

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND
SOUTHERN DIVISION**

STEMCELLS, INC. *et al.*

Plaintiffs,

v.

NEURALSTEM, INC.

Defendant.

Action No. 08:06–CV–1877—AW

MEMORANDUM OPINION

Plaintiffs StemCells, Inc. and Stemcells, California, Inc. (collectively, “StemCells”) filed this action against Neuralstem, Inc., Karl Johe, and I. Richard Garr, on July 24, 2006, alleging Neuralstem infringed several of StemCells’ patents in violation of 28 U.S.C. §§1, *et seq.* The parties have requested that the Court construe several claim terms that are in dispute in this case.

A. STANDARD OF REVIEW

Claim construction is decided by the court as a matter of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970-71 (Fed. Cir. 1995) (en banc), *aff’d* 517 U.S. 370 (1996). “The duty of the trial judge is to determine the meaning of the claims at issue, and to instruct the jury accordingly.” *Exxon Chem. Patents, Inc. v. Lubrizoil Corp.*, 64 F.3d 1553, 1555 (Fed. Cir. 1995) (citations omitted), *cert. denied*, 518 U.S. 1020, 116 S. Ct. 2554, 135 L. Ed. 2d 1073 (1996). In order to determine the meaning of a claim term, the Court should first look to the plain language of the claim and presume it carries its “ordinary and customary meaning.” *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1324 (Fed. Cir. 2002); *Vitronics Corp. v. Conceptoronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The ordinary and customary meaning is defined as the meaning that the claim term would have to a person having ordinary skill in the

art at the date the patent application in question was filed. *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*).

In order to ascertain the ordinary and customary meaning of a disputed claim term, the claims themselves must be thoroughly examined. If a claim term is used more than once throughout the patent, the “usage of a term in one claim can often illuminate the meaning of the same term in other claims.” *Markman*, 52 F.3d at 978. “Differences among the claims can also be a useful guide in understanding the meaning of particular claim terms.” *Id.* Further, the language used to separate the preamble of a claim from the body of a claim can offer insight into the claims’ meaning. *See Gillette Co. v. Energizer Holdings, Inc.*, 405 F. 3d 1367, 1371 (Fed. Cir. 2005). For example, “the word ‘comprising’ transitioning from the preamble to the body signals that the entire claim is presumptively open-ended.” *See id.* (citing *Crystal Semiconductor Corp. v. TriTech Microelectronics Int’l, Inc.*, 246 F.3d 1336, 1347 (Fed. Cir. 2001)). Finally, “the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.” *Phillips*, 415 F.3d at 1315.

If there is ambiguity as to the ordinary and customary meaning, it is proper for the Court to look to the specification in order to determine the “true intent and meaning of the language in the claims.” *Bates v. Coe*, 98 U.S. 31, 38 (1878); *see also Phillips*, 415 F.3d at 1316. The specification, in conjunction with the prosecution history and the prior art cited during the patent prosecution serve as intrinsic evidence and can be used to ascertain the true meaning of the disputed claim terms. *Phillips*, 415 F.3d at 1319-24. Preferred embodiments in the specification should be used to assist in determining the claim scope since these embodiments reflect the inventor’s desired use for his or her patent. However, if a proposed claim construction excludes a preferred embodiment from the claim scope, this construction is rarely correct. *Phillips*, 415 F.3d at 1316; *Anchro Wall Systems, Inc. v. Rockwood Retaining Walls, Inc.*, 340 F.3d 1298, 1308

(Fed. Cir. 2003). On the other hand, it is improper to read limitations from the specification into the claims unless the specification makes consistent and repeated statements leading to the “inescapable conclusion” that a limitation stated only in the specification is part of the claimed invention. *Phillips*, 415 F.3d at 1323. In order to add a limitation that excludes certain embodiments of the invention to a claim, there must be some “express disclaimer or independent lexicography in written description that would justify adding a negative limitation.” *Omega Eng’g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1322-23 (Fed. Cir. 2003).

In addition to the intrinsic evidence, dictionaries, expert testimony, and documents or prior art not part of the prosecution history may be used to determine the true meaning of a claim term, however, these documents are considered extrinsic evidence. *Id.* Although extrinsic evidence may be used to assist the court in determining the meaning of the disputed claim terms, intrinsic evidence will shed greater light onto what the term means to a person having ordinary skill in the art, and thus carries more weight than extrinsic evidence. *Id.* It is not necessarily important which order the Court consults these references in; what matters is that the Court gives the consulted sources the appropriate weight. *Id.* at 1324 (citing *Vitronics*, 90 F.3d at 1582). Because the Court must determine what the disputed claim terms would mean to a person having ordinary skill in the art at the time of invention, it is most important to understand the claim term in light of the invention’s scope, as determined by the claims themselves, the specification, the prosecution history and the prior art. *See id.* at 1319-24.

B. CLAIM CONSTRUCTION OF DISPUTED TERMS

a. “multipotent” (Term No. 4)

Found in the following claims: 1, 2, 8, 21, 34, 36, 37, 39, 40, 41, 43, 44, 45, 47, 54, 55, 56, 60, 61, 67, 70, 72, 75, 79, and 80 of the ‘832 patent; 1, 7, and 24 of the ‘418 patent; 9 and 24 of the ‘505 patent; 1 and 10 of the ‘346 patent; 1 and 10 of the ‘709 patent; and 1, 8, 9, and 22 of the ‘872 patent.

"multipotent"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
The progeny of a single neural stem cell have multiple differentiative pathways such as neurons, astrocytes (type 1 and type II), and oligodendrocytes.	When used in referring to a cell, means that the progeny of the cell have multiple differentiative pathways.

The parties' proposed constructions of this term are substantively similar in that both parties define the progeny of a multipotent cell to have "multiple differentiative pathways." The conflict between the two constructions arises because Neuralstem's proposed construction defines multipotent exclusively in terms of neural stem cells whereas StemCells prefers a broader definition of multipotent that is applicable to stem cells of a non-neural lineage. By referring only to neural stem cells, Neuralstem's construction of "multipotent" correctly includes the phrase, "such as neurons, astrocytes (type I and type II), and oligodendrocytes." The correctness of the examples is not in dispute as StemCells admits that Neuralstem's "construction is . . . applicable when the term 'multipotent' is used in conjunction with 'neural stem cells.'" Doc. No. 169, at 46. The prevailing issue is whether the term "multipotent" should refer to all cells or just neural stem cells.

The Court needs to look no further than the specification to determine the proper scope and thus proper construction of "multipotent." The '832 patent clearly supports Neuralstem's definition of the claim term. The specification states, "[t]he progenitor cells generated from a single multipotent neural stem cell are capable of differentiating into neurons, astrocytes (type I and type II) and oligodendrocytes. Hence, the neural stem cell is 'multipotent' because its progeny have multiple differentiative pathways." U.S. Patent No. 5,851,832 col.12 ll.59-64 (filed Dec. 22, 1998). Both parties' constructions are based on the specification; however, StemCells' definition of "multipotent" encompasses only a portion of the meaning given to the claim term in the specification. Neuralstem's construction of "multipotent" encompasses the

entirety of the specification giving the term a definition which includes the specific differentiative pathways of a multipotent neural stem cell’s progeny—neurons, astrocytes (type I and type II), and oligodendrocytes. The “multiple differentiative pathways” referenced in the specification and used in StemCells’ construction appear to simply summarize the specific types of pathways previously mentioned in the specification. Thus, adopting StemCells’ construction would require the Court to ignore the specific types of differentiative pathways that the specification has explicitly mentioned to characterize multipotent neural stem cells in favor of a summation of the pathways.

StemCells alleges that “multipotent” has “broader meanings and can be used to describe stem cells of a non-neural lineage Neuralstem’s proposed definition of ‘multipotent’ would therefore be completely at odds with the state of the art at the time of the filing.” Doc. No. 175, at 58. Assuming StemCells’ premise to be true, the Court finds it irrelevant as the Court believes that the patents-in-suit simply contemplate “progenitor cells generated from a single multipotent *neural* stem cell,” not stem cells of a non-neural lineage. ‘832 Patent col.12 ll.59-60. StemCells, in support of their premise, has cited an article from the *Immunology and Cell Biology* journal proving that at the time of the filing, the term “multipotent” applied to stem cells of a non-neural lineage, including “a multipotent hematopoietic (blood) cell.” Doc. No. 175, at 58. Yet, the Court is not persuaded because Neuralstem’s construction is not meant to be a broad definition, but rather only a definition applicable to the patents-in-suit. Further, the Court believes that the patentee understood the term “multipotent” to only describe stem cells of a neural lineage. The patent specification provides convincing evidence to support the Court’s conclusion that only neural stem cells were considered. Therefore, the Court believes that the patents-in-suit only describe neural stem cells, and thus the proper construction of the term “multipotent” does the same.

