UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

NOVARTIS VACCINES AND DIAGNOSTICS, INC., NOVARTIS PHARMA AG, and GRIFOLS WORLDWIDE OPERATIONS LIMITED,	:	18cv2434(DLC)
Plaintiffs,	:	OPINION AND ORDER
-v-	:	
REGENERON PHARMACEUTICALS, INC.,	:	
Defendant.	:	

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DENISE COTE, District Judge:

Novartis Vaccines and Diagnostics, Inc., Novartis Pharma AG, and Grifols Worldwide Operations Limited (together, "Novartis") commenced this action on March 19, 2018, against Regeneron Pharmaceuticals, Inc. ("Regeneron"), alleging infringement of United States Patent No. 5,688,688 (the "'688 Patent") entitled "Vector for Expression of a Polypeptide in a Mammalian Cell." This lawsuit is brought over three years after the expiration of the '688 Patent and almost seven years after the accused Regeneron products first entered the market.

The '688 Patent contains 24 claims and describes a biotechnology tool that allows researchers to modify cells to produce a desired protein by delivering foreign DNA into host cells. Pursuant to Markman v. Westview Instruments, Inc., 517 U.S. 370 (1996), the parties have presented their proposed constructions of five sets of the '688 Patent's terms. This Opinion construes the disputed terms. It adopts Regeneron's construction of the first two terms and Novartis's construction of the third and fourth terms. The remaining term requires no construction.

Background

The '688 Patent describes a bioengineering process for introducing foreign DNA into a host cell. The basic principles of molecular biology and genetic engineering that form the basis of the technology are not in dispute.[1] Before describing the '688 Patent, certain scientific principles relevant to the claim construction issues addressed in this Opinion are summarized here.

The Science of Vector Biotechnology

Deoxyribonucleic acid ("DNA") carries the genetic material for living organisms. DNA is made of sequences of four nucleotides (adenine, thymine, cytosine, and guanine).[2] Two long complementary strands of nucleotides are attached together and coil around each other, forming a double helix. One end of each strand is called the 5-prime (5') or "upstream" end, and the

[1] On September 24, 2018, both parties submitted declarations from retained experts presenting the scientific concepts relevant to the '688 Patent. The technical principles described in this Opinion are derived from these declarations and, to a lesser extent, from the parties' additional expert declarations submitted with their claim construction briefs.

[2] Each nucleotide pairs with another. For instance, adenine pairs with thymine. In ribonucleic acid ("RNA"), single stranded copies of DNA discussed in more detail below, the nucleotide uracil substitutes for thymine and pairs with adenine.

other is called the 3-prime (3') or "downstream" end. The two complementary strands run in opposite directions.

A gene is a unit of DNA; it is made up of a unique sequence of nucleotides; it is the basic unit of heredity. Through the genes, the order of nucleotides within DNA provides the information for building and maintaining an organism. In mammalian cells, strands of DNA composed of millions of nucleotides are packaged into thread-like structures within a cell's nucleus called chromosomes.

Proteins, or polypeptides, exist in every cell and perform a wide range of cellular tasks, including catalyzing chemical reactions, serving as antibodies, and performing tasks necessary for DNA replication. Many diseases are caused either by a cell's failure to synthesize a particular protein or by its failure to do so correctly. Biotechnology companies use proteins to detect disease and for therapeutic purposes. Proteins also play a role in the production of more protein, which is called protein expression. Proteins are made up of sequences of 20 different amino acids, which are attached together. A sequence of three nucleotides, referred to as a codon, codes for a specific amino acid.

Proteins are created and expressed through processes known as "transcription" and "translation." DNA within a cell's

nucleus is transcribed or copied onto a template, known as ribonucleic acid (“RNA”) or messenger RNA (“mRNA”), which then leaves the cell's nucleus, where it is translated or read by cellular machinery to produce a protein. A sequence of codons produces a particular order of amino acids, which are assembled to create a particular protein.

Regulatory DNA sequences send signals that initiate and affect transcription. A “promoter” region of DNA is a segment of DNA that signals where transcription starts. A “transcription initiation site” is the particular nucleotide where transcription begins. The promoter region is found near the front of the transcription initiation site and, diagramatically, is to the left (or "upstream” or “5’” direction) of the DNA sequence that is to be transcribed. An “enhancer” is a regulatory DNA sequence that influences the rate at which DNA is transcribed.

Nucleotides to the right of the transcription initiation site are described as located downstream, or in the 3’ direction, since transcription occurs in the 5' to 3' direction, copying a region of DNA until a polyadenylation signal occurs. This signal indicates where the transcription should end.

When RNA is initially transcribed from DNA it is known as precursor RNA. To be translated into protein, the precursor RNA

must be spliced to create mature RNA. An "intron" is a DNA sequence that does not code for proteins. It may include regulatory DNA sequences. After being copied from the DNA strand to the precursor RNA strand, the intron is cut out prior to protein expression. An "exon" is a DNA sequence that does code for proteins, that is not spliced out of the RNA strand, and that appears in the mature RNA. This processing occurs within the cell's nucleus.

"Vectors" are DNA molecules that deliver foreign DNA, or DNA not naturally found in a host cell, into a host cell. The process of vector delivery into host cells is called "transfection." After transfection of DNA sequences that code for proteins, the host cell may be able to produce the foreign protein encoded by the foreign DNA. The process of producing foreign proteins in host cells is known as "host cell expression."

The most commonly used vectors are plasmids. Plasmids are circular strands of DNA made up of a few thousand base pairs of nucleotides (a relatively small amount for DNA) that are found in some bacteria and exist apart from the bacteria's chromosomes.

Modern biotechnology has succeeded in inserting genes into plasmids. Enzymes known as restriction endonucleases cut open a

plasmid at a particular location; new DNA is inserted; and the plasmid is closed through a process known as ligation. This creates recombinant DNA. Recombinant DNA that is transfected or delivered into the host cell may be able, as noted above, to produce a foreign protein within the host cell.

Vectors can contain regulatory DNA sequences as well. These sequences send signals that can affect cell processes, such as the regulation of transcription or translation. The regulatory sequences added to a vector are often taken from mammalian viruses. Scientists are able to insert promoter, enhancer, and intron sequences from a mammalian virus into a vector. One source of regulatory DNA for vectors is the monkey or simian virus SV40; another is the human cytomegalovirus ("HCMV"). The '688 Patent describes a vector that includes both SV40 and HCMV DNA.

A cell replicates or copies itself in a process known as cell division. A parent cell divides into two daughter cells, which become parent cells in turn. Through this process a host cell's chromosomal DNA is replicated from generation to generation of cells. When bacteria cells divide, they replicate plasmids present in the parent cell in addition to the cell's chromosomal DNA. This is not the case in mammalian cell division.

When foreign DNA is transfected into a mammalian host cell through a vector, it can, in some cases, integrate into the host cell's chromosomes. If the foreign DNA integrates with the host cell's chromosomes, the foreign DNA will then be passed down from generation to generation when the cell divides. This process, in which the host cell successfully integrates the foreign DNA coding for a protein, allowing future generations of the cell to continue to express this protein, is known as stable expression.

