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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

REGENERON PHARMACEUTICALS, INC.,

Plaintiff,

-v-

MERUS B.V.,

Defendant.

14 Civ. 1650 (KBF)

OPINION & ORDER
(CLAIM CONSTRUCTION)

KATHERINE B. FORREST, District Judge:

Regeneron Pharmaceuticals, Inc. ("Regeneron") commenced this action against Merus B.V. ("Merus") and Ablexis LLC ("Ablexis"), on March 14, 2014, alleging infringement of U.S. Patent No. 8,502,018 (referred to as the "Patent" or the "'018 Patent"). On July 3, 2014, defendants responded to the complaint asserting, inter alia, invalidity and non-infringement. On November 3, 2014, Ablexis settled. The instant Opinion & Order constitutes the Court's determinations as to claim construction.

Claim construction is fundamentally concerned with determining what invention is covered by the patent-in-suit to assist the fact finder in considering ultimate issues: is the invention x or is it y? Do its boundaries end here or there? Must it be made this way, can it be made that way, or can it be made any way at all? And on. Put otherwise, before determining whether a patent has been infringed, one must understand the invention it seeks to cover. Given the resources

allocated to, and diverse outcomes of claim construction proceedings, it is plain that patent holders are frequently mistaken as to the nature and scope of their invention. While they believe (or assert) that they hold a patent disclosing one invention, claim construction may reveal quite another invention altogether. If a patent holder's view is overly broad, such position may reveal wishful thinking or short-sightedness during prosecution; no matter, claim construction reveals actual metes and bounds.

Regeneron and Merus are here engaged in this now somewhat routine exercise of debating what invention the Patent in fact discloses. Regeneron asserts that what the specification of the '018 Patent (the "Specification") repeatedly refers to as "the invention" is not that which is claimed. It asserts further that over the years, the Specification was mined for other inventions and claims than those here at issue, and that as a result, the claims in the '018 Patent are several steps removed from the language of the Specification itself. According to Regeneron, a few preferred embodiments, read as standing alone and removed from surrounding context, support its view of its claims here: that the '018 Patent – and Claim 1 as an example – broadly encompasses a genetically modified mouse with a particular gene segment (human unrearranged variable region) inserted at a particular location in a mouse (the immunoglobulin locus). Regeneron asserts that how it made the mouse is unimportant; the Patent merely discloses one possible method.

Construed as plaintiff asserts, Regeneron holds a patent to a mouse modified to include a human DNA sequence at the immunoglobulin locus, leaving the mouse

constant regions intact. (Transcript of 9/12/14 Proceedings, ECF No. 161 ("Transc.") 32:8-14.) The technology for making the mouse with such characteristics was, according to Regeneron, already known. (Transc. 33:11-16.) Thus, plaintiff asserts that it invented a mouse which can be genetically modified using any number of available methods, involving the insertion of a human or synthetic gene segment somehow at or near the immunoglobulin locus. Regeneron's construction posits a patent with extraordinarily broad reach.

By contrast, defendant Merus asserts that the invention disclosed in the '018 Patent is far narrower and ultimately bounded by the particular method for genetically modifying a mouse with which the Specification is principally concerned. Merus asserts that, for instance, Claim 1 discloses a mouse made only by a particular process. Merus characterizes the invention in Claim 1 as a product-by-process claim. Whether characterized as a product-by-process claim or simply defined by the Specification, Merus's point is the same: that Regeneron's '018 Patent concerns a mouse genetically modified in a specific way. Mice genetically modified in any number of different manners – but which ultimately share a similar genetic profile – are, according to Merus, outside of the Patent's scope. This debate as to scope pervades the parties' positions on claim construction. This Court generally agrees with the constructions Merus proposes, limiting the Patent to a far narrower scope than that asserted by Regeneron.

In connection with this claim construction proceeding, the Court received a number of written submissions including briefs and declarations from experts

skilled in the art.[1] (ECF Nos. 96, 103, 104, 105, 107, 108, 113, 114, 115, 116, 117, 123.) The parties' experts also appeared at a live hearing before the Court on September 12, 2014 during which they were subject to cross examination.[2] (ECF No. 161.)

Jeffrey Ravetch, M.D., Ph.D., submitted declarations and testified on behalf of Regeneron. Ravetch has substantial qualifications in the areas relevant to the technology in the '018 Patent. Notably, however, he submitted his initial declaration – in which he opines that each of the terms in dispute are unambiguous and would be well known to one skilled in the art at the time of application – without reviewing any of the Patent's prosecution history. (Transc. 62:15-16.) The bulk of Ravetch's declaration, as well as his presentation to the Court, concerned technical background in the area of molecular biology. Defendant does not dispute the technical "tutorial" aspects of Ravetch's presentation. (Transc. 80:19 – 81:06.) Ravetch's views on claim construction comprise fewer than 10 pages of his initial 56 page submission. As to each term at issue, Regeneron has taken the position that it needed no construction and was clear to one of ordinary skill in the art at the time.

Dr. Raphael Clynes submitted declarations and testified on behalf of Merus. Like Ravetch, he has substantial experience in the area. Clynes had read and

[1] The parties made a number of submissions – the last of which were filed after the hearing on claim construction. The matter became fully submitted only on September 22, 2014.
[2] Ablexis and Regeneron settled subsequent to the September 12, 2014 claim construction hearing. The Court therefore disregards Ablexis's submissions relating to claim construction and testimony elicited from its expert, William T. Garrard, Ph.D.

considered the prosecution history of the patent-in-suit in connection with his initial opinions. (Clynes Decl. ¶ 14.)

Both experts agree that the operative date from which they assess the meaning of claim terms is February 16, 2001 – the date of filing for U.S. Patent Application No. 09/784,859.

## I. THE PATENT AND RELATED TECHNOLOGY

The '018 Patent is entitled "Methods of Modifying Eukaryotic Cells."[3] It is a continuation-in-part of an application tracing back to an initial filing on February 16, 2001. The Abstract describes the invention as, "A method for engineering and utilizing large DNA vectors to target, via homologous recombination, and modify, in any desirable fashion, endogenous genes and chromosomal loci in eukaryotic cells." Subsequent to the February 2001 application, and prior to issuance of the '018 Patent, Regeneron obtained two other patents sharing the same Specification: U.S. Patent Nos. 6,586,251 and 6,596,541.[4]

The technology at issue in the Patent is described by Clynes as "the use of a particular method for generating genetically modified mice which may be used as a

[3] "Eukaryotic cells" are cells that have different compartments that serve distinct roles; for instance, chromosomes are housed within the cell nucleus. (Clynes Decl. n.2.) Eukaryotic cells comprise humans, mice and other higher order life; they are distinguished from bacteria which have no cellular compartments. (Clynes Decl. n.2.)

[4] Both of these patents largely concern method claims; Patent No. 6,596,541 also contains product-by-process claims related to a "method for creating and screening eukaryotic cells which contain modified endogenous genes or chromosomal loci". Regeneron asserts that the existence of these patents covering the method disclosed in the shared specification supports its view that the claims in the '018 Patent do not depend on the method used. This argument is based in rhetoric and not patent law. No principle of patent law provides that claims in any patent can, may or must be read apart from their accompanying specification. That claims are in a divisional or continuation-in-part patent does not alter these principles. In short, 35 U.S.C. § 112 applies to all patents and their respective claims.

research tool for drug discovery. The mice claimed by the '018 patent are engineered by a specific process to contain human DNA inserted in the genome of the mouse." (Clynes Decl. ¶ 17.)

As stated above, the parties generally agree on the basic principles of molecular biology and genetic engineering which inform the claims in the '018 Patent.[5] The Court refers to the declaration of Ravetch at ¶¶ 14-97 for basic technical background and shall not repeat most of the undisputed principles here. The Court includes below certain principles particularly relevant to the Court's determinations herein.

A. Certain Technical Principals

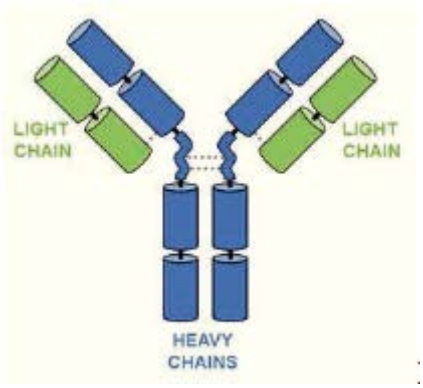
Deoxyribonucleic acid ("DNA") is a molecule in a cell which carries the genetic material for living organisms. DNA is capable of self-replication and synthesis. It consists of a double-stranded molecule that pairs in a double-helical structure: "One end of each strand is called the 5-prime (5') end, and the other is called the 3-prime (3') end." (Ravetch Decl. ¶ 15.) The 5-prime and 3-prime ends define the boundaries of a strand of DNA. DNA molecules are made up of chemical building blocks called "nucleotides". (Id. ¶ 16.) Nucleotides on the two strands of the double-helix pair with one another in complementary units called "base pairs" ("bp"). (Id.) The base pairings connect the individual DNA strands to each other to form the double-helix. (Id.) The unique sequence of bases on a given strand

[5] There are certain disagreements between the parties, including, inter alia, the possible size of synthetic DNA segments in 2001, and whether the boundaries of the immunoglobulin locus were known in 2001. Relevant disagreements are discussed infra.

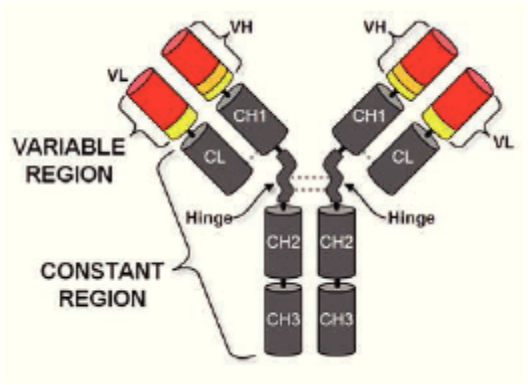
represents a code; a gene is a unit of DNA that includes the sequence of bases representing the codes for the amino acids that comprise a particular protein. (Id. ¶ 17.)

Genes are expressed by cells as proteins through processes commonly referred to as "transcription" and "translation". (Id. ¶ 18.) Before transcription and translation, the two strands of DNA that constitute a gene unwind from their double-helix configuration. (Id.) During "transcription", machinery in the cells reads the DNA sequence of one of the DNA strand's, nucleotide by nucleotide, and uses it as a template to produce an intermediate molecule called messenger RNA (abbreviated as mRNA). (Id.) The structure of a protein gives rise to its biologic activity. (Id. ¶ 19.)

