United States District Court,
E.D. Missouri, Eastern Division.

SIGMA-ALDRICH, INC., et al,
Plaintiffs.
v.
OPEN BIOSYSTEMS, INC,
Defendant.

No. 4:06-CV-754 CAS

Oct. 24, 2007.

Background: In suit for infringement of patents relating to a technique for altering lentiviruses so that they may be used as vectors to safely deliver beneficial genes to target cells for research and therapeutic purposes, owner and licensee filed motion for claim construction.

Holdings: The District Court, Charles A. Shaw, J., held that:
(1) term "lentiviral vector" meant a replication-defective viral vector that comprised a sequence of RNA or DNA nucleotides derived from a lentivirus, and
(2) term "capable of transducing" meant the ability to introduce and integrate genetic information carried by a viral vector into a cell.

Claims construed.

6,924,123, 7,056,699. Construed.

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MEMORANDUM AND ORDER ON CLAIM CONSTRUCTION

CHARLES A. SHAW**, District Judge.**

This patent infringement matter is before the Court on the Motion for Claim Construction filed by plaintiffs Sigma-Aldrich, Inc. ("Sigma") and Oxford Biomedica (UK), Ltd. ("Oxford") (collectively referred to as

"plaintiffs"). The defendant is Open Biosystems, Inc. ("Open" or "defendant"). The technology at issue relates generally to an area of microbiology and a technique for altering lentiviruses, a type of retrovirus,so that they may be used as vectors to safely deliver beneficial genes to target cells for research and therapeutic purposes. The Court conducted a claim construction hearing on August 21, 2007, and directed the parties to submit proposed orders regarding claim construction. For the reasons set forth below, the Court adopts the constructions proposed by plaintiffs.

The Court adopts the following constructions of disputed terms for the two asserted patents:

1. The term "lentiviral vector" is construed to mean "a replication-defective viral vector that comprises a sequence of RNA or DNA nucleotides derived from a lentivirus."

2. The term "lentiviral LTR-deleted vector" or "LLD vector" is construed to mean "a replication-defective vector based on a lentivirus in which (a) one or more LTR nucleotide sequences from the lentivirus, including at least one such nucleotide sequence that is involved in transcription, are not present, and (b) lentiviral LTR nucleotide sequences necessary for reverse transcription and integration are present."

3. The term "capable of transducing" is construed to mean "the ability to introduce and integrate genetic information carried by a viral vector into a cell."

4. The term "non-functional lentiviral 5' LTR promoter" is construed to mean "a lentiviral genetic sequence located at one end (called the 5' end) of the long terminal repeat that is not present or is no longer able to perform its normal function of initiating creation of RNA from DNA (transcription)."

I. Background

A. The Patents-at-Issue

Oxford is the owner by assignment of U.S. Patent Nos. 6,924,123 B2 ("the '123 patent") and 7,056,699 B2 ("the '699 patent"). The named inventors of these two patents are Drs. Susan Kingsman and Alan Kingsman, professors at the University of Oxford who formed Oxford to develop and commercialize gene-based medicines. Sigma holds an exclusive license to manufacture and sell products under these patents in certain defined research fields. Plaintiffs allege that Open's manufacture and sale of certain lentiviral vectors infringes claims 1-6 of the '123 patent and claims 1-9 of the '699 patent.

The claims of the two asserted patents are generally directed to viral vectors, which are genetically modified versions of existing viruses that can be used to carry beneficial genetic material into cells, such as for gene therapy. The vectors claimed in these patents are based on lentiviruses, which are a subgroup of retroviruses. The best-known lentivirus is the Human Immunodeficiency Virus (HIV), which causes AIDS.

The claimed lentiviral vectors are modified to prevent the lentiviruses from reproducing inside of cells, such as those inside of a patient being treated with a gene therapy. In other words, the lentiviruses are transformed from their dangerous natural or "wild-type" form into a beneficial and "neutered" form that can be used safely for gene therapy or research. As such, they are expected to be useful as a form of "smart bomb" to deliver new genetic material into specific cells, such as cells that do not divide or that divide slowly. One example is delivering the genes that produce dopamine into the brain cells of patients suffering from Parkinson's disease.

The '123 and '699 patents are directed to lentiviral vectors, which are modified lentiviruses. The inventors chose this particularly dangerous group of viruses to make their vectors because vectors made from lentiviruses have special properties that would make them uniquely suitable for the treatment of diseases, such as Parkinson's, which involve nerve cells. In order for gene therapy to help people with these types of diseases, the helpful or therapeutic gene has to be delivered to the cells where it is needed, which is what a vector does-it delivers the helpful gene. For diseases involving non-dividing cells such as nerve cells, lentiviruses are the only retroviruses that can deliver the helpful gene. The modifications the inventors made to the lentivirus permit the lentiviral vectors to introduce beneficial DNA into cells instead of introducing their own harmful viral DNA, and prevent the production of new viruses, thus avoiding infection and disease, such as AIDS. The end result is that a dangerous virus is turned into a helpful, safe vector. The inventors made their modifications to a part of the lentivirus called the "long terminal repeat" or "LTR." Because of this, the patent claims refer to the vector as a "lentiviral LTR-deleted vector."

The life-cycle of a wild-type lentivirus includes several stages. A lentiviral particle is lentiviral genetic material in the form of RNA encapsulated by a protein envelope. When a lentiviral particle infects a cell, it sheds this envelope and its RNA enters the cell. The lentiviral RNA is converted to lentiviral DNA, and this DNA is incorporated into the cell's DNA. FN1 The cell then makes viral RNA and viral protein from the incorporated viral DNA, along with making RNA and proteins from its own DNA. In this way, new viruses are produced to infect other cells. A vector has a similar life cycle except that it is modified so no progeny viruses can be created, and the inserted beneficial DNA is made instead of viral DNA. The ' 123 patent claims are directed to lentiviral LTR-deleted vector particles and the ' 699 patent claims are directed to the lentiviral LTR-deleted vectors generally.

FN1. RNA is an abbreviation for ribonucleic acid and DNA is an abbreviation for deoxyribonucleic acid. *See* Defendant's Stipulation, at 1.

B. The Background Technology

As explained in the uncontested testimony of Dr. Bryan Cullen,FN2 a cell stores in its genes the information it needs to function and replicate. Genes are genetic material composed of DNA. The genetic material of a cell is also known as its "genome." Genes contain the information required to make proteins.

FN2. Dr. Cullen appeared as an expert witness for co-plaintiffs Sigma and Oxford. He is the Director of the Duke University Center for Virology, the James B. Duke Professor of Molecular Genetics and Microbiology, and a research professor in medicine at the Duke University Medical Center. He testified via declaration and in person at the claim construction hearing. Except where explained below, neither Open nor its expert Dr. Tal Kafri (who testified via declaration only) disagrees with Dr. Cullen's explanation of the background technology.

DNA is a linear sequence of single-or double-stranded nucleotides called adenine, guanine, cytosine, and thymine. A string of nucleotides, in sequence, form a nucleic acid. Nucleotide sequences are typically read from left to right, with the left-hand side called the 5' end and the right-hand side called the 3' end. DNA is one type of nucleic acid, and it can be either single or double stranded. When DNA strands pair up, they are complementary; adenine pairs with thymine and guanine pairs with cytosine. The linear sequence of these nucleotides carries genetic information. RNA is the other type of nucleic acid. RNA is a linear sequence of

singleor, less often, double-stranded nucleotides,made up of adenine, guanine and cytosine similar to DNA, but with uracil instead of thymine. Like DNA, RNA carries genetic information.

RNA and DNA have different functions in the life cycle of a cell. DNA stores genetic information. Selected information in the DNA is copied to RNA, such as to make a protein encoded by the DNA. The process of going from DNA to RNA is called "transcription." Transcription begins at a site in the DNA called the promoter. A protein is made from the instructions in the RNA template, and the process of making (or "expressing") a protein from RNA is called "translation."

Viruses infect susceptible cells and take over the cellular transcription and translation machinery to trick the cell into making more viruses. Retroviruses are a unique type of virus because in a retrovirus, RNA stores the genetic information. The retroviral RNA is copied to DNA during the retroviral life cycle (called "reverse transcription"), so that the virus genome, now in DNA form, can insert itself into the DNA genome of a target cell (called "integration"). The integrated viral DNA is referred to as a "provirus." The cellular machinery is then hijacked to make new viruses from the integrated viral DNA.

Like all retroviruses, lentiviruses have a single-stranded RNA genome, which is reverse transcribed (copied) into double-stranded DNA when the virus infects a cell. This DNA form of the viral genome has matching nucleotide sequences called "long terminal repeats" or "LTRs" at both ends. Each LTR consists of three regions, known as the "U3," "R" and "U5" regions. The LTR components are present in the viral RNA, but are not identical at each end.