A vector may also express the protein within the host cell without the foreign DNA being integrated into the host cell's chromosomes. If the foreign DNA transfected into the host cell expresses the protein encoded in the foreign DNA within the cell without integration into the host cell's chromosomes, this is known as transient expression. Transient expression occurs when the vector replicates itself within the host cell, a process which may occur rapidly.[3] Eventually the daughter cells created through cell division will no longer contain the vector and no daughter cell will produce the protein of interest.

Most cells have limited life spans outside their natural environment. Certain mammalian cells are immortal in that they

[3] If a vector is transfected into a host cell where it cannot replicate, it may still briefly express the protein encoded in the vector.

are able to exist in cultures and divide and grow indefinitely. One type of immortal cell line useful in the biotechnology industry is the Chinese Hamster Ovary ("CHO") cell line. The two Regeneron products at issue in this lawsuit, Eylea and Zaltrap, both use a recombinant protein called aflibercept produced through a stable expression system in a CHO cell line. Eylea is used to treat Neovascular (Wet) Age-Related Macular Degeneration ("AMD"), Macular Edema Following Retinal Vein Occlusion ("RVO"), Diabetic Macular Edema ("DME"), and Diabetic Retinopathy ("DR") in patients with DME; Zaltrap is used to treat metastatic colorectal cancer.

The '688 Patent

As already noted, the title of the '688 Patent is "Vector for expression of a polypeptide in a mammalian cell". In other words, the '688 Patent describes a recombinant DNA technology used to express proteins in mammalian host cells. The '688 Patent contains 24 claims and was issued on November 18, 1997.

The specification emphasizes the use of the claimed invention in the production of recombinant Human Immunodeficiency Virus ("HIV") proteins that would be useful in efforts to diagnose and create a vaccine for HIV. For example, the specification's "Technical Field" section describes the patent's invention as

> directed to nucleotide sequences, such as DNA, encoding human immunodeficiency virus ["HIV"] polypeptides, the use of such nucleotide sequences in diagnostic procedures and in the production of recombinant protein, as well as the use of such proteins in diagnostic, prophylactic, and therapeutic applications.

The '688 Patent specification includes 59 drawing sheets, containing 31 figures, many of which are multi-part figures.

The specification also contains a list of examples. Each example concerns HIV. The examples are broken into eight categories, one of which is "Expression of HIV Polypeptides in Mammalian Cells." One example within this category, titled "2.3.2. Expression of gp120env using CMV IE-1 promoter", is of particular importance. It consists of two paragraphs and refers to a single figure in the specification, Figure 29, which is reproduced below. It is the only example that includes a vector with an HCMV promoter.

Example 2.3.2 describes the insertion of a coding region for an HIV protein, the gp120 polypeptide, into a mammalian cell expression vector, called "plasmid pCMV6a," in order to effect expression of the gp120 polypeptide at an increased rate. Plasmid pCMV6a is described as

> a mammalian cell expression vector which contains the transcriptional regulatory region from human cytomegalovirus immediate early region, HCMV IE1. The plasmid contains the SV40 polyadenylation region derived from pSV7d . . . ; the SV40 origin of replication . . . ; and the HCMV IE1 promoter. . . . The HCMV IE1 promoter region contains the region

> encoding the first exon (5′ untranslated), the first intron and the start of the second exon. . . .

(Emphasis supplied.)

The parties agree that this is the only example of a vector that falls within the claims that is diagrammed and described in the specification. The pCMV6a plasmid is depicted in Figure 29 of the specification.

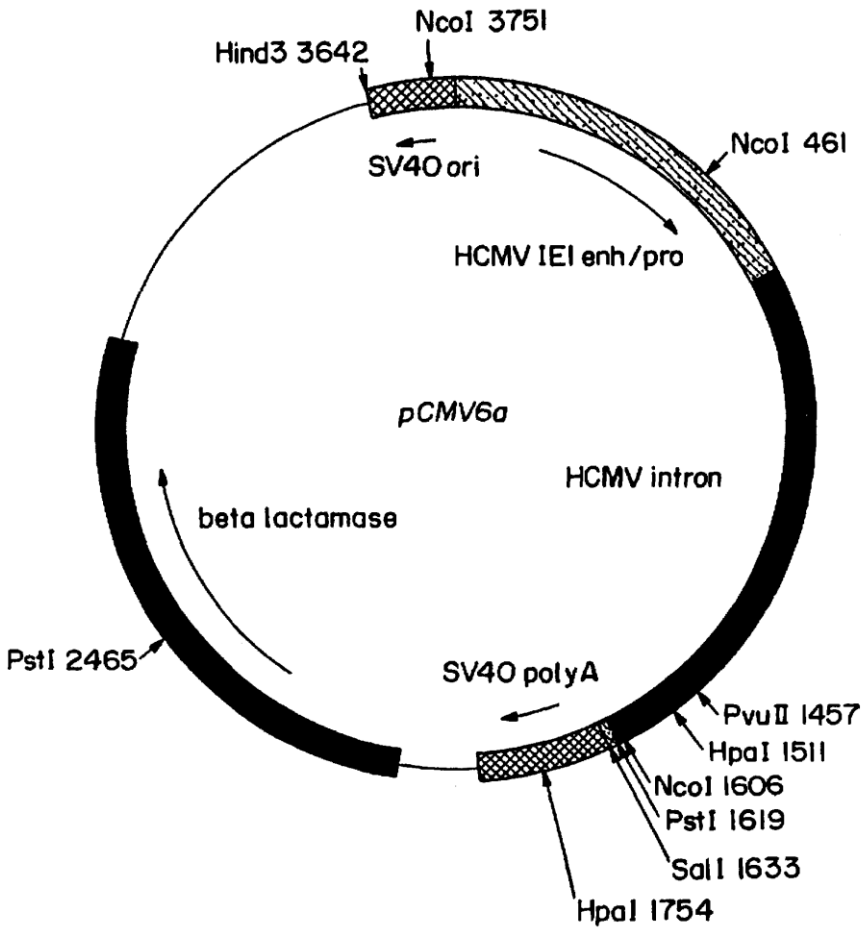


FIG. 29

Prosecution History of the '688 Patent

Novartis's predecessor in interest, Chiron Corporation ("Chiron"), filed the application for the '688 Patent on August 10, 1994. This application focused on the identification of DNA

sequences that could be obtained from HIV and products to express those sequences. It did not include claims to vectors. Between 1994 and 1997, the applicants overcame U.S. Patent and Trademark Office ("PTO") rejections to claims by amending the claims. The '688 Patent issued on November 18, 1997.

One amendment of significance to this litigation occurred in March of 1995. Chiron submitted amendments to the claims that added, for the first time, claims for a vector for expression of a polypeptide in a mammalian cell. It is the claims that Chiron added in 1995 that are at issue here, although as further amended in the ensuing years. Notably, Chiron continued to rely on the unrevised specification filed in August 1994 to support these additional claims.

