium is retarded through lowered secretions of PTH. *Id*. Calcium plays a key role in a variety of biological functions, including cell permeability, blood coagulation, transmission of nerve impulses, and normal muscle contraction. *Id* . at 1:16-19. Because PTH is a key regulator of calcium levels, accurate PTH measurement has proven to be important for a number of diseases. *Id*. (noting that "[s]erum PTH level is one of the most important index[es]" for a long list of disesases that include Paget's bone disease, primary hyperparathyroidism, and renal failure).

There are two reasons why determining the concentration of circulating, biologically active PTH levels in humans is particularly challenging. First, active PTH is found at extremely low levels in the bloodstream, normally 10 pg/mL to 40 pg/mL, and thus requires highly sensitive methods for detection. FN2 *Id*. at 1:60. Second, not all forms of the PTH hormone circulating in the bloodstream are biologically active. If a molecule of PTH is missing at least the first two amino acids at the "N-terminal" of its 84 amino-acid sequence, it loses all biological activity. *See* U.S. Pat. No. 6,030,790 at 1:10-20 (invalidated in Nichols Inst. Diag., Inc. v. Scantibodies Clinical Labs., No. 06-1087, 195 Fed. Appx. 947 (Fed.Cir. Sept.20, 2006) (unpublished)) ("However, upon the loss of the first amino acid, serine, the activity significantly decreases and is lost completely without the first two amino acids, serine and valine.") Blood serum in fact contains very large PTH fragments that are very similar to whole PTH in size, yet are biologically inactive because they are missing two or more amino acids at the N-terminus. *See, e.g., id*. at 2:28-30 ("hyperparathyroid patients and renal failure patients ... have significant endogenous concentrations of large, non-whole PTH fragments"); *id*. at 2:20-27, 1:43-48 (citing a 1998 article by LePage noting the discovery of "a large PTH fragment referred to as a 'non-(1-84) PTH' ... which is clipped closer to the N-terminal end of PTH"). Thus, any assay for detecting whole PTH must be able to distinguish intact, whole PTH molecules (variously referred to as "whole PTH," "wPTH," PTH (1-84), or (1-84) PTH) from these large, biologically inactive PTH fragments.

b. Assays for PTH

PTH "immunoassays" are tests that utilize custom-made antibodies that are specific for biologically active wPTH.FN3 One example is the immunoradiometric assay ("IRMA", or "sandwich assay") that is disclosed as a preferred embodiment of the ' 566 Patent. Id. 3:44-59.FN4 While the details of the assay protocol are not directly implicated by claim construction, the Court notes that the key to achieving accurate results in any PTH immunoassay is the antibody's *specificity* for whole PTH over N-terminal PTH fragments.

The experience with a previous generation of immunoassays for PTH highlights the need for na antibody that is highly specific for whole PTH. Prior to the invention claimed in the '566 Patent, a leading commercially available test kit, called the Nichols Allegro Intact PTH assay, purported to measure "intact" PTH, or "I-PTH" in blood serum. Id. at 2:12-15. However, the Nichols kit in fact reported PTH concentrations that were erroneously *higher* than the true values because the Nichols antibody would bind to PTH(7-84) and other large, inactive N-terminal PTH fragments present in the serum as well as binding to whole PTH molecules. *See* id. at 2:25-30. Such fragments are present in the blood serum but were not discovered until after the Nichols assay had been developed. *See, e.g.,* id. at 2:43-45. As a result, the term "I-PTH," used in connection with the Nichols assay, was abandoned in favor of new terminology. Id. at 2:25-27. Unfragmented, active PTH is now referred to as "whole PTH," (1-84) PTH, or "wPTH." *See* id. 1:6-8, 3:26-27. Likewise, biologically inactive PTH fragments that had been measured by I-PTH assays are now termed "interfering non-(1-84) PTH fragments."

B. The Invention

The '566 Patent is directed to antibodies specific for whole PTH, as well as related kits and methods for detecting whole PTH. Through the invention claimed by the '566 Patent, Scantibodies sought to succeed where the Nichols I-PTH kit failed by "detecting wPTH in a biological sample without detecting the non (1-84) large PTH fragment component of I-PTH." Id. at 2:43-45. Scantibodies' solution is to generate and isolate an antibody "specific for the initial sequence for wPTH ... VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID: NO 3) [amino acids 2-8 of PTH] ... wherein at least four amino acids are part of the antibody reactive portion of the peptide." '566 Patent at 2:47-52. By requiring binding to at least four of the amino acids in the PTH (2-8) region of wPTH, the '566 Patent ensures that the resulting antibody will not bind to PTH(7-84) or similar fragments that are missing at least four of the amino acids in the 2-8 region of PTH.FN5 *See* id. at 1:23-25 (noting the fragments in I-PTH are known to include the N-terminal fragments "cleaved about amino acids 5 to 8").

The '566 Patent teaches a two step process for generating the claimed antibody. First, an animal such as a goat is injected with an antigen (or "immunogen"), which is typically whole PTH or a fragment of PTH.FN6 *See* ' 566 Patent at 5:27-50. In response, the goat produces antibodies that are specific for this antigen. Some length of time after this immunization, the goats are bled and antiserum is extracted by removing the red blood cells. *Id*. This antiserum contains all the antibodies that have been generated by the animal, including all the antibodies that have been generated in response to the injected PTH antigen. Furthermore, the desired antibodies, those that bind to at least four amino acids in PTH(2-8), are a subset of these anti-PTH antibodies.

The second step of the process involves isolating these desired antibodies from the antiserum through "affinity purification". *See id;* ' 566 Patent at 5:53-67. In the purification step, an "initial peptide sequence," which is a short sequence of amino acids, is affixed to cross-linked agarose beads. This initial sequence typically consists of the first eight amino acids of PTH ("PTH(1-8)"), or a slightly shorter sequence (such as PTH(2-8), which is a sequence that is missing the first amino acid in PTH(1-8)). *See id*. at 4:50-55.FN7 The peptide-laden beads are then packed into a "separation column," a specialized kind of test tube. *See id*. at 5:16-21, 5:52-55. Next, the goat antiserum from the previous step is poured into the separation column. Antibodies that happen to be specific for the initial peptide sequence will then bind to the peptide-laden agarose beads. *See id*. *at* 5:57-59. These beads now contain the desired antibodies and can be isolated from the rest of the antiserum. *See id*. at 5:59-67.

Purified in this manner, the claimed antibodies can then be used in an appropriate immunoassay to detect concentrations of whole PTH in the bloodstream.

C. Procedural History

Scantibodies filed its Complaint on October 26, 2004, alleging that Immutopics' antibody kits infringed its U.S. Patent No. 6,689,566. During the course of discovery, Immutopics identified a prior art reference, known as the Colford Abstract FN8, which it claimed invalidated the ' 566 Patent. Immutopics notified Scantibodies of the existence of the Colford Abstract in an August 5, 2005 letter. *See* Sept. 20, 2005 Order Granting Plaintiff's Mot. to Stay Proceedings at 2. Subsequently, Scantibodies and later Immutopics filed separate requests for ex parte reexamination of the ' 566 Patent before the Patent & Trademark Office, which were consolidated into a single proceeding on February 16, 2006. *See* 5/24/2006 Office Action, Newboles Cl. Constr. Decl., Exh. B. at 2. Over Immutopics' objection, Judge George P. Schiavelli granted

Scantibodies' motion to stay the proceeding pending the outcome of ex parte reexamination. *See* Sept. 20, 2005 Order.

Ultimately, the claims of the '566 Patent survived reexamination in amended form. *See* PTO's Notice of Intent to Issue *Ex Parte* Reexamination Certificate, January 8, 2007, Newboles Cl. Constr. Decl., Exh. F. To overcome the Colford reference and other relevant prior art, Scantibodies amended independent claims 1, 20, and 22 (the kit and antibody claims-but not the method claims) to add two key limitations. Most importantly, it required that the antibody "specifically binds to whole parathyroid hormone but does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment." *See* Claims As Allowed After Re-Examination, Kasell Decl. Supp. Pl.'s Mot. P. Summ. J. on Defs.' Counterclaim of Patent Invalidity, Exh. B ("Reexamination Claims"). Scantibodies also added language to the kit and antibody claims that required that claimed antibodies be generated by the two-step process described in the previous section: "by immunizing a mammal with whole parathyroid hormone," collecting antiserum, and subsequently isolating the desired antibodies in the affinity purification step by "binding said antibody to at least four amino acids in the common sequence of human and rat PTH (1-8) sequence." *See* Reexamination Claims 1, 20, 22. Though the PTO has not, to date, issued the Reexamination Certificate itself, the validity of the claims no longer appears to be at issue in the reexamination proceeding.FN9

On March 5, 2007, the case was transferred to this Court for further proceedings. Subsequently, on November 13, 2007, Immutopics filed summary judgment motions on five grounds: failure to disclose the best mode known to the inventor, lack of enablement, obviousness, on-sale bar, and non-infringement. However, the Court concluded that evaluation of Defendants' motions for summary judgment, and particularly the motions for non-infringement and enablement, required construction of the claims as amended during reexamination. *See, e.g.,* Mem. P. & A. Supp. Pl.'s Opp'n to Defs.' Mot. Summ. J. of Non-Infringement, at 13 (suggesting the need for a *Markman* hearing). After a January 29, 2008 hearing on Immutopics' summary judgment motions, the parties agreed to the four disputed claim terms that were the subject of the *Markman* hearing.