The typical function of "B cells" is to make antibodies. Antibodies are also known as "immunoglobulins" and abbreviated as "Ig". (Id. ¶ 23.) They are a particular type of protein. They are typically depicted as having a structure shaped like the letter "Y". (Id. ¶ 24.) The Y structure consists of four chains of amino acids: two identical light chains and two identical heavy chains. Each light chain pairs with a partner heavy chain, and then each heavy-light chain pair associates with an identical heavy-light chain pair to form the "Y" structure. See Figure 1 below:




(Defs' Resp. Claim Constr. Br., ECF No. 103, at 7.) Each heavy chain and light chain is comprised of a "constant" region and a "variable" region. (Ravetch Decl. ¶ 25.) In both heavy chains and light chains of an antibody, the region at the tip of the "Y" is the "variable region". The other region on each heavy chain and light chain is called a "constant region". (Id.) While variable regions of antibodies differ extensively, the constant regions remain relatively the same within a given type. (Id. ¶ 29.) See Figure 2:

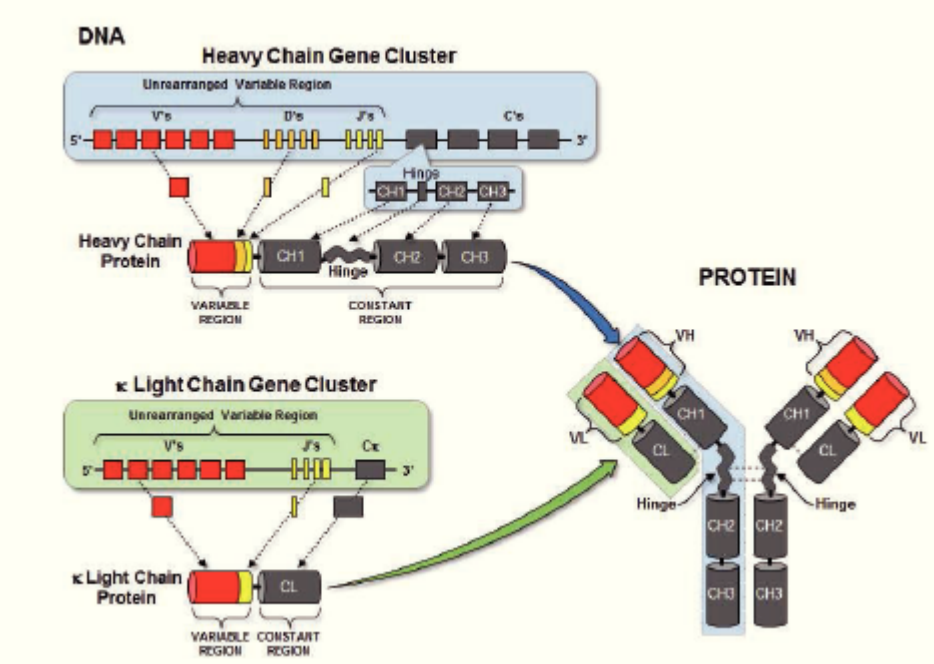



(Defs' Resp. Claim Constr. Br., at 7.)

Because antibodies are proteins composed of amino acids, they are encoded by genes composed of DNA nucleotides. (Id. ¶ 33.) The DNA that encodes antibody variable regions is assembled from separate gene "segments". (Id. ¶ 34.) A gene

that encodes the heavy chain variable region of an antibody is assembled from three gene segments, named variable (V or $V_H$), diversity (D or $D_H$) and joining (J or $J_H$) segments, where the subscript "H" indicates the gene segment that forms part of the antibody heavy chain. (Id.) A gene that encodes the light chain variable region of an antibody is assembled from two gene segments, named variable (V or $V_L$) and joining (J or $J_L$) segments, where the subscript "L" similarly indicates the light chain. (Id. ¶ 35.) These gene segments are joined together to form contiguous variable region gene segments (VDJ for heavy chains, and VJ for light chains) through DNA rearrangement mechanisms. (Id.)

In both humans and mice there is one gene locus containing the genetic material used for expressing heavy chains, and two gene loci containing genetic material used for expressing light chains. (Id. ¶ 36.) Through a process known as V(D)J recombination, the DNA sequence encoding a variable region of an antibody heavy or light chain is created at each Ig gene locus by selecting and joining together one each of the many V, D and J gene segments (for heavy chains) or V and J gene segments (for light chains) present at the locus. (Id. ¶ 44.) V(D)J recombination is referred to as "somatic recombination". (Id. at ¶ 49.) See Figure 3:




(Defs' Resp. Claim Constr. Br., at 8.)

There are – and at the time of the invention there already were – numerous methods for incorporating exogenous DNA into mice. (Id. ¶ 81.) The first method was the insertion of a "transgene" by random integration. (Id.) A "transgene" is a DNA sequence originating from outside the host organism. (Id.) One may create a "transgenic mouse" by injecting an exogenous DNA fragment into a fertilized mouse egg. (Id.) The DNA fragment is then incorporated spontaneously into a random chromosomal location in the genome of the embryo. (Id.) The exact location where the transgene DNA ends up in the genome is random. (Id. ¶ 82.) This process is known as "random integration". Random integration may result in the location of the added DNA in an area which is more or less transcriptionally active and can also disrupt or render nonfunctional DNA regions into which it integrates. (Id.) In

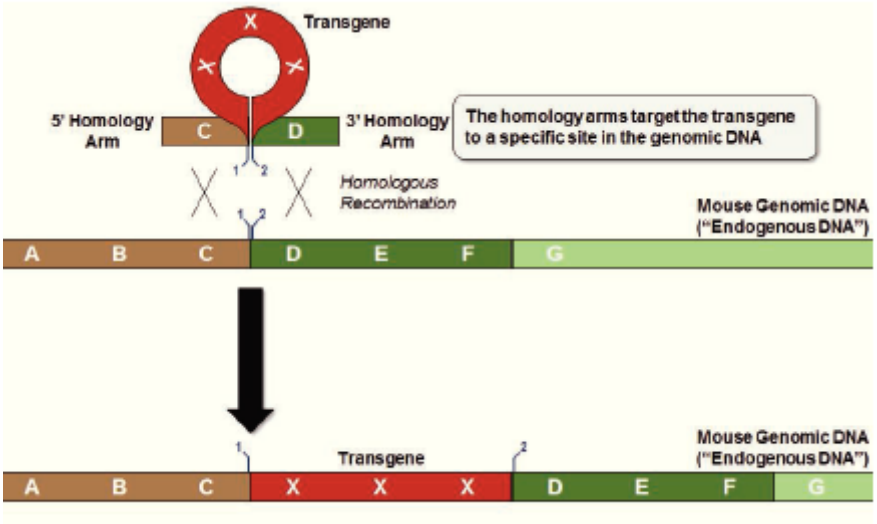
other words, the inserted DNA may or may not be where you want it to be in the mouse genome.

Non-randomized methods of genetic modification are referred to as "gene targeting". (Id. ¶ 83.) The key technique used for targeted gene modification is called "homologous recombination." (Id. ¶ 85.) The '018 Specification teaches a method of homologous recombination. A DNA construct, known as a "targeting vector" must be created to modify a gene using homologous recombination. (Id.) A "vector" is a vehicle which holds the DNA sequence to be incorporated into the mouse genome.[6] (Id.) To facilitate homologous recombination, the DNA sequence of interest is flanked by "homology arms"; these arms consist of DNA fragments that are substantially the same in sequence as the sequences that flank the target DNA sequence being replaced or augmented in the genome. (Id.) These arms allow the targeting construct to align with the host genome to ensure modification at the desired position. (Id.)

One wishing to exchange a number of variable gene segments of a mouse with their human equivalents, requires choosing a homology arm upstream (5') of the chromosomal fragment to be exchanged, and a homology arm downstream (3') of that fragment. (Id. ¶ 87.) These homology arms therefore flank the set of human variable gene fragments that one wishes to introduce into the mouse genome. (Id.)

[6] The '018 Patent refers to "large" DNA vectors; such vectors have a size of 20 kilobases ("kbs") or more. The size of a strand of DNA is referred by the number of base pairs ("bp"), including in terms of kilobase pairs (1kb= 1,000 base pairs) and megabase pairs (1 mb = 1,000,000 base pairs). (Clynes Decl. ¶ 27.) "LTVEC" is an acronym developed in the '018 Patent which stands for "large targeting vector for eukaryotic cells."

If homologous recombination occurs in the homology arms, the exchange of the mouse segments with their human counterparts has been accomplished. (Id.)[7] See Figure 4:




(Defs' Resp. Claim Constr. Br., at 9.)

Over time, it has been found that human gene segments are able to rearrange in a mouse to produce a broad spectrum of VDJ and VJ regions (for heavy and light chains) that are expressed in antibodies. (Id. ¶ 93.)

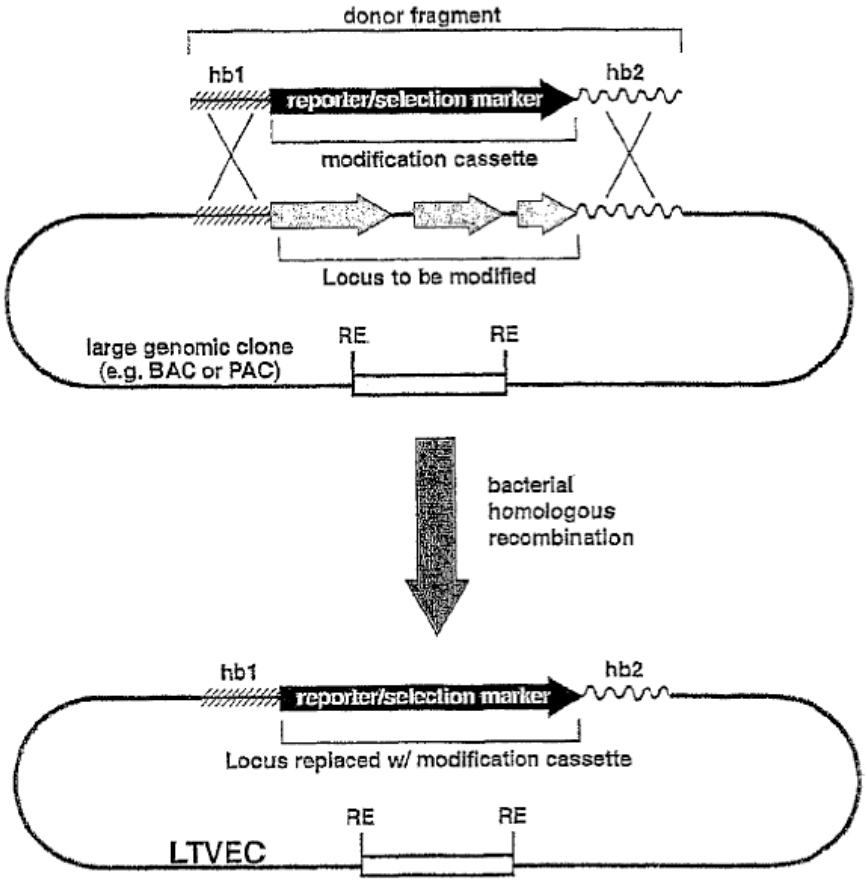
B. The '018 Patent

LTVECs – that is, large targeting vectors for eukaryotic cells – and the use(s) to which they are put in connection with homologous recombination, is at the core of the '018 Patent. LTVECs are "derived from fragments of cloned genomic DNA

[7] Certain stretches of DNA that are important in regulating transcription are referred to as "regulatory elements". "Promoters" are one such type. (Clynes Decl. ¶¶ 29-30.) Promoters are usually located at the 5', or upstream. Other regulatory elements may be located downstream or at the 3' end. (Clynes Decl. ¶ 30.) The boundaries of a gene are determined by the gene's regulatory elements located most upstream of the 5' end and most downstream of the 3' end of the coding sequence of that gene. (Clynes Decl. ¶ 30.) Thus, the boundaries of the 5' and 3' regulatory elements define the boundaries of the gene.

larger than those typically used by other approaches intended to perform homologous targeting in eukaryotic cells." ('018 Patent, 9:39-42.) As set forth above, as well as in the Specification, a "targeting vector" is a "DNA construct that contains sequences 'homologous' to endogenous chromosomal nucleic acid sequences flanking a desired genetic modification(s). The flanking homology sequences, referred to as the 'homology arms', direct the targeting vector to a specific chromosomal location within the genome. . ." ('018 Patent, 8:66-9:4.)

