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Pepper Hamilton LLP (Rochester)
70 Linden Oaks
Suite 210
Rochester, NY 14625

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SGAGIAS, MAGDALENE K	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STEVEN A. GOLDMAN, NEETA SINGH ROY, and TAKAHIRO NAKANO[1]

Appeal 2019-000909
Application 11/055,506
Technology Center 1600

Before DONALD E. ADAMS, ERIC B. GRIMES, and RACHEL H. TOWNSEND, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to an enriched or purified cell population, which have been rejected as indefinite and patent-ineligible. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM the rejection of some of the claims as ineligible for patenting, and enter a new ground of rejection on the same basis.

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[1] Appellant identifies the real party in interest as Cornell Research Foundation, Inc. Appeal Br. 2. We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

STATEMENT OF THE CASE

"Dopaminergic neurons, expressing transcription factors typical of midbrain, have been selectively induced from both murine and human ES [embryonic stem] cells." Spec. ¶ 4. Such induction, however, "has proven insufficient to achieve high levels of enrichment of dopaminergic neurons." *Id*.

The Specification reports on potentiation of "phenotypically-restricted neurons from human ES cells . . . by early exposure to fetal mesencephalic human glia to better replicate the *in vivo* environment of the fetal mesencephalon." *Id*. ¶ 85. A "line of human mesencephalic astrocytes . . . was generated. When coupled with previously established protocols for accentuating dopaminergic differentiation, mesencephalic glial co-culture indeed strongly potentiated dopaminergic neuronal differentiation from human ES cells." *Id*.

As a result, "tyrosine hydroxylase-expressing neurons were by . . . far the major neuronal phenotype produced, in comparison >60% of all neurons by 4 weeks." *Id*.[2] "This higher efficiency method of generating dopaminergic neurons from hES cells through mesencephalic astrocytic co-culture, yielded substantial enrichment of dopaminergic neurons and their progenitors." *Id*.

Claims 21, 45, 65, 69, 73–79, 81, 83–85, 90–93, 96, and 97[3] are on appeal. Claims 21, 73, and 76, reproduced below, are illustrative:

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[2] Neurons express βIII tubulin; dopaminergic neurons express both βIII tubulin and tyrosine hydroxylase. Spec. ¶ 22.

[3] Claims 66, 70–72, 87–89, 94, 95, 98, and 99 are also pending but are not rejected. Office Action mailed Nov. 17, 2016; Ans. 3, 40–41.

21. An enriched or purified population of human dopaminergic neurons produced by a method comprising:

providing a population of human embryonic stem cells;

inducing production of dopaminergic neuronal progenitor cells from the population of human embryonic stem cells;

selecting a promoter or enhancer which functions in human dopaminergic neuronal progenitor cells;

introducing a nucleic acid molecule encoding a marker protein under control of said promoter or enhancer into the induced population of human embryonic stem cells;

co-culturing the induced population of human embryonic stem cells with human astrocytes or human astrocyte conditioned media;

allowing the human dopaminergic neuronal progenitor cells in the co-culture to express the marker protein;

separating the cells expressing the marker protein from the induced population of human embryonic stem cells, whereby an enriched or purified population of human dopaminergic neuronal progenitor cells is isolated; and

differentiating the enriched or purified population of human dopaminergic neuronal progenitor cells into human dopaminergic neurons, wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-).

73. An enriched or purified population of human dopaminergic neurons produced by a method comprising:

providing a population of human embryonic stem cells;

inducing production of dopaminergic neuronal progenitor cells from the population of human embryonic stem cells;

co-culturing the induced population of human embryonic stem cells with human astrocytes or human astrocyte conditioned media;

separating dopaminergic neuronal progenitor cells from the induced, co-cultured population of human embryonic stem cells, whereby an enriched or purified population of human dopaminergic neuronal progenitor cells is isolated; and

differentiating the enriched or purified population of human dopaminergic neuronal progenitor cells into an enriched or purified population of human dopaminergic neurons, wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-).

76. An enriched or purified population of isolated human dopaminergic neurons, wherein the human dopaminergic neurons were induced from a population of human embryonic stem cells and wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-).

Claim 45 is similar to claim 21 but begins with the "selecting" step of claim 21, followed by "introducing a nucleic acid molecule encoding a marker protein under control of said promoter or enhancer into a population of human embryonic stem cells" and "inducing the population of human embryonic stem cells to produce a mixed population of cells comprising human dopaminergic neuronal progenitor cells"; the "co-culturing" and subsequent steps are the same in both claims.

The claims stand rejected as follows:

Claims 21, 45,[4] 65, 69, 73–79, 81, 83–85, 90–93, 96, and 97 under 35 U.S.C. § 112, second paragraph, as indefinite (Ans. 40), and

Claims 21, 65, 69, 73–79, 81, 83–85, 90–93, 96, and 97 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter (Ans. 3).