Reverse transcription of the viral RNA genome generates viral DNA with duplications of the U5 and U3 regions. This is the origin of the two identical LTRs that are characteristic of the DNA form of the viral genome. The R sequence is repeated at both ends of the viral RNA. The U sequences are different. U5 is the unique sequence that originates at the 5' end of the viral RNA, and U3 is the unique sequence that originates at the 3' end of the viral RNA. When the RNA genome is replicated as DNA by reverse transcription, the U5 and U3 regions are copied to both ends, resulting in an identical LTR at each end of the provirus.

In a retrovirus, the genes between the LTRs provide a blueprint for the virus, i.e., the genes direct the production of more virus. Simple retroviruses can only infect dividing cells, and cannot infect non-dividing cells. Non-dividing cells make up a large percentage of the cells in the body and include brain cells, muscle cells, and lung epithelia cells. Complex retroviruses such as lentiviruses can infect non-dividing and slowly-dividing cells; a property that makes them potentially attractive vectors.

In a lentiviral vector system, as opposed to a lentivirus, the viral genome is split into two or more parts: at least into (1) the vector and (2) the packaging components or packaging system. This is done so that the vector is "replication defective"-the packaging cells can produce vector particles that are infectious only once, and these resulting lentiviral vectors cannot cause production of vector particles after entering a target cell.

With the viral genome split in this way, its separate parts are provided to a packaging cell as DNA. When the vector is introduced to the packaging cell, all of the genetic material needed to produce vector particles is present; vector particles can be made, packaged and recovered from these cells. These particles can transduce a target cell, but they are replication defective or replication incompetent. New vector particles cannot be made in the target cell because the genome has been split.

One important use for lentiviral vectors is gene therapy. Gene therapy is based on replacing, altering or supplementing a gene that is absent or abnormal, and where the gene's absence or abnormality is responsible for a disease. For example, a lentiviral vector can be used to incorporate a normal DNA sequence into a cell as a substitute for the patient's own defective DNA, thereby allowing the cell to make normal protein from that DNA. This allows deadly viruses modified to become vectors to carry beneficial genes to target cells without risk that the virus will replicate in the human body. Lentiviral vectors are also important in research that will lead to effective gene therapies.

II. Legal Standards of Claim Construction

The United States Court of Appeals for the Federal Circuit has held that a court must first determine the meaning of relevant claim language to establish the scope of the patent's claims as a predicate for determining the core issues in actions of infringement and validity. *See* Markman v. Westview Inst. Inc., 52 F.3d 967, 979 (Fed.Cir.1995) (en banc), *aff'd,* 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). Claim construction is a matter of law reserved exclusively for the court. *See* Markman, 517 U.S. at 387, 116 S.Ct. 1384.

As the Federal Circuit articulated in its landmark decision in Phillips v. AWH Corp., to determine the correct claim construction, a court must follow, first and foremost, the words of the patent claim itself. It is a bedrock principle of patent law that the claims define the invention that the patentee owns, and the court may neither add words to nor subtract words from the claims in the process of construing them. Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed.Cir.2005) (en banc); TechSearch, L.L.C. v. Intel Corp., 286 F.3d 1360, 1373 (Fed.Cir.2002) (citing Perkin-Elmer Corp. v. Westinghouse Elec. Corp., 822 F.2d 1528, 1533 (Fed.Cir.1987)).

"[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms." Phillips, 415 F.3d at 1314. "In some cases, the ordinary meaning of claim language as readily understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." Id. "The inquiry into how a person of ordinary skill in the art understands a claim term provides an objective baseline from which to begin claim interpretation." Id. at 1313.

Claim terms "are generally given their ordinary and customary meaning," Phillips, 415 F.3d at 1312, unless the patentee demonstrates a clear intent to deviate from the plain and ordinary meaning, or to otherwise disavow claim scope. Id. at 1316. There is a heavy presumption that a claim carries its ordinary and customary meaning. *See* SunRace Roots Enterprise Co. v. SRAM Corp., 336 F.3d 1298, 1302 (Fed.Cir.2003). To overcome this presumption, the patentee must have "demonstrated an intent to deviate from the ordinary and accustomed meaning of a claim term by redefining the term or by characterizing the invention in the intrinsic record by using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *See* Teleflex, Inc. v. Ficosa N. Am., Corp., 299 F.3d 1313, 1327 (Fed.Cir.2002).

The claims must "be read in view of the specification, of which they are a part." Markman, 52 F.3d at 979. The specification "is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term." Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996). Courts must not, however, import limitations from the specification into a claim. Phillips, 415 F.3d at 1323.

It is not proper to limit what is claimed to preferred embodiments or specific examples in the specification if the patentee did not demonstrate a clear intent to deviate from the claim terms' ordinary meaning in that way, or to otherwise disavow the claim scope. Teleflex Inc. v. Ficosa N. Am., Corp., 299 F.3d 1313, 1326-28 (Fed.Cir.2002). Thus, the Court must interpret the claims in light of the specification, Markman, 52 F.3d at 979, but avoid impermissibly importing limitations from the specification into the claims. Comark Communs. v. Harris Corp., 156 F.3d 1182, 1186 (Fed.Cir.1998).

In SRI Int'l v. Matsushita Elec. Corp. of Am., 775 F.2d 1107, 1121 (Fed.Cir.1985), the Federal Circuit, in reversing a grant of summary judgment based on an overly narrow claim construction, succinctly explained why the claim construction analysis must focus on the claims and not the specification. The Court noted that although the District Court "correctly described the specification, ... the difficulty is this: claims are infringed, not specifications." Id. at 1121. The Court further stated:

When claim construction is required, claims are construable, as above indicated, in light of the specification, yet that claims are interpreted in light of the specification does not mean that everything expressed in the specification must be read into all the claims. If everything in the specification were required to be read into the claims, or if structural claims were to be limited to devices operated precisely as a specification-described embodiment is operated, there would be no need for claims. Nor could an applicant, regardless of the prior art, claim more broadly than that embodiment. Nor would a basis remain for the statutory necessity that an applicant conclude his specification with claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. It is the *claims* that measure the invention.

Id. (emphasis in original) (internal citations and quotations omitted).

In addition to consulting the specification, the Court "should also consider the patent's prosecution history, if it is in evidence." Markman, 52 F.3d at 980. "The prosecution history, which we have designated as part of the 'intrinsic evidence,' consists of the complete record of the proceedings before the PTO and includes the prior art cited during the examination of the patent." Phillips, 415 F.3d at 1317. "Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent. Furthermore, like the specification, the prosecution history was created by the patentee in attempting to explain and obtain the patent." Id. (internal citation omitted).

Courts may also rely on extrinsic evidence in construing claims. Extrinsic evidence is "all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." Markman, 52 F.3d at 980. "Within the class of extrinsic evidence, the court has observed that dictionaries and treatises can be useful in claim construction." Phillips, 415 F.3d at 1318. "Because dictionaries, and especially technical dictionaries, endeavor to collect the accepted meanings of terms used in various fields of science and technology, those resources have been properly recognized as among the many tools that can assist the court in determining the meaning of particular terminology to those of skill in the art of the invention." Id.

Similarly, expert testimony "can be useful to a court for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, to ensure that the court's understanding *of* the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." Id. Phillips confirms that expert testimony can be helpful to the Court in the claim construction process for a

variety of purposes and explains that it is only when expert testimony is "clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, the written record," or when the expert testimony is "conclusory" and "unsupported" that such testimony is "not useful" to the Court. Id. at 1318. Testimony of the inventor may also be helpful to the Court in the claim construction process in that an inventor is "a competent witness to explain the invention and what was intended to be conveyed by the specification and covered by the claims." Voice Techs. Group, Inc. v. VMC Sys., Inc., 164 F.3d 605, 615 (Fed.Cir.1999).

III. Claim Term Interpretation

The '699 patent claims "lentiviral vectors," and the '123 patent claims "lentiviral vector particles," a lentiviral vector in the form of a virus-like structure. The patents generally teach that these claimed lentiviral vectors are intended to be useful for providing gene therapy in humans for medical purposes and are not limited to research:

The invention further provides the use of retroviral vectors carrying the chimeric gene described herein, in gene therapy and in the preparation of a medicament *for* gene therapy*;* and *a method of performing* gene therapy on a target cell.... *The invention thus provides a gene delivery system for use in medicine*.

'123 patent, col. 4, ll. 17-27 (emphasis added).

The specification notes that Parkinson's disease "is an ideal candidate for gene therapy" to increase the production of dopamine in the brain, but that prior art vectors were generally inadequate for various reasons. Id. at col. 2, l. 44-col. 3, l. 39. It concludes that "[t]he present invention addresses these problems." Id. at col. 3, l. 40. *See also* id. at col. 3, ll. 57-59; col. 9, ll. 25-29; col. 11, l. 65-col. 12, l. 1 (discussing therapeutic uses of lentiviral vectors according to the invention); id., col. 12, ll. 64-65 (noting that claimed vectors have other useful applications "in addition to gene therapy").