All of the figures in the Specification show versions of homologous recombination with LTVECs of various types and sizes, none smaller than 20 kb. For instance, Figure 1 in the Specification shows a DNA "modification cassette" (or insert) being transferred by homologous recombination into a large targeting vector in a mouse's genome:




Figures 4A-4D show a human insert in a LTVEC of 200-300 kbs:

Figure 4A Human Ig heavy chain locus (total length ≈1Mb, not drawn to scale):

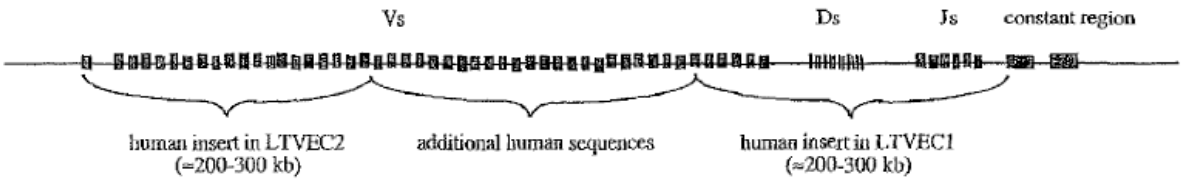



Figure 4B Mouse IG heavy chain locus (total length ≈1Mb, not drawn to scale) :

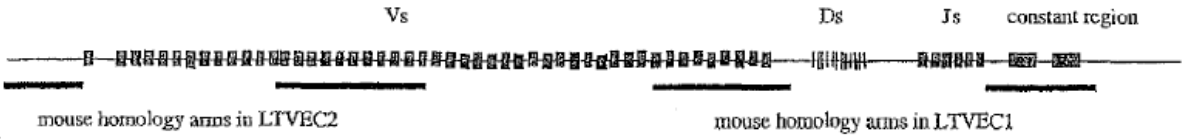



Figure 4C LTVEC2:

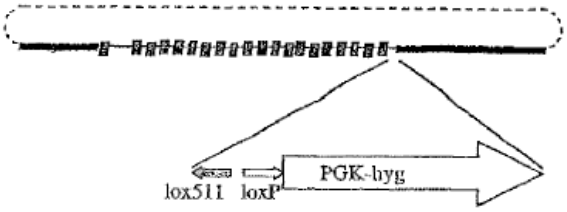
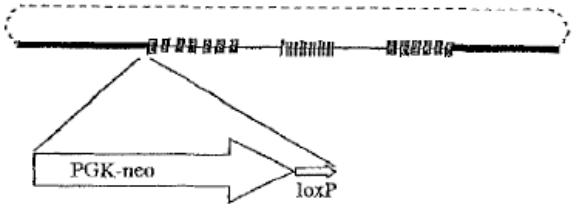



Figure 4D LTVEC1:




The Specification states that the "use of LTVECs provides substantial advantages" over current methods of homologous recombination. ('018 Patent, 1:37-38.) "LTVECs can be more rapidly and conveniently generated from available libraries of large genomic DNA fragments (such as YAC and BAC libraries)[8] than targeting vectors made using current technologies." ('018 Patent, 1:40-44.) "The present invention" is described as providing for "a rapid, convenient and streamlined method for systematically modifying virtually all the endogenous genes and chromosomal loci of a given organism." ('018 Patent, 1:51-54.)

[8] "YAC and BAC" libraries are able to produce artificial yeast and bacteria chromosomes. (Ravetch Decl. ¶ 96.)

The Specification describes prior genetic modification methods as limited by "size considerations" – the "size of the homology arms are restricted to less than 10-20 kb in total". ('018 Patent, 2:17-19.) Thus, the ability of the invention to "utilize targeting vectors with homology arms larger than those used in current methods" would be "extremely valuable". ('018 Patent, 2:21-23.) The use of "long regions of homology could increase the targeting frequency of "hard to target" loci in eukaryotic cells. . ." ('018 Patent, 2:31-33.) In terms of the prior art, the Specification notes there "is still a need for a rapid and convenient methodology that makes possible the use of targeting vectors containing large regions of homology so as to modify endogenous genes or chromosomal loci in eukaryotic cells". ('018 Patent, 2:59-63.) "In accordance with the present invention, Applicants provide novel methods that enable the use of targeting vectors containing large regions of homology so as to modify endogenous genes or chromosomal loci in eukaryotic cells via homologous recombination. Such methods overcome the [limitations in the prior art]". ('018 Patent, 2:64-67 – 3:2.)

In the summary of "the Invention," the Specification states, "In accordance with the present invention, Applicants have developed a novel, rapid, streamlined and efficient method for creating and screening eukaryotic cells which contain modified endogenous genes or chromosomal loci." ('018 Patent, 3:11-14.) The method uses LTVECs, introduces them into eukaryotic cells to modify the endogenous genes or chromosomal locus of interest, and analyzing the cell with an

assay for modification of the allele ("MOA assay"). ('018 Patent, 3:15-25.) The '018 Specification references a number of preferred embodiments including:

> "[A] method for genetically modifying an endogenous gene or chromosomal locus in eukaryotic cells [using LTVECs]" ('018 Patent, 3:27-30.)
>
> "Another embodiment of the invention is a method wherein the genetic modification to the endogenous gene or chromosomal locus comprises deletion of a coding sequence, gene segment, or regulatory element . . ." ('018 Patent, 3:40-43.)
>
> "An alternative embodiment of the invention is a method wherein the alteration of a coding sequence, gene segment, or regulatory element comprises a substitution, addition, or fusion . . . " ('018 Patent, 3:48-51.)
>
> "An additional preferred embodiment is one in which the LTVEC is capable of accommodating large DNA fragments greater than 20 kb, and in particular large DNA fragments greater than 100 kb." ('018 Patent, 3:67 – 4:3.)
>
> "Yet another preferred embodiment is a genetically modified eukaryotic cell that is produced by the method of the invention." ('018 Patent, 4:6-8.)
>
> "A preferred embodiment of the invention is a non-human organism containing the genetically modified endogenous gene or chromosomal locus produced by the method of the invention." ('018 Patent, 4:8-11.)
>
> "A preferred embodiment of the invention is a method for genetically modifying an endogenous gene or chromosomal locus of interest in mouse embryonic stem cells, comprising: [obtaining and using LTVECs] . . ." ('018 Patent, 4:65 – 5:16.)
>
> "Also preferred is a genetically modified mouse embryonic stem cell produced by this method; a mouse containing a genetically modified endogenous gene or chromosomal locus produced by this method; and a mouse produced from the genetically modified mouse embryonic stem cell." ('018 Patent, 5:16-21.)
>
> "Another preferred embodiment is a mouse containing a genetically modified endogenous gene or chromosomal locus of interest, produced by a method comprising the steps of: [obtaining and using LTVECs] . . ." ('018 Patent, 5:22-43.)
>
> "Also preferred is a transgenic mouse having a genome comprising entirely human heavy and light chain variable region loci operably linked to

> [entirely[9]] endogenous mouse constant region loci such that the mouse produces a serum containing an antibody . . . a transgenic mouse containing an endogenous variable region locus that has been replaced with an homologous or orthologous human variable locus, such mouse being produced by a method comprising [obtaining and using LTVECs] . . ." ('018 Patent, 7:24-54.)

All preferred embodiments set forth in the Specification reference the LTVEC method within the same paragraph.[10]

## II. TERMS AT ISSUE

Merus has requested that the Court construe the terms set forth below.[11] Regeneron has taken the position that no term requires construction; it has therefore offered no alternative construction.

1. A genetically modified mouse;
2. human unrearranged variable region gene segments;
3. inserted;
4. at;
5. endogenous mouse immunoglobulin locus;
6. linked / operably linked; and

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[9] A subsequent embodiment eliminates the word "entirely". ('018 Patent, 7:30-35.)

[10] Regeneron's position on claim construction requires reading the first two of this series of three preferred embodiments as disclosing a mouse genetically modified without regard to method. This position, and also as discussed below, focuses on the separation by semi-colon of the series of three preferred embodiments, with only the final embodiment (separated by a comma) directly connected to the LTVEC process. Regeneron's interpretation of this (long) sentence is incorrect. The series of three embodiments are purposefully linked together because of similarity, and as demonstrated by the absence of a period between them. To include two preferred embodiments not requiring reference to the LTVEC process with a third that does, would, in the context of the Specification, make no sense. No such dramatic differentiation between the embodiments is suggested.

[11] Ablexis separately requested that the term "a mouse constant region" be construed; as Ablexis has settled, the Court does not construe this term.

7. does not comprise a human immunoglobulin constant gene / lacks a human constant region gene

## III. APPLICABLE LEGAL STANDARDS FOR CLAIM CONSTRUCTION

Claim construction is generally a question of law for the Court. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 979 (Fed. Cir. 1995).[12] Determining the meaning of terms within a claim assists the fact finder in making subsequent and ultimate decisions as to, inter alia, whether an invention has in fact been infringed, or is in fact valid. The purpose of claim construction is to define terms so that the jury may be properly instructed. See Sulzer Textil A.G. v. Picanol N.V., 358 F.3d 1356, 1366 (Fed. Cir. 2004) ("[T]he trial court in a patent case must at minimum take steps to assure that the jury understands that it is not free to consider its own meanings for disputed claim terms and that the district court's claim construction, determined as a matter of law, is adopted and applied by the jury in its deliberation of the facts.").

In construing a term, the Court seeks to determine what that term would have meant to one "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." Phillips v. AWH Corp., 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc) (citations omitted). Although terms are generally construed as they would be understood by one of ordinary skill in the art, it is possible for a patentee to have set forth a particular and different meaning for a term within a claim; in such a case, the lexicography of

[12] There are certain instances, not relevant here, when this Court has been required to make factual findings in connection with some aspect of claim construction. See JobDiva, Inc. v. Monster Worldwide, Inc., No. 13 Civ. 8229 (KBF), 2014 WL 5034674 (S.D.N.Y. Oct. 3, 2014).

the patentee governs. See, e.g., Silicon Graphics, Inc. v. ATI Techs., Inc., 607 F.3d 784, 789 (Fed. Cir. 2010); Southwall Techs., Inc. v. Cardinal IG Co., 54 F.3d 1570, 1578 (Fed. Cir. 1995) ("The terms in a claim . . . are not given their ordinary meaning to one of skill in the art when it appears from the patent and file history that the terms were used differently by the applicant.").

A. Evidence Used in Claim Construction

The claims of a patent do not stand alone; they are part of "a fully integrated written instrument." Phillips, 415 F.3d at 1315 (citing Markman, 52 F.3d at 978). To interpret the meaning – including scope – of a patent's claims, a court may use intrinsic and, if necessary, extrinsic evidence. See Nazomi Commc'ns, Inc. v. Arm Holdings, PLC, 403 F.3d 1364, 1368 (Fed. Cir. 2005) (instructing courts to look to intrinsic evidence first). Intrinsic evidence includes the claims, the specification, as well as a patent's prosecution history. See All Dental Prodx, LLC v. Advantage Dental Prods., Inc., 309 F.3d 774, 780 (Fed. Cir. 2002) ("Foremost among the tools of claim construction is of course the claim language itself, but other portions of the intrinsic evidence are clearly relevant, including the patent specification and prosecution history."); see also Phillips, 415 F.3d at 1312 ("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.'" (quoting Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1115 (Fed. Cir. 2004))).