The remarks accompanying the amendments describe these new claims as "better defin[ing] . . . preferred embodiments of the[] claimed invention" and point to Example 2.3.2 and Figure 29 as support for the new claims.[4] In a petition to correct inventorship that accompanied the amendment, the applicants explained that the amendments and related inventorship correction were necessary in order to emphasize the construction of the plasmid pCMV6, which is described and depicted in Example

[4] In its remarks in 1995, Chiron also pointed to the first paragraph of Example 2.2.2, which describes preparation of an HIV gene of interest.

2.3.2 and Figure 29, respectively. As Chiron explained, at the time the original application was filed the emphasis had been on "identification of DNA sequences obtainable from HIV and the products of expression of such sequences," and the significance of this plasmid had been overlooked.

An October 1996 Chiron submission to the PTO is also of significance for this litigation. In the October 1996 communication, Chiron sought reconsideration of an April 1996 PTO rejection of some of its claims, including those for the expression vector added in March of 1995. In explaining its rejection, the PTO stated that the "applicants ha[d] yet to provide evidence that the broadly claimed invention . . . has written description in the application as originally filed." Chiron took the position that this ground of rejection was improper because "applicants have described the CMV IE-1 expression vector pCMV6a . . . found in the specification as filed at pages 57 and 58 [describing Example 2.3.2] and in Figure 29." Chiron went on to assert that its description of the pCMV6a vector was "sufficient to support all of applicants [sic] pending claims."

On April 25, 2006, a third party requested reexamination of the '688 Patent. On November 21, 2006, the PTO confirmed the patentability of Claims 4, 5, and 9, but rejected the other 21

Claims. In 2007, Novartis submitted additional amendments to the '688 Patent. Following some back and forth with Novartis and Novartis's November 2007 appeal of outstanding PTO rejections, the PTO confirmed all 24 claims in the '688 Patent, as amended, on September 25, 2009, and a reexamination certificate for the '688 Patent was issued on December 22, 2009.

The Disputed Terms

The parties disagree whether the '688 Patent describes a broad platform for expressing proteins in host cells, as Novartis contends, or only describes the specific vector that is illustrated in Figure 29, as Regeneron asserts. Among other things, they are litigating whether the '688 Patent covers the expression of proteins through a stable expression system, that is, through the integration of the foreign DNA with the chromosomes in a host cell's nucleus.

The parties dispute the construction of five sets of terms. Novartis asserts that four of these five terms require no construction. These terms appear throughout the '688 Patent's 24 claims. The first set of disputed terms, "vector" or "vector for expression," appears in Claims 1, 4, 5, 9, 13-16, and 19-24. The second set of disputed terms, "SV40 origin of replication" or "origin of replication," appears in Claims 1, 4, 5, 8, 9, 13, 15, 20, and 22. The third set of disputed terms, "upstream SV40

origin of replication," "an origin of replication operably linked upstream," and "upstream origin of replication," appears in Claims 1, 4, 5, 9, 20, and 22. The fourth disputed term, "isolated nucleic acid molecule," appears in Claim 17. The fifth and final set of disputed terms, "the first HCMV IE1 intron" or "the first intron," appears in Claims 1, 4, 5, 9, 13, 15, and 17.

All 24 claims, with the disputed terms underlined, are set forth below. In this litigation, Novartis asserts Claims 1, 2, 4, 5, 6, 8, 9, 13, 14, and 17 against Regeneron.[5]

> 1. A non-human mammalian host cell expression system for improved expression comprising a non-human mammalian host cell with a vector for expression of a polypeptide in a mammalian cell comprising a first polynucleotide sequence that comprises:
> a) an upstream SV40 origin of replication;
> b) a downstream SV40 polyadenylation region;
> c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, and

[5] Because of its impact on the scope of discovery in this litigation, in a February 8, 2019 stipulated order, Novartis withdrew any claim of infringement involving the '688 Patent's Claims 3, 7, 10-12, 15, 16, and 18-24. Novartis had not proceeded on those claims in prior infringement litigation against third parties, and therefore, was able substantially to comply with its disclosure obligations in this lawsuit by limiting its claims to those it previously pursued.

d) the polypeptide coding sequence encoding a heterologous polypeptide operably linked downstream of the transcription regulatory region.

2. The non-human mammalian host cell expression system of claim 1, wherein the polynucleotide sequence further comprises a linker that comprises a restriction site for insertion of the coding region of a polypeptide.

3. The non-human mammalian host cell expression system of claim 2, wherein the restriction site is a SalI site.

4. A vector for expression of a polypeptide in a mammalian cell comprising a first polynucleotide sequence that comprises:
a) an upstream SV40 origin of replication;
b) a downstream SV40 polyadenylation region; and
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3′ end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, wherein the SV40 polyadenylation region comprises the SV40 polyadenylation sequence present in plasmid pSV7d.

5. A vector for expression of a polypeptide in a mammalian cell comprising a first poly-nucleotide sequence that comprises:
a) an upstream SV40 origin of replication;
b) a downstream SV40 polyadenylation region; and
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3′ end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, wherein the SV40 origin of replication comprises the

SV40 origin of replication sequence present in plasmid pSVT2.

6. The non-human mammalian host cell expression system of claim 1, further comprising a selectable marker.

7. The non-human mammalian host cell expression system of claim 5, wherein the selectable marker is a polynucleotide sequence that encodes ampicillin resistance.

8. The non-human mammalian host cell expression system of claim 1, further comprising a bacterial origin of replication.

9. A vector for expression of a polypeptide in a mammalian cell comprising a first poly-nucleotide sequence that comprises:
a) an upstream SV40 origin of replication;
b) a downstream SV40 polyadenylation region; and
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, wherein the polynucleotide sequence comprises the HCMV sequences present in plasmid pCMV6ARV120tpa, ATCC Accession No. 68249.

10. The non-human mammalian host cell expression system of claim 2, further comprising a coding region that encodes a polypeptide, inserted at the restriction site.

11. The non-human mammalian host cell expression system of claim 10, further comprising a region encoding a signal sequence effective in directing the secretion of the polypeptide encoded by the coding region, positioned upstream from the coding region.

12. The non-human mammalian host cell expression system of claim 11, wherein the signal sequence is

derived from the human tissue plasminogen activator leader sequence.

13. A vector produced by the process comprising linking together in an operative manner:
a) a SV40 origin of replication;
b) a SV40 polyadenylation region;
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein said regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream therefrom; and
d) the polypeptide coding sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide operably linked downstream of the transcription regulatory region.

14. The vector of claim 13, wherein the vector is arranged in the same manner as plasmid pCMV6a.

15. A method for producing a non-human mammalian cell comprising a vector for expression of a heterologous polypeptide in a mammalian cell comprising:
a) providing a first polynucleotide molecule that comprises a SV40 origin of replication;
b) providing a second polynucleotide molecule that comprises a SV40 polyadenylation region;
c) providing a third polynucleotide molecule that comprises a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein said regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter;
d) linking the SV40 origin of replication, the SV40 polyadenylation region and the regulatory region from HCMV IE1 together to form a vector that is capable of effecting the transcription of a polypeptide coding sequence operatively linked downstream from the regulatory region;
e) operatively linking a heterologous polypeptide coding sequence downstream from the regulatory region; and
f) introducing the vector into a non-human mammalian cell.