OPINION

Definiteness

The Examiner concludes that claims 21, 45, 65, 69, 73–79, 81, 83–85, 90–93, 96, and 97 are indefinite, because

> [c]laims 21, 73, 76 recite steps out of order for the step 2 inducing production of dopaminergic neuronal progenitor cells from the population of human embryonic stem cells because it is not clear from the subsequent steps if induction is before or after the selecting step or introducing a nucleic acid step.

Ans. 40. The Examiner reasons that claim 45 similarly recites steps of "introducing a nucleic acid molecule encoding a marker protein" and "inducing" hES cells to produce a mixture of transfected and non-transfected cells, but concludes that

> [i]t is not clear if an enriched or purified population of human dopaminergic neuronal progenitor cells are produced in the inducing step because of the construction of the subsequent steps is not clear if every cell will become transfected so there is a mixture [of] transfected and non-transfected cells for the subsequent steps to ensue.

Id. at 41.

[4] The statement of the rejection does not include claim 45, but the Examiner addressed claim 45 in the body of the rejection. Ans. 40–41. Appellant addressed the indefiniteness rejection of claim 45. Reply Br. 16.

Appellant points out that "claim 76 does not recite an inducing, selecting, or introducing step" and "[c]laim 73 recites the inducing step, but does not recite the introducing or selecting steps," and therefore neither of these claims can be indefinite for the reason set out by the Examiner. Reply Br. 16.[5] We agree.

With respect to claims 21 and 45, Appellant argues:

> One of skill in the art would readily understand from reading the specification and examples of the present application . . . that the "selecting" and "introducing" steps can be carried out prior to, concurrently with, or subsequent to the "inducing" step. See '506 application at paras. [0058] – [0060]. Thus, a change in the ordered recitation of the steps in no way renders claims 21 and 45 indefinite. Rather the differing claims properly cover variations in the way the method of producing the claimed cell population can be carried out.

Reply Br. 16.

Again, we agree with Appellant. Claim 21 recites "introducing a nucleic acid molecule encoding a marker protein . . . into the induced population of human embryonic stem cells." Thus, claim 21 requires the inducing step to take place before the "introducing" step; otherwise, there would not be an "induced population" into which to introduce the nucleic acid molecule. Claim 45 recites "introducing a nucleic acid molecule encoding a marker protein . . . into a population of human embryonic stem cells," rather than into a mixed population produced by inducing the hES cells. The claim language simply requires a different order of steps.

[5] The Examiner withdrew the rejections set out in the Office Action mailed Nov. 17, 2016, and designated the rejections set out in the Answer as new grounds of rejection. Ans. 3, 40–41. Appellant responded to the new grounds of rejection in the Reply Brief.

In summary, we agree with Appellant that the Examiner has not "identifie[d] ways in which language in a claim is ambiguous, vague, incoherent, opaque, or otherwise unclear in describing and defining the claimed invention," and therefore has not shown that the claims are indefinite. *See In re Packard*, 751 F.3d 1307, 1311 (Fed. Cir. 2014). We reverse the rejection of claims 21, 45, 65, 69, 73–79, 81, 83–85, 90–93, 96, and 97 under 35 U.S.C. § 112, second paragraph.

Claim Interpretation

All of the claims on appeal are directed to a product: An enriched or purified population of human dopaminergic neurons.[6] "While the term 'population' is not defined in the specification, it is used throughout the specification consistent with its plain meaning to describe a grouping of multiple cells." Appeal Br. 14. We therefore give the term its broadest reasonable interpretation consistent with the Specification and its ordinary meaning: a group of cells. The claims are directed to a group of multiple (two or more) cells.

Each of the independent claims requires that the claimed cell population includes βIII tubulin positive cells; i.e., neurons. *See* Appeal Br. 17 ("the phrase 'βIII tubulin positive cells' refers to neurons"). Each of

[6] The Specification defines "enriched" and "purified" to refer to cell populations that are at least 90% or at least 99% pure, respectively, with respect to an index phenotype. Spec. ¶ 37. However, because the claims expressly require only 67.4 ± 12.1% βIII tubulin positive, TH^+ cells, we decline to read into the claims the 90% or 99% requirement that might be implied by the terms "enriched" and "purified." *See Sjolund v. Musland*, 847 F.2d 1573, 1581–82 (Fed. Cir. 1988) ("[W]hile it is true that claims are to be interpreted *in light of* the specification . . . , it does not follow that limitations from the specification may be read into the claims.").

the independent claims also requires that "at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-)."

Thus, the claims require that, of the neurons ("βIII tubulin positive cells") in the composition, no less than 67.4 ± 12.1% are dopaminergic neurons ("tyrosine hydroxylase positive (TH^+)"). *See* Appeal Br. 17 ("tyrosine hydroxylase is an identifying marker of a dopaminergic neuron"). The claims do not include an upper limit on the percentage of neurons in the composition that can be dopaminergic neurons, and therefore encompass a composition in which 100% of the neurons are dopaminergic neurons.

Each of the independent claims also states that, besides the TH^+ cells, "the remainder of the βIII tubulin positive cells in the enriched or purified population [are] tyrosine hydroxylase negative (TH^-)." Appellant argues that the claims should be interpreted to require a mixture of cell types. Appeal Br. 14.