Accordingly, the Court will adopt Neuralstem’s proposed construction of this claim term.

b. “culture medium” (Term No. 21)

Found in the following claims: 1, 2, 3, 4, 8, 21, 22, 30, 31, 32, 33, 34, 35, 38, 40, 44, 45, 46, 47, 48, 49, 52, 53, 54, 58, 69, and 77 of the ‘832 patent; 1, 3, 7, and 9 of the ‘418 patent; 1, 2, 3, 13, 14, 18, 19, 20, 25, and 26 of the ‘505 patent; and 1, 3, 5, 8, and 22 of the ‘872 patent.

"culture medium"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
Liquid capable of supporting cell growth and may contain serum or be serum-free.	A liquid or solid nutrient preparation capable of supporting cell cultivation; culture medium may contain serum or may be serum-free.

The parties agree that “culture medium” “support[s] cell growth and may contain serum or be serum-free”. The parties dispute whether “culture medium” should be defined as a liquid or both a liquid and “solid nutrient preparation.”

Neuralstem alleges that only a liquid form of “culture medium” should be included in the term’s construction because only the liquid form of “culture medium” is described in the specification. StemCells does not dispute Neuralstem’s contention that the specification fails to mention a solid nutrient preparation of “culture medium” as “[n]eural cells are typically cultivated in liquid culture media.” Doc. No. 169, at 49. However, StemCells believes that this omission from the specification does not lead to the conclusion that solid nutrient preparation should be excluded from the definition of “culture medium.”

On the contrary, StemCells argues that no precedential authority exists which mandates that “the specification must describe or provide examples in order to include an art-known embodiment into a claim term.” Doc. No. 175, at 54. StemCells claims “culture medium” includes solid nutrient preparation in its “ordinary and customary meaning as understood by one or [sic] ordinary skill in the art.” Doc. No. 169, at 48. StemCells cites the Concise Dictionary of Biomedical and Molecular Biology, *Id.*, and the journal article, *Growth of Cells on Solid Culture*

Medium, for the proposition that “[t]he art had already known that culture medium, standing alone, includes solid nutrient preparation.” Doc. No. 175, at 54. However, StemCells has attached no excerpt or passage from the article to support their proposition.

Without any further support from the record, the Court will first look to the specification for guidance as to the meaning of “culture medium” before consulting a dictionary. The specification is not ambiguous as it mentions only the liquid form of “culture medium,” thus clearly supporting Neuralstem’s proposed construction. StemCells does not dispute that the specification mentions only the liquid form of “culture medium.” Therefore, the Court will adopt Neuralstem’s proposed construction of this claim term.

c. “EGF-like ligands” (Term No. 25)

Found in the following claims: 5 of the ‘346 patent; and 5 of the ‘709 patent.

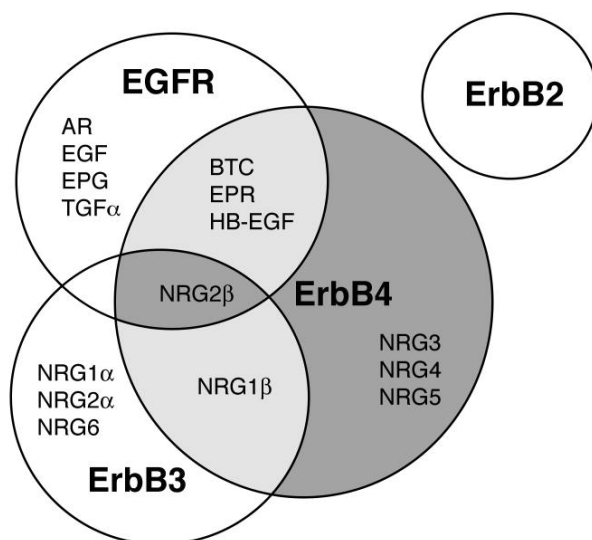
"EGF-like ligands"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
A compound structurally similar to EGF and binds to the EGF receptor.	A compound that is structurally similar to EGF; EGF-like ligands include, <i>e.g.</i> , EGF, TGF- α , betacellulin, heparin-binding epidermal growth factor, heregulin, cripto, and/or amphiregulin.

Neuralstem’s proposed definition of the claim term requires the EGF-like ligands to bind to the EGF receptor while StemCells’ proposed definition includes a list of examples of EGF-like ligands.

StemCells avers that the specification “clearly supports some of the EGF-like ligands listed by StemCells,” citing claim 4 of the ‘832 patent as support. Doc. No. 175, at 55. Claim 4 of the ‘832 patent identifies EGF, TGF- α , and amphiregulin as EGF-like ligands. *See* ‘832 Patent col.69 ll.36-39. StemCells further supports the examples included in their proposed construction by citing articles from *Progress in Growth Factor Research*, the *Journal of Mammary Gland Biology and Neoplasia*, and *Pharmacology & Therapeutics*. *See* Doc. No. 175,

at 56. While StemCells has supported the examples that are included in their proposed construction, it is important to note that StemCells’ definition only “include[s]” certain examples, meaning the list is not meant to be exclusive.

Neuralstem contends that by having the “EGF-like ligands bind to the EGF receptor (their proposed construction) gives meaning to ‘ligand’ which in the field of biochemistry means binding.” Doc. No. 171, at 42. Yet, StemCells opposes Neuralstem’s definition of this term on the grounds that “not all EGF-like ligands bind to the EGF Receptor.” Doc. No. 175, at 56. StemCells presents extrinsic evidence that clearly supports this notion in the form of a journal article entitled *Functional Selectivity of EGF Family Peptide Growth Factors: Implications for Cancer*. See *Id.* A figure from the article is presented below.



Kristy J. Wilson et al., *Functional Selectivity of EGF Family Peptide Growth Factors: Implications for Cancer*, 122 *Pharmacology & Therapeutics* 1 (2009) (figure 2). As posited by StemCells and demonstrated by the figure, “EGF-like ligands such as neuregulins do not bind to the EGF receptor.” Doc. No. 175, at 56.

The Court will adopt StemCells’ proposed construction of this claim term because there is ample support for all of the examples StemCells gave in their definition, the list of examples is

not meant to be exhaustive, and Neuralstem’s proposed construction does not appear to be scientifically accurate.

d. “neural stem cell(s)” (Term No. 37)

Found in the following claims: 1, 2, 8, 21, 34, 36, 37, 39, 40, 41, 43, 44, 45, 47, 54, 55, 56, 60, 61, 67, 70, 72, 75, 79, and 80 of U.S. Patent No. 5,851,832 (the ‘832 patent); 1 and 7 of U.S. Patent No. 7,115,418 (the ‘418 patent); 24 of U.S. Patent No. 7,361,505 (the ‘505 patent); 1 and 10 of U.S. Patent No. 6,294,346 (the ‘346 patent); 1 and 10 of U.S. Patent No. 7,101,709 (the ‘709 patent); and 1, 2, 3, 8, 9, 11, 12, 17, 22, 24, and 30 of U.S. Patent No. 6,497,872 (the ‘872 patent).

"neural stem cell(s)"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
A cell proliferated using the methods described in Examples 1-4.	An undifferentiated neural cell that (1) can be induced to proliferate and is able to divide essentially without limit; (2) is capable of self-maintenance, meaning with each cell division, at least one daughter cell will also be a stem cell; and (3) its non-stem cell progeny are progenitor cells capable of differentiating into neurons, astrocytes and oligodendrocytes.

It is clear from the ‘832 patent that the patentee provided a special definition for “neural stem cell(s).” Further, both parties agree that “[w]here, as here, a patentee sets out a special definition that definition is controlling.” Doc. No. 171, at 13. However, both parties claim that their proposed construction for “neural stem cell(s)” is the special definition provided by the specification.

The ‘832 patent discusses “neural stem cell(s)” in the following manner:

The capability of a cell to divide without limit and produce daughter cells which terminally differentiate into neurons and glia are stem cell characteristics. Accordingly, as used herein, the cells proliferated using the methods described in Examples 1-4 are termed ‘neural stem cells’. [sic] A neural stem cell is an undifferentiated neural cell that can be induced to proliferate using the methods of the present invention. The neural stem cell is capable of self-maintenance, meaning that with each cell division, one daughter cell will also be a stem cell. The non-stem cell progeny of a neural stem cell are termed progenitor cells. The

progenitor cells generated from a single multipotent neural stem cell are capable of differentiating into neurons, astrocytes (type I and type II) and oligodendrocytes.

'832 Patent col.12 ll.48-57. The examples to which the patent refers are:

Example 1
Dissociation of Embryonic Neural Tissue
14-day-old CD ₇ albino mouse embryos (Charles River) were decapitated and the brain and striata were removed using sterile procedure. Tissue was mechanically dissociated with a fire-polished Pasteur pipette into serum-free medium composed of a 1:1 mixture of Dulbecco's modified Eagle's medium (DMEM) and F-12 nutrient (Gibco). Dissociated cells were centrifuged at 800 r.p.m. for 5 minutes, the supernatant aspirated, and the cells resuspended in DMEM/F-12 medium for counting.