II. LEGAL STANDARD

"[T]he construction of a patent, including terms of art within its claim, is exclusively within the province of the court." Markman, 517 U.S. at 372. During claim construction, "[t]he words of a [patent] claim are generally given their ordinary and customary meaning," that is, "the meaning that the term would have to a person of ordinary skill in the art in question ... as of the [patent's] effective filing date." Phillips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed.Cir.2005) (*en banc*). Furthermore, the specification is "always highly relevant" in construing a claim. Id. at 1315. Where a claim term is disputed, the specification is in fact "the single best guide to the meaning of a disputed term" and will usually be dispositive as to its meaning. *Id*.

Extrinsic evidence in the form of expert testimony can also help educate the court concerning the invention and the knowledge of persons of skill in the art. Phillips, 415 F.3d at 1319. However, the Federal Circuit has cautioned against undue reliance on extrinsic evidence, which is "in general ... less reliable than the patent and its prosecution history." Phillips, 415 F.3d at 1318. Indeed, the use of extrinsic evidence is "unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." Id. at 1319. Expert testimony must also be disregarded where it is at odds with the intrinsic evidence, or where an expert's conclusory assertions as to the definition of a claim term are not supported by independent sources such as industry publications. Network Commerce, Inc. v. Microsoft Corp., 422 F.3d 1353, 1361 (Fed.Cir.2005) (citing Phillips, 415 F.3d at 1318). Ultimately, the decision as to the need for and

use of experts is within the sound discretion of the district court. InPro II Licensing, S.A.R .L. v. T-Mobile USA, Inc., 450 F.3d 1350, 1357 (Fed.Cir.2006).

III. CLAIM CONSTRUCTION

The parties dispute the meaning of the following four claim terms: (1) "specific for," (2) "specifically binds to whole parathyroid hormone," (3) "does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment" and (4) "not detecting an interfering non-(1-84) parathyroid hormone fragment."

Scantibodies and Immutopics agree that antibody specificity, binding, and detection are not defined by the '566 Patent. However, their competing claim definitions, detailed below, illustrate fundamentally different approaches to resolving their meaning. Scantibodies suggests that the intrinsic evidence lacks guidance simply because the concepts of antibody binding and specificity are already so well-known to persons having skill in the art that definitions of those terms are unnecessary. Pl.'s Br. Supp. Construction of Terms in Reexamination Claims ("Pl.'s Claim Constr. Br.") at 4 ("Indeed ... the only surprise would be if a definition *was* found in the record.") Dr. Monica Ranes-Goldberg, Scantibodies' expert, emphasizes that binding and specificity are relative concepts that are well understood in the art.

In contrast, Immutopics declines to offer a competing expert opinion because it believes that the intrinsic record, and in particular certain representations made during the reexamination, provide sufficient guidance as to the claim terms at issue to overcome the seeming ambiguity inherent in the ' 566 Patent. These intrinsic cues, it asserts, require that binding specificity be construed in absolute terms.

A. The Parties' Proposed Constructions

The parties have proposed the following claim constructions.FN10

Claim Term	Scantibodies' Construction	Immutopics' Construction
(1) specific for	The claimed antibody exhibits binding in the specified region (*i.e.*, 2-8 PTH) ***in whole PTH***[FN11] that is statistically significantly greater than the binding exhibited by the claimed antibody to any fragment of PTH not having at least four amino acids from the common sequence of human and rat PTH.	The binding of antibodies to PTH(2-8) with higher or increased affinity, as compared to the binding of the antibodies to whole PTH with weak binding or low affinity binding. The prosecution history, however, does not explain what the term "higher or increased affinity" means or what the term "weak binding or low-affinity binding" means.
(2) specifically binds to whole parathyroid hormone	The claimed antibody exhibits binding to whole PTH in a biological sample that is statistically significantly greater than the binding exhibited by the claimed antibody with any fragment of PTH in the sample not having at least four amino acids from the common sequence of human and rat PTH.	The antibody binds only to whole PTH and does not cross-react with non-whole PTH, even at extremely high concentrations of PTH fragments. For example, such an antibody must bind to whole PTH but not cross react with a PTH (7-84) fragment when such fragment is present at a concentration of 10,000 pg/ml. Further, the antibody that "specifically binds the whole parathyroid hormone" must be raised exclusively from the use of whole PTH (1-84) as an immunogen.
(3) does not	The claimed antibody exhibits	The antibody cannot bind to anything other than whole

specifically bind to an interfering non-(1-84) parathyroid hormone fragment	binding to one or more interfering non-(1-84) parathyroid hormone fragment(s) in a biological sample that is statistically significantly less than the binding exhibited by the claimed antibody to whole PTH in the sample.	PTH even at extremely high concentrations of fragments, such as concentrations of 10,000 pg/ml for PTH (7-84). Further, the antibody that "does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment" cannot be produced by any immunogen other than whole PTH (1-84), including but not limited to PTH (1-5), PTH (1-6), PTH (1-7), PTH (1-8), PTH (1-9), PTH (1-10), PTH (1-34), or PTH (1-38) as immunogens.
(4) not detecting an interfering non-(1-84) parathyroid hormone fragment	The claimed antibody exhibits binding to one or more interfering non-(1-84) parathyroid hormone fragment(s) in a biological sample that is statistically significantly less than the binding exhibited by the claimed antibody to whole PTH in the sample .	The antibody must not bind to anything other than whole PTH (1-84). It must not bind to PTH fragments, including PTH (1-34), even at extremely high concentrations of the specified fragments, such as concentrations of 10,000 pg/ml for PTH (7-84).

B. The Court's Construction

The Court begins with a clarification of two related terms often used to describe antibody binding: "binding affinity" and "specificity." Scantibodies' expert, Dr. Monica Ranes-Goldberg explains these terms in her declaration. Ranes-Goldberg Decl. para. 9. "Affinity" is a "quantitative measurement of an antibody's absolute binding strength with a particular antigen." Id. "Specificity" is a measure of an antibody's relatively greater binding affinity for one antigen versus another antigen. Id. Drawing on these definitions, if an antibody has a sufficiently greater tendency to bind a first antigen over a second antigen, it is said to be "specific for" the first antigen. The distinction between binding affinity and binding specificity permeates the rest of this Order.

1. "specific for"

"Specific for" appears in every independent claim in the patent. *See* Claims as Allowed after Re-exam of Patent No. 6,689,566 B1, Kasell Decl. Supp. Pl.'s Br. Supp. Construction of Terms in Reexamination Claims of U.S. Pat. No. 6,689,566, Exh. B ["Reexamination Claims"] (independent antibody claim 1; independent kit claims 20, 22; independent method claims 5, 13, 18, 25, 27). It serves as part of the following phrase: "[an] antibody or antibody fragment *specific for* an initial peptide sequence of whole parathyroid hormone wherein said initial peptide sequence consists of VAL-SER-GLU-ILE-GLN-LEU-MET (SEQ ID NO:3) FN12 ... wherein at least four amino acids in said initial peptide sequence are part of a reactive portion with said antibody".FN13 *See* Reexamination Claim 1 (emphasis added).

In Scantibodies' proposed definition of "specific for," binding between a claimed antibody and the 2-8 PTH region "in whole PTH" FN14 must be at a level "statistically significantly greater" than the binding between that antibody and "any fragment of PTH not having at least four amino acids from the common sequence of human and rat PTH." FN15 In contrast, Immutopics adopts the definition of "specific for" put forth by the patent examiner in her September 21, 2006 office action: that an antibody binds PTH (2-8) with "higher or increased affinity," as compared to the strength with which the antibody binds to whole PTH. However, Immutopics does not place much faith its own construction, concluding in its brief that "specific for" is

ultimately "indefinite and incapable of being construed" and that "the claim must be declared invalid rather than ascribed a speculative function." Immutopics, Inc. and Immutopics Int'l, LLC's Cl. Constr. Br. ("Defs.' Cl. Constr. Br.") at 6-7. FN16

The Court begins with its own analysis of this term in light of the role it plays in the '566 Patent. First, it establishes what binding affinities must be compared in order to define specificity in the context of "specific for." Since the claims teach that an antibody must be "specific for" PTH(2-8), it is logical to determine what it is not "specific for." Second, the Court also examines the level of specificity that is required under this claim term before turning to the parties' proposed definitions.

i. In light of the claim language and the specification, "specific for" is defined as an antibody's strong preference for the PTH(2-8) region of whole PTH over the rest of the whole PTH molecule.

