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MONTANARI, DAVID A

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte REN-HE XU and JAMES A. THOMSON

Appeal 2017-003146
Application 12/131,610[1]
Technology Center 1600

Before DEBORAH KATZ, JOHN E. SCHNEIDER, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to an *in vitro* culture comprising a substantially pure, replenishable population of synchronous primate trophoblast cells, which have been rejected as being directed to patent-ineligible subject matter. We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

STATEMENT OF THE CASE

"A trophoblast is a cell which is a precursor of the cells which participate in the formation of the human placenta." (Spec. ¶ 5.) "When an

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[1] Appellants identify the real party in interest as Wisconsin Alumni Research Foundation. (Appeal Br. 3.)

embryo begins differentiation, at the stage of a blastocyst, the cells in the inner cell mass are committed to form the cells which will become the embryo, while the outer cells of the blastocyst become committed to participate in the development of the placenta." (*Id.*)

"Stem cells are undifferentiated or only partially differentiated cells that have the capability to differentiate into a number of progenitor and mature cell lineages and types." (*Id.* ¶ 3.) "Primate embryonic stem cells are stem cultures created from embryos that survive indefinitely in culture and demonstrate the ability to differentiate into the major tissue types of the primate body." (*Id.* ¶ 4.) The present invention is directed to a culture of trophoblast cells derived from primate embryonic stem cells.

Claims 18 and 19 are on appeal. Claim 18 is representative and reads as follows:

> 18. An *in vitro* culture comprising a substantially pure, replenishable population of synchronous primate trophoblast cells, wherein the synchronous primate trophoblast cells express chorionic gonadotropin, are predominantly chorionic gonadotropin-beta (CG-β) positive, and are derived directly *in vitro* from undifferentiated primate embryonic stem cells exposed to a trophoblast inducing factor selected from the group consisting of bone morphogenetic protein 4 (BMP4), bone morphogenetic protein 2 (BMP2), bone morphogenetic protein 7 (BMP7), and growth and differentiation factor 5 (GDF5) without passing through an embryoid body stage.

(Appeal Br. 9.)

The following ground of rejection by the Examiner is before us on review:

Claims 18 and 19 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

DISCUSSION

The Examiner finds that claims 18 and 19 are not directed to patent eligible subject matter because they recite natural products, e.g., trophoblast cells and primate embryonic stem cells. (Ans. 2–3.) According to the Examiner, "the cells of the claimed invention are naturally occurring and derived." (*Id.* at 3.) The Examiner finds further "there is no difference between the primate trophoblast cells used in the claimed *in vitro* culture and naturally occurring cells, the primate trophoblast cells do not have markedly different characteristics, and thus are a 'product of nature' exception. (*Id.*; *see also id.* at 5 ("The population of primate trophoblast cells as claimed is indistinguishable from those that exist in nature.").)

The Examiner contends "[t]he only factors which can be examined under 101 in the claimed *in vitro* culture are those that are recited in the claim i.e. primate trophoblast cells. How the cells were obtained and the knowledge of culturing of them are not considered with respect to a composition." (*Id.* at 5.) The Examiner concludes that "[t]here are no other additional elements recited in the claims that would amount to significantly more than the judicial exceptions." (*Id.* at 4.),

We disagree with the Examiner's findings and conclusion that the claims are directed to patent-ineligible subject matter.

We analyze this case under the two-step framework described by the Supreme Court in *Mayo Collaborative Services v. Prometheus Laboratories,*

Inc., 566 U.S. 60 (2012) and *Alice Corp. v. CLS Bank Int'l*, 573 U.S. 208 (2014) taking into consideration the "2019 Revised Patent Subject Matter Eligibility Guidance" ("Revised Guidance"), issued by the Director of the USPTO on January 7, 2019, and which provides further details regarding how the Patent Office is to analyze patent-eligibility questions under 35 U.S.C. § 101. 84 Fed. Reg. 50–57 (Jan. 7, 2019).