The parties dispute the meaning of four terms found in the claims: (1) "lentiviral vector," (2) "lentiviral LTR-deleted vector" (or "LLD vector"), (3) "capable of transducing," and (4) "non-functional lentiviral 5' LTR promoter." The two asserted patents share an identical specification, and the contested terms are used consistently in both patents.

Independent claim 1 of the '123 patent (as corrected by a Certificate of Correction) is illustrative, with the four disputed terms underlined:

1. A *lentiviral vector* particle *capable of transducing* a non-dividing or slowly-dividing cell, said vector particle comprising a *lentiviral LTR-deleted (LLD) vector,* wherein the LLD vector comprises sequences sufficient for reverse transcription and integration, and wherein, upon transduction, the LLD vector comprises a *non-functional lentiviral 5' LTR promoter*.

Independent claim 1 of the '699 patent similarly reads:

1. A *lentiviral vector capable of transducing* a non-dividing or slowly-dividing cell, said vector comprising a *lentiviral LTR-deleted vector*.

A. The Meaning of "Lentiviral Vector"

[1] The term "lentiviral vector" appears in independent claim 1 of the ' 699 patent, and is included within the phrase "lentiviral vector particle" in independent claim 1 of the '123 patent. The parties agree (1) that a "lentivirus" is any retrovirus of the genus or subfamily *Lentivirinae,* (2) that a "vector" is a vehicle or agent which is designed to carry selected genetic material (DNA or RNA) in order to introduce the selected genetic material into a cell, and (3) that a "lentiviral vector particle" means "a lentiviral vector in the form of a virus-like structure comprising viral components that enable the introduction of genetic material into a cell." Joint Claim Construction and Pre-hearing Statement [Doc. 40], at 2; Def.'s Stipulation Regarding Agreed Upon Construction Of Terms And Phrases Formerly In Dispute [Doc. 95], at 1.

The parties agree generally that the lentiviral vectors of this invention are lentiviruses that have been altered to carry genetic material into a cell. *See, e.g.,* '123 patent, col. 9, ll. 8-11 ("[T]he vector according to the invention is based on a particular retrovirus, this may be a genetically or otherwise ... altered version of the retrovirus."); id. at col. 1, ll. 61-63 (noting that invention relates generally to "the development of retroviral vector systems based on lentiviruses, a small subgroup of retroviruses"); id. at col. 9, ll. 4-7 ("That the vector particle according to the invention is 'based on' a retrovirus means that it is derived from that retrovirus.").FN3

FN3. While the parties agree on the definition of the general term "vector," the Court is mindful of the fact that in the claims the terms are "lentiviral vector" and "lentiviral LTR-deleted vector." It is the terms as actually used in the patent claims that are for the Court to construe.

The parties disagree about whether the claimed "lentiviral vector" must be "replication defective," in other words, whether the virus must be neutered so that it can no longer make copies of itself and reproduce, such as after being administered to a patient for therapeutic purposes. Sigma and Oxford contend that the "lentiviral vector" claimed in the patents must be replication defective, so the term should be construed as "a *replication-defective* viral vector that comprises a sequence of RNA or DNA nucleotides derived from a lentivirus." Open urges a broader construction, that "lentiviral vector" means any type of "vector that is derived from a lentivirus," without a requirement that it be replication defective.FN4

FN4. Open had initially urged a narrower construction, that "lentiviral vector" be defined as "a vector that belongs to a group of retroviruses that cause 'slow disease' characterized by long incubation periods and chronic progressive phrases such as Human Immunodeficiency Virus (HIV)." Joint Claim Construction and Prehearing Statement [Doc. 40], at 3-4. It abandoned this position during claim construction briefing.

The Court agrees with Sigma and Oxford. The specification makes clear that "in any case" the vectors claimed in these patents "will be replication defective":

The retroviral vector according to the invention may be constructed according to the methods known in the art. It is desirable that the retroviral vector genome does not encode any unnecessary polypeptides, that is any polypeptides that are not required for achieving the effect the vector is designed for. *In any case, the retroviral vector will be replication defective.*

'123 patent, col. 10, ll. 48-54 (emphasis added).

This passage contains language of "manifest exclusion" that represents "a clear disavowal of claim scope."

Teleflex, 299 F.3d at 1327; *see also* Phillips, 415 F.3d at 1316 (noting that "the specification may reveal an intentional disclaimer, or disavowal, of claim scope by the inventor" which may be "regarded as dispositive" for interpreting a claim); Alloc, Inc. v. International Trade Comm'n, 342 F.3d 1361, 1370 (Fed.Cir.2003) (interpreting claim term narrowly where "the specification makes clear at various points that the claimed invention is narrower than the claim language might imply").

The inventors expressly limited their invention by emphasizing that "in any case" the vector claimed in the patents "will be" replication defective. This passage unambiguously states that "any" embodiment of the claimed lentiviral vector must be replication defective. *See* Astrazeneca AB v. Mutual Pharm. Co., 384 F.3d 1333, 1338-39 (Fed.Cir.2004) (holding that general term "solubilizer" in claims was limited where the specification unambiguously stated that the solubilizer must be a surfactant solubilizer). This statement in the specification is not discussing only a single embodiment among many, but is discussing every embodiment of the invention.

This is confirmed by the remainder of the specification. The specification discloses several different embodiments of vectors that are replication defective, but none are capable of replicating. *See* '123 patent at col. 5, ll. 51-54; col. 11, ll. 19-22, 30-36; col. 7, ll. 50-55, 63-65; col. 8, ll. 3-4; col. 9, ll. 45-53; col. 12, ll. 9-14; col. 14, ll. 15-31; Figs. 1-4 and 6. In every one of the disclosed embodiments, the vectors are replication defective.

This interpretation is also consistent with the stated purpose of the invention, which is to transform a potentially lethal lentivirus such as HIV into a beneficial lentiviral vector that can be used safely for gene therapy or research. If the vectors were allowed to replicate as the underlying viruses do in their natural state, they could cause serious harm to the patient, infect researchers or doctors, and spread disease to third parties. *See* '123 patent, col. 5, ll. 48-51 (noting that immunodeficiency viruses like HIV "inevitably bring with them safety considerations and prejudices").

Dr. Cullen testified that because of the risk of harm and disease, a vector that is replication defective is "absolutely essential" in a clinical setting. Deposition of Dr. Bryan R. Cullen ("Cullen Dep.") at 130:1-16. Dr. Cullen reiterated that non-replication-defective vectors "could not be used in any clinical setting because they would be dangerous." Transcript of Claim Construction Hearing ("Tr.") at 62:2-63:3. Dr. Susan Kingsman similarly explained in her deposition:

If [the vector] were not replication defective, it would be a virus, and you would not want to use a virus to modify cells or research for therapeutic purposes in the context of this invention. The whole art of making vectors is to convert viruses to replication defective entities.

Deposition of Dr. Susan M. Kingsman ("Kingsman Dep.") at 66:13-20.

Consistent with this goal, the specification emphasizes the importance of incorporating "safety aspects" into the vectors. '123 patent, col. 10, ll. 54-65. In particular, the vector should only have the "minimum retroviral material necessary to function." Id. These safety aspects are intended to prevent the "possible reconstruction of infectious virus particles," and thereby ensure that the vectors will remain replication defective. Id. FN5

FN5. This is further confirmed by the extrinsic evidence relied upon by Open. Although these references note that it is theoretically possible in other circumstances to use a lentiviral vector that is capable of replication, they emphasize that such vectors are highly disfavored. For example, one reference states

"generally" that vectors "are engineered to be replication-defective" for safety reasons. Buchschacher, Lentiviral Vector Systems for Gene Transfer (2003) (Def.'s Ex. G). Another reference notes that vectors capable of replicating "have not been as popular as replication-incompetent vectors" because they are only suitable for use in "avian species" or "a tissue culture dish," and not for use in "mammals." Current Protocols In Molecular Biology, Vol. 2, Supp. 36 (Def.'s Ex. H) at 9.9.6.

Open argues that the term "lentiviral vector" should be defined broadly as any "vector that is derived from a lentivirus." Open points to extrinsic evidence and asserts that the term "lentiviral vector" does not always mean a replication-defective vector in other circumstances "outside the context of these patents." Def.'s Br. at 16. While true, this is irrelevant because the claims must be interpreted within the context of these patents, not outside of them. *See* Phillips, 415 F.3d at 1319 (extrinsic evidence is "unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence").