The independent claims require an antibody that is "specific for" an " *initial peptide sequence* of whole parathyroid hormone" that "consists of" PTH(2-8). *See, e.g.,* Reexamination Claim 1 (emphasis added). Furthermore, it requires that "at least four amino acids in said *initial peptide sequence* " are part of the "reactive portion" that binds with the antibody. Id. While the ' 566 Patent's drafters might have more succinctly stated that the antibody should be "specific for at least four amino acids in PTH(2-8)," the focus on an "initial peptide sequence" is deliberate. "Initial peptide sequence" is a term of art in the '566 Patent and is well characterized in the specification. *See* '566 Patent at 4:48-67, 5:1-13 (characterizing the selection and synthesis of an "Initial Whole PTH Sequence Peptide" as the first step in isolating the desired antibodies). The written description permits the initial peptide sequence to be one of the following: (i) amino acids 1-8 of human PTH; (ii) amino acids 1-8 of rat PTH (in which the first amino acid is Alanine instead of Serine); (iii) "the common sequence" of rat and human PTH, i.e. amino acids 2-8, which are the same the same in human and rat.FN17 *Id*. at 4:50-55. In the claims, of course, the initial peptide sequence must "consist[ ] of" the last option, PTH(2-8).

The key to interpreting "specific for" is that the term "initial peptide sequence" has a dual purpose within the '566 Patent:

-> In its primary role, the initial peptide sequence is the peptide used for affinity purification-the process of isolating and purifying the claimed antibodies from goat antiserum. There, it is a short, standalone peptide affixed to an agarose bead in a separation column. Id. at 5:15-21, 5:52-67. Notably, no other amino acids of PTH are present during affinity purification. FN18

-> In its alternate form, the initial peptide sequence is part of the whole PTH molecule that is injected into the goat in order to generate antibodies. FN19 Id. at 5:27-34. Thus, in this context, "initial peptide sequence" merely refers to a particular region of whole PTH (i.e., amino acids 2-8 in the 84 amino acid sequence), rather than a standalone peptide. Id. Other amino acids of PTH are present: the initial peptide sequence is attached to the rest of the 84 peptide sequence that makes up whole PTH, i.e. amino acids 9-84.

Here, two facts about affinity purification aid in the Court's understanding of "specific for." First, the affinity purification step for isolating a claimed antibody necessarily precedes the use of that antibody to detect whole PTH. Second, the antibodies are isolated and purified based *solely* on their affinity for this standalone, initial peptide sequence. As a result, the antibodies claimed under the '566 Patent should bind the PTH(2-8) region *in whole PTH* just as strongly as they bind to PTH(2-8) as a standalone, affinity purification peptide. Because affinity for the initial peptide sequence is in fact the only criterion for

selecting the claimed antibodies, the presence of additional amino acids (i.e., 9-84) in whole PTH is irrelevant. An antibody "specific for" the initial peptide sequence required by the claims will bind with *substantially greater affinity* to 2-8 than to amino acids in 9-84.

Two facets of the claim language reinforce this conclusion. First, "consists of" is a close-ended phrase that permits the addition of no extra elements. *See* Vehicular Tech. Corp. v. Titan Wheel Int'l, Inc., 212 F.3d 1377, 1383 (Fed.Cir.2000) (contrasting "consisting of" with the open ended "comprising"). Thus, requiring an antibody that is "specific for" an initial peptide that "consists of" PTH(2-8) suggests it should not be specific for amino acids *elsewhere* in the whole PTH sequence. Additionally, the independent kit and antibody claims were amended during reexamination to require *explicitly* that the claimed antibodies be affinity purified with the PTH(2-8) peptide. *See* Reexamination Claims 1, 20, 22 ("and wherein said antibody ... is produced by immunizing a mammal with whole parathyroid hormone, collecting said antibody *... and isolating said antibody by binding said antibody to at least four amino acids in the common sequence of human and rat PTH(1-8) sequence* ") (emphasis added).FN20 Just as the antibody must bind to at least four amino acids of the PTH(2-8) initial peptide sequence *in whole PTH,* the amended language here requires that the antibody bind in exactly the same way to the PTH(2-8) initial peptide during affinity purification ("isolating said antibody").FN21 This further limitation, though not present in the original claims, explicitly ties together the two definitions of initial peptide sequence.

In sum, the analysis of "initial peptide sequence" answers two basic questions about the nature of specificity required by "specific for." First, the appropriate specificity comparison is between an antibody's affinity for the (2-8) region of whole PTH and its affinity for the rest of the whole PTH molecule-(9-84). Second, the antibody's *degree* of specificity for PTH(2-8) should be viewed in light of the fact that it was selected during affinity purification solely on its affinity for (2-8) as a standalone initial peptide.

ii. The "specific for" limitation deals only with the 'mechanics' by which an antibody binds to the N-terminal region of whole PTH.

The link between "specific for" and affinity purification illuminates that term's essential role in the claims. "Specific for" is a limitation that is concerned with the *mechanics* of antibody binding-mechanics that are influenced almost exclusively by the choice of initial peptide used in affinity purification.FN22 A separate claim limitation, one which implicates the remaining three claim terms at issue, addresses the ultimate *result* of antibody binding: that the antibody "specifically binds to" whole PTH "but does not specifically bind" to an interfering fragment (or alternately, that it detects whole PTH "while not detecting" an interfering fragment). Thus, "specific for" is *not* directed at accurate test results.

Thus, though the limitation on antibody binding mechanics provided by "specific for" and the "results" limitation imposed by the other three claim terms are both directed towards ensuring antibody "specificity" for whole PTH over interfering PTH fragments, they approach the problem from two different angles. Ideally they should reach the same result, and an antibody that binds to the N-terminal of whole PTH in a certain way will *necessarily* bind only to whole PTH while not specifically binding to interfering fragments. Indeed, the original antibody and kit claims contained only the "specific for" limitation, with no limitation as to results.FN23 But however confident the inventors of the ' 566 Patent may have been in their solution regarding binding mechanics, during reexamination Scantibodies added the phrase "specifically bind to whole [PTH] but does not specifically bind to an interfering ... fragment." This newly added limitation ensures, independently of "specific for," that a claimed antibody functions as it should.

iii. Scantibodies' definition is inconsistent with the Court's construction and provides no guidance as to the degree of specificity for wPTH.

Scantibodies' amended construction is fatally flawed for two reasons. First, it is inconsistent with the purpose and construction of "specific for" established by the Court. Second, the "statistically significantly greater" metric provides no substantive guidance in construing this term.

1. Scantibodies' definition of "specific for" erroneously addresses the 'result' of antibody binding, not its 'mechanics'.

Scantibodies' definition compares binding in the 2-8 PTH *region* of whole PTH with binding to PTH *fragments* missing at least four of the N-terminal amino acids between 2-8. This construction misapplies the concept of antibody binding specificity. It does not make sense to compare an antibody's affinity for a certain *region* within the whole PTH molecule (2-8) with its affinity for PTH *fragments* (which are entire molecules). Scantibodies is attempting to compare apples to oranges.

Moreover, Scantibodies cannot arrive at a valid definition of "specific for" even if it purports to compare apples to apples. For instance, Scantibodies' construction could be interpreted as a comparison of antibody affinity for the 2-8 *region* of wPTH versus affinity for the *corresponding region* of a PTH fragment "not having at least four amino acids from the common [2-8] sequence of human and rat PTH." As the Court's previous construction demonstrates, this is not the appropriate comparison for specificity. Scantibodies' definition compares antibody binding affinity for the N-terminal region of PTH across molecules, but "specific for" must compare affinity for one region within a single molecule (whole PTH) with another region in that molecule. Comparing specificities across differing molecules, while facially plausible, fails to take into account the usage of the phrase "initial peptide sequence" and its dual meaning in the context of the '566 Patent.