16. A method for producing the vector of claim 1, comprising introducing the vector into a host cell and allowing the host cell to generate a plurality of said vectors.

17. An isolated nucleic acid molecule comprising an enhanced promoter, wherein the enhanced promoter comprises the human cytomegalovirus immediate early region HCMV IE1 promoter and the first intron proximate to the 3' end of the HCMV IE1 promoter and wherein the enhanced promoter is operably linked to a nucleic acid sequence encoding a mammalian polypeptide or a heterologous mammalian virus polypeptide.

18. The nucleic acid molecule of claim 17, wherein the promoter region is derived from a subclone of human cytomegalovirus (Towne strain).

19. A vector for expression of a polypeptide in a mammalian cell, comprising the nucleic acid molecule of claims 17, wherein the nucleic acid molecule is capable of directing the transcription of a polypeptide coding sequence operably linked downstream of the nucleic acid molecule.

20. The vector of claim 19, further comprising an origin of replication operably linked upstream of the nucleic acid molecule.

21. The vector of claim 19, further comprising a polyadenylation region operably linked downstream of the nucleic acid molecule.

22. A vector for expression of a polypeptide in a mammalian cell, comprising:
a) an upstream origin of replication;
b) a downstream polyadenylation region; and
c) the nucleic acid molecule of claim 17 interposed between the origin of replication and the polyadenylation region, wherein the enhanced promoter region is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the promoter region.

23. A method for constructing the vector of claim 19, comprising operatively linking together the nucleic acid molecule and the polypeptide coding sequence.

> 24. A method for producing the vector constructed in claim 23, comprising introducing the vector into a host cell that is capable of replicating the vector and allowing the host cell to replicate the vector.

Discussion

"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." Aventis Pharm. Inc. v. Amino Chems. Ltd., 715 F.3d 1363, 1373 (Fed. Cir. 2013) (citation omitted). "When the parties raise an actual dispute regarding the proper scope of the[] claims, the court, not the jury, must resolve that dispute." 02 Micro Int'1 Ltd. v. Beyond Innovation Tech. Co., 521 F.3d 1351, 1360 (Fed. Cir. 2008).

In construing a patent claim, which is a question of law, courts "should look first to the intrinsic evidence of record, i.e., the patent itself, including the claims, the specification and, if in evidence, the prosecution history." Am. Calcar, Inc. v. Am. Honda Motor Co., Inc., 651 F.3d 1318, 1336 (Fed. Cir. 2011) (citation omitted). Courts, however, should not read meaning into claim language that is clear on its face. See Tate Access Floors, Inc. v. Interface Architectural Res., Inc.

expanded. See Terlep v. Brinkmann Corp., 418 F.3d 1379, 1382 (Fed. Cir. 2005).

Claim terms are generally given their "ordinary and customary meaning" as understood by a person of "ordinary skill in the art at the time of invention." Aylus Networks, Inc. v. Apple Inc., 856 F.3d 1353, 1358 (Fed. Cir. 2017) (citation omitted). The ordinary meaning of a claim term is its meaning "to the ordinary artisan after reading the entire patent." Id. (citation omitted).

If a claim term does not have an ordinary meaning, and its meaning is not clear from a plain reading of the claim, courts turn in particular to the specification to assist in claim construction. Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc., 711 F.3d 1348, 1361 (Fed. Cir. 2013). Through the specification, a patentee "can act as his own lexicographer to specifically define terms of a claim contrary to their ordinary meaning." Abraxis Bioscience, Inc. v. Mayne Pharma (USA) Inc., 467 F.3d 1370, 1376 (Fed. Cir. 2006) (citation omitted). "Usually, [the specification] is dispositive; it is the single best guide to the meaning of a disputed term." Power Integrations, 711 F.3d at 1361 (citation omitted). Since the purpose of the specification is "to teach and enable those of skill the art to make and use the

invention," it often provides "an example of how to practice the invention." Phillips v. AWH Corp., 415 F.3d 1303, 1323 (Fed. Cir. 2005). But, while courts use the specification "to interpret the meaning of a claim," they must "avoid the danger of reading limitations from the specification into the claim" itself. Id. Although the specification often describes specific embodiments of the invention, the Federal Circuit has repeatedly warned against confining the claims to those embodiments. Id.

The prosecution history may "inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution." Id. at 1317. Indeed, because the prosecution history includes the applicant's express representations made to the PTO examiner, it may be "of critical significance in determining the meaning of the claims." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir. 1996). "Any explanation, elaboration, or qualification presented by the inventor during patent examination is relevant" to claim construction. Fenner Investments, Ltd. v. Cellco P'ship, 778 F.3d 1320, 1323 (Fed. Cir. 2015). The prosecution history's instructive value is mitigated, however, by the fact that it "represents an ongoing negotiation between the PTO and the applicant ... [and] often

lacks the clarity of the specification." Phillips, 415 F.3d at 1317.

A court may also consider extrinsic evidence, such as dictionaries and treatises, but such extrinsic evidence is "generally of less significance than the intrinsic record." Takeda Pharma. Co. Ltd. v. Zydus Pharma. USA, Inc., 743 F.3d 1359, 1363 (Fed. Cir. 2014). If the meaning of the claim is clear from the intrinsic evidence alone, resort to extrinsic evidence is improper. Boss Control, Inc. v. Bombardier Inc., 410 F.3d 1372, 1377 (Fed. Cir. 2005).

35 U.S.C. § 112(b) requires that a patent specification "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor . . . regards as the invention." A patent that does not meet this requirement is said to be indefinite and is therefore invalid. Nautilus, Inc. v. Biosig Instruments, Inc., 572 U.S. 898, 901 (2014). A patent is invalid for indefiniteness "if its claims, 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." Id. Under Nautilus, the key question is whether the claims -- as opposed to particular claim terms -- inform a skilled reader with reasonable certainty about the scope of the

invention. Cox Commc'ns, Inc. v. Sprint Commc'n Co. LP, 838 F.3d 1224, 1231 (Fed. Cir. 2016) (citation omitted). Nevertheless, an indefiniteness analysis is "inextricably intertwined with claim construction" and training indefiniteness analysis on individual claim terms is a "helpful tool." Id. at 1232 (citation omitted). "Indeed, if a person of ordinary skill in the art cannot discern the scope of a claim with reasonable certainty, it may be because one or several claim terms cannot be reliably construed." Id.

"[A] court may not use the accused product or process as a form of extrinsic evidence to supply limitations for patent claim language." Wilson Sporting Goods Co. v. Hillerich & Bradsby Co., 442 F.3d 1322, 1331 (Fed. Cir. 2006). This rule, however, "does not forbid awareness of the accused product or process to supply the parameters and scope of the infringement analysis, including its claim construction component." Id.

Regeneron has proposed constructions of all five disputed terms.[6] Novartis puts forward a proposed construction purportedly reflecting the plain and ordinary meaning of "vector" and "vector for expression." Novartis asserts that construction of the four remaining terms is unnecessary. It

[6] Four of the five disputed terms comprise two or more phrases that the parties treat as substantially the same. For purposes of claim construction, these terms are construed together.

proposes in the alternative, however, a plain and ordinary meaning construction for each.