Example 2
Dissociation of Adult Neural Tissue
Brain tissue from juvenile and adult mouse brain tissue was removed and dissected into 500 µm sections and immediately transferred into low calcium oxygenated artificial cerebrospinal fluid (low Ca ²⁺ aCSF) containing 1.33 mg/ml trypsin, 0.67 mg/ml hyaluronidase, and 0.2 mg/ml kynurenic acid. Tissue was stirred in this solution for 90 minutes at 32° C.-35° C. aCSF was poured off and replaced with fresh oxygenated aCSF for 5 minutes. Tissue was transferred to DMEM/F-12/10% hormone solution containing 0.7 mg/ml ovomucoid and triturated with a fire polished pasteur pipette. Cells were centrifuged at 400 rpm. for 5 minutes, the supernatant aspirated and the pelleted cells resuspended in DMEM/F-12/10% hormone mix.

Example 3
Proliferation of Neural Stem Cells on Substrates

2500 cells/cm² prepared as in Example 1 were plated on poly-L-ornithine-coated (15 µg/ml;Sigma) glass coverslips in 24 well Nunclon (0.5 ml/well) culture dishes. The culture medium was a serum-free medium composed of DMEM/F-12 (1:1) including glucose (0.6%), glutamine (2 µM), sodium bicarbonate (3 mM), and HEPES (4-[2hydroxyethyl]-1-piperazineethanesulfonic acid) buffer (5 mM) (all from Sigma except glutamine [Gibco]). A defined hormone mix and salt mixture (Sigma) that included insulin (25 µg/ml), transferrin (100 µg/ml), progesterone (20 nM), putrescine (60 µM), and selenium chloride (30 nM) was used in place of serum. Cultures contained the above medium, hereinafter referred to as "Complete Medium" together with 16-20 ng/ml EGF (purified from mouse sub-maxillary, Collaborative Research) or TGFα (human recombinant, Gibco). After 10-14 days in vitro, media (DMEM only plus hormone mixture) and growth factors were replaced. This medium change was repeated every two to four days. The number of surviving cells at 5 days in vitro was determined by incubating the coverslips in 0.4% trypan blue (Gibco) for two minutes, washing with phosphate buffered saline (PBS, pH 7.3) and counting the number of cells that excluded dye with a Nikon Diaphot inverted microscope.

Example 4

Proliferation of Embryonic Mouse Neural Stem Cells in Suspension

Dissociated mouse brain cells prepared as in Examples 1 and 2 (at 1x10⁵ cell/ml) were suspended in Complete Medium with 20 ng/ml of EGF or TGFα. Cells were seeded in a T25 culture flask and housed in an incubator at 37° C., 100% humidity, 95% air/5% CO₂. Cells began to proliferate within 3-4 days and due to a lack of substrate lifted off the floor of the flask and continued to proliferate in suspension forming clusters of undifferentiated cells, referred to herein as "neurospheres". After 6-7 days in vitro the proliferating clusters (neurospheres) were fed every 2-4 days by gentle centrifugation and resuspension in DMEM with the additives described above.

'832 Patent col.34-35.

StemCells first argues that their proposed construction for "neural stem cell(s)" is a special definition explicitly provided by the specification. StemCells urges that "the entire specification, including specific examples, should be consulted rather than *selected snippets*." Doc. No. 175, at 20 (emphasis in original). By taking a holistic approach and reading the entire intrinsic record, StemCells' proposed construction comes from the entirety of the '832 patent cited above. Similarly, Neuralstem posits that the patentee set forth a special definition for "neural stem cell(s)" in the specification of the '832 patent which Neuralstem's proposed construction replicates. As support for their proposition, Neuralstem alleges that "the use of the

words ‘accordingly,’ ‘as used herein,’ ‘are termed,’ and the deliberate use of quotation marks around the term ‘neural stem cells’ all demonstrate that the patentee deliberately and precisely set forth a special definition.” Doc. No. 171, at 13-14.

StemCells acknowledges that “the inventors have included in the specifications at least four embodiments of the invention claim.” Doc. No. 169, at 18. However, StemCells also notes that the “infringed claims are not methods claims restricted to these preferred embodiments[,] and it would be error to read into these structural claims specific features of the method of manufacturing these cells.” *Id.* The Court is convinced by the intrinsic record that “neural stem cell(s)” is meant to be a claimed product rather than a method claim and should be read as such.

Yet, Neuralstem correctly cites *Sinorgchem Co., v. International Trade Commission*, 511 F.3d 1132 (Fed. Cir. 2007), for the proposition that when a term is “set off by quotation marks [it is] often a strong indication that what follows is a definition.” 511 F.3d at 1136. Further, Neuralstem provides numerous examples of language that often indicates a special definition is forthcoming such as “the word ‘term[ed]’ or the phrases ‘herein as,’ ‘hereinafter referred to as,’ ‘used herein,’ ‘as herein used,’ or its equivalent.” Doc. No. 178, at 4 (alteration in original). The cited portion of the ‘832 patent itself uses the phrase “as used herein.” ‘832 Patent col.12 ll.51. However, this method of claim construction is not absolute. The Court relies on precedent supporting the proposition that the “court must construe the disputed claim in view of the entire specification, including the drawings.” *See Medtronic Sofamor Danek USA, Inc. v. Globus Med., Inc.*, No. 06-4248, 2008 WL 732022, at *23 (E.D. Pa. Mar. 18, 2008) (citing *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995). As several courts have observed, “while examples disclosed in the preferred embodiment may aid in the proper interpretation of a claim term, the scope of a claim is not necessarily limited by such examples.” *E.g., STX, Inc. v. Brine, Inc.*, 37 F. Supp. 2d 740, 766 (D. Md. 1999) (quoting *Ekchian v. Home Depot, Inc.*, 104 F.3d 1299, 1303 (Fed. Cir. 1997).

Viewing the specification in its entirety, it appears to the Court that the patentee’s definition is more consistent with StemCells’ proposed construction. StemCells’ proposed construction appears to adopt a definition which considers the entirety of the patent and the properly claimed product, hence, not limiting this definition to the four embodiments cited. Moreover, the prosecution history of this patent supports StemCells’ proposed construction as the USPTO Board of Patent Appeals and Interferences held that “[n]eural stem cells are undifferentiated cells that can ‘divide without limit and produce daughter cells which terminally differentiate into neurons and glia.’” Ex Parte Weiss, No. 2006-0840, Doc No. 170-8, at 1-2 (B.P.A.I. May 9, 2006). Also, the Examiner’s definition of “neural stem cell(s)” being “an undifferentiated neural cell that can be induced to proliferate, and is capable of self-maintenance and multipotent” is more in agreement with StemCells’ definition than Neuralstem’s definition. Doc. No. 175, at 22.

In conclusion, the intrinsic record and the the prosecution history of the ‘832 patent is more consistent with StemCells’ proposed construction of this term. Therefore, the Court will adopt StemCells’ proposed construction of this claim term.

e. “consisting of” (Term No. 38)

Found in the following claim: 80 of the ‘832 patent.

"consisting of the undifferentiated progeny of a single human multipotent neural stem cell"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
All progeny of the single human multipotent neural stem cell are undifferentiated.	That the cluster does not contain cells other than the undifferentiated progeny of a single human multipotent neural stem cell, except for impurities ordinarily associated with cell culture prepared <i>in vitro</i> .

f. “consisting of” (Term No. 54)

Found in the following claims: 1, 13, 14, and 25 of the '505 patent.

"neurospheres consist of undifferentiated neural cells that are: nestin+ and; are glial fibrillary acidic protein (GFAP)-; neurofilament (NF)-; and myelin basic protein (MBP)-; and not nestin-"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
Neurospheres contain all undifferentiated neural cells. All of the undifferentiated neural cells stain positive for Nestin, and none of the undifferentiated neural cells stain positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein.	The neurospheres do not include cells other than undifferentiated neural cells, except for impurities ordinarily associated with culturing neurospheres, wherein the undifferentiated neural cells are characterized by the following: (1) positive immunocytochemistry staining of Nestin, and (2) negative immunocytochemistry staining of glial fibrillary acidic protein (GFAP), neurofilament (NF), and myelin basic protein (MBP), via standard immunocytochemistry techniques; "negative staining" means the signal of immune-staining does not exceed background level.

The preceding two claims are addressed together in the joint claim construction, and thus the Court will address them accordingly. First, the parties dispute whether “consisting of” as used in term number 38 can include “impurities ordinarily associated with cell culture prepared *in vitro*.” StemCells alleges that “[a]lthough the term ‘consisting of’ signifies the exclusion of unrecited steps or components, the exclusion is not absolute.” Doc. No. 175, at 12. StemCells cites the USPTO Board of Patent Appeals and Interferences as supporting their claim that “impurities ordinarily associated therewith” are not excluded from the term “consisting of.” Doc. No. 175, at 37. Neuralstem counters StemCells by stating that “[t]he Federal Circuit has held that ‘consisting of’ does not always include impurities.” Doc No. 178, at 24. However, Neuralstem seemingly accepts that some impurities “such as sugars, amino acids, water, serum, etc., would be acceptable” in the proposed construction. *Id.* at 25. The most important

discrepancy between the parties' proposed constructions is that Neuralstem believes "StemCells' construction appears to leave open the illogical possibility that *differentiated* cells could be within the scope of the 'consisting of' neurosphere claims." *Id.* (emphasis in original).