Scantibodies' approach (interpreted in this way) is also likely to create more uncertainty than it resolves. First, the comparison of binding affinities with "any fragment of PTH not having at least four amino acids from the common sequence" makes little sense. Why define "fragment of PTH" in terms of missing these amino acids, instead of using the term already used by the '566 Patent, "interfering non-(1-84) PTH fragment"? FN24 The two definitions are not identical, if for no other reason than that many or most of Scantibodies' "fragment[s] of PTH" contain N-terminal sequences that do not exist in nature.FN25 Unlike the term "an interfering ... fragment," "any fragment of PTH ..." does not require all the missing peptides to be contiguous, nor removed only from the extreme N-terminal end of PTH.FN26 Scantibodies' alternate formulation is also impractical. Because the term "any" (in "statistically significantly greater than the binding exhibited by the claimed antibody with *any* fragment of PTH ...") implies that the affinity for wPTH(2-8) must be greater than the affinity for the corresponding region in "any" *possible* "fragment of PTH", one must compute the binding affinities for dozens of hypothetical fragments, whose binding characteristics at the N-terminal are unknown, and comparing them with the affinity for the PTH(2-8) region of *whole PTH*.FN27

At the same time, Scantibodies cannot go further and render its construction logically consistent by requiring a comparison between the antibody's affinity for the *entire* whole PTH molecule with its affinity for PTH fragments "not having at least four amino acids" in the PTH(2-8) sequence. This interpretation would transform "specific for" from a limitation on the mechanics of antibody binding into one concentrated solely on the ultimate "result" of antibody binding, which is that a claimed antibody distinguish whole PTH from an interfering non-(1-84) PTH fragment. In the process, "specific for" would become a nearly FN28

redundant limitation which would swallow the three remaining terms at issue in this *Markman* order-"specifically binds to," "not specifically bind to an interfering ... fragment," and "not detecting an interfering ... fragment"-while continuing to provide no insight or guidance into the term "specific for." *See* Reexamination Claims 1 and 5. This interpretation, as well as the two previous ones, is unacceptable.

2. The requirement that affinity to PTH(2-8) be "statistically significantly greater" is also inconsistent with the basic purpose of "specific for" and adds nothing to the proposed construction.

Scantibodies' use of the term "statistically significantly greater" in its construction of "specific for" only further clouds the issue. This term is not supported by the patent specification and was not adequately explained at the *Markman* hearing on this issue. Dr. Ranes-Goldberg suggests that the term "statistically significantly" simply reflects the "concept that in a clinical context it is important that the antibody sufficiently discriminate between whole PTH and PTH fragments in a manner that provides a consistently reliable measurement based on a comparison with the appropriate positive and negative controls that are provided with the test kit." Ranes-Goldberg Decl. para. 12. FN29 But again, the need to sufficiently discriminate between whole PTH and PTH fragments is *already addressed* by other claim limitations which are directed to the "results" of antibody binding-the three remaining terms at issue in this *Markman* order. Such concerns have no place in a definition of "specific for," which focuses solely on the manner in which the antibody binds to whole PTH. Stripped of the window dressing of experimental controls and measurement reliability, Dr. Ranes-Goldberg's opinion provides no meaningful guidance on the level of specificity required in order for an antibody to be considered "specific for" PTH(2-8).

3. Scantibodies provides no justification for its questionable construction.

Scantibodies' construction does not flow either from the relative nature of antibody specificity, or from the requirement that "at least four amino acids in said initial peptide sequence" are "part of a reactive portion with said antibody"-a separate claim limitation that *follows* "specific for".FN30 Likewise, it finds no support in the specification. Furthermore, its construction does not even appear to be consistent with the understanding that Dr. Cantor, one of the named inventors of the ' 566 Patent and the founder of Scantibodies, demonstrated in this litigation only months earlier. *See* Thomas Cantor Decl. para. 7 (Dec. 18, 2007) ("So, for illustration only, if a peptide (e.g., wPTH) has a chain of 84 amino acids (from 1-84) and the antibody binds with amino acids 1-8 *more than it binds to 9-84,* we say that the antibody is *specific for* 1-8 ....") (emphasis added).

Scantibodies only provides the support of Dr. Ranes-Goldberg, who agrees that "[t]he critical comparison for the relevant specificity is to compare binding to the initial peptide sequence of whole PTH relative to a fragment that is missing some or all of this sequence." Ranes-Goldberg Decl. at para.para. 11, 13. But she provides no further justification for a position that contradicts the intrinsic record of the '566 Patent. In addition, Dr. Ranes-Goldberg fails to support her definition of "specific for" with sources outside of her declaration. *See* Network Commerce, Inc. v. Microsoft Corp., 422 F.3d 1353, 1361 (Fed.Cir.2005) (rejecting conclusory assertions by expert as to meaning of a claim term, where unsupported by independent evidence such as industry publications). Her definition in fact appears to be nothing more than a neat paraphrase of the proposed construction submitted by Scantibodies. *See id*. para. 11, 12.FN31 For these reasons, the Court gives no weight to her opinion on this claim term.

In short, no matter which way it is interpreted, Scantibodies' construction of "specific for" is inconsistent with the specificity framework established by the Court. It also obscures the real issue involved in construing this term: the *degree* of specificity that the antibody must possess for the 2-8 region of whole

PTH. Even though Scantibodies repeatedly emphasizes that specificity is a relative concept, such an argument does not transform it one that escapes definition entirely.FN32 In offering a proposed construction that addresses the wrong issues, Scantibodies provides no guidance at all.

iv. The examiner's definition of specificity, as interpreted by Immutopics, does not provide a coherent construction of "specific for."

In contrast to Scantibodies' expert-based approach, Immutopics' definition of "specific for" arises from the reexamination history, which is part of the intrinsic record. *See* Phillips v. AWH Corp., 415 F.3d at 1314 (prosecution history is part of intrinsic record); 35 U.S.C. s. 305 (stating that "reexamination will be conducted according to the procedures established for initial examination" after initial statutory period under s. 304).

The statement at issue arose during the September 21, 2006 Final Office Action, in which the patent examiner observed that the patent specification was "silent regarding the difference between the terms 'specific for' and 'binds to.' " *See* 9/21/2006 Final Office Action, Newboles Decl. Supp. Immutopics Cl. Constr. Br. Exh. D at 4-5. She then noted that it was also "silent regarding the relative affinities of the claimed antibodies." *Id*. On this latter point, the examiner then suggested a "default" definition for these relative affinities, stating, "in the absence of specification disclosure it is considered that the antibodies bind to the initial peptide sequence of PTH (SEQ ID NO: 3) with higher or increased affinity as compared to the whole PTH, and the binding of the claimed antibodies to the whole PTH sequence is interpreted as weak binding (or low affinity binding)." Immutopics derives its proposed construction almost verbatim: "the binding of antibodies to PTH(2-8) with higher or increased affinity, as compared to the binding of the antibodies to whole PTH with weak binding or low affinity binding."

The examiner's definition is confusing because it compares affinity for the "initial peptide sequence" of PTH(2-8) with the affinity for "the whole PTH sequence," and Immutopics does not attempt to clarify it. *See* Defs.' Claim Constr. Br. at 4 (stating without elaboration that " '[s]pecific for' means just what the Patent Examiner said it means"). Yet the Court's construction establishes that "specific[ity] for" the PTH(2-8) region requires a comparison of an antibody's affinity for that region with its affinity for the rest of wPTH *excluding that region*. The examiner's statement is especially puzzling given that the record shows that she did in fact understand the significance of an "initial peptide sequence". In the paragraph following her statement on relative binding affinities, the examiner stated that "[i]t is interpreted that the claimed antibodies specific to the initial peptide sequence of PTH ... would bind to the whole PTH ... since the wPTH comprises the initial peptide sequence." 9/21/2006 Office Action at 5. Though it is not entirely aligned with the Court's construction, these comments demonstrate that the examiner realized that an initial peptide sequence retains its identity even when it is part of the whole PTH molecule. In this light, the examiner's wording was merely imprecise: what she really meant was that the binding of the claimed antibodies to the whole PTH sequence *excluding the initial peptide sequence* is interpreted as weak binding.

Unlike the examiner, Immutopics fails to recognize the dual nature of an "initial peptide sequence," and insists that it must be a fragment.FN33 Interpreting the examiner's definition in this way renders it incoherent, however. The Court thus rejects Immutopics' construction of "specific for." Furthermore, because the claim language and specification adequately inform the meaning of "specific for", the Court does not need to consider Immutopics' argument that this term is, in fact, indefinite.FN34

While it is tempting (as the examiner suggested) to define "specific for" as requiring an antibody with

"higher or increased affinity" for PTH(2-8), but "weak" or "low affinity binding" to PTH(9-84), it would not bring additional clarity as to the degree of specificity here. The Court's construction already indicates that an antibody's affinity to amino acids 2-8 must be substantially greater than its affinity to amino acids 9-84 in wPTH. Thus, the terms "higher" and "weak" binding merely implicate a different perspective on binding specificity, rather than some difference in degree.