I. "vector"/"vector for expression"

Novartis proposes that the terms "vector" and "vector for expression" be afforded their plain and ordinary meaning, which Novartis asserts is "[a] DNA construct comprising transcriptional and translational initiation and termination regulatory signals and a sequence coding a polypeptide, wherein the regulatory signals are functional in a transformed or transfected host cell and effect expression of the polypeptide." Regeneron argues that these terms should be construed as "[a] DNA construct capable of introducing foreign DNA into a host cell for expression of that DNA." Regeneron is correct.

The claims, the specification, and the prosecution history indicate that the '688 Patent uses the terms vector and vector for expression to refer to a vector as that term is commonly understood by skilled artisans, that is, a DNA construct that is capable of introducing foreign DNA into a host cell so that the foreign DNA may be expressed within the cell. The use of this set of terms in the claims is illustrated by the following. Claim 1 describes a "vector for expression of a polypeptide in a mammalian cell." Claim 15 explains the "method for producing a non-human mammalian cell comprising a vector for expression,"

including "introducing the vector into a non-human mammalian host cell." Claims 16 and 24 describe "introducing the vector into a host cell" as a method for producing more of the vectors by, respectively, "allowing the host cell to generate a plurality of said vectors" and "allowing the host cell to replicate the vector."

The specification also describes the "vector [being] introduced into an appropriate host." For example, in the "Modes for Carrying Out the Invention" section, it explains that to "produce recombinant polypeptides, expression vectors will be employed. . . . The expression vector is introduced into an appropriate host where the regulatory signals are functional in the host."

Example 2.3.2 and Figure 29, the most significant example and figure in the specification, make clear that the claimed invention is a plasmid, which is the most commonly used vector for introducing foreign DNA into a mammalian host cell. Example 2.3.2 describes the creation of a plasmid which will transfect COS cells.[7] The invention is described as resulting in "a significant increase in expression" of a polypeptide in the host

[7] COS cells are monkey kidney cells.

cell. Figure 29 depicts a plasmid (to wit, pCMV6a), which is a vector for introducing foreign DNA into a host cell.

The prosecution history also reveals that the claimed invention is a plasmid. When it offered its 1995 amendment, Chiron explained that it had overlooked the importance of its original application's disclosure of the construction of plasmid pCMV6a and stated that the additional claims introduced in the amendment, which described this construction, represented its "preferred embodiment" of the patent's claims. In defending its patent, Chiron relied on Figure 29 and Example 2.3.2, which depict and describe a plasmid, as "sufficient" to support all of the patent's claims.

The parties agree that the terms "vector" and "vector for expression" refer to a DNA construct that can introduce foreign DNA into a host cell. Novartis complains, however, that Regeneron's construction will exclude "stably-integrated DNA vectors". That is true. The claims, specification, and prosecution history uniformly exclude a construction that would permit the term vector to refer to vector DNA that has been integrated into the host cell's chromosomes. Once the foreign DNA introduced through a vector into a host cell is successfully integrated into a host cell's chromosomes, that vector DNA is no longer a vector. While the construction of the term vector

adopted here may encompass vectors that result in either stable or transient expression of proteins in the host cell, the core feature of a vector is its ability to transfect the host cell. Typically, and as envisioned by the '688 Patent, a plasmid will serve as a vector to deliver foreign DNA into the host cell. Following transfection, vector DNA integrated into host cell chromosomes is not a vector or a vector for expression. It reflects a cellular change that resulted from use of a vector.

If it were appropriate to narrow the term vector to one associated with a single expression system, be it transient or stable, the evidence from the claims and specification (specifically, Example 2.3.2 and Figure 29) indicate that the '688 Patent was addressed to a vector that results in transient expression. There is no need, however, to narrow the definition of vector in this way. It is enough to define the essential feature of a vector as its ability to transfect a host and deliver foreign DNA into the host for expression.

In arguing for its preferred construction of the terms, Novartis does not point to the claims. Instead, it relies on a single declaration from the prosecution history and example 2.2.2 in the specification (not example 2.3.2). The declaration and example 2.2.2 refer to the use of CHO cells, which are used in the stable expression of proteins. During the reexamination

of the ‘688 Patent, a declarant for the inventors explained that during their research they had used COS and CHO cells as host cells to express proteins. Example 2.2.2 describes the expression of tPA/gp160, a gene, in both COS and CHO cells. It is the only example of a permanent cell line given in the ‘688 Patent and the example does not use the vector claimed in the ‘688 Patent. These references to research done during the creation of the invention are of limited assistance to Novartis for another reason as well. These references are entirely consistent with the construction adopted above. The two references describe using vectors, to wit plasmids, to create a permanent CHO cell line. They do not describe the permanent cell line, once created through the integration of vector DNA into the host cell’s chromosomal DNA, as containing vectors. Whether or not the inventors used a vector to create a permanent cell line in CHO cells in their research, a vector’s function and definition remains its ability to transfect a host cell in order to deliver foreign DNA that can be expressed in the host.

In a related argument, Novartis contends that the term vector should be construed to include vector DNA integrated into host cell chromosomes because the multiple references throughout the claims and specification to “mammalian host cell,” or “other mammalian host cell” indicate that the patentees contemplated introducing the claimed vector not just into COS cells, which

permit transient but not stable expression, but also into CHO cells, wherein integration of vector DNA into the cell's chromosomes is possible. The reference to mammalian host cells generally is too vague to bear the weight of Novartis's proposed construction. Example 2.3.2 refers specifically to COS cells, which are used for transient expression. Other mammalian cells also are used in transient expression; COS cells are not alone in allowing transient expression. In any event, even if it were possible to construe the '688 Patent as useful for stable expression, nothing in the claims, specification, or prosecution history indicates that the terms "vector" and "vector for expression" refer to vector DNA that has been integrated in a host-cell's chromosomal DNA through stable expression.

Novartis also appeals to what it describes as common sense. It implores rejection of Regeneron's proposed construction by pointing to the absurdity of describing a transfected vector as both "capable of introducing foreign DNA into host cells" and as capable of being replicated in the host cell.[8] Novartis emphasizes that once transfected, a vector would never be extracted from a host cell in order to be re-introduced into another host cell. This argument ignores the purpose of the

[8] While not discussed by Novartis, Claims 16 and 24 bring this supposed tension to the fore. They describe replication of vectors following transfection.

‘688 Patent, which describes a vector for expression of a polypeptide in a mammalian cell. The ‘688 Patent identifies the specific plasmid and the SV40 and HCMV regions that will be combined to create the invention’s vector for introducing the protein into the host cell. It explains that its invention results in improved expression of the foreign protein. Its focus is on the invention of a vector for transfection and improved expression. A skilled artisan would have understood the scientific processes at work and would have understood that improved expression of the protein, at least in transient expression, is achieved through replication of the plasmid within the host cell following transfection. There is no tension here.

The ‘688 Patent does not use the term “vector” to include a description of vector DNA integrated into a host cell’s chromosomal DNA. The terms “vector” and “vector for expression” are construed as “a DNA construct capable of introducing foreign DNA into a host cell for expression of that DNA.”