Neuralstem argues that "to give proper meaning to the phrase 'consisting of,' all cells must be undifferentiated." Doc. No. 171, at 33.

The Court recognizes the *Conoco, Inc. v. Energy & Environmental International, L.C.*, 460 F.3d 1349 (Fed. Cir. 2006), holding that "consisting of" permits the presence of "impurities that a person of ordinary skill in the relevant art would ordinarily associate with a component on the 'consisting of' list." 460 F.3d at 1360. Neuralstem seemingly concurs with this finding by accepting that some "common culture medium components . . . would be acceptable." Doc No. 178, at 25. Neuralstem's contention that differentiated cells should not be within the scope of the "consisting of" list because the "specification does not describe differentiated cells as impurities commonly associated with neurospheres" is not for a claim construction to determine. Doc No. 178, at 26. Neuralstem produces evidence that supports this notion; however, that evidence will be judged by the fact-finder. Regardless of whether Neuralstem is correct in finding that differentiated cells should not be considered an impurity, this Court is influenced by the precedence which includes impurities within a "consisting of" list. Therefore, the Court will adopt StemCells' proposed construction of this claim term.

Secondly, there are three disputes between the parties' proposed constructions for term number 54. First, the parties agree that "neurospheres do not include cells other than undifferentiated neural cells;" however, the parties again dispute whether the definition should include an exception for impurities. The Court uses the same logic described for term number 38 above and once again decides that precedent dictates that the impurities exception should be included within the "consists of" list. This determination favors StemCells' proposed construction.

Further, the parties dispute “whether any cell in the neurosphere may stain positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein.” Doc. No. 224, at 6. The Court surmises that Neuralstem is concerned with the phrase, “wherein the undifferentiated neural cells are characterized by the following: ... (2) negative immunocytochemistry staining of glial fibrillary acidic protein (GFAP), neurofilament (NF), and myelin basic protein (MBP), via standard immunocytochemistry techniques.” If differentiated cells are considered impurities and thus are included within the “consisting of” list, then Neuralstem is concerned whether these cells can test positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein. The Court, as first stated above for term number 38, does not think this is a matter for claim construction. It is for the fact-finder to determine whether differentiated cells may be considered impurities and thus “whether any cell in the neurosphere may stain positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein.” *Id.*

Finally, the parties dispute “whether the term ‘negative staining’ should be included.” *Id.* There is no argument within the record by either party for or against the inclusion of the phrase “negative staining.” The Court is persuaded by precedent that StemCells’ proposed construction is the better definition in regards to the first two disputes. Therefore, the Court will adopt StemCells’ proposed construction of this claim term.

g. “neurosphere(s)” (Term No. 41)

Found in the following claims: 1, 13, 14, 18, 25, and 26 of the ‘505 patent; and 1 and 11 of the ‘346 patent.

"neurosphere(s)"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction

A cluster of undifferentiated neural cells that have lifted off the floor of the container and continue to proliferate in suspension in the continued presence of a proliferation-inducing growth factor. Cells within a single neurosphere are clonally derived.

A cluster of undifferentiated cells wherein (1) the cells of a single neurosphere are clonal in nature because they are the progeny of a single neural stem cell and (2) in the continued presence of a proliferation-inducing growth factor precursor cells within the neurosphere continue to divide resulting in increase in the size of the neurosphere and the number of undifferentiated cells.

The term “neurosphere(s)” is described in multiple locations of the specification and is alluded to in numerous locations within the prosecution history of the patents-in-suit. The term “neurosphere(s)” was not a known scientific term at the time of the filing and the patentee failed to give one explicit definition for the term within the patents-in-suit. The parties’ proposed constructions differ because of the ambiguity associated with “neurosphere(s).” Neuralstem succinctly directs the Court to the differences in the parties’ proposed constructions of the term.¹ The parties’ primary disagreement is whether the definition of “neurosphere(s)” should include the “lifted off the floor” language. StemCells and Neuralstem both find support for their respective proposed constructions in the specification, patent history, and extrinsic evidence.

Neuralstem’s proposed construction relies upon Example 4 of the ‘832 patent:

Cells began to proliferate within 3-4 days and due to a lack of substrate lifted off the floor of the flask and continued to proliferate in suspension forming clusters of undifferentiated cells, referred to herein as “neospheres”.

‘832 Patent col.35. StemCells’ proposed construction relies upon the specification of the ‘832 patent:

Within 3-4 days in the presence of a proliferation-inducing growth factor, a multipotent neural stem cell begins to divide giving rise to

¹ Neuralstem highlights that there are differences in the parties’ proposed definitions stating, “[o]ne is that Neuralstem’s construction includes the concept that the cells must ‘lift[] off the floor of the container and continue to proliferate in suspension.’ This limitation is absent from StemCells’ construction. Another difference is that StemCells’ construction includes a limitation that the cells are proliferated ‘in the continued presence of a proliferation-inducing growth factor.’” Doc. No. 171, at 19.

a cluster of undifferentiated cells referred to herein as a “neurosphere”. The cells of a single neurosphere are clonal in nature because they are the progeny of a single neural stem cell. In the continued presence of a proliferation-inducing growth factor such as EGF or the like, precursor cells within the neurosphere continue to divide resulting in an increase in the size of the neurosphere and the number of undifferentiated cells.

‘832 Patent col.17 ll.5-14. The specification seemingly supports both parties’ proposed constructions. However, StemCells alleges that “Example 4 refers to ‘suspension’ culture [that] ‘due to a lack of substrate[]’ . . . the neurospheres would lift off the floor.” Doc No. 175, at 30. The Court believes that a limitation found within an embodiment of the invention should not limit the meaning of the term “neurosphere.”

Neuralstem supports the “lift off the floor” language by referring to extrinsic evidence from the first named inventor of the patent, Samuel Weis. Weis explained that “he (and co-inventor Brent Reynolds) ‘coined’ the term ‘neurosphere’ ‘to describe floating spheres of neural cells.’” Doc. No. 178, at 13.² Yet, Neuralstem seems to ignore the specification’s language that “[p]roliferation and perpetuation of the neural stem cell progeny can be carried out either in suspension cultures, or by allowing cells to adhere to a fixed substrate.” ‘832 Patent col.10 ll.61-64. Moreover, Neuralstem’s proposed construction is flawed in light of the fact that in several of the specification’s other provisions, the patentee explicitly defines a neural cell as one which

² Neuralstem offers the following interview exchange between Weis and an interviewer:

Q. Sure. What is a neurosphere?

* * *

A. So “neurosphere” was a term coined by Brent Reynolds and I think—I can’t remember if it was Brent or I, one of us, both—to describe floating spheres of neural cells.

* * *

Q. Sure. Well, what did you think the novel characteristics of neurospheres were?

* * *

A. So neurospheres were—we coined the term “neurospheres” as floating spheres of neural cells. Floating spheres of neural cells. Does that answer your question?

can proliferate in suspension or one which can adhere to a fixed structure. *See id.*; ‘832 Patent col.12 ll.12-15.

The Court is not willing to read a limitation into the claim at the expense of excluding other embodiments in the specification. Adopting Neuralstem’s proposed construction of the term “neurosphere(s)” would lead to this result. Further, StemCells’ definition of “neurosphere(s)” does not include any particular limitation and is more consistent with the patent’s specification in this case. Therefore, the Court will adopt StemCells’ proposed construction of this term.

h. “pure . . . consisting of” (Term No. 42)

Found in the following claims: 1, 13, 14, 18, 25, and 26 of the ’505 patent.

"pure in vitro cell culture composition . . . consisting of neurospheres and culture medium, wherein said neurospheres consist of undifferentiated neural cells"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
The culture composition contains only neurospheres and culture medium, and those neurospheres contain only undifferentiated neural cells.	An <i>in vitro</i> culture that does not include materials other than neurospheres and culture medium, except for impurities ordinarily associated with <i>in vitro</i> cell culture; and the neurosphere does not include cells other than undifferentiated neural cells, except for impurities ordinarily associated with culturing neurospheres.

The parties’ proposed definitions differ with respect to whether “pure” should include impurities or alternatively a substance with no impurities. The term “pure . . . consisting of” is not specifically defined in the patent. Thus, to determine the meaning of this term, the Court must look to the plain language of the claim and presume that it carries its ordinary and customary meaning. The ordinary and customary meaning is defined as the meaning that the claim term would have to a person having ordinary skill in the art at the date the patent

application in question was filed. *See Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc).

Neuralstem argues that logically “‘pure’ should [not] explicitly *include* ‘impurities.’” Doc. No. 171, at 29 (emphasis in original). In support of their argument Neuralstem cites Random House Webster’s College Dictionary for the proposition that “‘pure’ is something that is ‘free from adulterating or extraneous matter....’” *Id.*

StemCells, on the other hand, insists that “[t]he concept that a ‘pure’ culture is not 100% pure is well understood in the art.” Doc. No. 175, at 46. StemCells cites many examples where the term “pure” is used to connote 90%, 95%, 98%, and 99% purity within the scientific field.³ However, nothing in the briefs leads the Court to believe that this conclusion extends to all scientific matter, or specifically, the technology at issue in this case. Because none of these examples directly relates to neural stem cells, the Court is required to make an inference regarding purity that the Court is not willing to make.