Finally, Scantibodies raises a number of further objections to the examiner's statement, alternately characterizing it as an irrelevant discussion regarding the distinction between two similar terms, "specific for" and "binds to," *see* 3/24/2008 Hrg. Tr. at 3:6-9, 19-25, 4:1-6, 38:6-13; arguing that it is "directed to a form of the claims that no longer exists," Pl.'s Cl. Constr. Br. at 6 (emphasis omitted); and suggesting that the examiner did not understand the difference between the concepts of binding affinity and specificity, *see* Ranes-Goldberg Decl. para. 9. The Court need not consider these misguided objections in further detail because it declines to adopt the examiner's statement in its construction of "specific for." FN35

In conclusion, the Court rejects both parties' proposed constructions, and arrives at its own definition of "specific for," as " ***exhibiting substantially greater binding affinity for the PTH(2-8) region of whole PTH than for the PTH(9-84) region.***" In this definition, it is understood that the *magnitude* of specificity for PTH(2-8) is informed by the fact the antibody was selected during affinity purification based solely on its binding affinity for PTH(2-8) as a standalone peptide.

2. specifically binds to whole parathyroid hormone and does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment

The second and third claim terms are two parts of a single phrase added to independent Claims 1, 20, and 22 during reexamination: "and said antibody or antibody fragment specifically binds to whole parathyroid hormone but does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment." *See* Reexamination Claim 1, 20, 22 (kit and antibody claims). Though presented as two separate terms, they are two sides of the same coin and treated as such by the parties. The Court assumes that its construction of these two terms is purely advisory, as they appear only in the antibody kit claims-and those claims appear to be outside the scope of the parties' infringement dispute. FN36 However, the analysis of specificity is identical under these two terms and the final term, "not detecting an interfering non(1-84) [PTH] fragment," which does appear in the method claims.

Under "specifically binds," Scantibodies proposes that the claimed antibody must bind to whole PTH "in a biological sample" with an affinity that is "statistically significantly greater" than the affinity between the antibody and "any fragment of PTH in the sample not having at least four amino acids from the common sequence of human and rat PTH." It construes "does not specifically bind" as requiring the claimed antibody to bind to "one or more interfering non-(1-84) parathyroid hormone fragment(s) in a biological sample" with an affinity that is "statistically significantly less" than the affinity to whole PTH in the sample. Immutopics, on the other hand, proffers essentially the same definition for both claim terms: that "[t]he antibody binds only to whole PTH and does not cross-react with non-whole PTH, even at extremely high concentrations of PTH fragments." It also provides a quantitative threshold, drawn from the prosecution history: that an antibody must not specifically bind to the PTH (7-84) fragment even at "concentrations of 10,000 pg/mL". Immutopics further insists, as part of its proposed constructions for both claim terms, that PTH (1-84) is the only acceptable immunogen for generating the claimed antibodies.

As a threshold issue, the Court will not consider Immutopics' argument that both "specifically binds to" and

"not specifically bind" require the antibody to be "raised exclusively from the use of whole PTH (1-84) as an immunogen." FN37 All the claims that employ the two terms at issue *already* include an *explicit limitation* requiring the use of PTH (1-84) as the immunogen. *See* Reexamination Claims 1, 20, 22 (independent kit and antibody claims requiring that "said antibody ... is produced by immunizing a mammal with whole parathyroid hormone").FN38

i. Specificity in this context of these two terms entails a comparison between the antibody's affinity for whole PTH and its affinity for an interfering non-(1-84) PTH fragment.

A second threshold issue involves clarifying the relative affinities that must be considered in the context of "specifically binds" and "not specifically bind." Unlike the term "specific for," the claim language here provides the answer: the antibody must specifically bind to whole PTH while not specifically binding to an interfering non-(1-84) PTH fragment; in other words, it must have greater binding affinity for the former than for the latter. Accordingly, there is no reason why "specifically binds" should be defined differently than, or separately from, "not specifically bind." The two are linked: if an antibody binds to whole PTH with sufficiently greater affinity than it has for interfering PTH fragments, then both claim terms are satisfied. As Dr. Ranes-Goldberg testified for Scantibodies at the *Markman* hearing, the former term is just the "flip" side of the latter. 3/24/2008 Hrg. Tr. at 25:17.

While Immutopics' proposed constructions recognize this fact, Scantibodies' constructions do not: Scantibodies defines "specifically binds" in terms of "any fragment of PTH not having at least four amino acids," but it defines "not specifically bind" in terms of "an interfering non-(1-84) [PTH] fragment." As noted earlier, the two terms are not identical, and the use of "any fragment of PTH ..." presents various logistical problems, such as the need to calculate binding affinities for a whole class of hypothetical PTH peptides. Because of this potential for inconsistency, the Court rejects Scantibodies' construction of "specifically binds" (which employs this anomalous definition of a PTH fragment) and considers only its construction of "not specifically bind".

ii. The Court does not define the level of specificity for the two claim terms at issue because it cannot be characterized by either of the extremes proposed by the parties.

What constitutes specificity for whole PTH is the heart of the disagreement between Scantibodies and Immutopics with respect to the two claim terms at issue-as well as for the fourth claim term, "not detecting an interfering non(1-84) [PTH] fragment." The Court finds that neither party's definitions are satisfactory. Furthermore, because, neither the '566 Patent nor the prosecution history on reexamination adequately define specificity in this context, the Court does not arrive at a construction here.

1. Arguments

As with "specific for," Scantibodies proposes that the proper benchmark for specificity is statistical significance. Its definition of "not specifically bind," for example, is satisfied when an antibody's binding to interfering fragments is of "statistically significantly less" strength than the binding exhibited to whole PTH "in [a biological] sample." Dr. Ranes-Goldberg explains that statistical significance, which does not appear in the patent itself, refers "to a concept of how the antibodies would be used in a clinical setting." 3/24/2008 Hrg. Tr. at 19:25-20:1-2. Viewed from the perspective of a clinician who is measuring the level of whole PTH in a biological sample, an antibody is sufficiently specific if it is able to discriminate between whole PTH and any PTH fragments in the sample "in a way to provide measurement that is consistently reliable that would be meaningful to the clinician who was doing the test". Id. at 20:8-12. Scantibodies suggests that

this extrinsic standard is well-known in the art.

In stark contrast, Immutopics proposes an absolute, all-or-nothing definition of specificity for whole PTH. Under its definition, a claimed antibody must not bind to "anything other than whole PTH even at extremely high concentrations of [PTH] fragments." As its primary support, Immutopics points to published results by Dr. Gao that were cited by Scantibodies during reexamination.FN39 The Gao article reported that an antibody developed under Scantibodies' method (and presumably in accordance with the ' 566 Patent) displayed no cross reactivity with PTH (7-84) at concentrations of 10,000 pg/mL of the PTH(7-84) fragment.FN40 Immutopics now argues that, at the very least, Scantibodies is bound to this "10,000 pg/mL" standard in defining specificity for whole PTH.

2. Analysis

a. The Court declines to adopt Scantibodies' definition because it imposes essentially no restrictions on specificity.

Scantibodies' focus on the "clinical" context, and in particular, the need to accurately measure whole PTH in a biological sample, finds ample support in the '566 Patent. *See* '566 Patent at 1:6-9 ("The present invention relates to ... detecting [wPTH] in a biological sample."); 2:27-30 (noting that one problem presented by the prior art is that "hyperparathyroid patients and renal failure patients ... have significant endogenous concentrations of large, non-whole PTH fragments" which interfered with previous anti-PTH antibody testing kits). Providing "consistently reliable measurement based on a comparison with the appropriate positive and negative controls that are provided with the test kit," *see* Ranes-Goldberg Decl. para. 12, is certainly not inconsistent with the specification. *See also* Pl.'s Cl. Constr. Br. at 13 (echoing Dr. Ranes-Goldberg's emphasis on "consistently reliable" results). As Dr. Ranes-Goldberg explains, specificity values "only take on meaning in the context of the type of testing for which the antibody is being used." Ranes-Goldberg Decl. para. 7. However, by focusing exclusively on the the clinical context, Scantibodies and Dr. Ranes-Goldberg effectively propose a definition that places virtually no lower limit on the specificity for whole PTH.