II. “SV40 origin of replication”/“origin of replication”

Novartis claims that no construction is required for the terms “SV40 origin of replication” and “origin of replication,” but alternatively, that they should be construed as “[a] region of DNA that originates from simian virus 40 and is a signal for

initiation of replication of DNA" or "[a] region of DNA that is a signal for initiation of replication of DNA." Regeneron asserts that these terms should be construed as "[a] region of [SV40] DNA that is directing replication of the vector in the host cell." The parties essentially dispute whether the term origin of replication should be construed to indicate only a structural component or also the component's functionality, that is, whether it is a site that directs replication. Consideration principally of the claims, but also of the specification and prosecution history indicate that the terms should be construed as Regeneron proposes.

Throughout the claims, the term "SV40 origin of replication" or "origin of replication" is listed as the first element of the claimed vector for expression of a polypeptide in a host cell. Claim 1 emphasizes that the claim is for a "system for improved expression." That improved system for expression is a vector that is comprised first of "an upstream SV40 origin of replication," and then additional downstream components. Claims 13 and 20 also refer to the origin of replication as linked in an "operative manner" or "operably linked" to other elements. Claim 13, for example, describes "A vector produced by the process comprising linking together in an operative

manner: a) a SV40 origin of replication" and the other core elements of the claimed vector.[9]

A skilled artisan would understand that the reference to the SV40 virus was relevant to the understanding of the vector's functionality in the host cell. It is undisputed that an SV40 origin of replication, which comes from a monkey or simian virus, is functional in certain primate cells, such as COS cells, and not in CHO cells. There is a species incompatibility problem that prevents SV40 from directing DNA replication in rodent cells, such as the CHO cells. The claimed invention, therefore, would only result in "improved expression" through incorporation of an SV40 origin of replication, as Claim 1 claims, if the SV40 origin of replication is functional in the host cell.

Examination of the specification reinforces a construction of these terms that includes not just the identification of their location on the vector but also a description of their capacity to function as part of the invention. Example 2.3.2 describes the plasmid at issue, pCMV6a, as containing an "SV40

[9] These other elements are: "b) a SV40 polyadenylation region; c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1 . . . and d) the polypeptide coding sequence encoding a mammalian polypeptide . . . ."

origin of replication." The example describes the use of pCMV6a as borne out of an "effort to improve the expression of [the gene] gp120 in COS and other mammalian cell types." It describes using the plasmid to transfect a COS cell, which resulted in a "significant increase in expression" of the sought-after protein. Figure 29 also identifies the plasmid pCMV6a as containing an upstream SV40 origin of replication and a downstream SV40 polyadenylation region.

The prosecution history of the '688 Patent further supports a construction of the term "origin of replication" to include functionality. In 1996, the PTO rejected a claim that described an origin of replication that is "homologous to a SV40 origin of replication sequence." According to the PTO, without the inventors explaining the meaning of "homologous" or "what elements of the recited polynucleotides are relevant to its function . . . one of skill might obtain a homologous sequence devoid of function." Chiron's subsequent amendment of its claims removed the term "homologous to" and described instead a vector "comprising the SV40 origin of replication."

Novartis opposes a construction of these terms that would require them to also function. It asserts that the terms refer simply to a region of DNA that is a structural component of the

plasmid. In making this assertion it relies principally on the following arguments.

First, Novartis points out that an SV40 origin of replication does not always function. Prior to transfection into the host cell, when the vector exists only in a test tube, the SV40 origin of replication is nonfunctional. This argument misconstrues the patent. The claims describe an expression system in a "host cell." The origin of replication's functionality is only necessary "in the host cell." There is no tension, therefore, between the SV40 origin of replication being non-functional outside a host cell and Regeneron's proposed construction of the claims, which requires it to be functional in a host cell.

Next, Novartis asserts that the specification contemplates use of CHO host cells, and therefore, must have contemplated an SV40 origin of replication that would be non-functional in certain host cells. There is no support for this construction in the claims. Indeed, the patent's emphasis on the invention of an improved expression system and on the SV40 origin of replication as a key component of the invention indicate otherwise. As described above, the specification's single example of stable expression in CHO cells did not involve either

the plasmid described in Example 2.3.2 or depicted in Figure 29 or an SV40 origin of replication.

In arguing that the specification supports its interpretation, Novartis points to language in example 2.3.2 that indicates that the vector would be used in COS "and other mammalian cell types". This language provides at best very weak support for the Novartis construction. Example 2.3.2 refers specifically to COS host cells, and there is no dispute that SV40 functions in some primate host cells other than COS cells.

Next, Novartis refers, unconvincingly, to a sentence in the background section of the specification which addresses the creation of recombinant polypeptides. The sentence explains that in a microorganism (i.e., not in a mammalian host cell) the vector for expression may differ from the cloning vector. There is reference to the possibility that the expression vector "may or may not include a replication system which is functional in the expression host."[10] This sentence is not included in example 2.3.2, the sole example that describes the claimed invention, and does not refer to either SV40 or the plasmid depicted in

[10] The sentence at issue reads: "For expression in microorganisms.[sic] the expression vector may differ from the cloning vector in having transcriptional and translational initiation and termination regulatory signal sequences and may or may not include a replication system which is functional in the expression host."

Figure 29. Moreover, this sentence says little more than the following: replication systems may not be a component of a vector. Here, the invention does include a replication system. It includes the SV40 origin of replication and claims an "improved" expression system in the host cells. It would be nonsensical for the inventors to insist throughout the claims on the inclusion of this particular origin of replication if it were not an essential feature of the invention's improved expression system.

Novartis also supports its argument that the SV40 origin of replication listed in the claims can be nonfunctional in some host cells by pointing to example 2.2.2, describing prior research in which a plasmid was used to transfect both COS cells and CHO cells. As already discussed, this example does not include reference to an SV40 origin of replication, or to the plasmid at issue in Figure 29 and discussed in Example 2.3.2.[11] The disclosure in the specification of research that created a stable CHO cell line through use of a vector for expression other than the one described in the claims and embodied in Figure 29 does not assist Novartis.

[11] Novartis states that this example describes an expression vector containing an SV40 origin of replication. The passage, however, refers to transfection of CHO cells using plasmids involving the SV40 early promoter, not the SV40 origin of replication.

In sum, Novartis's proposed construction is at odds with the plain language of its claims, whether those claims are read individually, read together, or read in context with the specification and prosecution history. Accordingly, the terms "SV40 origin of replication" and "origin of replication" are construed as "a region of [SV40] DNA that is directing replication of the vector in the host cell."

III. "upstream SV40 origin of replication"/"an origin of replication operably linked upstream"/"upstream origin of replication"

Novartis contends that no construction of the terms "upstream SV40 origin of replication," "an origin of replication operably linked upstream," and "upstream origin of replication" is required. Alternatively, Novartis contends they should be construed as "5' of the transcription regulatory region from human cytomegalovirus immediate early region hCMV IE1." Relying principally on Figure 29, Regeneron proposes that these terms be construed as "[a]n [SV40] origin of replication that is proximal to and 5' of the human cytomegalovirus immediate early region HCMV IE1 transcription start site, with no polypeptide coding sequence interposed." Novartis's proposed construction is correct; its construction avoids adding limitations not found in the claims.