Every inventor is required to disclose the invention so as to "allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."

Billups-Rothenberg, Inc. v. Associated Regional and University Pathologists, Inc., 642 F.3d 1031, 1036 (Fed. Cir. 2011); 35 U.S.C.A. § 112 ("The specification shall contain a written description of the invention, and of the manner and process of making and using it"). The "written description requirement exists to ensure that inventors do not 'attempt to preempt the future before it has arrived.'" Billups-Rothenberg, 642 F.3d at 1036 (citing Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993)). The written description requirement precludes premature claims and requires the disclosure of an actual invention. Novozymes A/S v. DuPont Nutrition Biosciences APS, 723 F.3d 1336, 1345 (Fed. Cir. 2013).

Claims must be read in light of the specification. See Phillips, 415 F.3d at 1315. The purposes of the specification are to teach and enable those of skill in the art to make and use the invention and to provide a best mode for doing so. Id. at 1323. One skilled in the art is "deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Id. at 1313. The specification is always "highly relevant" to claim construction analysis; it is the "single best guide to the meaning of a disputed term." Id. at 1315 (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996) (internal quotation mark omitted)); see also On Demand Mach. Corp. v. Ingram Indus., Inc., 442 F.3d 1331, 1338, 1340 (Fed. Cir. 2006) ("[T]he scope and outer boundary of claims is set by the patentee's description of his invention," and "the claims cannot be of broader scope than the invention that is set forth in the specification.").

"[W]hen the scope of the invention is clearly stated in the specification, and is described as the advantage and distinction of the invention, it is not necessary to disavow explicitly a different scope." On Demand, 442 F.3d at 1340. The specification therefore provides guidance as to the meaning of claims – and how they should be construed – even if such guidance is not in a definitional format. Id. (citing Bell Atlantic Network Svcs., Inc. v. Covad Comms. Group, Inc., 262 F.3d 1258, 1268–69 (Fed. Cir. 2001)); Network LLC v. Centraal Corp., 242 F.3d 1347, 1352 (Fed. Cir. 2001) ("[Plaintiff's] argument that the district court improperly limited the scope of Claim 1 by importing the caching and pulling functions from the specification misperceives the role of claim construction in an infringement analysis. The role is neither to limit nor to broaden the claims, but to define, as a matter of law, the invention that has been patented . . .").

Examples of courts construing terms based on the specification in a manner that limits claim scope are useful (as that is what the Court similarly does here). In On Demand, the Federal Circuit found that since "the focus of the [] patent is immediate single-copy printing and binding initiated by the customer and conducted at the customer's site," the district court erred in construing the term "customer" more broadly to include anyone who buys goods or services. On Demand, 442 F.3d at 1340. The Federal Circuit relied upon the fact that the specification "repeatedly reinforces its usage of the term 'customer' as the retail consumer." Id.

In Biogen, Inc. v. Berlex Labs., Inc., 318 F.3d 1132 (Fed Cir. 2003), the Federal Circuit addressed whether the broad language of certain claims directed to the production of human beta interferon protein in Chinese hamster ovary cells were correctly construed as limited to the use of a single DNA "construct." The construct was to introduce both a selectable marker gene and the human interferon gene into the host cell. Id. at 1133-34. Among the claims at issue were Nos. 66 and 68:

> 66. A Chinese hamster ovary cell having incorporated therein an expressible gene encoding human á- or â-interferon, or a progeny thereof.
>
> 68. A Chinese hamster ovary cell having incorporated into its chromosome an expressible gene encoding human interferon, or a progeny thereof.

Id. at 1334. It was conceded that these claims did not mention the use of a single DNA construct. Id. at 1135. Based on the specification, prosecution history and expert testimony, however, the district court construed all claims as requiring use of a single construct. Id. In particular, both the district court and Federal Circuit deemed it critical that the specification discussed only a single DNA construct. Id. Berlex, the patent holder, argued that it was irrelevant to the cell claims whether transformation of the Chinese hamster ovary cell is achieved by single or multiple constructs. Id. Biogen responded that except for a few undeveloped sentences, the entire specification was directed solely to the invention whereby a single DNA construct is used to carry linked interferon and marker genes into the Chinese hamster ovary cell. Id. at 1136. The district court and Federal Circuit agreed. The Federal Circuit repeated the established rule that "'when the claims are written

more broadly than the disclosure warrants' they may be construed 'to preserve the validity of the claims with respect to their original intended scope.'" Id. at 1140 (quoting Texas Instruments, Inc. v. Int'l Trade Comm'n, 846 F.2d 1369, 1371-72 (Fed. Cir. 1988)).

Similarly, in Honeywell Intern., Inc. v. ITT Indus., Inc.. 452 F.3d 1312 (Fed. Cir. 2006), the Federal Circuit affirmed the district court's construction of the term "fuel injection system component" as limited to a fuel filter. The Federal Circuit agreed with the district court that the written description was limited to fuel filters and addressed problems in fuel filter design. Id. at 1314. Both the Federal Circuit and district court found it significant that the specification referred to a fuel filter as "the invention" in several places. Id. at 1316. The patent holder, Honeywell, argued that the district court erred in its construction – and that it had improperly imported a limitation from the specification into the claims, thereby improperly limiting the scope of the claims. Id. at 1317. The Federal Circuit disagreed. Citing Phillips, 415 F.3d at 1315, it reiterated that the claims cannot go further than the invention disclosed in the specification. Id. at 1318. "The public is entitled to take the patentee at his word and the word was that the invention is a fuel filter." Id.; see also Netcraft Corp. v. Ebay, Inc., 549 F.3d 1394, 1398 (Fed. Cir. 2008) (while use of the phrase "the present invention" does not automatically limit the meaning of claim terms in all circumstances, it may when read as such in the context of the specification and prosecution history).

Claim construction that limits the scope of a claim may, therefore, be based on the scope implicit in the specification rather than explicit disavowal. Astrazeneca AB v. Mutual Pharmaceutical Co., Inc., 384 F.3d 1333, 1339-40 (Fed. Cir. 2004) (lexicography does not require rigid formalism such as "I define _____ to mean _____,"; the specification may define claim terms by implication). The specification acts as a dictionary even when it defines terms by implication and not an explicit statement of redefinition. Bell Atl. Network Svcs., 262 F.3d at 1268.

Somewhat in tension with the above is another core principle: that a specification should not be read so as to limit a claim. See Absolute Software, Inc. v. Stealth Signal, Inc., 659 F.3d 1121, 1136-37 (Fed. Cir. 2011) (declining to import a limitation into the claim where a portion of specification identified the purported limitation as one of "two optional features" despite earlier references in the specification requiring the invention to include both features); Netword, 242 F.3d at 1352. Thus, although specifications contain one or more examples of the embodiment of an invention, they need not contain every possible embodiment, and courts should not read into the claims limitations based on the embodiments in the specification. See Phillips, 415 F.3d at 1323; see also Innogenetics, N.V. v. Abbott Labs., 512 F.3d 1363, 1371-72 (Fed. Cir. 2008) ("[The defendant] argues that a patent can never be literally infringed by embodiments that did not exist at the time of filing. Our case law allows for after-arising technology to be captured within the literal scope of valid claims that are drafted broadly enough."). The reconciliation between these principles is – in practice – based on whether

disclosures imply the sought breadth, including (for instance) additional embodiments or not.

Several aspects of the patent prosecution history can be of significant use during claim construction. Statements the patentee may have made in connection with patent prosecution are binding if used to obtain patentability. See Teleflex, Inc. v. Ficosa N. Am. Corp., 299 F.3d 1313, 1326 (Fed. Cir. 2002) ("[T]he prosecution history (or the file wrapper) limits the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance." (quoting Standard Oil Co. v. Am. Cyanamid Co., 774 F.2d 448, 452 (Fed. Cir. 1985) (internal quotation marks omitted))); see also Kripplez v. Ford Motor Co., 667 F.3d 1261, 1266 (Fed. Cir. 2012) ("A patentee's statements during reexamination can be considered during claim construction, in keeping with the doctrine of prosecution disclaimer."). The prosecution history provides evidence of how the patentee understood and explained his invention to the Patent Office. Phillips, 415 F.3d at 1317.

Statements made by a patentee during prosecution prevent claim terms from becoming ever-changing as the need and situation changes. See Southwall Techs., 54 F.3d at 1578 ("A patentee may not proffer an interpretation for the purposes of litigation that would alter the indisputable public record consisting of the claims, the specification and the prosecution history, and treat the claims as a 'nose of wax.'").

Courts should generally construe claims so as to preserve their validity. See Amgen Inc. v. Hoechst Marion Roussel, Inc., 469 F.3d 1039, 1042 (Fed. Cir. 2006); Phillips, 415 F.3d at 1327. If a claim is fairly susceptible of two constructions, the construction which will secure to the patentee his (or an) actual invention should be adopted. Smith v. Snow, 294 U.S. 1, 14 (1935); Amgen, 469 F.3d at 1042. Consistent with those principals, the Court cannot enlarge the claims beyond the limitations imposed by the patentee. Amgen, 469 F.3d at 1042; Phillips, 415 F.3d at 1319.

Parties do not always agree, as is the case here, that a particular claim requires construction. There are numerous instances in which one party asserts that the plain and ordinary meaning informs one of ordinary skill in the art of all that he or she needs to know, while an opposing party disputes that position. In such cases, the Court ordinarily should construe the claim. See O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., 521 F.3d 1351, 1361 (Fed. Cir. 2008) ("A determination that a claim term 'needs no construction' or has the 'plain and ordinary meaning' may be inadequate when . . . reliance on a term's 'ordinary' meaning does not resolve the parties' dispute. . . . In this case, . . . claim construction requires the court to determine what claim scope is appropriate in the context of the patents-in-suit.").

B. Product-by-Process Claims

Claims may be written or construed to contain both a product and a process; such claims are referred to as "product-by-process" claims. Product-by-process

claims are often – but not always – written in a format of "x product, manufactured by y process." See, e.g., Abbott, 566 F.3d at 1286; Southwall Techs., 54 F.3d at 1576. In product-by-process claims, both the product and the process terms separately and together serve as limitations in defining infringement. Abbott Laboratories v. Sandoz, Inc., 566 F.3d 1282, 1291 (Fed. Cir. 2009) (en banc). When claims are written to include both a product and process, the process detailed thereby is as much a part of the invention as the resulting product. Id. at 1293 ("'process terms in product-by-process claims serve as limitations in determining infringement.'") (quoting Atlantic Thermoplastics Co., Inc. v. Faytex Corp., 970 F.2d 834, 846-47 (1992)); see also Anderson Corp. v. Fiber Composites, LLC, 474 F.3d 1361, 1372 (Fed. Cir. 2007).