We disagree. The claims do not recite any upper limit on the percentage of βIII tubulin positive, TH^+ cells. The claims also do not recite any minimum percentage of TH^- cells (or a required minimum of any other type of cells). And, because "at least 67.4 ± 12.1%" includes 100%, the claims do not otherwise require the presence of cells other than dopaminergic neurons. For example, if the "at least" language was not present, and the claims were limited to a population "wherein 67.4 ± 12.1% of βIII tubulin positive cells in the population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the

population being tyrosine hydroxylase negative (TH^-),” the claim language might support Appellant’s position, because it would require at least 100 – (67.4 +12.1) = 20.5% of the population to be cells other than βIII tubulin positive, TH^+ cells.

However, as written the claims encompass a composition in which 100% of the βIII tubulin positive cells are TH^+ cells (and 0% are TH^-); i.e., the “remainder” of βIII tubulin positive cells is zero. Thus, under the broadest reasonable interpretation of the claim language, no TH^- cells are required to be present in the composition.

Claims 21, 45, and 73 also state that the composition is “produced by a method comprising” certain steps. “Product-by-process” claim language limits the scope of a product claim to the extent that the process affects the structure of the claimed product. *See In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985) (“The patentability of a product does not depend on its method of production. If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.”).

In this case, the Examiner finds that “[t]here is no indication in the specification that the claimed process imparts any structural, functional, or otherwise markedly different characteristics to the claimed population of dopaminergic neurons that makes them different from naturally occurring dopaminergic neurons.” Ans. 5. The Examiner thus concludes:

> The claimed invention comprises entirely naturally occurring components (human dopaminergic neuron cells). These naturally occurring products are naturally occurring dopaminergic neurons that are present in natural *in vivo* environment such as fetal mesencephalon tissue. The claimed

> invention is merely a cell culture comprising naturally occurring human dopaminergic neurons.

Id. at 6.

Appellant does not point to any structural or phenotypic difference between naturally occurring human dopaminergic neurons and dopaminergic neurons produced by the process recited in the claims. *See, e.g.,* Appeal Br. 7 ("an enriched or purified population of human dopaminergic neurons having a hitherto unattained purity"), *id*. at 14 ("dopaminergic neurons are known and . . . the objective of the subject invention is to achieve an enriched population of dopaminergic neurons").

The Specification states that the goal of the disclosed process was to replicate as closely as possible the natural environment of dopaminergic neurons during development in vivo. For example, the Specification states that "no studies to date have attempted to mimic developmental dopaminergic induction from ES cells with mesencephalic glia. This has in part been due to the scarcity of native human fetal mesencephalic glia, and the lack of available lines of these cells." Spec. ¶ 4. The Specification states that the "invention relates to a new strategy for improving the efficiency of dopaminergic neurogenesis from human ES culture, using co-culture with telomerase-immortalized human fetal mesencephalic astrocytes during sonic hedgehog ('SHH')/FGF8-mediated neuronal induction." *Id*. ¶ 12. *See also id*. at ¶ 85:

> In this study, it was asked if the generation of phenotypically-restricted neurons from human ES cells could be potentiated by early exposure to fetal mesencephalic human glia *to better replicate the in vivo environment of the fetal mesencephalon*. . . . When coupled with previously established protocols for accentuating dopaminergic differentiation,

> mesencephalic glial co-culture indeed strongly potentiated dopaminergic neuronal differentiation from human ES cells.

(Emphasis added.)

In summary, Appellant has pointed to no evidence, in the Specification or elsewhere, showing that the dopaminergic neurons produced by the processes recited in the claims differ from their naturally occurring counterparts. The evidence of record therefore supports a finding that human dopaminergic neurons produced by the processes recited in the claims on appeal do not differ markedly from naturally occurring human dopaminergic neurons.

Patent-Eligibility

Claims 21, 65, 69, 73–79, 81, 83–85, 90–93, 96, and 97 stand rejected as being "directed to a composition of matter namely cells, which is directed to a natural phenomenon . . . which does not recite additional elements that amount to significantly more than the judicial exception." Ans. 3. The Examiner finds that the claimed cell populations

> are not markedly different in structure from a naturally occurring product. In particular, the claims are directed to an enriched or purified population of human dopaminergic neurons . . . wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-) are naturally occurring products.

Id. at 4. "[T]he cells of the claimed invention are a natural product that is not markedly different in structure from naturally occurring enriched isolated dopaminergic neurons." *Id*. at 5. The Examiner acknowledges that some of the claims are in product-by-process format but finds that "[t]here is no

indication in the specification that the claimed process imparts any structural, functional, or otherwise markedly different characteristics to the claimed population of dopaminergic neurons." *Id*. "There is no disclosure or evidence on this record that the method for producing the dopaminergic neuron populations provide[s] a population of human dopaminergic neurons with a significant difference over the population" known in the art. *Id*. at 6.