We first examine whether the composition of claim 18 is directed to a law of nature. Not every claim that involves natural products is directed to patent-ineligible subject matter. As the Supreme Court noted "[t]he rule against patents on naturally occurring things is not without limits, . . . for 'all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas,' and 'too broad an interpretation of this exclusionary principle could eviscerate patent law.'" *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 589 (2013) (quoting *Mayo*, 566 U.S. at 71). Thus, "[d]iscoveries that possess 'markedly different characteristics from any found in nature' [] are eligible for patent protection." *In re Roslin Institute*, 750 F.3d 1333, 1336 (Fed. Cir. 2014 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980)). As our reviewing Court noted in *Roslin*, the claim to "a live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats" was patent-ineligible because the clone "is an exact genetic replica . . . and does not possess 'markedly different characteristics'" from the donor parent. *Roslin*, 750 F.3d at 1337 ("Dolly's genetic identity to her donor parent[,which parent is acknowledged to be unpatentable,] renders her unpatentable."). The Court explained that "the word 'cloned' in the pending claims connotes genetic

identity, and the claims say nothing about a phenotypic difference between the claimed subject matter and the donor mammals." *Id.* at 1338. The Court further noted that "[a]ny phenotypic differences between Roslin's donor mammals and its claimed clones are the result of 'environmental factors,' Appellant's Br. 21, uninfluenced by Roslin's efforts" and thus, the phenotypic differences were nature's handiwork, not "any effort of the patentee." *Id.*

Claim 18 requires that the *in vitro* culture comprises a substantially pure, replenishable population of synchronous trophoblast cells that are derived directly *in vitro* from undifferentiated primate embryonic stem cells and do not pass through an embryoid body stage. In determining that this culture is a patent-ineligible product of nature, the Examiner first contends that because the trophoblast cells are derived from a living tissue, "the cells of the claimed invention are naturally occurring and derived." (Ans. 3.) We find the record evidence does not support the Examiner's finding as to either points. That is, while it is true that trophoblasts are naturally occurring, the claimed trophoblasts are not naturally occurring. Moreover, that the cells are derived from embryonic stem cells that are natural products is immaterial, as the claimed trophoblasts derived therefrom are not themselves naturally occurring and possess markedly different characteristics than naturally occurring trophoblasts that are not simply "nature's handiwork", as will be explained.

Trophoblasts are naturally established in mammalian embryogenesis from the blastomere. (Ireland[2] 527.)[3] The blastomere can also form cells of the inner cells mass (ICM). (*Id.*; *see also* Spec. ¶ 5.) Embryonic stem cells, unlike trophoblasts, are derived naturally from the ICM. (Spagnoli[4] 1.) Moreover, trophoblasts are not naturally produced by embryonic stem cells.[5] When cultured *in vitro*, primate embryonic stem cells can form an embryoid body. (Spec. ¶ 4.) An embryoid body comprises undifferentiated pluripotent stem cells and differentiated cell types, which "spontaneously give rise to a mixed population of differentiated cell types including trophoblasts." (Golos Dec.[6] ¶ 9.) However, embryoid bodies are not naturally occurring, they arise in culture. (Spagnoli 1–3; *see also* Golos Dec. ¶ 9.)

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[2] Ireland, Visualizing Human Biology, 3rd Ed. Wiley and Sons Inc. (2008). This reference was cited by the Examiner during prosecution of the present application on appeal in a Notice of References Cited dated October 7, 2014 and was referenced in the Non-Final Office Action accompanying that Notice. (Non-Final Office Action dated Oct. 7, 2014, at 3).

[3] Trophoblasts are the outer cells of the blastocyst and participate in the development of the placenta. (Spec. ¶ 5.)