In further support of their proposed construction, StemCells cites *Johns Hopkins University v. Cellpro, Inc.*, 152 F.3d 1342 (Fed. Cir. 1998), for the proposition that the reality of the technology at issue is that only a purity level of 85-90% can be reached. *See* 152 F.3d at 1355-56. The Court is not persuaded by StemCells’ argument as *John Hopkins University* was debating the term “substantially free” and not “pure.” *See id.* at 1355. Further, the court in *John Hopkins University* supported the inclusion of impurities largely because of the intrinsic record,

³ (1) StemCells offers the product brochure of Miltenyi Biotech to demonstrate that absolute purity is scientifically unrealistic. Stemcells states, “In the Results and Discussions sections, the actual purities of cell cultures were reported as >90% (page 8), 95% (page 22), or 98% (page 14).” Doc No. 175, at 46.

(2) StemCells references a journal article entitled *A Pure Population of Lung Alveolar Epithelial Type II Cells Derived from Human Embryonic Stem Cells* where “the purity of the cell culture was reported as >99%.” *Id.*

(3) StemCells references another journal article entitled *Comprehensive Protocols to Isolate, Characterize, and Culture pure-population of Multi-potent Stem Cell from Mouse Epidermis* where “the purity of the cell culture was reported as >90%.” *Id.*

with the court noting that the “only disclosed embodiment of the claimed cell suspension[] is highly indicative of the scope of the claims.” *Id.* Here, the Court finds no such support within the intrinsic record for StemCells’ proposition that impurities should be included within the definition of “pure.”

As such, the Court is convinced by the extrinsic evidence presented by Neuralstem that “pure” should not include impurities. Therefore, the Court will adopt Neuralstem’s proposed construction of this term.

i. “consists essentially of” (Term No. 43)

Found in the following claims: 10 of the ’346 patent.

"neural cell population consists essentially of the progeny of a single multipotent neural stem proliferated in vitro"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
The neural cell population is clonally-derived.	The neural cell population contain the progeny of a single multipotent neural stem cell that are proliferated in vitro, and do not contain other types of cells that would materially affect the basic characteristic of the neural cell population.

The parties agree that this term is “a neural cell population that contains only the progeny of a single multipotent neural stem cell population that is clonally-derived.” Doc No. 171, at 37. From the briefings, it is apparent to the Court that the parties disagree over the inclusion of impurities, a very similar disagreement to those had for term numbers 38, 54, and 42. The contested language reads, “and do not contain other types of cells that would materially affect the basic characteristic of the neural cell population.” Neuralstem alleges that this language imports an improper legal standard into the claim, while Stemcells argues that this language is appropriate because any other interpretation of the claim would require that “the neural cell population contain clonally-derived cells *only*, and nothing else, i.e. that the cell population is 100% pure.” Doc. No. 175, at 42 (emphasis in original).

StemCells’ proposes that the term “limit[s] the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s) of the claimed invention. Doc. No. 175, at 43. The court in *AFG Industries, Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239 (Fed. Cir. 2001), interpreted “consisting essentially of” to ““exclude[] ingredients that would materially affect the basic and novel characteristics of the claimed composition’. The phrase is open to ‘unlisted ingredients that do not materially affect the basic and novel properties of the invention.’” 239 F.3d at 1245 (citations omitted). In short, the case law clearly supports StemCells’ proposed construction.

Neuralstem purports that the interpretation of “consisting essentially of” in *AFG Industries, Inc.* “is an improper legal standard that has no place in claim construction” because the court in *AFG Industries, Inc.* construed what “consisting essentially of” meant within the context of the patents-in-suit. Doc. No. 171, at 37. The Court finds that *AFG Industries, Inc.* applied the correct legal standard as many other courts have applied a similar definition of “consisting essentially of” without placing the term within the context of the patents-in-suit. *See Kim v. ConAgra, Foods, Inc.*, 465 F.3d 1312 at 1319-20 (Fed. Cir. 2006); *PPG Industries v. Guardian Industries Corp.*, 156 F.3d 1351 at 1354 (Fed. Cir. 1998).

Neuralstem next argues that “StemCells’ construction falls short . . . as it does not recite what the basic and novel characteristics of the claimed neural stem cell population might be.” Doc. No. 178, at 29. This is so because the “patent applicant may . . . alter the typical meaning of ‘consisting essentially of’ through disclaimers made during prosecution or statements in the specification that define the basic and novel characteristics of the claimed invention” and StemCells’ has failed to do so. *Id.* at 28. The Court finds no validity in this argument as “patentee[s] *can* alter [the] typical meaning” of the term “consisting essentially of,” but of course are never obliged to do so. *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335 at 1343-44 (Fed. Cir. 2009) (emphasis added).

Finally, Neuralstem opposes StemCells’ proposed construction because it may include non-clonally derived cells, and “[n]on-clonally derived cells would materially affect the basic characteristics of a neural stem cell population of clonally derived cells.” Doc. No. 178, at 29. If the Court chooses to accept StemCells’ proposed construction, then it is an issue for the fact-finder to determine if non-clonally derived cells materially affect the basic characteristics of the neural cell population. Thus, if Neuralstem’s contentions are true, then non-clonally derived cells will not be included no matter which proposed construction is chosen.

The Court is persuaded by the prior case law that clearly supports StemCells’ proposed construction of “consists essentially of.” Therefore, the Court will adopt StemCells’ proposed construction of this term.

j. “cluster” (Term No. 44)

Found in the following claims: 37, 38, and 80 of the ‘832 patent; and 1 of the ‘346 patent.

“cluster” or “cluster of cells” or “cluster of human cells” or “a cluster of proliferated neural cells”	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
An aggregate of cells where cells are in contact with one another.	An aggregate of cells wherein individual cells are in contact with at least one other cell.

The parties agree that a “cluster” is an “aggregate of cells.” The parties differ as to the scope of the physical contact element of cells in a cluster. Neuralstem’s proposed construction requires that the cells in a cluster are “in contact with one another.” Contrarily, StemCells alleges that the definition of cluster does not mandate that all cells in a cluster touch one another. StemCells purports that “cluster” means “an aggregate of cells wherein individual cells are in contact with at least one other cell.”

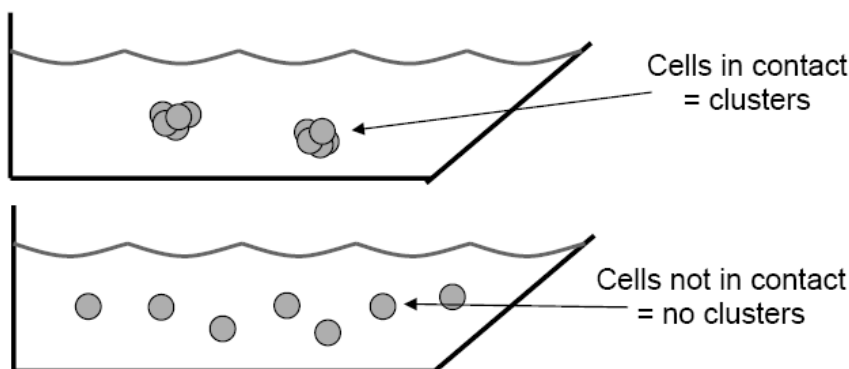
In short, Neuralstem believes a “cluster” of cells must be “in contact with one another” while StemCells believes each cell must contact “at least one other cell.” StemCells’ definition

is clear. A “cluster” is created when every cell is touching “at least one other cell” within the cluster. Neuralstem opposes StemCells’ definition because it “leave[s] open the possibility that a linear conformation of cells reads on the claim term.” Doc No. 227, at 12. Further, Neuralstem alleges that “[a] line of cells—whereby each cell is in contact with two cells to form a chain—is clearly not what was intended by the applicants during prosecution.” *Id.* Neuralstem supports their argument by referencing an excerpt from Figure 1 of the ‘832 patent:



‘832 Patent fig. 1 (excerpt). The Court recognizes that this lone excerpt is not a “chain” as described by Neuralstem and thus would run contrary to StemCells’ definition. However, the Court refuses to limit the term “cluster” to exclude chains based solely on the single excerpt from Figure 1 above. Neuralstem does not make any other arguments within the record to support the claim that a chain should not be included within the definition of “cluster.”

Further, Neuralstem’s proposed construction featuring the language, “in contact with one another,” is ambiguous. As StemCells correctly points out, Neuralstem insinuates that “‘contact with one another’ would require physical contact so that each cell is touching all other cells in the cluster” Doc. No. 175, at 60. Yet, Neuralstem clearly cannot be positing such a definition as the excerpt above and Neuralstem’s own example below indicate.



Doc No. 171, at 24. In both figures there are cells within each cluster that are not touching all other cells within the cluster. In summation, Neuralstem’s argument for eliminating “chains” indicates that their definition requires more contact within a cluster than a “chain” would provide, which is essentially any cell contacting two other cells. Yet, Neuralstem’s illustration and referenced excerpt indicate that their definition requires less contact within a cluster than the contact of all cells with one another.