The inventors acknowledged that in the prior art, other researchers had sometimes used vectors that were capable of replicating. The inventors expressly ruled out these types of vectors as part of their invention because such vectors were unsafe and therefore unsuitable for therapeutic purposes. The inventors emphasized that "in any case" the only vectors they claimed in these patents were replication defective. '123 patent, col. 10, ll. 48-54. In so doing, the inventors stated that they were not seeking to claim more than they were entitled to. They only claimed "replication-defective" lentiviral vectors.

Open also urges the Court to ignore the inventors' unambiguous disclaimer because it only appears in "one sentence." Defendant's Br. at 16; Tr. at 35:10-13. The Court is unaware of any authority requiring more than "one sentence" to create a disclaimer where that language is clear. To the contrary, the Federal Circuit has rejected the notion that "rigid formalism" is necessary for a disclaimer. Astrazeneca, 384 F.3d at 1339.

Open further argues that only some of the claims require lentiviral vectors that are replication defective. Some claims, such as claim 1 of the '123 patent, provide that the claimed lentiviral vector must have a "non-functional lentiviral 5' LTR promoter." Other claims, such as claim 1 of the '699 patent, do not have this limitation. Open contends that the vectors in these later claims do not need to be replication defective.

This argument is without merit. The specification teaches that "in any case" the lentiviral vectors "according to the invention," i.e., the vectors in these claims, "will be replication defective." The claim language Open points to is "non-functional 5' LTR promoter," not "replication defective."These terms are not synonymous. The patent specification explains that a non-functional lentiviral 5' LTR promoter is one way, but is not the only way, to make a lentiviral vector replication defective. The specification also discloses other ways to make lentiviral vectors that are replication defective, as explained below.

The claims reflect these different embodiments that are disclosed in the specification. In some claims, such as claim 1 of the '123 patent, the claimed vector must specifically have a "non-functional lentiviral 5' LTR promoter." This claim language only provides further guidance about a particular way to make the vector replication defective, not *whether* the vector is replication defective.

In other claims, such as claim 1 of the '699 patent, the language is broader and includes any type of lentiviral LTR-deleted vector that is replication defective. These claims are not limited to the "non-functional lentiviral 5' LTR promoter" embodiment, but can include vectors made replication defective through other methods.FN6

FN6. This interpretation is also consistent with the prosecution history. During prosecution, the inventors amended claim 1 of the '123 patent to add the limitation that it includes a "non-functional lentiviral 5' LTR promoter." Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13) at 4. The inventors explained that the purpose of the amendment was to "further clarify" that the vector "is no longer capable of ... replication" because it includes this feature. Id. at 6. The inventors did not suggest, however, that this was the only way of making a vector that was replication defective, or that such a vector would be capable of replication unless it had this particular limitation.

Accordingly, the Court construes "lentiviral vector" as used in these claims as meaning "a replication-defective viral vector that comprises a sequence of RNA or DNA nucleotides derived from a lentivirus."

B. The Meaning of "Lentiviral LTR-deleted (LLD) Vector"

[2] The term "non-functional lentiviral 5' LTR promoter" appears only in the claims of the '123 patent. Sigma and Oxford contend that this term means "a lentiviral genetic sequence located at one end (called the 5' end) of the long terminal repeat that is not present or is no longer able to perform its normal function of initiating creation of RNA from DNA (transcription)." Open contends that this term means "a lentiviral genetic sequence located at one end (called the 5' U3 region) of the long terminal repeat that is no longer able to perform its normal function of initiating creation of RNA from DNA (transcription)."

The parties disagree about two points. First, the parties disagree about whether this term is only limited generally to the "5' end" or specifically to the "5' U3 region." As discussed earlier, the "5' U3 region" is a more specific location within the 5' LTR. Claim 1 refers to the "5'" end and, by its own terms, is not limited to the "5' U3 region." The "U3 region" is an extraneous limitation that the Court will not read into the term.

The parties agree that the phrase "lentiviral LTR-deleted vector" (or "LLD vector") is a term coined by the inventors acting as their own lexicographers. The phrase did not have an ordinary meaning in the relevant art at the time the applications for the asserted patents were filed. The phrase appears in all claims of the '123 and '699 patents.

"LTR" is an abbreviation for "long terminal repeat," referring to the sections at either end of the viral genome. According to the specification, each LTR contains three distinct regions, known as the "U3," "R" and "U5" elements. *See* '123 patent, col. 6, ll. 41-46 ("The LTRs ... are identical [nucleotide] sequences that can be divided into three elements, which are called U3, R and U5."). This is depicted in Figure 1 of the '123 patent. In lentiviruses such as HIV, the LTRs regulate the functions of reverse transcription, integration and transcription. *See* '123 patent, col. 6, ll. 31-37; Tr. at 67:12-19.

The parties agree generally that the term "lentiviral LTR-deleted vector" refers to a vector in which some portion of the LTRs has been deleted or modified, rather than one in which the LTRs have been deleted entirely. In other words, some nucleotide sequences found in the LTR of the original virus are no longer present in the claimed vector.

The parties dispute which portions of the LTR are deleted or modified. Open points to an embodiment that discloses substitution of the R region, and concludes that "lentiviral LTR-deleted vector" must be limited to a vector in which the entire R region has been substituted.

Sigma and Oxford contend that "lentiviral LTR-deleted vector" is not limited to this one embodiment, but instead to a vector in which "at least one such nucleotide sequence that is involved in transcription" is removed from or replaced in the LTR, while the other nucleotide sequences necessary for reverse transcription and integration are left intact. Sigma and Oxford contend that this definition encompasses all of the embodiments disclosed in the specification. The Court agrees with Sigma and Oxford.

The specification emphasizes that the vector must have three key characteristics to be safe and effective for gene therapy uses described throughout the specification:

1. The vector must have nucleotide sequences that make it capable of reverse transcription. This allows the RNA in the vector to be transcribed into beneficial DNA after it enters the host cell.

2. The vector must have nucleotide sequences that make it capable of integration. This allows the beneficial DNA to insert itself into the host cell's DNA after entering the nucleus. Once the beneficial DNA has been integrated, the cell can begin manufacturing proteins that serve a therapeutic purpose (such as by potentially making dopamine in brain cells for a patient who has Parkinson's disease).

3. The vector *must not* have at least one lentiviral LTR nucleotide sequence involved in transcription.

If a vector lacks either of the first two characteristics, it will be unable to deliver effective gene therapy. The third characteristic, deleting at least one lentiviral LTR nucleotide sequence involved in transcription, allows the vector to be safely used to deliver gene therapy. The specification teaches that these properties define a lentiviral vector that is "LTR-deleted" according to the invention.

The invention begins with the genome of a lentivirus, but creates a safer vector by either deleting or replacing various genetic sequences in the LTR. '123 patent, col. 9, ll. 4-8. This includes removing or replacing at least one original nucleotide sequence that is involved in transcription. *See* '123 patent, col. 7, ll 50-55, 63-65; col. 8, ll. 3-4; col. 9, ll. 45-53; col. 12, ll. 9-15; col. 14, ll. 15-31; Figs. 1-4 and 6. These deleted LTR sequences can be either "promoter" or "enhancer" sequences, both of which help to control transcription. '123 patent, col. 6, ll. 35-38, 48-49, 51-55.

At the same time, the specification teaches that the LTRs must not be modified to the extent that they are unable to engage in reverse transcription and integration. It teaches that these functions are necessary "in order to function as a vector":

As will be evident, *in order to function as a vector,* the lentiviral LTR-deleted vector according to the invention *will need to have a reverse transcription system* (compatible reverse transcriptase and primer binding sites) *and an integration system* (compatible integrase and integration sites) allowing conversion to the provirus and integration of the double-stranded DNA into the host cell genome.

'123 patent, col. 8, ll. 59-65 (emphasis added); *see also* id. at col. 8, ll. 6-8, 27-30, 37-39, 42-45, 47-51; col. 9, ll. 11-14; col. 13, l. 58-col. 14, l. 3; col. 14, ll. 11-12; Figs. 1-4 and 6. The specification defines a lentiviral LTR-deleted vector as a vector in which some nucleotide sequences from the LTRs have been substituted or removed while others have been retained. These changes must remove at least one lentiviral LTR nucleotide sequence involved in transcription, but still allow the vector to engage in reverse transcription and integration, which are essential "to function as a vector."

This interpretation is confirmed by the claims themselves and by the prosecution history. During prosecution, the inventors amended claim 1 of the '123 patent to clarify the role of the "lentiviral LTR deleted vector." The amended claim emphasizes the importance of allowing reverse transcription and integration while blocking replication. *See* Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13 FN7), at 4.

FN7. Citations to "Pls.' Ex." are to the declaration and supplemental declaration of Paul M. Zagar, Docket Nos. 87 and 102. Citations to "Def.'s Ex." are to the declaration of Michael J. Hickey, Docket No. 96.