There is a clear and direct relationship between the principles which inform a court's determination of when a specification limits breadth of a patent, and when a product claimed may be limited by the process by which it was made. Whether described by reference to one set of cases (limited by the specification, see e.g., On Demand, 442 F.3d at 1340; Phillips, 415 F.3d at 1315; Vitronic, 90 F.3d at 1582) or the other (product-by-process claims, see e.g., Anderson, 474 F.3d at 1372; Atlantic Thermoplastics, 970 F.2d at 846-47) the point is the same: a product claimed is limited by that which has been disclosed in the specification.[13] In all events, the patent can be no broader than the outer boundaries of the specification.[14]

[13] "Disclosed" here refers to the invention, not merely a listing of preferred embodiments.
[14] In Andersen Corp. v. Fiber Composites, LLC, 474 F.3d 1361 (Fed. Cir. 2007), the Federal Circuit found that the district court's limitation of the product (a pellet) to compositions with certain properties was not unduly narrow. Id. at 1367. The case involved two groups of patents: one covered

C. Indefiniteness

"[A] patent's claims, viewed in light of the specification and prosecution history, [must] inform those skilled in the art about the scope of the invention with reasonable certainty." Nautilus, Inc. v. Biosig Instruments, Inc., 134 S. Ct. 2120, 2129 (2014); see also Interval Licensing LLC v. AOL, Inc., No. 2013-1282, 2014 WL 4435871, at *5 (Fed. Cir. Sept. 10, 2014) ("Although absolute or mathematical precision is not required, it is not enough, as some of the language in our prior cases may have suggested, to identify 'some standard for measuring the scope of the phrase.'").

This requirement is referred to as "definiteness." It embodies the important function of "appris[ing] the public of what is still open to them." Id. (quoting Markman, 517 U.S. at 373) (internal quotation marks omitted). The requirement that a claim be precise enough to afford clear notice of what is claimed thereby eliminates the temptation to later inject ambiguity into the scope of a patent. Id. ("[A]bsent a meaningful definiteness check, . . . patent applicants face powerful incentives to inject ambiguity into their claims."). A claim which fails to meet the "reasonable certainty" requirement is indefinite, see id., and thus not entitled to

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compositions capable of being extruded into structural members, and another covered the extruded structural members themselves. In construing this second group, the Court limited the scope of the composite structural members to those including an intermediate step of pelletization or linear extrusion. Id. at 1375. The court observed that "[t]he specification ... indicates that the claimed physical properties of the composite structural members are attributable to the process that is used to make them, a process that includes pelletization." Id. at 1372." In other words, the Federal Circuit found that the portions of the specification describing how the physical properties of the claimed composite structures are obtained make clear that the formation in a particular manner is not merely a preferred embodiment but is rather a critical element of the process that produces the structures. Id. at 1367.

patent protection, see United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 233 (1942) ("To sustain claims so indefinite as not to give the notice required by the statute would be in direct contravention of the public interest which Congress therein recognized and sought to protect.").

Patents entitle the holder to a presumption of validity of its claims. See 35 U.S.C. § 282 ("A patent shall be presumed valid."). As a result, a party seeking to have a claim declared "indefinite" must present clear and convincing evidence. Tech. Licensing Corp. v. Videotek, Inc., 545 F.3d 1316, 1338 (Fed. Cir. 2008) ("To the extent there are any factual findings upon which a trial court's indefiniteness conclusion depends, they must be proven by the challenger by clear and convincing evidence.").

## IV. THE COURT'S CONSTRUCTIONS

Merus's proposed constructions share a common theme: that the method of genetically modifying eukaryotic cells described in the Specification is an essential limitation on the metes and bounds of the claims. As discussed above, Merus asserts that the "genetically modified mouse" is not made by any process other than the LTVEC method disclosed. Plaintiff Regeneron asserts that while that method is disclosed in the Specification, the invention set forth in the claims is not defined by that method; that is, the mouse, in Claim 1 for instance, may have been genetically modified by some other (non-LTVEC) method.

The legal principles set out above are directly applicable to the parties' respective arguments. Such principles include: First, the law is clear that the

claims define the invention. See Liquid Dynamics Corp. v. Vaughan Co., Inc., 355 F.3d 1361, 1368 (Fed. Cir. 2004). Second, a patentee is not entitled to more than he has disclosed in the specification. Phillips, 415 F.3d at 1315. Third, while the specification is the most important guide to understanding the claims, see Multiform Desiccants Inc. v. Medzam Ltd., 133 F.3d 1473, 1478 (Fed. Cir. 1998), a court should not read limitations in the specification into the claims, see Liebel–Flarsheim Co. v. Medrad, Inc., 358 F.3d 898, 904 (Fed. Cir. 2004). And, sifting through these principles, whatever the metes and bounds of an invention are, the inventor is entitled to its full breadth. See TI Group Automotive Systems (North America), Inc. v. VDO North America, LLC, 375 F.3d 1126, 1138 (Fed. Cir. 2004). The Court is mindful of the following principles as well: patents serve a critical public notice function, see Johnson & Johnston Associates v. R.E. Service Co., 285 F.3d 1046, 1052 (Fed. Cir. 2002) (en banc), and that the public must be able to read the claims in light of the specification and be able to understand that as to which the inventor has exclusive rights, see Nautilus, 134 S. Ct. at 2129. At oral argument on claim construction, Regeneron's counsel posed the question, "who owns the silence?" (Transc. 248:12-14.) These principles lead to the following conclusion: if there was truly silence and no disclosure, the public owns the silence; if there was actual or implicit disclosure, the patentee owns the silence.

As to each of the terms set forth below, Regeneron asserts that no construction is necessary, that the plain and ordinary meaning is clear to one skilled in the art at the time. Merus disagrees, as does this Court. Regeneron's

position ignores that "plain and ordinary meaning" concerns both technical concepts (what a word means) and scope (how far does that meaning extend). In taking the position that the terms required no construction, Regeneron focused only on "what the words mean" – and very little on scope. Of course, that is an agreed starting point – and often an endpoint when the specification does not dictate otherwise. But, as here, when the specification may be read to define boundaries as to those otherwise ordinary terms, that too must be taken into account.

Fundamentally, the parties' disputes on claim construction are not so much as to English and technical meaning as to scope. When the parties dispute the meaning as well as scope of terms, it is the Court's role to resolve that dispute. O2 Micro Int'l Ltd., 521 F.3d at 1361. The Court generally construes each of the disputed terms as Merus proposes: when the claim terms are read in overall context of the Patent, there is no doubt that the scope of the '018 Patent is far narrower than Regeneron asserts. All claim terms must be read in light of the LTVEC method that is at the heart of the invention.

A. "A genetically modified mouse"

Merus asserts that the term "a genetically modified mouse" should be construed as "A transgenic mouse produced by the process of using LTVECs to modify embryonic stem cells and using a quantitative assay to detect modification of allele in those cells." (Joint Cl. Constr. Chart ("JCC") at 1.) According to Merus, this term defines the product created by the method described in the remainder of the

claim.[15] Regeneron asserts that this term requires no construction and that a person of ordinary skill in the art would understand the term "genetically modified mouse" without further definition. (Ravetch Decl. ¶ 101.) The dispute here is as to scope: the question is the extent to which the breadth of otherwise clear terms is informed by the Specification and other intrinsic evidence. There is no real dispute that in terms of the plain meaning, one of ordinary skill in the art at the time would generally understand that a "genetically modified mouse" is a mouse that has been genetically modified in some way. Here, the nature of the dispute between the parties means that the exercise of claim construction requires more than this. It requires asking how those words are understood against the intrinsic evidence. In that regard, it is clear that Merus's proposed construction is correct.

The entire Specification and history of the '018 Patent supports that each of these words refer to a mouse, the genes of which have been modified, using the particular method described in the Specification. Basic principles of claim construction support the Court's view. First, it is axiomatic that a patentee cannot claim more than that which he has invented. On Demand, 442 F.3d at 1340. Second, the specification is always highly relevant to claim construction and is usually the single best guide. Vitronics, 90 F.3d at 1582. Third, when claims are worded more broadly than the disclosure warrants, they may be construed to

[15] Merus refers to this term and, for instance, Claim 1, as identifying a product-by-process claim. As discussed above and infra, whether described as a product-by-process claim or limited to that which was disclosed in the Specification, the end result is the same.

preserve the validity of the claims with regard to their intended scope. Biogen, 318 F.3d at 1140.[16]

The phrase "genetically modified mouse" is not a term written in a vacuum. See Phillips, 415 F.3d at 1315. It is written against the detailed Specification. The Specification is almost exclusively concerned with the use of large targeting vectors ("LTVECs") – larger than those used in the prior art – for homologous recombination. (Clynes Decl. ¶¶ 70-71.) There is no genetic modification described as part of the invention which does not use LTVECs and the LTVEC method.[17] Thus, it would be contrary to a host of basic principles of claim construction to read this term as somehow having a broader meaning than that implicitly or explicitly disclosed in the Patent. Indeed, if the Court were to agree with Regeneron's asserted scope, it would violate the principle that claims should be construed so as to preserve their validity, see Amgen Inc., 469 F.3d at 1042, because such breadth would violate the written description requirement.

Regeneron relies very heavily on Example 3 to support the breadth of its view of scope. Notably, Example 3 is entitled "Use of LTVECs to Produce Chimeric and Human Antibodies". ('018 Patent, 19:35-40.) Regeneron's focus is on only a portion of the content in Example 3; and based on this portion – ignoring the title of the section and what immediately follows – asserts that this portion functions as a

[16] To the extent claims exceed their disclosure, they may be subject to an invalidity determination pursuant to 35 U.S.C. § 112.

[17] As Clynes notes, the use of LTVECs constituted the key to the inventions. (Clynes Decl. ¶ 60.) Multiple references in the Specification describe the critical use of LTVECs in connection with the invention. Figures 4A-4D demonstrate that role.

"specification within a specification": that is, that this portion is sufficient to disclose, on a standalone basis, the genetically modified mouse claimed. The argument reads the section entitled "Brief Description" ('018 Patent, 20:36-21:60) as if it were unconnected to the following section, "Materials and Methods" ('018 Patent, 21:61-24:24). The two sections are intertwined; and Regeneron's reading therefore distorts the Patent. First, as stated, Example 3 is entitled "Use of LTVECs to Produce Chimeric and Human Antibodies"; second, following the "Brief Description" section, the "Materials and Methods" section discloses steps necessary to do precisely that to which the title refers. LTVECs are integral to that process. To the extent the particular steps are exemplar only, that allows the use of LTVECs with other steps – fewer steps or more steps – but not the elimination of LTVECs altogether. LTVECs, in other words, may be used in a number of ways to do the same thing.

Textual support for the Court's narrowed construction is found throughout the Specification. The Specification differentiates the invention disclosed from prior art and references the problem it solves in terms of the use of LTVECs. As Clynes states, the "theory of the '018 patent is that using longer than normal homology arms to produce a targeting vector will cause that vector to insert a larger fragment of cloned genomic DNA (as opposed to synthetic DNA) than previously thought possible." (Clynes Decl. ¶ 61.) For instance, the Specification states outright that the use of LTVECs provides "substantial advantages over current methods" ('018 Patent, 1:37-43; Clynes Decl. ¶ 25); and "Applicants contend that the novelty of the

method of the invention lies in the unique combination of those steps and techniques coupled with the never-before-described method of introducing a LTVEC directly into eukaryotic cells to modify a chromosomal locus, and the use of quantitative MOA assays . . . This novel combination represents a significant improvement over previous technologies . . .” (see ’018 Patent, Example 3, 19:35-24:24, as discussed supra) (see also Clynes Decl. ¶¶ 56-59, 71-72).