Though experiment and protocol design and the reliability of results are preconditions for obtaining accurate measurements of whole PTH levels, they do not address the actual issue-an antibody's *inherent* specificity for whole PTH. The Nichols Allegro kit provides a good example: as a commercially available kit for detecting levels of intact PTH in biological samples, it would obviously include well-designed instructions and protocols regarding proper use, and would provide "consistent," "reliable," and "statistically significant" results (in the ordinary meaning of that term) purportedly measuring concentrations of unfragmented PTH. Yet the Nichols antibody fails to distinguish the 7-84 PTH fragment from whole PTH, and hence, does not specifically bind to whole PTH because it binds as strongly to whole PTH as to that particular interfering non-(1-84) fragment. *See* '566 Patent at 2:1-40 (describing the shortcoming of the Nichols Allegro kit). In that situation, reproducibility, consistency, or the presence of positive or negative controls simply are not at issue. They are external factors that have nothing to do with the inherent binding propensities of a given antibody.

By failing to define specificity for whole PTH over fragments, Scantibodies has chosen a definition that imposes an incredibly low threshold on the two claim terms at issue. Its definition requires only that an antibody bind to an interfering PTH fragment with " *statistically significantly less* " strength than the strength with which it binds whole PTH. This definition would encompass, for example, a slightly improved version of the Nichols antibody whose affinity for PTH(7-84) is weakened by a small, but consistently

measurable amount, yet whose affinity for wPTH remains the same. This improved antibody would exhibit "statistically significantly less" binding to PTH(7-84) than it would to whole PTH, and thus under Scantibodies' definition would "not specifically bind to an interfering non-(1-84) [PTH] fragment." FN41 Yet it would not be useful as an assay for wPTH. Clearly, this is not an acceptable definition of specificity.

b. Immutopics' definition of specificity for whole PTH is unreasonably restrictive and not supported by the prosecution history.

At the other extreme, Immutopics contends that binding to PTH fragments is never acceptable. By requiring that an antibody be *absolutely* specific for whole PTH, however, Immutopics would essentially read the word "specifically" out of the phrase "not specifically bind." Moreover, the prosecution history on reexamination does not support Immutopics' construction. Nothing in the record "expressly says that ... binding to the undesirable PTH (7-84) fragment cannot occur even at concentrations of 10,000 pg/mL," *see* Defs.' Cl. Constr. Br. at 9.

In both its July 24, 2006 and November 10, 2006 Amendments, Scantibodies cited the 10,000 pg/mL figure from Gao in making an argument designed to overcome a rejection based on the Colford reference. *See* 7/24/2006 Scantibodies Amendment, Newboles Cl. Constr. Decl., Exh. C at 29; 11/10/2006 Amendment, Newboles Cl. Constr. Decl., Exh. E at 16-17. However, Scantibodies employed the Gao reference, in *both* the July and November filings, primarily to demonstrate that the " *Nichols* intact PTH IRMA" displayed "nearly 100% cross-reaction" with the 7-84 fragment. *See* 7/24/2006 Scantibodies Amendment at 29; 11/10/2006 Amendment at 16-17. While the quote from Gao also contrasted Nichols' high cross-reactivity with the lack of cross-reaction in Scantibodies' own assay "even at a PTH (7-84) concentration of 10,000 pg/mL," the mention of that figure was incidental to Scantibodies' actual point, which was an awkward attempt to distinguish the Colford reference by way of the Nichols reference. FN42

Prosecution history disclaimer requires a clear and unambiguous disavowal of claim scope during prosecution in order to obtain claim allowance. Salazar v. Procter & Gamble Co., 414 F.3d 1342, 1344 (Fed.Cir.2005). Here, the intrinsic record demonstrates that this was neither a clear and unambiguous disclaimer, nor a statement made in order to obtain claim allowance. First, Scantibodies simply did not make a clear and unambiguous statement committing itself to the 10,000 pg/mL figure; its argument would not have suffered (further) if the 10,000 pg/mL figure had been left out. Second, even if that figure constituted an unambiguous statement, the examiner did not rely on it in allowing the claims over Colford. The argument that Scantibodies made regarding Colford in its 11/10/2006 Amendment was *exactly* the same as the one it made on July 24, 2006. Yet the earlier argument had already been vigorously rebuffed by the examiner. *See* 9/21/2006 Office Action at 10-14, 32-35 ("[The Colford] PTH(1-7) antibody binds only to the intact PTH (showed only one peak.) Thus, [it] does not bind to the interfering PTH fragment ."). Rather, the evidence suggests that the examiner ultimately allowed the claims over Colford after Scantibodies amended the kit and antibody claims to require an antibody that is generated by *immunization with whole PTH*. *See* 11/10/2006 Amendment at 2 (amending claims); *id*. at 15 (noting that Colford does not explain what immunogen it used to generate its PTH(1-7) antibody).

Thus, Scantibodies' usage of the Gao reference in the reexamination record does not suggest that 10,000 pg/mL provides an appropriate metric for specificity. Because it is incapable of supporting even that specific limitation on the claims, Immutopics may not use it for the even more stringent proposition that a claimed antibody may not bind to interfering fragments to any degree whatsoever.

In conclusion, the specification and prosecution history do not support either party's construction as to the level of required specificity.FN43 Scantibodies, in particular, has not shown through extrinsic evidence that statistical significance is a level of binding specificity that is well recognized in the art. Without more compelling intrinsic evidence or extrinsic evidence regarding how the level of specificity might be defined by one skilled in the art relevant to the ' 566 Patent, the Court cannot determine the degree of specificity for whole PTH.FN44

3. not detecting an interfering non-(1-84) parathyroid hormone fragment

The claim term "not detecting an interfering non-(1-84) [PTH] fragment" appears in every method claim and was not amended during reexamination. *See* ' 566 Patent, Claims 5, 13, 18, 25, 27 (independent method claims). The parties propose virtually the same definition for this term as for their proposed constructions of "does not specifically bind"; indeed, they agree that "binding" and "detection" are related terms. *See, e.g.*, Mem. P. & A. Supp. Pl.'s Opp'n to Defs.' Mot. for Summ. J. of Non-Infringement at 9 (stating that "detection is directly associated with 'binding' " and that an antibody's ability to detect a particular antigen "proportional to the antibody's affinity for binding to" that antigen). For this reason, as with "specifically binds ... not specifically bind," the Court declines to reach a construction with respect to the level of specificity required for whole PTH over fragments.

IV. CONCLUSION

The Court reaches the following constructions of the terms:

1. "Specific for" is defined as ***exhibiting significantly greater binding affinity for the PTH(2-8) region of whole PTH than for the PTH(9-84) region.***

2. "Specifically binds to whole parathyroid hormone but does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment" cannot be defined by the Court because the level of specificity for whole PTH over interfering fragments is indeterminate. An absolute standard, which would preclude all binding to interfering fragments, is inappropriate. The proper standard is clearly relative, but the Court is unable to determine a measure of the degree of relativity.

3. "Not detecting an interfering non-(1-84) parathyroid hormone fragment" is similarly indeterminate.

IT IS SO ORDERED.

FN1. Amino acids are the building blocks of all proteins (including hormones). A peptide is a linear sequence of amino acids. Every peptide sequence begins at the "N-terminal" of the peptide and ends at the "C-terminal". The amino acids in a peptide sequence are numbered beginning at the N-terminal (starting with 1) and ending at the C-terminal. Due to the varying chemical and structural properties of each amino acid in the sequence, a peptide in vivo will not remain a linear sequence, but typically folds into a particular three-dimensional shape, or conformation, which determines the peptide's function and biological properties. *See* DAVID NELSON AND MICHAEL COX, LEHNINGER PRINCIPLES OF BIOCHEMISTRY 115-116, 126-129 (3d ed.2000).

FN2. A picogram (pg) is 1 x 10^{-12} gram, or one-millionth of one-millionth of a gram. Thus, a concentration

of 10-40 pg per milliliter is vanishingly small.

FN3. Antibodies are Y-shaped proteins that are derived from the immune system. They are produced by an organism's immune system in response to the introduction of a foreign substance, termed an "antigen", into the bloodstream. Every antibody has the ability to bind to a particular epitope, or three-dimensional shape. *See GENERALLY* JAMES GODING, MONOCLONAL ANTIBODIES: PRINCIPLES AND PRACTICE 6-10 (2D ED.1986).