The inventors further explained that this amendment was made to "correlate with the function of the LLD vector" as disclosed in the specification:

[T]he claims have been amended to recite language that *correlates with the function of the LLD vector*. For example, the vector sequences maintained in the LLD vector are *only those sufficient for reverse transcription and integration of the virus*. The claim amendments further clarify that the LLD vector *is no longer capable of transcriptional control/virus replication* because, upon transduction, the vector comprises a non-functional lentiviral 5' LTR promoter.

Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13) at 6 (emphasis added).

The inventors emphasized that the "lentiviral LTR-deleted vector" was not limited to any one embodiment depicted in the specification or figures, such as Figure 1. *See id*. Rather, this term should be construed broadly as including a vector with any modifications to the LTR, as long as "the sequences sufficient for the reverse transcription and integration of the lentivirus are maintained" and some other portions, i.e., those for transcription, "are not maintained." *Id*.

The specification discloses that HIV vectors in the prior art used HIV LTRs that were not active in the absence of a viral protein called Tat. *See* '123 patent, col. 2, ll. 10-12. HIV LTRs have a sequence in their R region called TAR. *See* id. at col. 2, ll. 19-22; col. 7, ll. 13-15; col. 7 l. 66-col. 8, l. 2. TAR by itself may weakly inhibit the HIV LTR promoter, but binding of the Tat protein to TAR causes transcription from the HIV LTR promoter to increase approximately one hundred-fold. Second Declaration of Dr. Bryan R. Cullen ("Second Cullen Decl.") [Doc. 101] at para. 6; Tr. at 21:1-4, 68:19-21. Thus, efficient transcription from the HIV LTR promoter requires Tat. Second Cullen Decl. para. 5. The problem with supplying Tat is that it complicates the system and may have cancer-causing properties. '123 patent, col. 2, ll. 39-43. The specification states that one aim of the invention is to modify the LTRs in such a way as to avoid the need for using Tat. '123 patent, col. 2, ll. 22-24.

The specification discloses at least three ways to make a lentiviral LTR-deleted vector. Each of these embodiments shows a modification to the LTRs that removes at least one lentiviral LTR nucleotide sequence involved in transcription and eliminates dependence on Tat, but still allows reverse transcription and integration:

1. ***Replace the R region.*** The specification discloses that the R regions of the LTRs can be replaced. *See, e.g.,* '123 patent, col. 8, ll. 5-6. This embodiment overcomes the problems with supplying Tat by replacing the lentiviral R region where TAR is located. *See, e.g.,* id., col. 7, l. 63-col. 8, l. 2. There is no need to

supply Tat to the system because there is no TAR rendering the LTR promoter dependent on Tat.

2. ***Delete part of the U3 region.*** The specification also discloses that there are "alternative ways" of achieving the same result. It teaches that one way is to delete part of the U3 region from the 5' LTR to create a "self-inactivating" vector:

There are *alternative ways* of achieving a single transcription unit vector, however. The vector genome *could be designed as a self-inactivating vector* (Yu et al., 1986 PNAS 83, 3194) in which *part of the 3' U3 sequences are deleted* so that the transduced vector genome has a non-functional 5' LTR promoter.

'123 patent, col. 9, ll. 43-48 (emphasis added).

In this embodiment, the LTR promoter is removed and the vector instead relies on an internal promoter (located between the LTRs). *See* '123 patent, col. 9, ll. 49-54. There is no LTR promoter whose expression is dependent on the binding of Tat to TAR.

3. ***Replace the U3 region.*** The specification discloses a third embodiment that achieves the same results by replacing the U3 region (except for sequences necessary for integration) with a promoter from a cell or another virus. *See, e.g.,* '123 patent, Figs. 1, 2, 6; col. 14, ll. 13-21; Tr. at 67:22-68:4. The non-lentiviral promoter is not dependent on Tat for efficient gene expression. *See, e.g.,* '123 patent, col. 7, ll. 50-55. Thus, the need to provide Tat is removed.

These three disclosed embodiments for overcoming the Tat problem are not mutually exclusive.FN8 Although any one embodiment by itself avoids Tat, embodiments can be combined for added safety. For example, the specification states that "a straightforward way to achieve the desired vector LTRs" includes both the R region replacement and U3 region replacement embodiments:

FN8. The specification also recognizes that these disclosures are merely "examples" that are "not intended to limit the invention to specific embodiments described." Id., col. 4, ll. 36-39. It further explains that the figures offer "generalized" illustrations that depict the "principle" of the invention. Id., col. 4, ll. 42-52; col. 5, ll. 12-14.

A straightforward way to achieve the desired vector LTRs is therefore *to replace the lentiviral R regions and as far as possible the U3 region,* but leaving essential lentiviral sequences present such as a short sequence of the U3 region necessary for integration.
Id., col. 8, ll. 4-8. Using this embodiment, both TAR (in the R region) and the lentiviral LTR promoter (in the U3 region) have been replaced. Open argues that this statement limits the invention to the R region replacement embodiment. It does not. Two other embodiments, i.e., " *way[s]* to achieve the desired vector LTRs," are disclosed. The R region replacement embodiment and the U3 region deletion embodiments can also be combined, as acknowledged by Open. Tr. at 103:16-19. Each one of these embodiments alone is an example of a way to make a vector "LTR deleted." Tr. at 20, 22, 27, 67-69.

Dr. Cullen testified that the ' 123 and '699 patents teach three separate ways to make an "LTR deleted" vector. *See* Tr. at 20-22, 27, 67-69. His testimony is consistent with the specification, and is contrary to Open's contention that the specification limits the claims to a single embodiment-even though three possible embodiments are disclosed. Open did not cross examine Dr. Cullen or offer contrary testimony, even though

its own expert, Dr. Tal Kafri, was present at the hearing.

The specification teaches that "lentiviral LTR-deleted vector" is a lentiviral vector in which the LTRs have been modified from those of the original wild-type lentivirus. The modified LTRs must still function to allow reverse transcription and integration, which are essential for gene therapy, while simultaneously lacking at least one lentiviral LTR nucleotide sequence involved in transcription. This interpretation is supported by the prosecution history, the claims' language and Dr. Cullen's testimony. Sigma and Oxford's construction is therefore correct.

Open contends that "lentiviral LTR-deleted vector" is limited to only the one embodiment above in which the R region is replaced. This would exclude the two other preferred embodiments disclosed in the specification (the "replace the U3 region" and the "delete the U3 region" embodiments), as well as any other alternatives for creating a lentiviral LTR-deleted vector. The Federal Circuit has emphasized that "[a] claim construction that excludes a preferred embodiment is rarely, if ever, correct." Pfizer, Inc. v. Teva Pharms. USA, Inc., 429 F.3d 1364, 1374 (Fed.Cir.2005) (quoting SanDisk Corp. v. Memorex Prods., Inc., 415 F.3d 1278, 1285 (Fed.Cir.2005)) (internal alterations omitted). Moreover, Open's definition contains no requirement that the lentiviral LTR-deleted vector be capable of reverse transcription or integration, which are essential "in order to function as a vector". '123 patent, col. 8, ll. 59-65.

Open offers three arguments in support of its proposed interpretation. First, Open argues that the specification contains "magic words" (i.e., "manifest words of exclusion") that limit the claim term to the single embodiment with a replaced R region. Tr. at 75:1-4, 84:10-14. Open contends that this language identifies the "replace the R region" embodiment as "the invention," to the exclusion of any other embodiments. Open argued at the claims construction hearing:

Let's look at Column 8, lines 9 through 10.... "The invention is outlined in Fig. 1. The vector system is designated Lentiviral LTR-Deleted (LLD) vector." The magic words. "The invention is outlined in Fig. 1."

Tr. at 84:7-11.

The Court disagrees with Open's argument. Figure 1 discloses two embodiments: (1) R region replacement, and (2) U3 region replacement. Open also argued that Figures 2-4 and 6 limited the invention to the R region replacement embodiment. Tr. 87:20-90:8. This cannot be the case because these figures also show two embodiments.

The specification explains that there are "alternative ways" of creating a lentiviral LTR-deleted vector that do not involve changing the R region. Id., col. 9, ll. 43-45. The specification points to the "delete the U3" embodiment as one such "alternative way." Id., col. 9, ll. 45-48. The specification also discloses a third embodiment of replacing the U3 region. Each of these three embodiments meets the definition of a "lentiviral LTR-deleted vector" as it modifies the LTR in a way that allows reverse transcription and integration, but removes at least one lentiviral LTR nucleotide sequence involved with transcription. Id., col. 8, ll. 59-65.