The Examiner finds that Freed[7] "teaches the presence of human dopaminergic neurons in mesencephalic tissue." *Id*. The Examiner finds that Brundin[8] "teaches an enriched population of human nigrostriatal dopaminergic neurons isolated from 11.5 week fetal mesencephalon tissue." *Id*.

The Examiner reasons that, "[w]hile the claims are to a population, . . . the statutory nature of the invention is based on the cells within the population. If the cells of the population are not significantly different from the naturally occurring cells, then, the specific percentage cell population claimed is not significant[ly] different from the naturally occurring population taught by Freed and Brundin." *Id*. at 7. That is, "[t]he particular percentage of human nigrostriatal dopaminergic neurons within the population provides no significant difference over the same cells taught by Freed and Brundin." *Id*. "Neither enrichment no[r] purity is seen as altering the dopaminergic neurons to markedly different characteristics from the natural dopaminergic neurons." *Id*.

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[7] Freed et al., "Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's Disease," *N. Engl. J. Med.* 344(10):710–719 (2001).
[8] Brundin et al., "Human fetal dopamine neurons grafted in a rat model of Parkinson's disease: immunological aspects, spontaneous and drug-induced behaviour, and dopamine release," *Exp. Brain Res.* 70:192–208 (1988).

Appellant argues that "the closest naturally occurring counterpart to the claimed cell population is the population of mesencephalic cells described by Brundin," which was isolated by dissection of fetal mesencephalon tissue and "does not employ *any* steps intended to alter the naturally occurring fetal brain cell composition." Reply Br. 5. Appellant cites Freeman[9] as evidence that "dissected human central mesencephalon tissue grafts comprise dopaminergic neurons (~3–10%)," along with non-dopaminergic neurons. *Id*. Appellant argues that "[t]he enriched fraction of dopaminergic neurons in the claimed cell population relative to the fraction of dopaminergic neurons in the corresponding natural cell population of Brundin . . . renders the claimed cell population markedly different." *Id*. at 7.

Appellant also argues that the "compositional difference between the claimed cell population and its closest natural counterpart cell population underlies a key *functional* difference between the two populations . . . the cell population's ability to survive upon engraftment." *Id*. Specifically, Appellant argues that "upon striatal implantation of the claimed cell population . . . , nearly 20% of the donor-derived dopaminergic neurons had survived." *Id*. at 7–8. "Engraftment of Brundin's isolated population of ventral mesencephalic cells . . . resulted in only about 5% donor dopaminergic cell survival rate after engraftment." *Id*. at 8. Appellant argues that "having markedly more dopaminergic neurons, . . . imparts enhanced therapeutic utility to the claimed cell population as compared to the naturally occurring tissue derived cell population of Brundin." *Id*.

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[9] Thomas B. Freeman and Patrik Brundin, "Important Aspects of Surgical Methodology for Transplantation in Parkinson's Disease," in *Restorative Therapies for Parkinson's Disease*, Chap. 8, pp. 131–165 (2006).

Appellant also argues that "[a] finding of patent eligibility of the claimed cell population under the second prong of *Alice* is supported by existing case law." *Id*. at 14. "[T]he claimed cell population is not produced by isolating and purifying dopaminergic neurons from their natural source. . . . Rather, production of the claimed cell population from hESCs is the result of significant human ingenuity and intervention." *Id*. at 15. Appellant argues that

> the recitation of the human activities (i.e., the hand of man) that are used to produce the claimed enriched or purified population of human dopaminergic neurons in each of the independent claims . . . , in combination with the recited enriched number of dopaminergic neurons in the resulting population, together add significantly more to transform the nature of these claims into patent eligible subject matter under the second prong of *Alice*.

Id.

Principles of Law

Section 101

Patent-eligible subject matter is defined in 35 U.S.C. § 101. An invention is patent-eligible if it claims a "new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101. The Supreme Court, however, has carved out exceptions to what would otherwise appear to be within the literal scope of § 101, e.g., "[l]aws of nature [and] natural phenomena" such as products of nature that are considered "building blocks of human ingenuity." *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208, 216 (2014) (citing *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576 (2013) and *Mayo Collaborative Servs. v. Prometheus Labs, Inc.*, 566 U.S. 66 (2012)). "[T]he 'manifestations of laws of nature' are 'part of the storehouse of knowledge,' 'free to all men and reserved exclusively to

none.'" Manual of Patent Examiner Procedure ("MPEP") § 2106.04(b)(I) (quoting *Funk Brs. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). "When a law of nature or natural phenomenon is claimed as a physical product, the courts have often referred to the exception as a 'product of nature.'" MPEP § 2106.04(b)(II).

The Supreme Court has established a two-step framework for "distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts." *Alice*, 573 U.S. at 217. "First, we determine whether the claims at issue are directed to . . . [a] patent-ineligible concept[]." *Id*. "If so, . . . we consider the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id*. (quoting *Mayo*, 566 U.S. at 78–79).