In addition, Claim 1 when read holistically, itself uses process terms such as “modified”, “inserted” and “linked.” These process words support the requirement that some process has occurred to create the “genetically modified mouse”. This process is not a mystery, it is described and referenced throughout the Specification: the Specification discloses a method of “inserting” the DNA, the size of the DNA segment, when to get it, as well as a method to obtain the linkage of a human gene segment to a mouse constant region, and thereby to accomplish the genetic modification of the mouse. The Specification refers to no other process besides the LTVEC process described.

In addition, the Specification itself tells the reader what the invention is: there are over 20 instances in which the Specification refers to the “method of the invention” (see, e.g., ’018 Abstract, “A method for engineering and utilizing large DNA vectors . . . as well as the use of these cells to generate organisms bearing genetic modification”; ’018 Patent, 1:46-50, 1:51-54; 2:64-67; 3:2-7; 3:11-14; 4:3-6, 4:6-8; 4:8-11, 4:11-14, 10:39-42, 12:40-45, 15:5-8, 15:17-32, 15:52-54, 15:55-64, 17:66-18:2, 18:46-49, 18:52-56, 18:59-19:3); every disclosure of a prophetic transgenic

mouse refers to the method (see, e.g., '018 Patent 7:24-54, 15:55-66, "such mouse being produced by a method" refers back to a "transgenic mouse").

When there are disputes as to what the invention is, courts often refer to what the specification stated on the subject, in particular by using phrases such as "the present invention". See Trading Techs. Int'l, Inc. v. eSpeed, Inc., 595 F.3d 1340, 1353-54 (Fed. Cir. 2010); Edwards Lifesciences LLC v. Cook, Inc., 582 F.3d 1322, 1330 (Fed. Cir. 2009); NetCraft, 549 F.3d at 1398 ("[W]e agree with the district court that the common specification's repeated use of the phrase 'the present invention' describes the invention as a whole."); Honeywell, 452 F.3d at 1318; SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1343 (Fed. Cir. 2001). When a method is used to describe how to prepare "the present invention", a court may construe the product with reference to the process. See, e.g., Verizon Services Corp. v. Vonacre Holdings Corp., 503 F.3d 1295, 1308 (Fed. Cir. 2007) ("When a patent thus describes the features of the 'present invention' as a whole, this description limits the scope of the invention"); In re Fenofibrate Patent Litig., No. 11 MDL 2241 (JSR), 2011 WL 10901800 at *2-6 (S.D.N.Y. Aug. 23, 2011).

The prosecution history also supports the Court's construction. The "invention" is referred to as a "method" more than a dozen times by both Regeneron and the examiner (see Clynes Decl. Ex. 15, '176 Appl., July 26, 2012, Reply to Non-Office Action, at 8, 9; Ravetch Reply Decl. Ex. 3, '176 Appl., Oct. 11, 2012, Final Rejection, at 14, 15; Ravetch Reply Decl. Ex. 6, '176 Appl., Jan. 11, 2013, Reply to

Final Office Action, at 11; Ravetch Reply Decl. Ex. 4, '176 Appl., Feb. 1, 2013, Advisory Action, at 18.) Moreover, in addressing the draft claims reciting the term "genetically modified mouse", the applicants drew a distinction between the prior art and the "claimed method" or a mouse made by the claimed method. (Clynes Decl. ¶¶ 76-77.) For instance, in responding to a rejection, as anticipated, of claims very similar to those here, the applicants stated,

> "[N]o teaching, motivation, suggestion, or pressure to develop a method for making a human variable/mouse constant antibody from an endogenous mouse locus through rearrangement of germline sequences at the endogenous locus was recognized in the art at the time the application was filed."
>
> "The claimed method is not a combination of prior art elements, according to known methods."
>
> 'The claimed method does not represent use of a known technique employed in similar gene targetings to improve the Lonberg method."

(Clynes Decl. ¶ 77, Ex. 15, '176 Appl., July 26, 2012, Reply to Non-Final Office Action, at 8-9.)

Regeneron itself relied upon its own VelocImmune mouse during patent prosecution; the VelocImmune mouse is made with the LTVEC method. (Clynes Decl. ¶¶ 79-80; Transc. 130:21-131:1.) In January 2013, applicants relied on the success of the VelocImmune mouse to argue the claims that ultimately issued in the '018 Patent were not obvious. (Clynes Decl. ¶ 78, Ex. 16, '176 Appl., Jan. 11, 2013, Reply to Final Office Action, at 11-12.) The applicants asserted that the claimed method results in a particular mouse with certain characteristics. Id. And, that "[m]ice made according to the pending claims . . ." exhibit certain characteristics.

Id. Further, applicants submitted an exhibit describing that the mice were made with the VelociGene and VelociMouse technologies. (Clynes Decl. ¶¶ 79-80.)

Read in context, the term "genetically modified mouse" can only refer to a mouse modified using the LTVEC process. Whether this limitation is described in terms of the scope of the Specification (and that the inventor cannot claim more than he has discovered), or as a product-by-process claim is ultimately beside the point. The bottom line result is the same.

B. "human unrearranged variable region gene segments"

Merus asserts that the term "human unrearranged variable region gene segments" should be construed as "A contiguous stretch of cloned human genomic DNA containing variable region gene segments (V, D and J for the heavy chain / V and J for the light chain) in germline configuration, i.e. as it is in the human genome before the development of B cells." (JCC at 1; Transc. 131:15-132:1.) Regeneron argues that this term requires no construction. (Ravetch Decl. ¶ 103.) The issue is, again whether the terms are limited in scope by virtue of the Specification and other intrinsic evidence. They are. The Court agrees with Merus's proposed construction.

The disputes as to this term breaks into three parts: (1) whether the DNA segments are human DNA – that is, taken or cloned from a human host – or may be synthetic, and (for instance) created from a library of DNA sequences (see, e.g., Clynes Decl. ¶¶ 86-87); (2) what the term "unrearranged" means; and (3) whether the "variable region gene segments" requires one contiguous segment of the V, D

and J region or whether the V, D and J segments may be assembled one by one and stitched together.

1. human vs. synthetic

As to the first issue: the Specification, read as one of ordinary skill in the art at the time, requires the DNA segment to be human (that is, taken from or cloned from a human); it may not be synthetic. The key legal principle is that the specification must be read according to the standard of what it meant to one skilled in the art as of the application date. W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1556, (Fed. Cir. 1983). That date is February 16, 2001. It is not appropriate to read the Specification as of a later point in time. At that time, synthetic DNA was not compatible with LTVECs: in 2001 synthetic DNA segments were just too short. The '018 Patent describes LTVECs as larger than prior art genetic segments – which were typically between 10-20 kb. (See, e.g., '018 Patent, 2:17-20: describing limitations of prior art as "restricted to less than 10-20 kb in total." '018 Patent, 2:64-3:2, 3:67-4:3: describing the invention as "targeting vectors containing large regions of homology . . . to overcome the above-described limitations. . .".) In February 2001, synthetic DNA was not typically used to create DNA segments of greater than 20 kbs. In his declaration, Clynes stated that synthetic DNA could only achieve a length of 10 kb in 2001; and that lengths of 20-100 kb of synthetic DNA were not achieved until 2004-08. (Clynes Decl. ¶ 103.) In 2001, DNA synthesis was still in its infancy and producing synthetic DNA fragments greater than a few kb long via this method was difficult and could not be

readily accomplished by one of ordinary skill in the art. (Id. ¶¶ 50, 101-103.) As of that time, persons of skill in the art had not synthesized fragments of DNA larger than 10 kb, which is smaller than either of the homology arms to be integrated when using the LTVEC method. (Id. ¶ 103.) To have created larger synthetic DNA segments would have consumed significant resources and time by those of *extraordinary* skill in the art. (Id.) The Specification is clear that LTVECs require much larger fragments. The '018 Specification was therefore referring to human – not synthetic – DNA. That technical advances now allow synthetic DNA in larger sizes – and make LTVECs of synthetic DNA now possible – does not itself alter the invention. The invention is construed as of 2001 – not some later date. See Novozymes A/S, 723 F.3d at 1345 (the written description requirement precludes premature claims).

Moreover, the Specification supports the DNA as human: the only DNA sequences disclosed in the Specification are cloned human DNA – not synthetic DNA. (See '018 Patent, 7:24-30, 22:5-14, 24:4-6). The '018 Patent teaches the benefit of human sequences. ('018 Patent, 21:54-60.) At the hearing, Clynes explained that the use of synthetic DNA was inconsistent with the '018 Patent as the patent language indicated "the intent is to move the entire human locus". (Transc. 129:20-130:5.) Indeed the Specification, including Example 3 (a prophetic example), confirms human genomic DNA. ('018 Patent, 24:4-6, 7:24-30.) The Specification in fact teaches away from synthetic DNA "the method of the invention makes possible the precise modification of large loci that cannot be accommodated

by traditional plasma-based targeting vectors because of their size limitations." ('018 Patent, 10:39-42.) Nowhere does the specification describe use of DNA synthesis. (Clynes Decl. ¶ 97.)

The Specification also describes transformation with cloned genomic human DNA: "One embodiment of the invention is a method of replacing, in whole or in part, a non-human eukaryotic cell, an endogenous immunoglobulin variable region gene locus with an homologous or orthologous human gene locus comprising: a) obtaining a large cloned genomic fragment containing, in whole or in part, the homologous or orthologous human gene locus…" ('018 Patent, 5:44-50) (emphasis added). And "comprising entirely human heavy and light chain variable region loci…" ('018 Patent, 7:24-30) (emphasis added).

Finally, the '018 Patent never discloses the use of synthetic DNA to target the endogenous mouse immunoglobulin locus. As discussed above, while there were size limitations on synthetic DNA segments, they did exist – and if the applicants wanted to allow for synthetic DNA and likely anticipated technical advances, they could easily have done so.

In addition, Merus asserts that Regeneron distinguished the '018 Patent from the use of "synthetic loci" during prosecution. The PTO rejected the claims as anticipated by Lonberg & Kay. Plaintiff distinguished the '018 Patent from Lonberg on the basis that, "The cited portions of Lonberg leave no doubt whatsoever that the Lonberg mouse construction instructions were to build a transgenic mouse that makes fully human antibodies from transgenes that are distant from endogenous

mouse immunoglobulin loci, i.e., they are synthetic loci randomly inserted into the mouse genome. . .” (Clynes Op. Decl., Ex. 16, ’176 Appl., January 11, 2013, Reply to Final Office Action, at 5-6.)

2. Unrearranged

Turning to the word “unrearranged”, Merus asserts that it means the DNA sequence is in “germline configuration”, that is, prior to any rearrangement or recombination occurring through the natural process of B-cell development. (Clynes Decl. ¶¶ 91, 105; Transc. 131:20-132:1.) Merus takes issue with DNA segments reorganized in a lab as constituting an “unrearranged” segment. Regeneron asserts that “unrearranged” means just that; it is not rearranged but is “capable of rearranging.” Regeneron further asserts that, as used in reference to the V segment, “unrearranged” refers to the configuration wherein the V segment is not recombined so as to be immediately adjacent to a D or J segment. Regeneron’s position construes the term “unrearranged” more broadly than the clear implications of the Specification.