[4] Spagnoli et al., *Guiding embryonic stem cells towards differentiation: lessons from molecular embryology*, 16 Current Opinion in Genetics & Development 1–7 (2006). Spagnoli was cited by Appellants during prosecution of the application on appeal and relied on in the After Final Response filed March 27, 2014. (After Final Response at 4.)

[5] Thus, the claimed trophoblasts are not "naturally derived" from embryonic stem cells, *i.e.*, they are induced to form in *in vitro* culture.

[6] Declaration of Thaddeus G. Golos, dated April 6, 2015. The Golos Declaration was submitted by Appellants during prosecution with the response filed April 7, 2015. (*See* Response to Non-Final Office Action at 3.)

The Examiner next contends that the "nature-based products, *i.e.*, a population of primate trophoblast cells" of the *in vitro* culture have the same genotype and phenotype and structure as naturally occurring cells and "[h]ow the cells were obtained" is not considered with respect to such product claims. (Ans. 3, 5.) It is true that "[t]he patentability of a product does not depend on its method of production" in the context of determining patentability over the prior art. *In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985).[7] However, as discussed above, if the product made by the recited process is established to result in a product that has markedly different characteristics from any found in nature, then it is patent-eligible, notwithstanding further evaluation for patentability over prior art. Thus, the relevant question, with respect to the § 101 issue here, is whether the claimed *in vitro* culture of primate trophoblast cells that are required to be a substantially pure, replenishable population of synchronous trophoblast cells that are derived directly *in vitro* from undifferentiated primate embryonic stem cells and do not pass through an embryoid body stage are markedly different from naturally occurring trophoblast cells, *i.e.*, trophoblast cells from a blastomere. *See Roslin*, 750 F.3d 1339 (concluding "[t]here is nothing in the claims, or even in the specification, that suggests that the clones are distinct in any relevant way from the donor animals of which they are copies."). As Appellants point out Dr. Golos's testimony supports a conclusion that "it was well understood in the field that human placenta-

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[7] However, to the extent that certain structure is implied by the process steps, that must be considered, *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979), as should any evidence of unexpected properties compared to the prior art product, *see, e.g.*, *In re Marosi*, 710 F.2d 798, 802 (Fed. Cir. 1983).

derived trophoblasts do not proliferate *in vitro*[, rather such] *in vivo*-derived trophoblasts form a non-replenishable, terminally differentiated trophoblast population." (Appeal Br. 7 (citing Golos Dec. ¶¶ 7, 9).) Golos explains that placenta derived trophoblasts "do not proliferate . . . when cultured in vitro." (Golos Dec. ¶ 7.) Rather, such cells "terminally differentiate" when cultured *in vitro*. (*Id.*) Golos explains that cells that are "incapable of replication" *in vitro* are not "replenishable" *in vitro*. (*Id.*)

Golos also explains that while there where methods known for synchronizing cells in culture, synchronized cells are "artificially induced." (Golos Dec. ¶ 8 (citing Jackman[8].) Golos also states: "No isolated substantially pure population of synchronized, replenishable human trophoblasts exists in nature." (Golos Dec. ¶ 9.)

In short, we find the foregoing evidences that trophoblast cells from nature when cultured *in vitro* are not replenishable, and synchronicity of cells in culture is artificially induced, *i.e.*, not natural. As a consequence, we conclude that the claimed *in vitro* culture of replenishable, synchronous primate trophoblast cells derived from undifferentiated primate embryonic stem cells without passing through an embryoid body stage are markedly different from naturally occurring trophoblast cells.

Therefore, we reverse the Examiner's rejection of claims 18 and 19 as being directed to patent-ineligible subject matter.

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[8] Jackman, Cell Cycle Analysis: *Methods for Synchronizing Cells at Specific Stages of the Cell Cycle*, in Current Protocols in Cell Biology, 8.3.1–8.3.20 (1998).

SUMMARY

We reverse the rejection of claims 18 and 19 under 35 U.S.C. § 101 as being directed to patent-ineligible subject matter.

REVERSED