The United States Patent and Trademark Office ("PTO") issued the 2019 Revised Patent Subject Matter Eligibility Guidance ("Revised Guidance"), indicating how the PTO would analyze patent eligibility under the Supreme Court's two-step framework. 84 Fed. Reg. 50 (January 7, 2019). In response to received public comments, the Office issued further guidance on October 17, 2019, clarifying the 2019 Revised Guidance. USPTO, *October 2019 Update: Subject Matter Eligibility* (the "October 2019 Update") (available at https://www.uspto.gov/sites/default/files/documents/peg_oct_2019_update.pdf).

Under the Revised Guidance, in determining what concept the claim is "directed to," we first look to whether the claim recites any judicial exceptions, including laws of nature, natural phenomena, and/or abstract

ideas. 84 Fed. Reg. at 53–54 ("Step 2A, Prong One"). If it does, then we look to whether the claim recites additional elements that integrate the recited judicial exception into a practical application. *Id*. at 54–55 (citing MPEP § 2106.05(a)–(c), (e)–(h)) ("Step 2A, Prong Two").

Only if a claim (1) recites a judicial exception and (2) does not integrate that exception into a practical application, i.e., it is found to be "directed to" a judicial exception, do we then look to whether the claim contains an "'inventive concept' sufficient to 'transform'" the claimed judicial exception into a patent-eligible application of the judicial exception. 84 Fed. Reg. at 56; *see also Alice*, 573 U.S. at 221 (quoting *Mayo*, 566 U.S. at 82).

Claims alleged to be patent-ineligible because they recite products of nature are properly analyzed under the framework of the Revised Guidance. *See* 84 Fed. Reg. at 54 n.20 ("This notice does not change the type of claim limitations that are considered to recite a law of nature or natural phenomenon. For more information about laws of nature and natural phenomena, including products of nature, see MPEP 2106.04(b) and (c).").

Revised Guidance Step 2(A), Prong 1

Following the Revised Guidance, we first consider whether the claims recite a judicial exception; i.e., whether they set forth or describe a product of nature in accordance with the guidance in MPEP § 2106.04(b) and (c). Revised Guidance, 84 Fed. Reg. at 54; October 2019 Update, at 1.

Each of independent claims 21, 73, and 76 recites a population of human dopaminergic neurons. Dopaminergic neurons are naturally occurring human cells. *See, e.g.,* Brundin 203, left col. ("[T]he normal number of DA [dopamine] neurons in a human mesencephalon have been

estimated at around 450000."). As discussed previously with regard to claim interpretation, Appellant has not pointed to evidence, in the Specification or elsewhere, showing that the human dopaminergic neurons recited in the claims are different from naturally occurring human dopaminergic neurons. Thus, the evidence of record supports a finding that the rejected claims recite a product of nature, which is a judicial exception to patentable subject matter. *See Association for Molecular Pathology v. Myriad Genetics Inc.*, 569 U.S. 576, 580 (2013) ("[A] naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.").

Revised Guidance Step 2(A), Prong 2

Although Appellant's claims recite a product of nature, they would still be patent-eligible if "the claim[s] as a whole integrate[] the recited judicial exception into a practical application of the exception." 84 Fed. Reg. 54. The analysis includes "[i]dentifying whether there are any additional elements recited in the claim beyond the judicial exception(s)" and "evaluating those additional elements individually and in combination to determine whether they integrate the exception into a practical application." *Id.* at 54–55. The analysis of whether the claim integrates the judicial exception into a practical application includes "[i]dentifying whether there are any additional elements recited in the claim beyond the judicial exception(s)" and "evaluating those additional elements individually and in combination to determine whether they integrate the exception into a practical application." *Id.* at 54–55.

Here, in addition to human dopaminergic neurons—also referred to as βIII tubulin positive cells that are tyrosine hydroxylase positive (TH^+)—each

of independent claims 21, 73, and 76 recites "[a]n enriched or purified population . . . wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-)."

As previously discussed (*supra* footnote 6), we interpret the preambles' recitation of "enriched or purified" as simply referring to the "at least 67.4 ± 12.1%" dopaminergic neurons recited in the claims, because interpreting those terms as defined in the Specification would read in a 90% or 99% purity limitation that is contrary to the express limitations of the claims. And, also as previously discussed, we interpret a "population" to mean a group of multiple—at least two—cells.

With regard to "the remainder of the βIII tubulin positive cells in the enriched or purified population," as previously discussed, we interpret the claim language to encompass a homogeneous population of dopaminergic neurons; i.e., a population containing no remainder of TH^- cells. This is the broadest reasonable interpretation of the claims because (a) the claims do not recite an upper limit to the percentage of TH^+, βIII tubulin positive cells, and "at least 67.4 ± 12.1%" reads on 100%; (b) the claims do not recite any minimum required percentage of TH^-, βIII tubulin positive cells; and (c) the claims do not recite any other required cell types in the population.

In addition, independent claims 21 and 73 each recites "human dopaminergic neurons produced by a method comprising" certain steps. As previously discussed with regard to claim interpretation, Appellant has not pointed to any structural or phenotypic properties of human dopaminergic neurons produced by the recited methods that distinguish them from

naturally occurring human dopaminergic neurons, and the Specification does not describe any such properties. Thus, the product-by-process language of claims 21 and 73 does not represent an additional element that integrates the recited naturally occurring product into a practical application of the judicial exception.