The Court believes that Stemcells’ proposed construction of the term “cluster” makes the most sense in light of the ordinary meaning of the term. Therefore, the Court will adopt StemCells’ proposed construction of this term.

k. “adherent” (Term No. 45)

Found in the following claims: 21 and 48 of the ‘832 patent; 6 and 12 of the ‘418 patent; 6, 12, and 23 of the ‘505 patent; and 1 of the ‘709 patent.

“adherent” or “adherent cell culture” or “adherent culture”	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
Cells grown on and attached to a substrate surface not maintained in an undifferentiated state.	A culture in which the cells are attached to the surface of a substrate surface.

The parties’ only disagreement is in regards to the phrase, “not maintained in an undifferentiated state.” Neuralstem argues that StemCells’ proposed construction would permit neural stem cells to proliferate in an undifferentiated state. Neuralstem alleges StemCells’ proposed construction is flawed because the patent specification “includes *no examples* of growing cells in an adherent culture and maintaining those cells in an undifferentiated state.” Doc No. 171, at 26 (emphasis in original). Further, Neuralstem believes that the prosecution history of the family of patents in dispute supports the inclusion of the phrase, “not maintained in an undifferentiated state.”

StemCells responds to Neuralstem's objections by alleging that Neuralstem uses improper means of inserting limitations into the term by using omissions to support their proposed constructions and by "teaching away." Doc. No. 175, at 68. StemCells alleges that the specification demonstrates that neural stem cells and their undifferentiated progeny can be proliferated as adherent culture. In *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, (Fed. Cir. 2004), the court rejected the argument that "if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment Even when the specification describes only a single embodiment, the claims of the patent 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." 358 F.3d at 906. Reviewing the specification at issue in this case, the Court does not believe that the patentee demonstrated a clear intention to limit the claim using "words or expressions of manifest exclusion." *Id.* Therefore, simply because the patent may not include examples of growing cells in an adherent culture and maintaining those cells in an undifferentiated state, the Court is not willing to interpret "adherent" as prohibiting cells from proliferating in this manner.

However, the Court does believe that the prosecution history of the patent supports Neuralstem's proposed construction. The purported sister application, Application Serial No. 10/199,830 ("the '830 application"), to the '832 patent had the exact specification as the patents-in-suit. The Examiner rejected the '830 application on the grounds that the specification "fail[ed] to provide an enabling disclosure teaching how to proliferate the undifferentiated multipotent neural stem cells on an adherent substrate in the presence of at least one proliferation-inducing growth factor 'without inducing differentiation.'" Doc. No. 171, at 27. StemCells abandoned the '830 application after it was rejected on the above-mentioned basis. Neuralstem treats this abandonment as a concession by the patentee that the Examiner's objections were true. Neuralstem uses this purported prosecution history to support their view

that the ‘832 patent regards the term “adherent” to be “cells grown on and attached to a substrate surface not maintained in an undifferentiated state.” *Id.* at 28. StemCells avers that “abandoning a patent application is not an admission that the Examiner is right.” Doc. No. 175, at 66.

In *Laitram Corp. v. Morehouse Industries, Inc.*, 143 F.3d 1456 (Fed. Cir. 1998), the court articulated that “when two patents using the same claim term both stem from the same parent patent application, the prosecution histories of both are relevant to an understanding of the term in both patents.” 143 F.3d at 1460 n.2 (citing *Jonsson v. Stanley Works*, 903 F.2d 812, 818 (Fed. Cir. 1990)). The ‘830 application is a sister application of the ‘832 patent and thus the Court believes that the prosecution history of the ‘830 application is persuasive. The examiner rejected the ‘830 application because the application does not teach how to “proliferate neural stem cells on an adherent substrate, as recited in the claims, while maintaining the cells in the undifferentiated state.” Doc. No. 172-9, at 4. The Court is persuaded that Neuralstem’s proposed construction is correct because of the prosecution history provided by the Examiner’s rejection of the sister ‘830 application. The Court emphasizes that the patentee’s abandonment of the ‘830 application is in no way a concession on the part of the patentee.

Therefore, the Court will adopt Neuralstem’s proposed construction of this term.

I. “purified” (Term No. 46)

Found in the following claims: 24 of the ‘505 patent; 1 of the ‘346 patent; and 1 of the ‘709 patent.

“purified” or “the neural cell population is purified” or “a purified population of multipotent neural stem cells”	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
All cells in culture are multipotent neural stem cells.	The cells are separated from at least some of the cells with which they are naturally associated; purified does not require the cell population to be homogeneous.

The parties disagree as to whether “purified” requires a homogenous neural stem cell population. This is a similar disagreement to those had for term numbers 38, 54, 42, and 43. Neuralstem’s proposed construction requires homogeneity while StemCells’ proposed construction does not.

StemCells supports their proposed construction by referencing language from the reexamination of the ‘346 patent and the USPTO Board of Patent Appeals and Interferences.

The patentee stated the following during the reexamination of the ‘346 patent:

The undifferentiated neural cell populations are “purified and enriched in the number of multipotent neural stem cells compared to primary human neural tissue” since these populations have a greater proportion of multipotent neural stem cell in the culture than primary human neural tissue.

Doc. No. 175, at 47. The patentee’s use of “purified” supports StemCells’ allowance for heterogeneity, evidenced by the fact that two cell types are included in the definition of “purified”—both neural stem cells and primary human neural tissue. Moreover, the prosecution history supports StemCells’ proposed construction as the USPTO Board of Patent Appeals and Interferences gave the following definition for “purified” during the prosecution of the ‘505 patent:

We interpret “purified” to mean cells are separated from at least some of the cells with which they are naturally associated; purified does not require the cell population to be homogeneous.

Doc. No. 169, at 29.

Neuralstem contends that the USPTO Board of Patent Appeals and Interferences’ interpretation of “purified” is not controlling because “the USPTO is required to use a different standard for construing claims than that used by district courts.” Doc. No. 171, at 30. Further, Neuralstem insists that the Court “must consult the specification, prosecution history, prior art, and other claims to determine the proper construction of the claim language.” *Id.* The Court agrees with Neuralstem that the USPTO Board of Patent Appeals and Interferences’

interpretation is not controlling and that the Court must consult the intrinsic record to determine the proper construction of “purified.” However, in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc), the court held that “the prosecution history, which [they] 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. Like the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent.” 415 F.3d at 1317 (citations omitted). Therefore, this Court will treat the USPTO Board of Patent Appeals and Interferences’ interpretation of “purified” as intrinsic evidence. Further, the patentee’s own understanding of “purified” as demonstrated during the reexamination of the ‘346 patent is additional intrinsic evidence supporting StemCells’ proposed construction.

Neuralstem argues that “to accept the view that purified somehow means unpurified would be an illogical construction.” Doc. No. 171, at 31. Neuralstem cites Random House Webster’s College Dictionary to prove “the ordinary meaning of purified is ‘to make pure; free from pollutants or contaminants.’” *Id.* at 30. Neuralstem made a nearly identical argument for their proposed construction of term number 42, “pure . . . consisting of.” The Court found in favor of Neuralstem’s proposed construction of “pure . . . consisting of” because Neuralstem’s extrinsic evidence was more persuasive than StemCells’ extrinsic evidence. Here, StemCells has provided intrinsic evidence directly from the prosecution history which is more compelling than extrinsic evidence in the *Markman* analysis. Therefore, the Court will adopt StemCells’ proposed construction of this term.

m. “Nestin(+)” (Term No. 47)

Found in the following claims: 1 and 7 of the ‘418 patent; and 1, 13, 14, 18, 25, and 26 of the ‘505 patent.

"Nestin(+)" or "stain positive for nestin" or "Nestin(-)"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction

<p>Nestin(+) or “stain positive for nestin”: positive staining by immunocytochemistry using an antibody that binds Nestin, including but not limited to the Rat 401 antibody;</p> <p>Nestin(-): no specific staining by immunocytochemistry using an antibody that binds Nestin, including but not limited to the Rat 401 antibody;</p> <p>“specific staining” means that the signal is above background noise level.</p>	<p>Nestin(+) or “stain positive for nestin”: positive staining by immunocytochemistry using an antibody that binds Nestin;</p> <p>Nestin(-): no specific staining by immunocytochemistry using an antibody that binds Nestin;</p> <p>“specific staining” means that the signal is above background noise level.</p>
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The parties’ proposed constructions are almost identical. The parties dispute whether the phrase, “including but not limited to the Rat 401 antibody,” should be included within the definition. StemCells alleges that citing Rat 401 antibody as an example in this definition “would mean that a cell that stains negative for Rat 401 antibody would be Nestin (-).” Doc. No. 175, at 52. However, the “Rat 401 is not a ‘universal’ antibody [because i]t does not bind to cat, monkey, or human Nestin.” *Id.* Thus, StemCells argues that it is improper to include Rat 401 because if it is used to stain human neural stem cells the results will be negative, yet human neural stem cells are Nestin(+).