Open also argues that the discussion concerning the "replace the R region" embodiment is found in a section entitled "detailed description of the invention," and contends that as a result this embodiment must represent the entire "invention." Open's argument is contradicted by language expressly stating that this section only provides "examples" that are "not intended to limit the invention," as well as by the disclosure of other

embodiments in the same section, including the "delete the U3" and "replace the U3" embodiments. '123 patent, col. 4, ll. 36-40; *see also* id., col. 18, ll. 29-34 (reiterating that the specification only discloses "preferred embodiments," and noting that "many other variations thereof are possible" by a person of ordinary skill in the art).FN9

FN9. Open also relies on discussions of particular embodiments in other sections, such as one section entitled "examples." The specification likewise clarifies that this section only discloses "specific embodiments" that are "not intended to limit the invention." Id., col. 13, ll. 38-40.

Open further argues that the claims must be limited to embodiments that have particular "advantages" disclosed in the specification. *See, e.g.,* ' 123 patent, col. 12, ll. 6-14 (discussing the "advantage of removing the HIV expression signals"). This is without merit. Just as claims are not limited to specific preferred embodiments, they are not limited to embodiments that feature particular "advantages." Such advantages may explain why some embodiments are preferred, but do not define the invention or the scope of the claims. *See* Phillips, 415 F.3d at 1327 ("Although deflecting projectiles is *one of the advantages* of the baffles of the [asserted] patent, the patent does not require that [the baffles] always be capable of performing that function." (emphasis added)); *see also* Ventana Med. Sys., Inc. v. Biogenex Labs., Inc., 473 F.3d 1173, 1181 (Fed.Cir.2006) ("each claim does not necessarily cover every feature disclosed in the specification"); E-Pass Techs., Inc. v. 3Com Corp., 343 F.3d 1364, 1370 (Fed.Cir.2003) ("An invention may possess a number of advantages or purposes, and there is no requirement that every claim directed to that invention be limited to encompass all of them.").
Open's argument is also refuted by the prosecution history, in which the inventors explained that there were many ways of creating a lentiviral LTR-deleted vector. *See* Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13), at 6. The inventors specifically noted that "Figure 1 is exemplary, and in no way limits the scope of the claims." *Id*. In other words, the inventors anticipated and cautioned against Open's interpretation that "the invention" is confined to what is shown in Figure 1. In context, both the specification and file history make clear that the discussion of the "replace the R" embodiment is merely one preferred embodiment, rather than a limitation on the breadth of the claims.

There is no language that can be construed as "manifest words of exclusion or restriction" reflecting "a clear disavowal of claim scope" to restrict the meaning of lentiviral LTR-deleted vector. *See* Teleflex, 299 F.3d at 1327. Unlike the language of manifest exclusion that explains the claimed vectors must be replication defective, there is no suggestion here that "in any case" the claimed lentiviral LTR-deleted vector "will have" a replaced R region. Instead, the specification discloses the substitution of the R region as part of one "straightforward" way to create a lentiviral LTR-deleted vector, discloses "alternative ways" of creating a lentiviral LTR-deleted vector, and cautions that all of these are only "examples" that are "not intended to limit the invention."

Although the specification expressly discloses at least three different embodiments of the lentiviral LTR-deleted vector, Open proposes a construction that would exclude two of the embodiments. Even if the specification disclosed only a single embodiment, it would not be appropriate to confine the claims to that embodiment:

We do not import limitations into claims from examples or embodiments appearing only in a patent's written description, even when a specification describes very specific embodiments of the invention or even describes only a single embodiment, unless the specification makes clear that "the patentee ... intends for the claims and the embodiments in the specification to be strictly coextensive."

JVW Enters., Inc. v. Interact Accessories, Inc., 424 F.3d 1324, 1335 (Fed.Cir.2005) (quoting Phillips, 415 F.3d at 1323); *see also* Ventana Med. Sys. v. Biogenex Labs., Inc., 473 F.3d 1173, 1181-82 (Fed.Cir.2006) (rejecting argument that inventor had "implicitly defined" a claim term as being limited to a particular feature disclosed in each of the embodiments); Phillips, 415 F.3d at 1323 ("In particular, we have expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment." (citations omitted)); Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc., 381 F.3d 1111, 1117 (Fed.Cir.2004) ("even where a patent describes only a single embodiment, claims will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction" (internal quotations omitted)).

Open relies on cases in which a broad term was interpreted narrowly because the specification disclosed only one embodiment, criticized prior art based on other embodiments, and unambiguously stated that the one embodiment defined the invention claimed in the patent. *See, e.g.,* C.R. Bard, Inc. v. U.S. Surgical Corp., 388 F.3d 858, 860-61 (Fed.Cir.2004) (interpreting the term "plug" narrowly where the specification "unequivocally" defined this term as meaning a "pleated plug" in the Summary of the Invention section, the specification did not disclose any other embodiments, and the inventors emphasized to the Patent Office that the claims were limited to a pleated plug to overcome prior art); FN10 *see also* Honeywell Int'l, Inc. v. ITT Indus., Inc., 452 F.3d 1312, 1318-19 (Fed.Cir.2006) (interpreting "fuel injection system component" narrowly where the specification repeatedly emphasized that the invention was limited to a "fuel filter," and the specification did not disclose any other types of fuel injection system components or suggest that the fuel filter was only a preferred embodiment); Astrazeneca, 384 F.3d at 1338-40 (interpretingterm "solubilizer" narrowly where specification expressly states that the solubilizer must be a particular type of solubilizer and "clearly disavows" other types of solubilizers as unsuitable for the invention); Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1097-1102 (Fed.Cir.2003) (interpreting term "chromosomally integrated" narrowly where the specification disclosed only one embodiment, and referred to that embodiment expressly as the invention in the Summary of the Invention); SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1342-44 (Fed.Cir.2001) (interpreting term as limited to a particular configuration where the specification defined the term as such in the Abstract, criticized prior art that had different configurations, described this configuration in the Summary of the Invention as being the invention, and stated unequivocally that "all embodiments of the present invention contemplated and disclosed herein" are limited to this configuration).

FN10. The court emphasized that disclaimers in sections such as the "Summary of the Invention" or the "Abstract" carry particular weight because they preface the entire specification. C.R. Bard, 388 F.3d at 864 ("Statements that describe the invention as a whole are more likely to be found in certain sections of the specification, such as the Summary of the Invention."). This rule does not apply to statements, like those relied on by Open here, found in the "Detailed Descriptions" of the invention or of the preferred embodiment.

[3] The type of limiting language described in the foregoing cases is not present in the patents here. As the Federal Circuit stated in Liebel-Flarsheim Co. v. Medrad, Inc., a narrow claim construction is appropriate in cases where "there were specific reasons dictating a narrow claim construction beyond the mere fact that the specification disclosed only a single embodiment or a particular structure." 358 F.3d 898, 907 (Fed.Cir.2004). The Federal Circuit ruled that disputed claims should not be limited to particular

embodiments absent a "clear disavowal of claim scope in either the written description or the prosecution history." Id. at 912; *see also* Phillips, 415 F.3d at 1323 (citing Liebel-Flarsheim with approval).

Unlike the cases cited by Open, the inventors here did not demonstrate any intent for the claims and embodiments "to be strictly coextensive," Phillips, 415 F.3d at 1323, or provide a "clear disavowal of claim scope." Liebel-Flarsheim, 358 F.3d at 912. The Court therefore declines to limit the claims to only one embodiment. *See* Saunders Group, Inc. v. Comfortrac, Inc., 492 F.3d 1326, 1332 (Fed.Cir.2007) (refusing to limit claims to one embodiment absent "a clear intention to limit the claim scope"); Intamin, Ltd. v. Magnetar Techs., Corp., 483 F.3d 1328, 1335 (Fed.Cir.2007) (refusing to limit terms to one embodiment where "the overall context of the patent ... does not specifically disavow" alternative ways of practicing the invention); Phillips, 415 F.3d at 1324-28 (refusing to limit term "baffles" to a specific embodiment disclosed in the specification).

Second, Open argues that plaintiffs' proposed construction of "lentiviral LTR-deleted vector" would render other language in the claims superfluous, because claim 1 of the '123 patent already states that the vector "comprises sequences sufficient for reverse transcription and integration." The Court disagrees.

[4] One rule of claim construction provides that "a claim construction that gives meaning to all the terms of the claim is preferred over one that does not do so." Merck & Co., Inc. v. Teva Pharms. USA, Inc., 395 F.3d 1364, 1372 (Fed.Cir.2005). This is a useful rule of construction but "is not inflexible." Power Mosfet Techs., L.L.C. v. Siemens AG, 378 F.3d 1396, 1410 (Fed.Cir.2004). "[W]here neither the plain meaning nor the patent itself commands a difference in scope between two terms, *they may be construed identically*." Id. (citing Pickholtz v. Rainbow Techs., Inc., 284 F.3d 1365, 1373 (Fed.Cir.2002)) (emphasis added). Even if Open's argument is correct, however, such redundancy would not change the meaning of "LTR deleted" because the patents do not command a different result.