In summary, the additional elements recited in the claims, considered individually or in combination, do not integrate the recited, naturally occurring human dopaminergic neurons into a practical application of the judicial exception.

Revised Guidance Step 2(B)

Finally, the Revised Guidance directs us to "evaluate the additional elements individually and in combination . . . to determine whether they provide an inventive concept (i.e., whether the additional elements amount to significantly more than the exception itself)." 84 Fed. Reg. at 56.

Here, the only elements recited in the claims, other than the naturally occurring cells, are discussed above with regard to claim interpretation and the Step 2(A), Prong 2 analysis. In a nutshell, each of claims 21, 73, and 76 require a population—i.e., at least two cells—that can all be human dopaminergic neurons that do not differ markedly, if at all, from naturally occurring dopaminergic neurons. The requirement for a "population" of at least two naturally occurring cells does not provide an inventive concept such that the claim amounts to more than the judicial exception itself. *See, e.g.*, *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 759–760 (Fed. Cir. 2014) (A claim to "[a] pair of single-stranded DNA primers" was found to be "not distinguishable from the isolated DNA found patent-ineligible in *Myriad*").

Appellant's Arguments

Appellant argues that the claimed cell population is markedly different from the closest naturally occurring counterpart. Specifically, Appellant argues that "the closest naturally occurring counterpart to the claimed cell population is the population of mesencephalic cells described by Brundin," which was isolated by dissection of fetal mesencephalon tissue and comprised only 3–10% dopaminergic neurons. Reply Br. 5.

Appellant argues that "[a] comparison of the claimed cell *population* to the cell *population* of Brundin, rather than a comparison of the individual cells within the populations as done by the examiner, shows that the claimed population exhibits markedly different characteristics from its naturally occurring counterpart population." *Id*. at 6. Specifically, "[t]he enriched fraction of dopaminergic neurons in the claimed cell population relative to the fraction of dopaminergic neurons in the corresponding natural cell population of Brundin . . . renders the claimed cell population markedly different." *Id*. at 7.

This argument is unpersuasive, because the claims are not limited to any minimum size of cell population and therefore encompass a "population" of as few as two human dopaminergic neurons. Claims 21 and 73 *do* require that the dopaminergic neurons be made by the recited processes but, as discussed above, the evidence of record does not show that human dopaminergic neurons produced by the recited processes differ in any way from naturally occurring dopaminergic neurons in the human body.

The closest naturally occurring counterpart to the claimed population is a human dopaminergic neuron in the body. In *Myriad*, for example, claim 1 recited "'[a]n isolated DNA coding for a BRCA1 polypeptide,' which has

'the amino acid sequence set forth in SEQ ID NO:2.'" *Myriad*, 569 U.S. at 584. The Court held that

> [t]he *Chakrabarty* bacterium was new "with markedly different characteristics from any found in nature." . . . In this case, by contrast, Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.

Id. at 590–591.

Thus, the Court compared the claimed "isolated DNA" encoding BRCA1 with the naturally occurring BRCA1 gene, and concluded that separating the gene from its surrounding genetic material did not make it patent-eligible in the way that Chakrabarty's "markedly different" bacterium was patent-eligible. Similarly here, the dopaminergic neurons in the claimed population have not been shown to be different, much less markedly different, from naturally occurring human dopaminergic neurons, and the fact that the claims require a "population" of at least two human dopaminergic neurons does not make the claimed invention amount to significantly more than the judicial exception itself.

Appellant argues that "[t]he circumstances underlying this appeal make the present case completely distinguishable from *Myriad*. Firstly, . . . the claimed cell population was not isolated from surrounding cells and tissue of the mesencephalon like the DNA of *Myriad* was isolated from its surrounding genetic material." Reply Br. 8.

> Rather, the claimed cell population was induced from a population of hESCs. While it is the final cell population that is assessed for patentability, the claimed feature of the cell population that structurally distinguishes it from its closest naturally occurring cell population, i.e., the increased percentage of dopaminergic neurons, is attributable to the method of production employed.

Id. at 9.

This argument is unpersuasive. The *Myriad* Court did not compare the claimed "isolated DNA coding for a BRCA1 polypeptide," with the BRCA1 gene as it occurs in nature; specifically, as part of a chromosome, inside a nucleus, in a cell. Rather, the Court held that, despite the need to break chemical bonds in order to separate the gene from its natural environment, the claimed DNA was patent-ineligible. *See Myriad*, 569 U.S. at 587 ("[C]ovalent bonds at both ends of the segment must be severed in order to isolate segments of DNA. This process technically creates new molecules."); *id*. at 591 ("[S]eparating that gene from its surrounding genetic material is not an act of invention."). Similarly here, the naturally occurring counterpart for the claimed population of two or more human dopaminergic neurons is a human dopaminergic neuron, not the macroscopic tissue sample dissected from fetal mesencephalon that is described by Brundin. Just as in *Myriad*, the population of dopaminergic neurons claimed here is patent-ineligible because it was not markedly different from its natural counterpart.