Neuralstem correctly argues that the patent specification “clearly indicates that Rat401 is an antibody available to identify nestin.” Doc. No. 171, at 49.⁴ StemCells does not dispute this point as the specification is very clear. However, StemCells replies by arguing that “claim construction does not require to read [sic] everything in the specification into the claims.” Doc. No. 175, at 53. The Court will follow the specification which specifically states that Rat 401 is an antibody that can be used to identify nestin. Moreover, Neuralstem is not reading a limitation into the patent as StemCells contends. The language that Neuralstem uses, “including, but not limited to,” clearly allows for other antibodies besides Rat 401 to be used in testing for nestin.

Therefore, the Court will adopt Neuralstem’s proposed construction of this term.

⁴ The specification for patent ‘832 explicitly states, “Antibodies are available to identify nestin, including the rat antibody referred to as Rat401.” ‘832 Patent col.17 ll.21-22.

n. “of . . . lack” (Term No. 52)

Found in the following claim: 7 of the '418 patent.

<p>"a culture of undifferentiated neural cells . . . said undifferentiated neural cells stain positive for nestin and said undifferentiated neural cells lack differentiated neural cells that do not stain positive for nestin and that stain positive for the differentiated neural cell markers neurofilament, glial fibrillary acidic protein, neuron specific enolase, and myelin basic protein"</p>	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
<p>Culture containing all undifferentiated neural cells. All of the undifferentiated neural cells stain positive for nestin, and none of the undifferentiated neural cells stain positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein.</p>	<p>(1) The culture that contains undifferentiated neural cells, wherein the undifferentiated neural cells are characterized by positive immunocytochemistry staining of Nestin, and</p> <p>(2) the culture does not contain detectable level of differentiated neural cells, wherein the differentiated neural cells are characterized by negative staining of nestin, and positive staining of neurofilament, glial fibrillary acidic protein, neuron specific enolase, and myelin basic protein via standard immunocytochemistry techniques.</p>

o. “of” (Term No. 55)

Found in the following claim: 1 of the '418 patent.

<p>"a culture of undifferentiated neural cells . . . wherein said undifferentiated neural cells are nestin+ and are glial fibrillary acidic protein (GFAP)-; neurofilament (NF)-; neuron specific enolase (NSE)-; and myelin basic protein (MBP)"</p>	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
<p>Culture containing all undifferentiated neural cells. All of the undifferentiated neural cells stain positive for nestin, and none of the undifferentiated neural cells stain positive for neurofilament, glial fibrillary acidic protein, neuron specific enolase, or myelin basic protein.</p>	<p>The culture contains undifferentiated neural cells, wherein the undifferentiated neural cells are characterized by the following:</p> <p>(1) positive immunocytochemistry staining of Nestin, and</p> <p>(2) negative immunocytochemistry staining of glial fibrillary acidic protein (GFAP), neurofilament (NF), and myelin basic protein (MBP), via standard immunocytochemistry</p>

techniques;

“negative staining” means the signal of immune-staining does not exceed background level.

Term numbers 52 and 55 will be addressed together as these terms are addressed simultaneously in the joint claim construction. Once again, Neuralstem and StemCells dispute whether the constructions should be completely pure or include impurities. In this instance, the dispute is whether any differentiated neural cells should be included within a culture.

Neuralstem argues that the constructions should reflect 100% purity by only including undifferentiated cells.⁵ StemCells contends that “the term ‘of’ should be construed as being open-ended” and thus allowing for “additional, unrecited elements.” Doc. No. 175, at 40.

StemCells avers that “of” is an open-ended rather than a closed-ended transitional phrase. In support of this premise, StemCells argues that they are “unaware of any case law stating that if a claim fails to mention element A, then it could only encompass element B.” *Id.* In addition, StemCells correctly claims that “[a]lthough the ‘classical’ open-ended transitional phrase, ‘comprising,’ is not used, the Federal Circuit and the USPTO have allowed the use of other transitional phrases.” *Id.* Yet, neither the Federal Circuit nor the USPTO have construed the term “of” as an open-ended transitional phrase. Neuralstem argues that StemCells’ proposed construction broadens the definition “to cover an invention that is nowhere described in the patents-in-suit” and that the Court “cannot now rewrite the claims” to do just that. Doc. No. 171, at 36. The Court is persuaded by the wording in claim 7 of the ‘418 patent which reads, “undifferentiated neural cells lack differentiated neural cells” Doc. No. 171, at 35. The Court believes this passage best shows the intended scope of the claim terms, a scope which does not include differentiated cells.

⁵ Neuralstem alleges, “A plain reading of these claims leads one of the ordinary skill to conclude that they are directed to proliferating a culture of undifferentiated neural cells for one simple reason—the claims fail to mention ‘differentiated cells.’” Doc. No. 171, at 36.

StemCells argues that “because the transitional phrase is not close-ended [sic], ‘lacking differentiated cells’ is not the same as ‘undifferentiated cells only.’” Doc. No. 175, at 40. Thus, the claim does not exclude “additional, unrecited elements.” *Id.* While the Court acknowledges StemCell’s argument that “there are technological limitations to the purification techniques,” *Id.* at 41, the Court has already held that without intrinsic evidence to prove otherwise, purity should have its ordinary meaning, thus excluding elements not expressly called for in the claim.

Finally, Neuralstem’s proposed construction is nearly identical to the specification of the ‘418 patent which reads as follows:

[U]ndifferentiated neural cells lack differentiated neural cells that do not stain positive for nestin and that stain positive for the differentiated neural cell markers neurofilament, glial fibrillary acidic protein, neuron specific enolase, and myelin basic protein . . .

Doc. No. 171, at 35. Compare the ‘418 patent with Neuralstem’s proposed construction:

All of the undifferentiated neural cells stain positive for nestin, and none of the undifferentiated neural cells stain positive for neurofilament, glial fibrillary acidic protein, neuron specific enolase, or myelin basic protein.

It is apparent to the Court that when the ‘418 patent describes the types of differentiated neural cells that it lacks, Neuralstem imports this definition into their own constructions of the claim terms.

The Court believes these claim terms were not intended to be open-ended and that Neuralstem’s proposed constructions are the most consistent with the ‘418 patent. Therefore, the Court will adopt Neuralstem’s proposed constructions of these terms.

p. “consist of . . . lack” (Term No. 53)

Found in the following claims: 18 and 26 of the ‘505 patent.

"neospheres consist of undifferentiated neural cells that stain positive for nestin and said neurospheres lack differentiated neural cells that do not stain positive for nestin but that stain positive for the differentiated neural cell markers, neurofilament, glial fibrillary acidic protein and myelin basic protein"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
Neurospheres contain all undifferentiated neural cells. All of the undifferentiated neural cells stain positive for nestin, and none of the undifferentiated neural cells stain positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein.	(1) The neurospheres do not include cells other than undifferentiated neural cells, except for impurities ordinarily associated with culturing neurospheres, wherein the undifferentiated neural cells are characterized by positive immunocytochemistry staining of Nestin; and (2) The neurospheres do not contain detectable level of differentiated neural cells, wherein the differentiated neural cells are characterized by negative staining of nestin, and positive staining of neurofilament, glial fibrillary acidic protein, neuron specific enolase, and myelin basic protein via standard immunocytochemistry techniques.

Neuralstem and StemCells “disagree on whether (1) the neurospheres must contain any differentiated cells; (2) whether any cell in the neurosphere may stain positive for neurofilament, glial fibrillary acidic protein, or myelin basic protein; (3) whether the phrase ‘negative staining’ should be included; and (4) whether phrase [sic] ‘detectable level’ should be included.” Doc. No. 224, at 12. The Court has addressed the first three concerns above in its discussion of term numbers 38 and 54, which are nearly identical to the present term “consist of . . . lack.” To summarize, the Court is persuaded by the precedent provided by the *Conoco v. Energy & Environmental International* court which permits the presence of certain impurities within a “consisting of” list. *See Conoco, Inc. v. Energy & Env'tl. Int'l, L.C.*, 460 F.3d 1349, 1360 (Fed. Cir. 2006). Therefore, the Court prefers StemCells’ proposed construction for the first three disputes.

Dispute number four is original to this term. Neuralstem opposes the phrase, “the neurospheres do not contain detectable level of differentiated neural cells.” Neuralstem alleges that the words “detectable level” are “nowhere found in the patents-in-suit.” Doc. No. 171, at 33. The Court feels that “detectable level” is to be defined by someone of ordinary skill in the art, and as such, may go before the fact-finder. Therefore, the Court will adopt StemCells’ proposed construction of this term.

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Dispute number four is original to this term. Neuralstem opposes the phrase, “the neurospheres do not contain detectable level of differentiated neural cells.” Neuralstem alleges that the words “detectable level” are “nowhere found in the patents-in-suit.” Doc. No. 171, at 33. The Court agrees with Neuralstem’s logic that “if a type of cell is not ‘detectable,’ then for all practical purposes it does not exist.” *Id.* The phrase, “detectable level,” creates confusion within the definition and the phrase requires a definition of its own. Therefore, the Court will partially adopt StemCell’s proposed construction of this term. The definition will read as follows:

The neurospheres do not include cells other than undifferentiated neural cells, except for impurities ordinarily associated with culturing neurospheres, wherein the undifferentiated neural cells are characterized by positive immunocytochemistry staining of Nestin.

q. “transplant” (Term No. 56)

Found in the following claims: 1 and 22 of the '872 patent.