There is no such redundancy or conflict between the proper construction of lentiviral LTR-deleted vector and its use in the claims. Claim 1 of the ' 123 patent provides:

1. A lentiviral vector particle capable of transducing a non-dividing or slowly-dividing cell, said vector particle comprising a lentiviral LTR-deleted (LLD) vector, wherein the LLD vector *comprises sequences sufficient for reverse transcription and integration,* and wherein, upon transduction, the LLD vector comprises a non-functional lentiviral 5' LTR promoter.

(Emphasis added).

Through this language, the inventors merely reiterated what was already said in the specification and file history concerning the definition of lentiviral LTR-deleted vector. The specification says that the lentiviral LTR-deleted vector must be capable of reverse transcription and integration, and that is repeated for added clarity in the language of the claim. The inventors stated that their amendment was for consistency with the specification, even though they professed that it was not necessary. *See* Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13), at 4, 6.

[5] There is no conflict between the correct interpretation of this term and the claim scope. As in the Power Mosfet case, it is entirely proper to construe these terms coextensively where that interpretation is fully supported in the specification and file history. *See* 378 F.3d at 1410. It would be improper for the Court to adopt an interpretation that flies in the face of the specification and file history merely to avoid some

overlap with the claim language. *See also* Nystrom v. TREX Co., 424 F.3d 1136, 1142 (Fed.Cir.2005) (affirming construction of the term "board" to mean a "piece of elongated construction material made from wood cut from a log" even though it rendered "wooden decking board" in a dependent claim surplusage).

Further, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." Phillips, 415 F.3d at 1314. This language in claim 1 of the '123 patent *further reiterates* that this is an important part of how the term is defined. The repetition in this definition of "lentiviral LTR deleted vector" does not create superfluous language, but supports the definition advanced by Sigma and Oxford.

Open's proposed construction would lead to inconsistent results with claim 1 of the '699 patent. This claim provides that the vector comprises a lentiviral LTR-deleted vector, as defined in the specification and file history:

1. A lentiviral vector capable of transducing a non-dividing or slowly-dividing cell, *said vector comprising a lentiviral LTR-deleted vector*.

(Emphasis added). The examiner of this patent found this language to be straightforward by itself, and therefore did not request any further clarification. This claim does not have additional language about "reverse transcription" or "integration" because those requirements are already included in the definition of lentiviral LTR-deleted vector.

The specification teaches that reverse transcription and integration are essential "in order to function as a vector." '123 patent, col. 8, ll. 59-65. Under Open's construction of lentiviral LTR-deleted vector, there is no requirement that the vector must be capable of reverse transcription and integration. Under Open's construction there would be no requirementthat the vectors in claim 1 of the '699 patent be capable of these essential functions. Such an interpretation is contrary to the unambiguous language in the specification, and cannot be correct. Sigma and Oxford's construction is consistent with the specification and with the claim language. Even if this construction did render some claim language repetitious, such a construction is permissible. *See* Power Mosfet, 378 F.3d at 1410.

Third, Open argues that the definition of "lentiviral LTR-deleted vector" must be limited in view of an earlier patent issued to the Kingsmans, U.S. Patent No. 6,235,522 ("the '522 patent"). The '522 patent also relates generally to lentiviral vectors, but is not formally related to the two asserted patents. This patent uses the term "lentiviral LTR-deleted vector" once in its specification as a general description of a modified lentiviral vector, but never uses this term in the claims. *See* '522 patent, col. 6, ll. 32-33.

During prosecution, the examiner rejected certain claims of the pending '699 patent for double patenting as anticipated by the earlier '522 patent. The inventors filed a terminal disclaimer to overcome this rejection. Open takes this as an admission that the vectors in the two asserted patents must be limited to what is claimed in the '522 patent.

The Court disagrees. The filing of a terminal disclaimer is not an "admission" of any sort about the scope of a claim. *See* Ventana, 473 F.3d at 1184 n. 4 (rejecting argument that terminal disclaimer "represents an admission by the inventors equating all claims of the [one] application to all claims of the [the other] Patent"); Quad Envtl. Techs. Corp. v. Union Sanitary Dist., 946 F.2d 870, 874 (Fed.Cir.1991) ("the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection.").

Even if the '699 patent were anticipated by the '522 patent, this would not limit the claims of the '699 patent. To the contrary, the '699 patent could be anticipated but simultaneously be broader and claim additional subject matter (such as different embodiments of LTR-deleted vectors). Indeed, the '522 patent does not use the term "lentiviral LTR-deleted vector" in its claims, but rather uses entirely different terms to describe its claimed vectors. *See* Ventana, 473 F.3d at 1184 n. 4 (noting that arguments concerning scope of other patent "are irrelevant" where the claims used different language).FN11

FN11. Moreover, the term "lentiviral LTR-deleted vector" is clearly defined in the specifications and file histories of the '123 and '699 patents themselves. The '522 patent has no familial relationship with the two asserted patents and therefore is not relevant for claim interpretation. *See* Goldenberg v. Cytogen, Inc., 373 F.3d 1158, 1167-68 (Fed.Cir.2004) (holding that district court erred by interpreting patent based on unrelated patent to the same inventor, emphasizing the "distinct line between patents that have a familial relationship and those that do not."); Texas Digital Sys., Inc. v. Telegenix, Inc., 308 F.3d 1193, 1211 (Fed.Cir.2002) (noting that prosecution history of unrelated patent "sheds no light" on proper interpretation of patent at issue). To the extent that the '522 patent uses the term differently from the two asserted patents, the two asserted patents must control. *See* Young Dental Mfg. Co., Inc. v. Q3 Special Prods., Inc., 112 F.3d 1137, 1143 (Fed.Cir.1997) ("The specification that is relevant to claim construction is the specification of the patent in which the claims reside.").

The Court construes "lentiviral LTR-deleted vector" or "LLD vector" as meaning "a replication-defective vector based on a lentivirus in which (a) one or more LTR nucleotide sequences from the lentivirus, including at least one such nucleotide sequencethat is involved in transcription, are not present, and (b) lentiviral LTR nucleotide sequences necessary for reverse transcription and integration are present."

C. The Meaning of "Capable of Transducing"

[6] The parties agree that "transducing" is a word commonly used in the field, although they dispute its precise definition, and agree that its plain meaning as understood by one of skill in the art of reading the specification and claims should apply. The parties agree that "capable of transducing" means at a minimum that genetic material can be "introduced" into the nucleus of a cell. "Introduction" means that the RNA from the viral vector first enters the cell, is reverse transcribed into DNA, and then crosses the nuclear membrane and enters the nucleus of the cell.

The principal disagreement is whether the transduction ends with the entry of DNA into the nucleus of a cell, or also includes "integrating" DNA into the cell's genome (DNA) after it enters the nucleus. Sigma and Oxford contend that "capable of transducing" means that the lentiviral vector has the ability to both "introduce" the genetic material into the nucleus and "integrate" it into the cell's DNA. Open proposes a more general definition, that "capable of transducing" means only that the vector is "able to transfer genetic material into the nucleus of a cell," and is silent concerning integration. The Court agrees with Sigma and Oxford.

The terms "transduction," "transducing," and "capable of transducing" are not expressly defined in the specification. The specification discloses that prior lentiviral vectors were capable of transducing cells and integrating into the host cell's DNA. *See* '123 patent, col. 2, ll. 10-12 ("The HIV-based vectors produced to date result in an integrated provirus in the transduced cell that has the HIV LTRs at its ends."). The

specification distinguishes between "infection"-getting into the cell-and "transduction," which includes integration:

The lentivirus of the invention provides the ability to infect and transduce non-dividing and/or slowly-dividing cells. During the infection process, lentiviruses form a pre-integration complex.... The complex is able to pass across the nuclear membrane of the target cell, by means of signal sequences in the proteins.

'123 patent, col. 5, ll. 29-35.

The specification goes on to explain that "integration" is essential in order to provide effective gene therapy, which is a stated goal of the invention. As explained in the specification and confirmed by Dr. Cullen, the purpose of the invention is to modify the genome of a diseased cell so that the cell can produce (or "express") beneficial proteins, such as dopamine for a patient with Parkinson's disease. *See, e.g.,* id., col. 2, l. 60-col. 3, l. 40; col. 3, ll. 63-66; col. 4, ll. 26-27; col. 9, ll. 25-27; col. 13, ll. 48-55; Declaration of Dr. Bryan R. Cullen, Docket No. 87 ("Cullen Decl."), at para. 15-16; Tr. at 19:14-17. The cells will only express beneficial proteins in significant quantities if the vector becomes integrated with the host cell's DNA.

In other words, if the vectors merely enter the nucleus without integrating into the DNA, as suggested by Open, they will be useless for therapeutic purposes or related research. This is confirmed by the language in the specification and file history discussed above emphasizing that the LTRs must remain capable of "integration," not only "introduction." '123 patent, col. 8, ll. 59-65; *see also* id., ll. 6-8, 27-30, 37-39, 47-51; Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13), at 6. Thus, in order to carry out a stated purpose of the invention, gene therapy, and related research, transduction must include both introduction and integration.