The Specification itself never uses the term “unrearranged” – it only references DNA rearrangement as the natural process that occurs during B-cell development – not prior to B-cell development. (’018 Patent, 19:42-50; 20:41-43.) A comparison of Claim 1 to Claim 6 highlights the existence of some difference between the parties’ constructions. Claim 6 claims human variable region gene segments are “capable of rearranging” to form the gene (’018 Patent, 29:39-41); Claim 1 refers only to “unrearranged.” Claim 6 would therefore be superfluous if

Claim 1's reference to "unrearranged" meant the same thing. (Compare Claim 1 to Claim 6.) Courts are to construe terms so as to retain their validity – and redundancy would require the elimination of Claim 1 or 6. Biogen, 318 F.3d at 1140.

The difference between the two positions – Regeneron's and Merus's – amounts to a difference between whether unrearranged requires "germline configuration". (Regeneron asserts "no", Merus asserts "yes"). Clynes stated that immunology literature as of 2001 supports his (and Merus's) view of the distinction. (Clynes Decl. ¶ 107.) Immunology textbooks as of 1999 and 2000 use "unrecombined" as synonymous with "unrearranged" and rearranged as occurring during the development of B-cells (also known as "somatic recombination"). According to Clynes, engineered DNA, or DNA that is reorganized in a lab prior to being inserted into a mouse, would not have been considered by one of ordinary skill in the art to be "unrearranged." (Id. ¶ 109.)

The prosecution history also supports the Court's construction. (Id. ¶¶ 110-113.)[18] The applicants distinguished between "human rearranged variable region gene segments inserted at endogenous mouse loci" versus randomly inserted synthetic loci. (Id. ¶111.) In doing so, the applicants effectively indicated that their invention was different from prior art that had used randomly inserted synthetic loci.

[18] European proceedings also support the Court's construction. (Clynes Decl. ¶¶ 114-115.)

3. Variable Region Gene Segments

The debate between the parties as to "variable region gene segments" relates to whether the DNA at issue may be "stitched together" or should be contiguous. The point of the LTVEC method is that the variable region gene segment would be contiguous. It is a "fundamentally different approach to use an engineered construct to stitch together various bits from the human genome to create a smaller recombination substrate . . ." (Transc. 134:6-8.) As described above, "variable region gene segments" encompass variable region DNA that is the V, D, and J gene segments for the heavy chain and V and J gene segments for the light chain. That is, the phrase "variable region" captures these gene segments as a group versus as individual (V, D, or J) gene segments. When the applicants wanted to use the word "segments" (as they did in Claim 20), they did so. The Court construes "variable region" to have meaning rather than being a synonym for individual V, D, or J gene segments.

Support for this construction is found throughout the Specification. The Specification describes obtaining the human DNA as contiguous human genomic DNA obtained from BACs that span the entire VDJ region of the human heavy chain locus. ('018 Patent, 22: 5-15, "Large insert (BAC) clones spanning the entire VDJ region of the human heavy chain locus are isolated. . .") Figure 4A similarly refers to DNA swaths including all of the V, D and J segments.

Clynes agrees that the genomic DNA must be contiguous and he relates to the point of the invention: the use LTVECs, which permit targeted insertion of a

large swath of cloned human DNA, had not previously been possible. (Clynes Decl. ¶ 95.) The invention obviates the need to produce a genetically modified mouse by using smaller and restructured fragments of variable gene segments such as in Fig. L. (Id.) This benefit is demonstrated through the initial step of obtaining "Large Genomic DNA Clone Containing the Gene(s) or Chromosomal Locus (Loci) of Interest." ('018 Patent, 11:15-16.) As Clynes explained at the hearing, "the patentees wished to take the entire human immunoglobulin locus without any modification and drop it into the mouse genome." (Transc. 132:5-7) (emphasis added).

In addition, the inventors distinguished the "variable region gene segments" made by the claimed method from one using a minilocus: "The VelocImmune technology . . . encompasses a method of generating a high specificity fully human antibody to a select antigen . . . In an alternative approach, others have utilized a 'minilocus' approach in which an exogenous Ig locus is mimicked through inclusion of individual genes from the Ig locus. . ." (Id. ¶¶ 125, 128 (emphasis added)); see also Clynes Op. Decl. Ex. 31, '103 Patent, 10:42-45, 10:60-63.) Clynes also refers to a variety of Regeneron internal documents to show that at the time of the invention, the inventors did not possess an invention covering insertion of individual V, D and J segments. (Clynes Decl. ¶¶ 121-124.)

C. "inserted"

Merus asserts that the term "inserted" should be construed as "One step addition of DNA, without replacing or deleting any native DNA as a result of the

addition." (JCC at 2.) Regeneron asserts that this term requires no construction. (Ravetch Decl. ¶ 110.) With that said, Regeneron also asserts that the term "inserted" may implicitly include a "deletion" of a DNA fragment or the "replacement" of a host DNA fragment with a fragment DNA sequence. The Court agrees with Merus's construction.

Regeneron's broad construction is inconsistent with the ordinary meaning of the term "inserted." To "insert" something requires but a single step. (Clynes Decl. ¶ 140.) In addition, differences between Claim 1 and Claim 11 support the term "insertion" as equivalent to "placement of a DNA fragment in" – and not "placement of a DNA fragment in, subsequent to or preceding the deletion or replacement of . . .": Claim 1 allows only for insertion and Claim 11 allows for insertion, deletion or replacement.

In addition, the Specification supports a distinction between the single insertion step and a multi-step process. When different steps were involved, they were specifically called out: "The region to be modified and replaced using bacterial homologous recombination can range from zero nucleotides in length (creating an insertion into the original locus) to many tens of kilobases (creating a deletion and/or replacement of the original locus)." ('018 Patent, 12:14-18, Clynes Decl. ¶ 141.)

The Specification also refers to other instances in which insertions, deletions and replacement or substitution are called out separately: "'Gene targeting' is the modification of an endogenous chromosomal locus by the insertion into, deletion of,

or replacement of the endogenous sequence via homologous recombination using a targeting vector." ('018 Patent, 9:12-15, Clynes Decl. ¶ 143.) And "[t]his modification of allele (MOA) includes, but is not limited to, deletions, substitutions, or insertions of as little as a single nucleotide or deletions of many kilobases spanning a gene(s) or chromosomal loci of interest, as well as any all possible modifications between these two extremes." ('018 Patent, 9:45-50.) (See also '018 Patent, 3:40-48, 12:14-18.)

The prosecution history of the '018 Patent further supports the Court's construction. (See, e.g., Clynes Decl. ¶ 144.) For example, applicants in the '234 application in 2000 distinguished between deletion, alteration, insertion, and replacement. The method of Claim 1 distinguished between "insertion of a new coding sequence, gene segment, or regulatory element; creation of a conditional allele; or replacement of a coding sequence or gene segment from one species." (Id.) (emphasis added).

Clynes stated that as of 2001, skilled artisans distinguished between three types of modifications by homologous recombination: deletion, insertion and replacement. (Clynes Decl. ¶¶ 51, 142.) His review of the '018 Specification was consistent with the recognition of this distinction. (Id. ¶ 53) ('018 Patent, 9:12-15; 9:40-50). He stated that textbooks and basic dictionaries of biological terms also distinguished between these terms. (Clynes Decl. ¶ 53.)

D. "at"

Merus asserts that term "at" should be construed as "Into the locus, as opposed to near the locus, by the locus or around the locus." (JCC at 2.) Regeneron asserts that this term requires no construction. The issue between the parties again concerns scope: the more leeway as to the word "at", the broader the scope. The Court agrees with Merus's proposed construction.

The term "at" is used in the final phrase of Claim 11: "wherein the mouse constant region is at an endogenous mouse immunoglobulin locus." (See Clynes Decl. ¶ 147.) According to Clynes, "[g]iven that the mouse constant region exists within the locus, it is clear that is what the patentees intended by the use of the word "at". (Id.) (emphasis added). Regeneron's own expert, Ravetch, concedes that the term "at" is equivalent to the term "within". The term "at" therefore defines a boundary as "within the bounds of the locus". (Id. ¶ 149; Ravetch Op. Decl. ¶ 114; Reply Decl. ¶ 145.)

The prosecution history of the '018 Patent uses "at" and "in" the locus interchangeably: "None of the cited paragraphs [in the prior art] suggest or even hint at placing unrearranged human immunoglobulin gone segments at an endogenous mouse locus, much less a functional endogenous mouse locus. . . . There is absolutely no hint or suggestion in Lonberg to employ a functional endogenous mouse locus having inserted unrearranged human immunoglobulin variable region gene segments in the functional locus." (Clynes Decl. ¶ 148, citing Ex. 16, '176 Appl., January 11, 2013 Reply to Final Office Action, at 5-6.)

Figure 4B of the '018 Patent shows the constant region in the locus.

Nothing in the intrinsic evidence suggests a construction of the word "at" as "near", "around" or "by" the locus. There is not, for instance, any description of insertion near to or in general proximity of the locus of interest.

E. "endogenous mouse immunoglobulin locus"

Merus asserts that the term "endogenous mouse immunoglobulin locus" is indefinite. (JCC at 2.) It argues that the size, sequence and borders of the immunoglobulin locus was undefined the time the application was filed on February 16, 2001. (Clynes Decl. ¶ 150.) According to Merus, the intrinsic evidence provides no clarity. Regeneron argues that this term has sufficient definition and in fact requires no construction at all. (Ravetch Decl. ¶¶ 110-114.) The Court agrees with Merus that there is clear and convincing evidence that as of 2001 the metes and bounds of the locus were not identified with reasonable certainty; the scope of the term also lacks reasonable certainty and is therefore indefinite. Put otherwise, if one skilled in the art did not know with reasonable certainty where the 5-prime of the immunoglobulin locus was, the insertion of the genomic DNA segment might not fall within the locus at all – defeating the point of the invention. Lack of boundaries is particularly important when comparing prior art methods of random integration with the advance that the LTVEC method is supposed to bring: targeted genetic modification. In such context, being "in the vicinity" but not actually "in the locus" is not enough and does not reflect the invention: without adequate

information as to the 5-prime, one skilled in the art could not practice the invention or be certain that he was not infringing it.

The endogenous mouse immunoglobulin locus is the chromosomal location where the DNA that regulates and encodes the heavy chain and two light chains are present. (Clynes Decl. ¶ 151.) The Specification never uses the term "endogenous mouse immunoglobulin locus" and never informs the reader how to find the immunoglobulin locus. It mentions the use of "structural or functional data" to select "a" locus ('018 Patent, 11:17-22, "[a] gene(s) or locus (loci) of interest can be selected based on specific criteria, such as detailed structural or functional data, or it can be selected in the absence of such detailed information as potential genes or gene fragments become predicted through the efforts of the various genomic sequencing projects . . ."), but provides no specific data for locating the "endogenous mouse immunoglobulin locus," nor does it suggest that genomic sequencing has predicted its location. (Clynes Decl. ¶ 155.) In particular, the 3' and 5' borders are not provided in the Specification and the number of variable region gene segments are not provided.