"transplanting said multipotent neural stem cell progeny to said host" or "transplanting said one or more cells to said host"	
Neuralstem's Proposed Construction	StemCells' Proposed Construction
Transferring multipotent neural stem cell progeny to a host so that the transferred cells survive, migrate to appropriate locations within the host tissue, and form appropriate neural connections with neighboring cells.	Administering the multipotent neural stem cell progeny to the host (e.g., injecting the cells to a neural region of the host).

Each party has one distinct issue with the other’s proposed construction. Neuralstem contends that “administer” is not synonymous with “transplant” and thus the two cannot be used interchangeably. StemCells believes “a result that can be achieved does not mean that such result must be achieved.” Doc. No. 175, at 70. As such, Neuralstem’s requirement that “the transferred cells survive, migrate to appropriate locations within the host tissue, and form appropriate neural connections with neighboring cells” only pertains to successful transplantations, not all transplantations. Thus, StemCells believes that “Neuralstem’s proposed construction improperly reads a limitation from a preferred embodiment into the claims.” *Id.*

First, the Court will address whether “administer” and “transplant” are synonymous. StemCells references the ‘832 patent specification where they allege that the two words are being used interchangeably. Specifically, they cite the following passage, bolding text to support their arguments:

Transplantation can be done bilaterally, or, in the case of a patient suffering from Parkinson’s Disease, contralateral to the most affected side. Surgery is performed in a manner in which

particular brain regions may be located, such as in relation to skull sutures, particularly with a stereotaxic guide. Cells are delivered throughout any affected neural area, in particular to the basal ganglia, and preferably to the caudate and putamen, the nucleus basalis or the substantia nigra. **Cells are administered** to the particular region using any method which maintains the integrity of surrounding areas of the brain, preferably by injection cannula.

Doc. No. 175, at 68-69 (emphasis in original). The Court does not believe this supports StemCells' argument that the two terms are synonymous. The synonymous relationship between the terms appears attenuated at best.

According to Neuralstem, the specification does not use "transplant" and "administer" interchangeably. Neuralstem cites the specification of the '832 patent to highlight the difference between the two terms:

Neural stem cell progeny when *administered* to the particular neural region preferably form a neural graft, wherein the neuronal cells form normal neuronal or synaptic connections with neighboring neurons, and maintain contact with transplanted or existing glial cells which may form myelin sheaths around the neurons' axons and provide a trophic influence for the neurons. As these *transplanted* cells form connections, they re-establish the neuronal networks which have been damaged due to disease and aging.

Doc. No. 171, at 39 (emphasis in original). Neuralstem contends that administered cells that "are able to [form and maintain normal neuronal connections with neighboring neurons] are referred to as 'transplanted cells.'" *Id.* However, StemCells references this exact passage in support of their argument that the two terms are synonymous. The Court agrees with StemCells in that the passage seemingly supports the theory that the two terms are interchangeable. The Court is persuaded by the phrase, "[a]s these transplanted cells form connections" *Id.* This infers that the cells to which the specification refers have not yet formed the "normal neuronal connections" that Neuralstem equates with transplanted cells. *Id.*

Neuralstem cites several other passages in support of their premise including another portion of the specification:

To date, treatment for CNS disorders has been primarily via the administration of pharmaceutical compounds. Unfortunately, this type of treatment has been fraught with many complications including the limited ability to transport drugs across the blood-brain barrier and the drug-tolerance which is acquired by patients to whom these drugs are administered long-term

Recently, the concept of neurological tissue grafting has been applied to the treatment of neurological disease such as Parkinson's Disease. *Neural grafts may avert the need not only for constant drug administration, but also for complicated drug delivery systems which arise due to the blood-brain barrier.* However, there are limitations to this technique as well. First, cells used for transplantation which carry cell surface molecules of a differentiated cell from another host can induce an immune reaction in the host. *In addition, the cells must be at a stage of development where they are able to form normal neural connections with neighboring cells.*

Doc. No. 227, at 7-8 (emphasis in original). This passage supports Neuralstem's premise that "transplant" and "administer" are not synonymous. Ultimately, the use of this term in the specification is ambiguous, with different portions of the specification supporting both parties' arguments. The Court is not persuaded by either parties' argument.

Second, the Court will address whether "Neuralstem's proposed construction improperly reads a limitation from a preferred embodiment into the claims." Doc. No. 175, at 70.

StemCells again references the specification in support of their argument:

Neural stem cell progeny when administered to the particular neural region **preferably form a neural graft**, wherein the neuronal cells form normal neuronal or synaptic connections with neighboring neurons, and maintain contact with transplanted or existing glial cells which may form myelin sheaths around the neurons' axons, and provide a trophic influence for the neurons. As these transplanted cells form connections, they re-establish the neuronal networks which have been damaged due to disease and aging.

Id. at 69-70 (emphasis in original). This excerpt supports StemCells' argument that the requirements Neuralstem adopts as part of their proposed construction are actually requirements for a preferred embodiment and not the claim itself.

Neuralstem counters StemCells by referencing the '872 patent history. Neuralstem contends that both the Examiner and patentee “understood the term ‘transplant’ to be distinct from ‘administer.’” Doc. No. 171, at 39. The Examiner rejected all claims in an Office Action that reads as follows:

The claims of the instant invention are broad in that they encompass all neural stem cell progeny and it is not apparent from the specification that any and all neural stem cell progeny can be obtained and transplanted as claimed. Also, the claims are broad in that they read on any transplantation site and it is not clear from [sic] the specification that these cells could be transplanted to any site within an organism.

Doc. No. 171, at 39. Neuralstem contends that “[i]f ‘transplant’ simply meant ‘administer,’ then the Examiner’s enablement rejection would have been nonsensical” because cells can be administered to any location within an organism. *Id.* Neuralstem then references the patentee’s reply to the Examiner’s enablement rejection:

The Examiner’s § 112, 1st ¶ rejection is also based on the assertion that “it is not apparent from the specification” that neural stem cell progeny can be “transplanted as claimed.” However, the specification shows that neural stem cell progeny can be **successfully transplanted** into animals, where they survive, migrate to appropriate locations within the host tissue, and form appropriate neural connections with neighboring cells.

Id. at 40 (emphasis added). Neuralstem believes this passage proves that the patentee understood “transplant” to mean more than “administer.” StemCells recognizes the patentee’s preferred embodiment which defines successfully transplanted cells as ones that survive and migrate to appropriate tissues. However, Stemcells also avers that this is a preferred embodiment of the invention, and that inserting limitations, as they claim Neuralstem does, would be improper. StemCells alleges, “[s]uccessfully [sic] integration of the transplanted cells is the desired result, and the Applicant demonstrated that such result can be achieved to meet the 112 enablement rejection. However, a result that can be achieved does not mean that such result must be achieved.” Doc. No. 175, at 05. The Court is persuaded by the overwhelming precedent in

favor of StemCells’ position which is appropriately worded by the *Kara Technology Inc. v. Stamps.com Inc.*, 582 F.3d 1341 (Fed. Cir. 2009) courts finding that “the patentee is entitled to the full scope of his claims, and we will not limit him to his preferred embodiment or import a limitation from the specification into the claims.” 582 F.3d at 1348.

The Court believes that the requirements Neuralstem imposes on the term “transplanted” are only found for successful transplantations with the Court believing successful transplantations are a preferred embodiment. As such, the Court is not willing to limit the claim to a preferred embodiment. Also, while the term “administer” may not be defined by the specification, there is ample support for both parties’ positions. Because the Court is not willing to create its own definition, the Court must choose between two imperfect choices. When comparing the two proposed constructions, the Court is most uncomfortable with limiting a claim to a preferred embodiment. Therefore, the Court will adopt StemCells’ proposed construction of this term.

CONCLUSION

Having construed the individual claim terms, the Court refers the parties to the table below for a quick reference to the claim terms which the Court has adopted. This litigation will proceed pursuant to the most recent Scheduling Order issued in this case (Doc. No. 225).

Table of Definitions

Term Number	Term (as found in Doc. No. 224)	Neuralstem	StemCells
4	"multipotent"	X	
21	"culture medium"	X	
25	"EGF-like ligands"		X
37	"neural stem cell(s)"		X
38	"consisting of"		X
54	"consisting of"		X
41	"neurosphere(s)"		X
42	"pure . . . consisting of"	X	
43	"consists essentially of"		X
44	"cluster"		X

45	adherent	X	
46	"purified"		X
47	"Nestin(+)"	X	
52	"of . . . lack"	X	
55	"of"	X	
53	"consist of . . . lack"		X
56	"transplant"		X

August 11, 2011
Date

/s/
Alexander Williams, Jr.
United States District Judge