This conclusion is also consistent with the extrinsic evidence, which generally defines "transduction" as requiring both introduction into the nucleus and integration into the host cell's DNA. For example, Sigma and Oxford offered an article from 1996 from the Proceedings of the National Academy of Sciences USA, that is directed to a "lentiviral vector suitable for in vivo gene delivery." Naldini, et al., Proc. Natl. Acad. Sci. USA 93; 11382 (1996) (Pls.' Ex. 19). The article states that "[t]ransduction occurs by integration of the vector genome." Id.

Open itself cites extrinsic evidence that emphasizes integration into the DNA is essential for gene therapy:

Because of the way replication-defective retroviral vectors are designed, virus particles containing vector genomes can be produced and can be used to infect target cells. The vector genome then undergoes reverse transcription and *integration into the cell's genome,* where it can *express the foreign gene(s) of interest,* but is unable to replicate an additional time and spread to other cells[.]

Buchschacher, Lentriviral Vector Systems for Gene Transfer (2003) (Def.'s Ex. G) at 6 (emphasis added). Integration "into the genome" means that the vector is integrated with the host cell's DNA, where it is used to express genes, i.e., make proteins based on those genes.

Another reference cited by Open states that transduction requires integration. *See* Steadman's Medical Dictionary (26th ed. 1995) (Def.'s Ex. R) at 1837 ("Transfer of genetic material (and its phenotypic expression) from one cell to another by viral infection."). Dr. Cullen testified that this definition implicitly

requires integration, particularly in the context of the patents, because gene expression (or "phenotypic expression") can only occur if the virus has integrated with the DNA. Tr. at 63:13-65:22.

At the claim construction hearing, Open produced for the first time a 1990 publication by Stevenson to support its position that integration is not necessary for expression in HIV. *See* Tr. at 54:22-55:3. In response to the Stevenson paper, Dr. Cullen testified that by 1996, before the Oxford invention, it was known that integration is critical for gene expression. This is shown in the 1996 paper from the National Academy of Sciences, Pls.' Ex. 19: "if [the researchers] had lentiviral vector that cannot integrate, they did not get perceptible expression of the protein of interest." Id. at 63:4-64:11; Naldini, et al., Proc. Natl. Acad. Sci. USA, 93; 11382 (1996). Open did not challenge Dr. Cullen or present rebuttal testimony from its expert on this matter.

The weight of the extrinsic evidence, including Dr. Cullen's testimony, supports Sigma and Oxford's position that "transduction" in the context of these patents requires "integration." To the extent that the Stevenson reference uses a different definition of "transduction," it is inconsistent with the term's use in the patents. *See* Phillips, 415 F.3d at 1319 (extrinsic evidence is "unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence").FN12

FN12. Open also notes testimony by one of the inventors, Dr. Susan Kingsman, in which she agreed that "in the general field outside of this patent" the term "transducing" does not "always" require integration. She further explained that "in the context of this patent," transduction always requires both introduction and integration. Kingsman Dep. at 99:2-15. The parties have offered extrinsic evidence showing that integration is part of transduction and extrinsic evidence showing that integration is not part of transduction. This makes the use of the term transduction "in the context of the patent" all the more critical. To the extent that Dr. Kingsman merely acknowledged the uses of "transduction" in contexts that are inconsistent with this term's use in these patents, this testimony is likewise not relevant to construction of the patents.

Open argues that including integration as part of "transduction" would render portions of claim 6 of the '699 patent superfluous. Claim 6 depends from claim 2, which in turn depends from claim 1. These claims read:

1. A lentiviral vector capable of transducing a non-dividing or slowly-dividing cell, said vector comprising a lentiviral LTR-deleted vector.

2. The lentiviral vector according to claim 1, further comprising a nucleotide sequence encoding a protein of interest.

. . . . .

6. A method of performing gene delivery on a target cell comprising the steps of:

a) transducing the target cell with the lentiviral vector according to claim 2; and

b) delivering the nucleotide sequence to the target cell.

Open asserts that "delivering the nucleotide sequence to the target cell" in step (b) of claim 6 means integration and argues that if "transducing" includes integration, the step of "delivering the nucleotide

sequence" in step (b) would be superfluous with "transducing" in claim 1 and step 6(a).

The Court disagrees. The claims themselves reveal no problem of superfluous language. Claim 1 of the patent says that the vector is "capable of transducing" a cell. In the method of claim 6, step (a) explains that this vector actually transduces the cell. Step (b) further states that in so doing, the nucleotide sequence of claim 2 is actually and successfully delivered to the target cell. There is nothing superfluous, and the plain meaning of the terms is preserved.

Open relies on Bicon, Inc. v. Straumann Co., 441 F.3d 945 (Fed.Cir.2006), in which the Federal Circuit declined to adopt a claim interpretation that "would [require] the public to look past the plain language of the claims and guess whether a detailed description of a structural feature in a claim is superfluous." Id. at 951. Here, the Court would have to look past the plain language of the claim to adopt Open's "superfluous" argument. The Court declines to do so. The Court finds that Open misreads Bicon, in which "superfluous" meant assigning no meaning at all to a claim term, rather than assigning the same meaning to two claim terms. *See* id. at 950 (under patentee's proposed claim construction, " 'a frusto-spherical basal surface portion' ... has no role in the claim and thus is entirely superfluous").

In addition, if the claim did contain superfluous language, the general preference to avoid superfluous language in claims is not strong enough to cause the Court to overlook the plain meaning of the term "transducing" in the context of the patents. *See* Power Mosfet, 378 F.3d at 1410 ("[W]hile interpretations that render some portion of the claim language superfluous are disfavored, where neither the plain meaning nor the patent itself commands a difference in scope between two terms, they may be construed identically.").

Consequently, the Court construes "capable of transducing" as meaning "the ability to introduce and integrate genetic information carried by a viral vector into a cell."

D. The Meaning of "Non-functional Lentiviral 5' LTR Promoter"

[7] The term "non-functional lentiviral 5' LTR promoter" appears only in the claims of the '123 patent. Sigma and Oxford contend that this term means "a lentiviral genetic sequence located at one end (called the 5' end) of the long terminal repeat that is not present or is no longer able to perform its normal function of initiating creation of RNA from DNA (transcription)." Open contends that this term means "a lentiviral genetic sequence located at one end (called the 5' U3 region) of the long terminal repeat that is no longer able to perform its normal function of initiating creation of RNA from DNA (transcription)."

The parties disagree about two points. First, the parties disagree about whether this term is only limited generally to the "5' end" or specifically to the "5' U3 region." As discussed earlier, the "5' U3 region" is a more specific location within the 5' LTR. Claim 1 refers to the "5'" end and, by its own terms, is not limited to the "5' U3 region." The "U3 region" is an extraneous limitation that the Court will not read into the term.

Second, the parties disagree about whether the "non-functional" description means that the sequence is simply "no longer able to perform its normal function," or whether it also includes a sequence that is "not present."

The term "non-functional lentiviral 5' LTR promoter" was added to claim 1 through an amendment during the prosecution history. *See* Amendment and Response to Office Action dated Oct. 21, 2004 (Pls.' Ex. 13),

at 4-6. To support this amendment, the inventors cited the specification as follows: "part of the 3' U3 sequences are deleted so that the transduced vector genome has a nonfunctional 5' LTR promoter." Id.

According to Dr. Cullen, the promoter in the 3' U3 region becomes the 5' LTR promoter upon transduction. Cullen Decl. at para. 160. The specification and prosecution history therefore show that deletion of the 5' LTR promoter, i.e., making it "not present," is one means of rendering it non-functional. Thus, in the context of the patent, "non-functional" includes "not present." Moreover, there is no disclaimer or disavowal that would prohibit deleting all of the promoter sequences, as opposed to deleting only some portion of the promoter sequences. *See, e.g.,* '123 patent, col. 8, ll. 5-8 (deleting all of U3 except short sequence necessary for integration).

The Court agrees with Sigma and Oxford that "non-functional lentiviral 5' LTR promoter" is properly construed as "a lentiviral genetic sequence located at one end (called the 5' end) of the long terminal repeat that is not present or is no longer able to perform its normal function of initiating creation of RNA from DNA (transcription)."

IV. Conclusion

For the foregoing reasons, the Court concludes that the constructions of the disputed terms and phrases proposed by plaintiff are correct, and adopts those constructions.

Accordingly,

IT IS HEREBY ORDERED that Plaintiffs' Motion for Claim Construction is **GRANTED** as set forth in this Memorandum and Order. [Doc. 86]

For the foregoing reasons, the Court concludes that the constructions of the disputed terms and phrases proposed by plaintiff are correct, and adopts those constructions.

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