FN4. The assay disclosed in the '566 Patent calls for two different antibodies. The first is a "signal" or "tracer" antibody, which is specific for the intact N-terminal region of wPTH, *see* '566 Patent at 3:52-53, 4:33-34, and which in addition has been radioactively labeled, *see id*. 4:6-22 (describing protocol for labeling antibody with Iodine-125 radioisotope). The other antibody is a "capture antibody", which is typically specific for the other end of a PTH molecule (the C-terminal end)-the end which is present in both biologically active and inactive PTH molecules. *Id*. at 3:53-57. The "capture" antibody is attached to a solid support, such as the wall of a test tube or vial. *Id*. at 3:51-52, 4:30-32. When a biological serum sample is poured into the test tube, all PTH molecules, biologically active or not, will bind to the "capture" antibodies lining the walls of the tube. *Id*. at 4:30-32. The "signal" antibody is also added to the test tube and binds only to the "captured" PTH molecules that are biologically active. *Id*. at 4:32-39. After washing away any signal antibodies that are not bound to captured PTH, *id*. at 4:38-39, one can measure the amount of radioactivity emitted by the radioactively labeled signal antibodies to determine the amount of biologically active PTH in the sample. *Id*. at 4:41-47 ("Radioactivity on the [sides of the test tube], which amount corresponds to the quantity of wPTH present, is measured using a gamma counter.").

FN5. This approach does not appear to preclude binding to *any* biologically inactive N-terminal fragment, such as PTH(3-84), which is only missing the first two amino acids. An antibody that binds to PTH amino acids 3, 4, 5 and 6, for example, would bind to at least four amino acids in the PTH(2-8) common sequence, but it would not be able to distinguish whole PTH from the PTH(3-84) fragment. Indeed, distinguishing all N-terminal PTH fragments from whole PTH does not appear to be the goal of the '566 Patent, which is apparently content to solve the problem presented by the Nichols Allegro kit: avoiding to the PTH (7-84) fragment. Yet even if PTH (7-84) is in fact the most common N-terminal PTH fragment present in the blood, it was already known at the time of filing of the ' 566 Patent that inactive fragments as large as (3-84) could interfere with a PTH assay, because loss of the first two amino acids would abolish biological activity.

FN6. Because the goal is to generate antibodies that are specific for the N-terminal region of whole PTH, common sense dictates that the immunogen that is injected into the goat should *at the very least* include that intact N-terminal region.

FN7. As explained later in this order, the choice of "initial peptide sequence" is critical to determining precisely which antibodies will be isolated from the goat antiserum.

FN8. J.W. Colford, M. Salvati, et al., Isolation and Characterization of Large Molecular Weight Fragments

of PTH, Newboles Claim Construction Decl., Exh. G (abstract and presentation materials presented at 79th Annual Meeting of the Endocrine Society, June 11-14, 1997).

FN9. *See* Dec. 28, 2007 Order Denying Scantibodies' Motion for Partial Summary Judgment on Defendants' Counterclaim of Patent Invalidity.

FN10. *See* Joint Statement of Contentions Re: Meaning of Terms in Reexamination Claims of U.S. Pat. No. 6,689,566.

FN11. The phrase "in whole PTH" was not present in the parties Joint Statement of Contentions. However, Scantibodies proposed this amendment during its presentation at the March 24, 2008 claim construction hearing, which had been recommended by their expert, Dr. Ranes-Goldberg.

FN12. This spells out the (2-8) sequence in whole PTH.

FN13. Method claims 5, 13, and 18 involve some minor variations in wording, but employ "specific for" in the exact same manner as in every other independent claim.

FN14. Immutopics vigorously objects that Scantibodies' three-word amendment, "in whole PTH," following "the specified region (i.e. 2-8 PTH)" is a radical alteration of Scantibodies' proposed construction. *See* Transcript of March, 24, 2008 Claim Construction Hearing ("3/24/2008 Hrg. Tr.") at 10:8-14.

FN15. The phrase, "common sequence of human and rat PTH" is defined in the patent specification as the PTH(2-8) sequence (identified above as SEQ ID NO. 3), which is the same in both rat and human. *See* '566 Patent at 4:50-55. It does not refer to any other parts that the human and rat PTH sequences may have in common.

FN16. Because "specific for" is present in every independent claim of the '566 Patent, a finding of indefiniteness would result in every claim being declared invalid.

FN17. More correctly, the written description allows the "initial peptide sequence" to be "at least four amino acids in the common sequence, absent the first amino acid," meaning that it can be up to three amino acids shorter than PTH(2-8). However, the claims require that the initial sequence "consist of" PTH(2-8); and the kit and antibody claims further require that the antibody be isolated by binding to at least four amino acids of PTH(2-8).

FN18. During the briefing on Immutopics' pending summary judgment motions, Immutopics pointed out

that Scantibodies had in fact used PTH(1-9) as an affinity purification peptide in its tests and had in fact never experimented with PTH(1-8), *see* '566 Patent Fig. 5 (stating the use of a "[anti-]PTH(1-8) Antibody"), or PTH(2-8) which is required by the claims. However, whatever relevance this fact may have to Immutopics' motions for summary judgment for lack of enablement and failure to disclose best mode, it has no bearing on claim construction. The Court must interpret the patent on its own terms.

FN19. The '566 specification permits the antigen to be one of several things: the "initial peptide sequence" by itself; "incorporated" into another peptide-either "a non PTH peptide having a molecular weight ... of between about 5000 and 10,000,000"; or "as part of the wPTH complete sequence." '566 Patent at 5:27-34. Because the goal of the '566 Patent is to generate and isolate antibodies specific *to whole PTH,* it makes the most sense to use *whole* PTH as the antigen. (The second option, in particular, appears to be impractical.) Indeed, the antibody and kit claims-but not the method claims-were amended during reexamination to *require* an antibody that is "produced by immunizing a mammal with whole parathyroid hormone" and no other antigen. *See* Reexamination Claims 1, 20, and 22; *see also* 9/21/2006 Office Action at 40-41 (allowing method claims over the prior art, thus obviating need for amendment).

FN20. This additional claim limitation is not present in the method claims because the examiner allowed those claims without amendment. *See* 9/21/2006 Office Action at 40-41 (accepting Scantibodies' arguments that method claims were not obvious over Kohno in light of Bouillion); *see also* 7/24/2008 Scantibodies amendment at 39-48 (arguments overcoming rejections over Bouillion). The Court's analysis of "specific for," however, remains relevant to all the claims, including the method claims.

FN21. As noted earlier, human and rat PTH(1-8) have in common their PTH(2-8) sequence (also identified by the claims as "SEQ ID NO:3"). Thus, "the common sequence of human and rat PTH(1-8)" is another way of referring to PTH(2-8).

FN22. There are only two variables in the two step method for generating and purifying a claimed antibody: the choice of immunogen, and the choice of affinity purification peptide. However, the latter is the more important one. Even if the immunogen is whole PTH, the only way to ensure that antibodies are specific for the *N-terminal* of whole PTH is to use an appropriate affinity peptide.

FN23. Thus, prior to the reexamination the independent kit and antibody claims only contained a requirement as to the mechanics of antibody binding: as long as the antibody bound 4 amino acids of PTH(2-8), the claim would read upon that antibody even if it could not distinguish whole PTH from PTH fragments. *Compare* '566 Patent, Claims 1, 20, 22, *with* Reexamination Claims 1, 20, 22. In contrast, the method claims always required "not detecting an interfering non-(1-84) [PTH] fragment."

FN24. The discrepancy between these two different definition for "fragments" is also reflected in Scantibodies' proposed constructions of "specifically binds" and "not specifically bind." The former definition refers to "any fragment of PTH not having at least four amino acids", yet the latter references "an interfering non-(1-84) parathyroid hormone fragment." The use of two definitions is likely to create

inconsistency and confusion.

FN25. PTH(6-84) through PTH(9-84) fall within this definition, but to reach even this result, one must also assume that amino acid 1 in these hypothetical fragments is also missing, even though Scantibodies' proposed construction does not expressly require it. Otherwise, the resulting PTH fragment will have a sequence such as 1-6-7-8-9-..., or 1-7-8-9-..., and *none* of the PTH fragments defined by Scantibodies would be ones found in nature. Moreover, even if Scantibodies' definition of "fragment of PTH" is confined to the (6-84) through (9-84) PTH fragments found in nature, it omits other real N-terminal PTH fragments: (5-84), (4-84), and (3-84). It is unreasonable to exclude these fragments given that *any* PTH fragment missing the first N-terminal two amino acids is biologically inactive and thus could interfere with the detection of active (1-84)PTH.

FN26. For example, a PTH molecule that is missing amino acids 3, 5, 7, and 8 satisfies Scantibodies' definition. This leaves amino acids 2, 4, 6, and 9-84, resulting in the sequence 2-4-6-9-10-11-... (again, assuming that amino acid 1 is also missing). Another example would be a PTH molecule that is missing amino acids 3, 4, 5, 6, 7, 8. The PTH sequence in that fragment would be -2-9-10-11-... It appears that the vast majority of sequences not having at least 4 amino acids in this region do not exist in nature (all of them, in fact, except PTH(6-84) through PTH (9-84)).