Throughout the claims, "upstream" is used in conjunction with the directional terms "downstream" and "interposed between." For example, Claims 4, 5, and 9 describe a "vector for expression of a polypeptide in a mammalian cell comprising . . . an upstream SV40 origin of replication; . . . a downstream SV40 polyadenylation region; and . . . a transcription regulatory region from [HCMV IE1] . . . interposed between" the two. A skilled artisan would understand "upstream" to mean in the 5' direction, and, in the context of the rest of the claim language, would understand that the HCMV IE1 material was interposed between the SV40 origin of replication and the downstream SV40 polyadenylation region.[12]

This same orientation of the elements appears in the specification in Figure 29, which is referred to as depicting "[t]he map of pCMV6a" in Example 2.3.2. It should be noted as well, however, that Regeneron's proposed construction is a literal description of the plasmid shown in Figure 29, which is reproduced earlier in this Opinion. The figure places the three elements next to each other on the circular plasmid with no intervening elements or space appearing between them.

[12] As described above, during replication, DNA is transcribed from the upstream/5' to the downstream/3' direction.

The prosecution history indicates that the relative positions of the elements recited in the claims was important to the PTO. Directional cues were added to the claims in October 1995 after the PTO rejected previously applied-for claims "because the arrangement of the elements in relation to each other [was] unspecified." In its amendment responding to this rejection, Chiron explained that the addition of "upstream" and the other directional terms "recite[d] the relative arrangement of the elements in the polynucleotide sequence," and stated that support for this amendment can be found in Figure 29, which depicts the pCMV6a plasmid.

Regeneron's proposed construction would restrict the patent in at least two ways. It requires that the SV40 origin of replication be "proximal" to the HCMV IE1 region. It also provides that "no polypeptide coding sequence" is "interposed." The patent, however, provides instructions about the directional relationship and sequence of the elements in the vector. It does not eliminate the possibility of other material appearing between the three constituent elements. Regeneron's limitations are therefore rejected.

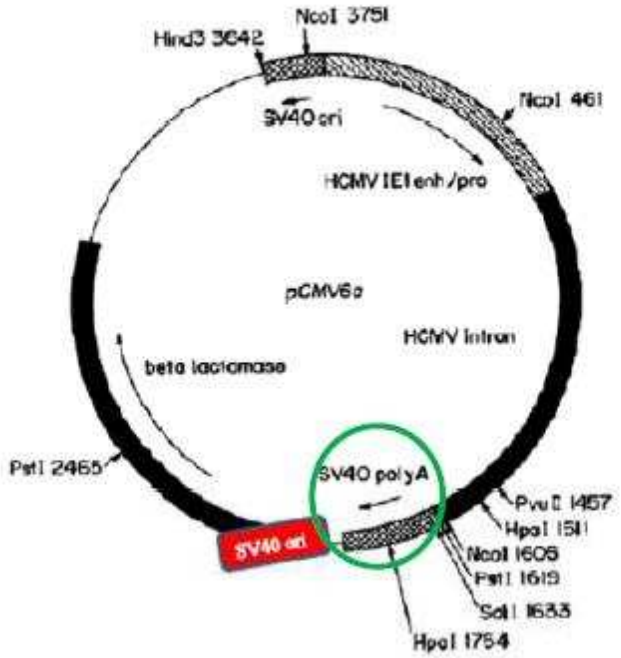
Regeneron argues that because Figure 29 is the sole embodiment of the invention, the construction of the disputed terms should include the limitations it suggests. Aside from

this figure, however, nothing in the '688 Patent indicates that the patentees intended to include the restrictions that Regeneron suggests. Moreover, Figure 29's inclusion of other elements on the plasmid not mentioned in example 2.3.2 or the claims, such as restriction enzyme sites and a beta lactamase gene, indicate that the inventors contemplated that their claimed expression vector could include elements not explicitly listed in the claims. Absent other support for these limitations, Regeneron's proposed restrictions fail.

Regeneron also argues that the patent is indefinite without the restrictions it suggests. Regeneron contends that, because of the circular shape of the plasmid in Figure 29, when a claim indicates upstream or 5' of the origin of replication it is indicating everything in the counterclockwise direction from the starting point. As one proceeds around the plasmid, this includes a point that is also "downstream" of the origin of replication. Regeneron asserts that its use of the word "proximal" in its proposed construction remedies this indefiniteness. Regeneron illustrates this indefiniteness with a hypothetical plasmid that includes an SV40 origin of replication located at approximately 6:30 on the circular plasmid and an HCMV IE1 transcription start site located at about 12:30 on the plasmid. In such a plasmid, Regeneron contends, the SV40 origin of replication could reasonably be

described as either "upstream" or "downstream" of the HCMV IE1 start site. It also argues that placement of the SV40 origin of replication upstream of another gene, which in its example is the beta lactamase gene, means that, while technically upstream of, it would no longer be linked to, the HCMV IE1 regulatory region.

Figure 29 (modified and circle added):



In the context of the entire set of claims, the use of "upstream" is not so ambiguous as to render the claims indefinite. While in a round structure, such as a plasmid, anything upstream could also technically be downstream, a

skilled artisan would reasonably understand that "upstream" refers to a direction, that is, 5' along a stretch of DNA or in the opposite direction of the direction of transcription. Reading the claims together, they describe the SV40 origin of replication as upstream from the SV40 polyadenylation region, with the HCMV IE1 interposed between them, such that transcription would move from the origin of replication to the HCMV interposed region and on to the polyadenylation region. The claims require that the arrangement result in improved expression of the foreign DNA through the operative linking of the designated elements. This is sufficiently definite.

Regeneron's proposed construction would improperly import limitations to the claims in the '688 Patent. Accordingly, "upstream SV40 origin of replication," "an origin of replication operably linked upstream," and "upstream origin of replication" are construed as "5' of the transcription regulatory region from human cytomegalovirus immediate early region hCMV IE1."

IV. "isolated nucleic acid"

Novartis argues that no construction of "isolated nucleic acid" is required and alternatively that it should be construed as "a segment of DNA nucleotides existing separate from other hCMV components normally associated with hCMV." Regeneron asserts that this term should be construed as "[a] purified

nucleic acid molecule free of cellular components including other nucleic acid molecules." Novartis's proposed alternative construction is correct.

Claim 17, the only claim in which word "isolated" is used, explains that the described "isolated nucleic acid molecule compris[es] an enhanced promoter" made up of the HCMV IE1 promoter and the "first intron proximate to the 3' end" of the promoter. It adds that the "enhanced promoter" is operably linked to other listed elements.

Subsequent claims incorporate claim 17 by reference. For example, Claim 19 describes a vector for expression of a polypeptide "comprising the nucleic acid molecule" of Claim 17 that is capable of directing transcription of a polypeptide coding sequence "operably linked" downstream. Claim 22 describes a vector for expression of a polypeptide comprising "an upstream origin of replication," "a downstream polyadenylation region," and "the nucleic acid molecule of Claim 17 interposed between" them.