The lack of information as to the location of the locus reflects the absence of such information in 2001. The record before the Court reveals that, as of 2001, the boundaries of that locus were not known. In terms of the regulatory regions, there is limited disclosure for the 3' and none for the 5'. Literature demonstrates that in 2001 the 5' border was not known. (See Clynes Op. Decl., Ex. 5, 46, 47, 50; Ravetch Reply Decl., Ex. 41.) For instance, in 2006 – five years after the Application was

filed – Pawlitzsky et al. stated that "the 5' border of IgH and its flanking region have not been characterized." (Clynes Op. Decl., Ex. 46.) And in 2006, Johnston et al. stated, "The mechanisms that regulate variable (V) gene selection during the development of the mouse IgH repertoire are not fully understood, due in part to the absence of the complete locus sequence." (Clynes Op. Decl., Ex. 47.) As late as 2011, Ebert et al. wrote, "In contrast, regulatory elements other than the VH gene promoters are not yet known . . ." (Clynes Op. Decl., Ex. 50.) Regeneron's internal documents suggest that the inventors did not in fact know the length of the locus. (Clynes Decl. ¶ 43, Ex. 51, Lab Notebook of Dr. Stevens, June 20, 2001, "the boundaries for the endogenous mouse immunoglobulin loci were not known in 2001, though it was generally known that they were located somewhere within chromosomes 12 (heavy), 6 (kappa) and 16 (lambda)".) Ravetch concedes that the size of the locus was unknown. His shifting positions reflect the general uncertainty: his opening declaration referred to 2.3 megabases, but that number was changed to 2.741 megabases in his deposition. In 2014, Murphy et al. referred to it as 2.6 megabases.[19] (Ravetch Depo. at 265-66, "Q: why do you think the '018 inventors directed people to use the SEQ ID NO. 5-6, which have nothing to do with the endogenous mouse immunoglobulin locus, to replace the locus? . . . A: . . . My interpretation is it shouldn't be there.") He then testified that the correct SEQ ID that one would use to locate the homology arms to target the mouse immunoglobulin locus was not provided for in the patent. (Id. at 264-65.) Ravetch

[19] At his deposition in this matter, Ravetch testified that he believes that the 1 megabase size cited in the Specification was a typographical error. (Ravetch Depo., at 223).

also testified that certain functions involved in Ig locus regulation were unknown at the time. (Id. at 276-77.)

As for locus size, Figures 4A-4D cite to SEQ ID No: 5 and 6, which concern "OCR 10", which has no relation to the mouse immunoglobulin locus. ('018 Patent, 8:32-35) (Transc. 77:10-14, 78:13-15). At his deposition, Ravetch conceded this point. The locus length is described as approximately 1 megabase ('018 Patent, Figure 4A-4D); however, the information the Specification provides is simply wrong. (Ravetch Depo., at 223.) Other literature refers to the locus as at least twice that length; the prosecution history refers to the length as between 1 megabase and 3 megabases; Regeneron's "VelocImmune" mouse, which it asserted was the commercial embodiment of the invention, references the DNA insert into a region of 3 megabases. (VelcoImmune Exhibit ('176 Application)) (Clynes Decl. ¶¶ 155, 159, 166; Transc. 136:3-15). Ravetch conceded that as of the date of the invention, the 5' region of the heavy chain locus had not yet been physically mapped but that it was known that a V gene segment from the J558 V gene segment family was at the 5' end of the locus. (Ravetch Reply Decl. ¶ 139; Transc. 137:2-10.)

To add to the ambiguity, one skilled in the art attempting to practice (or avoid) the invention in the '018 Patent also lacks information as to the strain of mouse to which the immunoglobulin locus related. There is significant diversity in strains of mice and diversity in the IgH locus between different strains. Without knowing the particular strain of mouse the inventors used, one skilled in the art could not know the metes and bounds of the invention. (See Clynes Decl. ¶¶ 33, 179;

Clynes Opp. Decl. Ex. 52, referring to the European Opposition against EP 1360287, and Regeneron's July 16, 2014 response to the oppositions, Statement of Craig H. Bassing, Ph.D. (Ex. D. 78) at ¶18.) Ravetch conceded that there are strains of mice the genome of which have likely not yet been characterized. (Ravetch Depo., at 270).[20]

The Supreme Court has set forth the standard for indefiniteness as an instance in which a claim, "read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." Nautilus, 134 S.Ct. at 2124. The term "endogenous mouse immunoglobulin locus" was not defined in 2001. One would have had to guess and be lucky to get it right. The "reasonable certainty" required by the Supreme Court is lacking. [21]

F. "linked" and "operably linked"[22]

Merus asserts that the term "linked" should be construed as "covalently bonded", and that the term "operably linked" should be construed as "covalently bonded such that the rearranged human variable region causes the expression of the mouse constant region gene." (JCC at 2, 3; Clynes Decl. ¶ 182.) Regeneron

[20] The Specification makes it clear that both the regulatory and coding segments of the locus were at issue. See Figure 4B; see also Ravetch Depo., at 241-42.)

[21] Regeneron argues that questions of indefiniteness should await a later stage of the proceedings – and not be resolved as a part of claim construction. That argument, however, asks this Court to either arrive at a construction for a term which is indefinite – or to ignore its responsibilities during claim construction. It will do neither. If during claim construction, it becomes clear that a claim cannot in fact be construed due to indefiniteness, there is no legal principle for the Court to withhold its determination on that issue. See, e.g., Teva Pharm USA, Inc. v. Sandoz, Inc., 723 F.3d 1363, 1367-69 (Fed. Cir. 2013).

[22] These terms are found in Claims 8, 11-19.

asserts that this terms requires no construction. (Ravetch Decl. ¶ 115.) The issue concerns scope: Merus arguing for narrower scope and Regeneron broader. The Court agrees with Merus's proposed construction.

Linked nucleotide bases comprise a DNA sequence. (Clynes Decl. ¶ 183.) Nucleotide bases are connected to each other by a chain of covalent bonds to form a DNA sequence. (Id.) A complementary sequence of DNA is linked by hydrogen bonds; the interaction between the two sequences gives DNA its double-helix shape. (Id.) Every nucleotide on a given sequence is linked to other nucleotides via a phosphate backbone and linked to the complementary strand of DNA via hydrogen bonds. (Id. ¶ 184.) Thus, "linked" has several potential meanings to one skilled in the art:

- covalent bonds linking a DNA sequence
- hydrogen bonds linking one strand to its complimentary strand
- linkage of one nucleotide base to another
- linkage of nucleotide bases as links of a chain

(Id.) The Patent reads:

> Claim 8: The mouse of claim 1, wherein rearrangement of the human variable gene segments in the mouse results in a variable region that comprises a rearranged human variable region gene **linked** to a mouse constant region gene.
>
> Claim 11: A genetically modified mouse, comprising in its germline human unrearrangcd variable region gene segments **linked** to a mouse constant region gene, wherein the mouse lacks a human constant region gene, and wherein the mouse constant region gene is at an endogenous mouse immunoglobulin locus.

> Claim 18: The mouse of claim 11, wherein rearrangement of the human variable gene segments in the mouse results in a variable region that comprises a rearranged human variable region gene **operably linked** to a mouse constant region gene.

('018 Patent, 29:45-48, 29:54-59, 29:30:35-38.) According to Clynes, one of ordinary skill in the art is 2001 would read the claims here against the Specification as using the word "linked" to mean that covalent bonds exist between and among nucleotides in a given sequences. (Clynes Decl. ¶ 185.) Thus, Claims 8 and 11 require that the human variable region gene be covalently bonded to the mouse constant region gene (versus some other form of linkage).

The term "operably linked", as used in Claim 18, includes a limitation ("operably") and therefore must be narrower than "linked" generally. This is based on the legal principles referred to above that courts should construe claims so as to be valid, see Biogen, 318 F.3d at 1140, and give meaning to each term, see Cohesive Techs., Inc. v. Waters Corp., 543 F.3d 1351, 1368 (Fed. Cir. 2008). The term "operably linked" appears in the Specification in the context of a preferred embodiment in Claim 18: "a transgenic mouse having a genome comprising entirely human heavy and light chain variable region loci **operably linked** to entirely endogenous mouse constant region loci such that the mouse produces a serum containing an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation." ('018 Patent, 7:24-30.)

In the prosecution history, the inventor states: "'operably linked' implies that (transcriptional) activity of the gene loci is linked. The term 'operably linked' is commonly used when refers to the linkage between a promoter and a gene as the

promoter directs transcription of the gene . . .” (Clynes Op. Decl., Ex. 53, Feb. 27, 2006 Non-Final Office Action, at 12.)

Based on the intrinsic and extrinsic evidence, “operably linked” indicates a functional relationship between the “rearranged human variable region gene” and a “mouse constant region”. (Clynes Decl. ¶ 187.)

G. “does not comprise a human immunoglobulin constant gene” and “lacks a human constant region gene”[23]

Merus asserts that both of these terms should be construed as “The mouse lacks DNA that regulates or encodes a constant region gene that originates from a human (i.e., genomic)”. (JCC at 3.) Merus further argues that the term “a constant region gene” means DNA that regulates and encodes a constant region. Regeneron asserts that this claim does not require construction. (Ravetch Decl. ¶¶ 119-121.) The dispute here generally (but not entirely) mirrors that discussed above in connection with the term “human unrearranged variable region gene segments”. (Clynes Decl. ¶ 135.) Here, however, instead of requiring use of cloned genomic DNA that originates from a human, these claims require its absence. (Id.)

There is no definition or description of this term in the Specification or prosecution history. Plaintiff has not provided any way to decide whether a sequence of DNA can be considered “human” based on sequence similarity.

One question is whether what must be lacking or absent is a human constant region gene or whether it can be synthetic but have a sequence found in humans.

[23] These terms are found in dependent Claim 10 (“The mouse of claim 1, wherein the mouse does not comprise a human immunoglobulin constant gene”), independent Claim 11 (“lacks a constant region gene”) and dependent Claims 12-19.

The use and import of the term "human" is, however, different in these claims from that in, for instance, Claim 1. In Claim 1, the human DNA sequence at issue is inserted using a LTVEC. The size limitations of DNA sequences in 2001 are one basis of the Court's determination that human means not synthetic in that context. As used in these claims here, however, the size of the sequence is irrelevant as it must be absent. Thus, this rationale is not equivalent between the terms. The Court finds no reason why the absence of the human DNA sequence cannot be both the absence of both human and synthetic (in human sequence) DNA.

It is true that terms should generally be construed consistently across claims. See Southwall Techs., 54 F.3d at 1579; Rexnord Corp. v. Laitram Corp., 274 F.3d 1336, 1342 (Fed. Cir. 2001). However, that principle gives way when logic and particular context dictate otherwise. See Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1327-29 (Fed. Cir. 2006) (construing the claim term "gap" as having different meanings in different claims based on those claims' different geometrical contexts); Epcon Gas Sys., Inc. v. Bauer Compressors, Inc., 279 F.3d 1022, 1030-31 (Fed. Cir. 2002) (interpreting "substantially" in two different ways where term was used in "two contexts with a subtle but significant difference").

The Court agrees, however, that what must be lacking is the entire, contiguous region of the constant gene. In other words, if a human or synthetic constant gene segment is present, that is not inconsistent with these claims. (See

discussion of "regions" above). Thus, the Court here interprets "region" as it did above as contiguous (V, D and J) versus as segments.

Accordingly, the Court constues this term as "The Mouse lacks DNA that regulates or encodes a constant region gene that originates from a human or is in human sequence."

## V. CONCLUSION

The Court's determinations as to claim construction are as set forth above.

SO ORDERED.

Dated: New York, New York
November 21, 2014

KATHERINE B. FORREST
United States District Judge