FN27. The language of Scantibodies' construction suggests that Scantibodies might consider an antibody to be "specific for" PTH(2-8) if the affinity for 2-8 of whole PTH was greater than the affinity for the corresponding N-terminal region in any *single* "fragment of PTH." It is unreasonable to define an antibody's specificity for PTH in relation only to one PTH fragment, as this would allow the antibody to bind some other fragment with greater affinity than whole PTH-yet still be considered specific for whole PTH.

FN28. The "specific for" limitation, twisted in this way, would not have complete identity with the "specifically bind to whole [PTH] but ... not specifically bind to an interfering non-(1-84) fragment" limitation because Scantibodies' "fragment of PTH not having at least four amino acids" is not the same as "an interfering non-(1-84) fragment".

FN29. Dr. Ranes-Goldberg reiterated this testimony at the *Markman* hearing. *See* 3/24/2008 Hrg. Tr. at 30:18-25, 31:1-23.

FN30. Scantibodies does not explain why it is necessary to compare an antibody's binding affinity to PTH(2-8) in whole PTH to its affinity for a fragment in which that separate and independent claim term has been negated.

FN31. Dr. Ranes-Goldberg states that " 'specific for' means this antibody has a greater tendency to bind an initial peptide sequence of whole PTH relative to a fragment of PTH that is missing all or some of this initial peptide sequence." *Id*. para. 11. She then explains that by "greater tendency," she means the same

thing as Scantibodies' "statistically significantly greater." *Id*. para. 12.

FN32. To support her construction of Dr. Ranes-Goldberg protests that it is "not possible to assign absolute numbers to these relative descriptions of 'greater' or 'lesser' [binding] because they only take on meaning in the context of the type of testing for which the antibody is being used." *Id*. para. 12. Yet specificity is "determined by [an antibody's] relative binding affinities," which are "quantitative measurement[s]." Ranes-Goldberg Decl. para.para. 8, 9. This suggests that it is entirely possible to arrive at a concrete value for antibody specificity for one antigen over another.

FN33. *See* 3/24/2008 Hrg. Tr. at 10:16-25 (objection by Immutopics' counsel that Scantibodies' amendment, which added "in whole PTH" after "binding in the specified region (i.e., 2-8 PTH)," would "radically" alter Scantibodies' proposed construction) ("[with the amendment,] you would have differences between binding the whole versus fragments [instead of just] *these fragments* versus fragments") (emphasis added).

FN34. The thrust of Immutopics' claim construction brief suggests that Immutopics chose a confusing interpretation of the examiner's statement precisely in order to drive home its argument on indefiniteness. The Court notes, however, that invalidity based on s. 112, para. 2 indefiniteness was not among the five grounds for summary judgment that Immutopics brought before this court.

FN35. The Court does note the following. First, the examiner *was,* in fact, speaking to the concept of specificity and not to any supposed distinction between "specific for" and "binds to." Her statement mentions neither of those phrases. Rather, it speaks of "the relative affinities of the claimed antibodies," *see* 9/21/2006 Office Action at 5, which Dr. Ranes-Goldberg recognizes as a textbook definition of "specificity." *See* Ranes-Goldberg Decl. at para. 9. Second, it is clear that the examiner understood the distinction between binding affinity and specificity. *See* 9/21/2006 Office Action at 6 ("Examiner agrees with the Patentee's assertions, that the antibody specificity is based on the binding affinities.") Lastly, Scantibodies did not, in fact, address the examiner's concerns through by amending the claims. Scantibodies subsequently added the word "specifically" in front of "binds to," but left the term "specific for" alone. *See* 11/10/2006 Scantibodies Amendment at 2, 5-6.

FN36. The antibody and kit claims contain the claim limitation, added during reexamination, that the antibody must be produced by immunizing with (1-84) PTH and affinity purified with (2-8) PTH. *See* Reexamination Claims 1, 20, 22. Yet Immutopics contends that its antibodies are generated by (i) immunizing with (1-34) PTH and (ii) affinity purifying with (1-13) PTH. *See* Transcript of January 29, 2008 Hearing ("1/29/2008 Hrg. Tr.") at 54:17-18. If true, then Immutopics is incapable of infringing either the antibody or kit claims of the '566 Patent. Scantibodies effectively conceded at the January 29 hearing that it had no independent evidence that Immutopics immunized with whole PTH (1-84) instead of PTH (1-34). 1/29/2008 Hrg. Tr. at 32:17-34:9, 62:14-63:4. *See also* 3/24/08 Hrg. Tr. at 36:21-25 ("we've already admitted in open court that if an antibody is produced and it's not produced in immunization by 1 to 84, it's not going to infringe any of the antibody or kit claims ... that's not true of the method claims").

FN37. Immutopics contends that Scantibodies disclaimed the use of other immunogens by arguing during reexamination that certain prior art antibodies did not "specifically bind to" whole PTH because they were not raised with wPTH. In response to rejections over Magerlein, Tampe, and Adermann, Scantibodies had argued that it is "there is a strong probability, or at least possibility" that antibodies raised by immunization with antigens other than whole PTH would not be specific for whole PTH. Other than the posture in which this supposed disclaimer was made, the choice of immunogen appears to have no direct relevance to antibody specificity for whole PTH over PTH fragments. *See* 11/10/2006 Amendment at 22, 24, 26-27.

FN38. Notably, Immutopics does not argue that this limitation should be imposed upon the method claims, which, unlike the kit and antibody claims, do not expressly require that an antibody be raised by immunization with whole PTH. Immutopics' proposed construction for the fourth claim term, "not detecting an interfering ... fragment", a term which is found only in the method claims, does not include the limitation here.

FN39. Gao et al., *J. Bone Miner. Res., 16(4):* 605-14 (2001).

FN40. This is a high concentration of fragment; for reference, normal levels of *whole* PTH in the blood serum in humans range from 10 pg/mL to 40 pg/mL. *See* '566 Patent at 1:60.

FN41. To provide a numerical example, consider an antibody whose affinity for PTH(7-84) is 30% as strong as its affinity for whole PTH. This antibody would be 30% as likely to bind to PTH(7-84) as to whole PTH; and in a sample containing equimolar amounts of whole PTH and PTH(7-84), the antibody would have a 30% error rate in measuring the concentration of whole PTH. No one would describe this antibody as having specificity for whole PTH. Yet as long as the binding it exhibits to PTH(7-84) is "statistically significantly less" than the binding exhibited to the whole PTH in the sample, and the experiment is conducted with appropriate positive and negative controls so as to achieve "consistently reliable" measurements, Scantibodies' definition of the term "does not specifically bind to an interfering non-(1-84) parathyroid hormone fragment" would be satisfied.

FN42. Scantibodies distinguishes Colford as follows: (1) Jensen, who was apparently linked to the authors of the 1997 Colford reference, presented a poster at a conference in 1996. Jensen is not listed as an author on the 1997 Colford reference. (2) In the poster, Jensen suggested that the results achieved by his research group's anti-PTH antibody were "higher or comparable" to Nichols' results. (3) Because Nichols does not distinguish an interfering fragment, and because Colford gives results that are "higher or comparable" to the Nichols results, it follows that Colford, like Nichols, also does not distinguish an interfering fragment and does not anticipate the '566 Patent. The flaws in this logic are staggering. The data in the Colford reference itself clearly demonstrate that the authors had generated an antibody capable of distinguishing a PTH fragment, called PTH (beta), from whole PTH (labeled PTH (alpha)). *See* Colford Abstract, Newboles Cl. Constr. Decl., Exh. G. Yet rather than address the prior art on its own terms, Scantibodies' argument is based on an isolated, ambiguous phrase taken out of context from a different piece of prior art. Scantibodies' argument can be characterized only as a smear by implication. However, it does not constitute a prosecution disclaimer.

FN43. The reason why the degree of specificity cannot be determined for "specifically binds ... not specifically binds," as compared to "specific for," is that the latter was present in the original patent and draws support from the specification. That is not true of the claim limitations here.

FN44. It is worth noting, in general terms, that specificity in this context is directed towards detecting the concentration of whole PTH in a biological sample. Thus, an antibody must be sufficiently specific for whole PTH over interfering fragments as to generate results that are "meaningful to the clinician," 3/24/2008 Hrg. Tr. at 20:8-12. *See also* Colford Decl. para. 3 ("In other words, when a patient's blood is tested for PTH, it is important that the measurement of the concentration of wPTH in the blood be as specific as possible. If both wPTH and ... 'interfering' fragments ... are detected ... the measurement for wPTH will be inaccurate.")

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