The specification includes the term "isolated" throughout its text. Most often, this term is used to describe the process of extracting a particular sequence of DNA from the rest of its native DNA. For example, in describing how to obtain an "oligonucleotide probe," the specification explains that

> [v]iral RNA from HIV may be isolated from the supernatant of cells infected (e.g., HIV-1 or HIV-2) in culture and the high molecular weight materials precipitated and the DNA removed, for example employing DNASE. The residual RNA may then be divided into molecular weight fractions, where the fraction associated with the molecular weight of the retrovirus is isolated.

(Emphasis supplied.) Such descriptions demonstrate an understanding of "isolated" that entails separating sequences of nucleic acids from their native context.

The word "isolated" in Claim 17 should be construed to refer to a nucleic acid molecule that has been "isolated" or removed from its source DNA. Once removed from its native context it may be spliced into a new environment and "interposed between" two other nucleotide regions, as described in Claim 22.

Regeneron's proposed construction of the term "isolated nucleic acid" would essentially read claims, such as 19 and 22 that contemplate the "isolated nucleic acid" as linked to other DNA segments in the plasmid, out of the patent. It also fails to account for that portion of Claim 17 which explains that the isolated nucleic acid is "operably linked" to a nucleic acid sequence encoding a polypeptide.

According to Regeneron, the practical dispute between the parties' proposed constructions centers on whether vector DNA integrated into the chromosomes of a host cell could be considered "isolated" nucleic acid. Regeneron contends that

isolated DNA is the opposite of vector DNA in a cell's chromosome and that any construction of the term should make clear that an "isolated nucleic acid molecule" is separate from all other cellular components. Regeneron's focus is misplaced. The invention's use of the term isolated refers to the process through which the molecule was derived; it does not describe its functionality or physical connection to other molecules into which it is integrated either in the vector or after, potentially, its integration with a host cell's chromosomes.

The patent uses the term isolated to refer to a DNA sequence separated from its native context. "Isolated nucleic acid" is therefore construed as "a segment of DNA nucleotides existing separate from other hCMV components normally associated with hCMV."

V. "the first HCMV IE1 intron"/"the first intron"

Novartis asserts that "the first HCMV IE1 intron" and "the first intron" require no construction and that alternatively they should be construed as "[t]he noncoding region of the hCMV IE1 gene between the first and second exons." Regeneron contends that these terms should be construed as "[a]ll or a portion of the first HCMV IE1 intron." Novartis is correct that no construction is needed.

The claims use the disputed terms in describing a component of the claimed vector's transcription regulatory region. This regulatory region is described in Claims 1, 4, 5, 9, 13, and 15 as including "the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter."

Example 2.3.2 in the specification uses the term "first intron" when describing the pCMV6a plasmid that is the subject of Figure 29. The specification states:

> Plasmid pCMV6a is a mammalian cell expression vector which contains the transcriptional regulatory region from human cytomegalovirus immediate early region, HCMV IE1. . . . The HCMV IE1 promoter region contains the region encoding the first exon (5' untranslated), the first intron and the start of the second exon (where the Sa1I site was created by in vitro mutagenesis).

(Emphasis supplied.)

As shown above, Figure 29 diagrams the relationships described in Example 2.3.2. The HCMV intron is darkened and appears downstream of the HCMV promoter.

The prosecution history also sheds light on the proper construction of the terms. Chiron amended its claims in October 1996 to add the term "first intron" in response to a PTO rejection. Specifically, Chiron added a description of the vector's transcription regulatory region as including the "first hCMV IE1 intron proximal to the 3' end of the HCMV IE1

promoter." In adding this term, Chiron distinguished its patent from one whose elements included a "portion" of an intron.[13]

About ten years later, however, Novartis's communications with the PTO made an ambiguous reference to the importance of a portion of the first intron. Responding to the PTO's November 2006 rejection on re-examination of certain of the '688 Patent claims, Novartis represented that its claimed invention produced "higher than expected levels of expression due to the inclusion of portions of the first intron." This statement about productivity, however, does not clearly assert that the claimed invention requires that only a portion of the intron be included in the invention. Novartis may simply be crediting its invention's efficacy to the functioning of a portion of the first intron. Indeed, the PTO's response suggests that it understood Novartis's claimed invention to include the "entire"

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[13] The PTO's rejection was based on a patent for an invention by Cornelia Gorman ("the Gorman Patent"). Chiron explained that unlike its amended claims, which included the term the "first intron", "Gorman fails to teach or suggest an expression vector which contains the first HCMV IE1 intron."

The Gorman Patent describes a transient expression system for expression of recombinant proteins through the use of expression vectors. The specification for the Gorman Patent includes one example of an expression vector that includes a description of "[t]he vector pF8CIS containing the cytomegalovirus enhancer . . . and promoter . . . , the cytomegalovirus splice donor site and a portion of an intron, the Ig variable region intron and splice acceptor site, the cDNA encoding factor VIII and the SV40 polyadenylation site." (Emphasis supplied.)

intron, not just a portion of it. The PTO stated that "the instant claims (e.g. instant claim[] 17) are not limited to the entire first intron proximate to the 3' end of the HCMVE IE 1 promoter and thus the instant claim would encompass [another patented expression vector] which contains intron nucleotides proximate to the 3' end of the HCMV IE 1 promoter as well as pXEP22 which contains the entire intron." This statement appears in the PTO's March 29, 2007 second rejection on re-examination of some of the '688 Patent claims. (Novartis later resolved the PTO's rejection of this claim on other grounds unrelated to the scope of reference to the first intron.)

The parties agree that intron sequences are noncoding sequences of DNA. There is, in fact, no disagreement between the parties as to the definition of "intron". The parties' only disagreement regarding the disputed terms is whether the first HCMV IE1 intron or first intron must be construed to include the entire first intron of the gene or whether it could refer as well to only a portion thereof.

The plain language of the claims suggests that the disputed terms encompass the entire first intron and nothing in the patent itself suggests that "the first [HCMV IE1] intron" should be understood to also encompass only a part of this DNA construct. This reading is confirmed by Chiron's October 24,

1996 amendment and communication with the PTO, which together indicate that "the first HCMV IE1 intron" should be read to mean only the entire first HCMV IE1 intron. By emphasizing that meaning, Chiron distinguished its invention from claims in another patent, the Gorman Patent.

Regeneron's asserted construction rests almost exclusively on the 2006-2007 prosecution history described above. That prosecution history, however, does not unambiguously support Regeneron's construction.

In sum, Regeneron's construction is at odds with the plain and ordinary meaning of the terms "the first HCMV IE1 intron" and "the first intron." That ordinary meaning refers to the entirety of the intron, and not to both the entirety and a portion of the intron. That ordinary meaning is not overcome by ambiguous language in the prosecution history. The terms have a clear meaning to a person of ordinary skill in the art. Accordingly, there is no need to construe these terms.

Conclusion

The disputed terms, as set forth in the parties' claim construction submissions, are construed as set forth above.

SO ORDERED:

Dated: New York, New York
March 20, 2019

DENISE COTE
United States District Judge