Appellant also argues that this case is distinguished from *In re Roslin Inst. (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2014), because "[t]he claims of *Roslin* were directed to a 'live-born *clone* of a pre-existing, non-embryonic, donor mammal, . . .'." Reply Br. 9. Appellant argues that, "[i]n contrast, . . . the present invention is directed to a 'population of cells,' where the population of cells is different from any naturally occurring cell population." *Id*.

The only "naturally occurring cell population" that Appellant attempts to distinguish from the claimed one, however, is Brundin's macroscopic tissue sample. Appellant has not pointed to evidence showing that the

individual human dopaminergic neurons in the claimed population differ from the same cells as they naturally occur. Thus, Appellant has not shown that claimed "population" of two or more cells is markedly different from a product of nature.

Appellant argues that "it is understood in the art that gene expression profiles differ between cells of different origin." Reply Br. 11. Appellant argues that Shin[10] compared "(i) human neural stem cells derived from embryonic stem cells and (ii) human neural stem cells derived from fetal tissue, and found that >2,000 genes are differentially expressed between these two 'identical' neural stem cell populations." *Id*. Appellant argues that "Shin demonstrates that cells, by virtue of what they are derived from, in particular cells derived from embryonic stem cells versus fetal tissue, possess markedly different gene expression profiles." *Id*. Appellant argues that "there is no requirement . . . [to] show a phenotypic difference in the cells of the claimed population in order for the population to be considered patent eligible." *Id*. at 12.

We are not persuaded. It is possible that the processes recited in the claims *might* result in cells that are markedly different—for example, phenotypically—from their naturally occurring counterparts as a result of different gene expression patterns. However, Appellant has not pointed to any persuasive evidence in the record showing that the product-by-process limitations of the claims do, in fact, define cells that differ markedly from naturally occurring human dopaminergic neurons. Shin's evidence of gene

[10] Shin et al., "Whole Genome Analysis of Human Neural Stem Cells Derived from Embryonic Stem Cells and Stem and Progenitor Cells Isolated from Fetal Tissue," *Stem Cells* 25:1298–1306 (2007).

expressions patterns for two types of cells, neither of which is claimed here, does not distinguish the claimed cell population from a product of nature.

Appellant also argues that the "compositional difference between the claimed cell population and its closest natural counterpart cell population underlies a key *functional* difference between the two populations. This functional difference involves the cell population's ability to survive upon engraftment to replace the dopaminergic neurons lost during a disease like Parkinson's disease." Reply Br. 7. Appellant argues that the Specification shows that, using the claimed cell population, "nearly 20% of the donor-derived dopaminergic neurons had survived" when assessed ten weeks after transplantation into rats, whereas "[e]ngraftment of Brundin's isolated population of ventral mesencephalic cells . . . resulted in only about 5% donor dopaminergic cell survival rate after engraftment." *Id*. at 7–8.

This argument is also unpersuasive, because it is based on the same flawed comparison of the claimed cell population to the cell sample, isolated by dissection, that is described by Brundin. As previously discussed, the claimed cell population can be as small as two cells and can be composed only of dopaminergic neurons. Thus, the closest naturally occurring counterpart is a single human dopaminergic neuron, not a tissue sample cut from fetal brain tissue.

In addition, we do not find the cited evidence to support a finding that the claimed dopaminergic neurons differ functionally from dopaminergic neurons found in nature. Appellant points to the Specification's description of "implantation of the claimed cell population into 6-OHDA-lesioned host brains." Reply Br. 7, citing Spec. ¶¶ 76–79. Appellant states that "[w]hen assessed at 10 weeks after transplantation, nearly 20% of the donor-derived

dopaminergic neurons had survived (*i.e.*, the average density of TH^+ dopaminergic neurons was 27,185 ± 4,226/mm^3 out of a total of average of 136,726 ± 27,185 donor-derived hNA^+ nuclei/mm^3)." *Id*. at 7–8.

Paragraphs of the Specification 76–78, cited by Appellant, describe the 6-OHDA rat model of Parkinson's Disease (¶ 76) and tests conducted on transplanted and non-transplanted rats (¶¶ 77, 78). Paragraph 79 states that the brains of transplanted animals were assayed for the number of cells engrafted and the number of xenografted (human) cells expressing TH. Spec. ¶ 79. The Specification states that human ("hNA+") nuclei were found at 136,726 ± 27,185 hNA+ nuclei/mm^3. *Id*. "The average density of the TH^+ cells was 27,185 ± 4,226/mm^3." *Id*.

Consistent with Appellant's argument, 27,185 is 19.9% of 136,726. However, that number represents the percentage of dopaminergic neurons (TH^+) cells among all of the human (hNA+) cells in the grafts. It is not the percentage of dopaminergic neurons, among the total dopaminergic neurons engrafted, that survived implantation.

Appellant's argument does not point to where the Specification describes the number of cells implanted into each of the 6-OHDA-lesioned rat. The Specification does state that, after rats were lesioned with 6-OHDA, "rats from one group were transplanted with cells (approximately 500,000 cells/3 μls of HBSS)." Spec. ¶ 67. Even if that statement refers to the same experiments described in paragraphs 76–79, however, it does not describe what cells were implanted, or what percentage of the implanted cells were dopaminergic neurons. Thus, the evidence of record does not support Appellant's position that the claimed population of human dopaminergic neurons are markedly different from naturally occurring human

dopaminergic neurons by virtue of their increased survival after transplantation.

Finally, Appellant argues that "patent eligibility of the claimed cell population under the second prong of *Alice* is supported by existing case law." Reply Br. 14. Appellant argues that "the human activities (*i.e.*, the hand of man) that are used to produce the claimed enriched or purified population . . . in combination with the recited enriched number of dopaminergic neurons in the resulting population, together add significantly more to transform the nature of these claims into patent eligible subject matter under the second prong of *Alice*." *Id*. at 15.

This argument is unpersuasive. "[H]uman activities (*i.e.*, the hand of man)," in Appellant's words, were also required to produce the isolated DNA claimed in *Myriad*. The Court acknowledged that isolating DNA requires "separating a specific gene or sequence of nucleotides from the rest of the chromosome," which "technically creates new molecules." *Myriad*, 569 U.S. at 587. The Court held, however, that "separating that [BRCA1] gene from its surrounding genetic material is not an act of invention." *Id*. at 591. That is, "Myriad did not create anything," and specifically not something, like Chakrabarty's bacterium, that was markedly different from what was found in nature. *Id*. at 590–591. The Court expressly stated that "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." *Id*. at 596. Similarly here, Appellant's population of human dopaminergic neurons is not patent-eligible simply because the cells have been made by the recited processes, in the absence of evidence that the resulting cells differ from those found in nature.

New Ground of Rejection

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection: Claim 45 is rejected under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

Claim 45 reads as follows:

45. An enriched or purified population of human dopaminergic neurons produced by a method comprising:

selecting a promoter or enhancer which functions in said human dopaminergic neuronal progenitor cells;

introducing a nucleic acid molecule encoding a marker protein under control of said promoter or enhancer into a population of human embryonic stem cells;

inducing the population of human embryonic stem cells to produce a mixed population of cells comprising human dopaminergic neuronal progenitor cells;

co-culturing the induced population of human embryonic stem cells with human astrocytes or human astrocyte conditioned media;

allowing the human dopaminergic neuronal progenitor cells in the co-culture to express the marker protein;

separating the cells expressing the marker protein from the mixed population of cells, whereby an enriched or purified population of human dopaminergic neuronal progenitor cells is isolated; and

differentiating the enriched or purified population of human dopaminergic neuronal progenitor cells into an enriched or purified population of human dopaminergic neurons wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-).

The process recited in claim 45 is similar to that recited in claim 21, except that in claim 21, human embryonic stem cells are (a) induced to produce dopaminergic neuronal progenitor cells, and then (b) a nucleic acid

encoding a marker protein is introduced into the induced population of cells, whereas in claim 45, (a) a nucleic acid encoding a marker protein is introduced into human embryonic stem cells, and then (b) the cells are induced to produce a population of cells comprising dopaminergic neuronal progenitor cells. In both processes, the net result of these steps is the same: dopaminergic neuronal progenitor cells having a nucleic acid encoding a marker protein introduced into them. The remainder of the two claims is the same: the resulting cells are subjected to the same subsequent steps, and finally differentiated into the claimed "population of human dopaminergic neurons wherein at least 67.4 ± 12.1% of βIII tubulin positive cells in the enriched or purified population are tyrosine hydroxylase positive (TH^+), with the remainder of the βIII tubulin positive cells in the enriched or purified population being tyrosine hydroxylase negative (TH^-)."

In short, claims 21 and 45 carry out the same process steps, albeit in a slightly different order, and result in the same, claimed, population of cells. Therefore, the discussion above regarding claim 21, and the conclusion that it is directed to patent-ineligible subject matter, applies equally to claim 45.

We only apply the new ground of rejection to independent claim 45. We leave it to the Examiner, upon return of this application to the examining corps, to determine whether any of the claims that depend from claim 45 should also be rejected under 35 U.S.C. § 101. *See* MPEP § 1213.02 ("[S]ince the exercise of authority under 37 CFR 41.50(b) is discretionary, no inference should be drawn from a failure to exercise that discretion.").

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed	New Ground
21, 45, 65, 69, 73–79, 81, 83–85, 90–93, 96, 97	112, ¶ 2	Indefiniteness		21, 45, 65, 69, 73–79, 81, 83–85, 90–93, 96, 97	
21, 65, 69, 73–79, 81, 83–85, 90–93, 96, 97	101	Eligibility	21, 65, 69, 73–79, 81, 83–85, 90–93, 96, 97		
45	101	Eligibility			45
Overall Outcome			21, 65, 69, 73–79, 81, 83–85, 90–93, 96, 97		45

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. . . .

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

AFFIRMED-IN-PART; 37 C.F.R. § 41.50(b)