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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KIM O'CONNOR and KATIE RUSSELL

Appeal 2019-006318
Application 13/992,953
Technology Center 1600

Before RICHARD M. LEBOVITZ, ULRIKE W. JENKS, and MICHAEL A. VALEK, *Administrative Patent Judges*.

JENKS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] files this appeal from Examiner's decision to reject claims directed to a method of identifying human multipotent mesenchymal stem cells as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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[1] Appellant identifies the real party in interest as "The Administrators of the Tulane Educational Fund." Appeal Br. 1. We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42(a).

STATEMENT OF THE CASE

According to the Specification, bone marrow is a promising source of mesenchymal stem cells (MSC). Spec. ¶ 5. "Single-cell analysis has revealed that MSCs [derived from bone marrow] are a heterogeneous mixture of cells that differ in their stage of lineage commitment and extent of differentiation." *Id.*

Claims 6, 8, 9, 11, 13, 14, and 21–30[2] are on appeal, and can be found in the Claims Appendix of the Appeal Brief. Claim 6 is representative of the claims on appeal, and reads as follows (bracketing and numbering added for reference convenience):

> 6. A method of identifying human multipotent mesenchymal stem cells capable of high proliferation that have a cell doubling time of 30-hours or less, comprising the steps of
> [1] collecting mesenchymal stem cells;
> [2] measuring the expression of NG2; and
> [3] *isolating* the mesenchymal stem cells having a colony forming efficiency of greater than 40% with high expression of NG2 *by selecting the mesenchymal stem cells having high antibody binding capacity (ABC) of anti-NG2 antibodies of at least 100,000 molecules of anti-NG2 antibodies per mesenchymal stem cell*.

Appeal Br. 22 (Claims Appendix) (emphasis added).

Claim 6 recites three active steps: (1) collecting mesenchymal stem cells, (2) measuring expression of NG2, and (3) selecting cells "having high antibody binding capacity (ABC) of anti-NG2 antibodies of at least 100,000 molecules of anti-NG2 antibodies per mesenchymal stem cell." The other independent claims, claims 11, 21, and 26, recite a similar three step cell

[2] Claims 10, 15, 33–36, and 41–44 are withdrawn from consideration. Appeal Br. 3.

identification method that also requires selection of cells based on ABC values, but using either different starting tissue or a different combination of markers.

REJECTIONS

Appellant requests review of the following grounds of rejection made by Examiner:

I. Claims 6, 9, 21, 22, 24, and 25 under pre-AIA 35 U.S.C. 103(a) as unpatentable over Crisan[3] in view of Kozanoglu[4] and Stallcup;[5]

II. Claims 9, 11, 14, 26, 27, 29, and 30 under pre-AIA 35 U.S.C. 103(a) as unpatentable over Crisan in view of Kozanoglu, Stallcup, and Silva Meirelles;[6]

III. Claim 8 under pre-AIA 35 U.S.C. 103(a) as unpatentable over Crisan in view of Kozanoglu, Stallcup, and Shiels;[7]

IV. Claim 13 under pre-AIA 35 U.S.C. 103(a) as unpatentable over Crisan in view of Kozanoglu, Stallcup, Silva Meirelles, and Shiels;

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[3] Crisan et al., *A Perivascular Origin for Mesenchymal Stem Cells in Multiple Human Organs*, 3 CELL STEM CELL 310–13 (2008) ("Crisan").
[4] Kozanoglu et al., *Human bone marrow mesenchymal cells express NG2: possible increase in discriminative ability of flow cytometry during mesenchymal stromal cell identification*, 11 CYTOTHERAPY 527–33 (2009) ("Kozanoglu").
[5] Stallcup, *The NG2 proteoglycan: Past insights and future prospects, 31 J. Neurocytology*, 423–35 (2002).
[6] da Silva Meirelles, *In Search of the In Vivo Identity of Mesenchymal Stem Cells*, 26 STEM CELLS 2287–99 (2008) ("Silva Meirelles").
[7] Shiels et al., US 2009/0274663 A1, published Nov. 5, 2009 ("Shiels").

V. Claim 23 under pre-AIA 35 U.S.C. 103(a) as unpatentable over Crisan in view of Kozanoglu, Stallcup, and Lin;[8] and

VI. Claim 28 under pre-AIA 35 U.S.C. 103(a) as unpatentable over Crisan in view of Kozanoglu, Stallcup, Silva Meirelles, and Lin.

I.–VI. Obviousness over Crisan, Kozanoglu, and Stallcup

Because all six rejections rely upon the teaching of Crisan, Kozanoglu, and Stallcup regarding identifying human pluripotent mesenchymal stem cells with a high proliferation potential, the same issue is dispositive for all of these rejections, so we will consider the rejections together. We elect claim 6 as representative.

Examiner finds that "pericytes [taught in Crisan] have multilineage mesodermal potential and therefore adheres to the strict definition of mesenchymal stem cells (MSCs)." Ans. 3. Examiner finds that Crisan uses fluorescence-activated cell sorting (FACS) for cell selection. *Id.* Examiner finds that "Crisan teaches monitoring the CD146 and NG2 express[ion] over several passages." *Id.* Examiner acknowledges that "Crisan does not specifically teach using the method to select mesenchymal stem cells, or the properties of the selected cells." *Id.* at 4.

Examiner relies on Kozanoglu for teaching that "human bone marrow mesenchymal stem cells that express NG2 can be isolated using flow cytometry and antibodies specific to NG2." Ans. 4. Examiner relies on Stallcup for teaching "that NG2 functions to promote proliferation in cells." *Id.*

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[8] Lin et al., US 2007/0128722 A1, published June 7, 2007 ("Lin").

Examiner concludes that based on the combination of references one of skill in the art would have been motivated to use Crisan's method of sorting cells expressing high specific antibody and apply the sorting to MSC cells expressing NG2. Ans. 6. Examiner finds that "[t]he recitation of 'having a colony forming efficiency of greater than 40%' and 'ABC of anti-NG2 antibodies of at least. . . .' are inherent properties of the cells. . . . For these reasons it appears that the MSCs expressing NG2 are identical to the claimed cells, and therefore that they would have the same inherent properties of the claimed cells." *Id*. at 4.

Appellant argues that the Examiner did not address the claim requirement that the selection of cells is based on "ABC values of at least 100,000 molecules of anti-NG2 antibodies per MSC [which] is the numerical cut off as the selection criteria." Appeal Br. 11; Reply Br. 3. In addition, Appellant contends that "[t]he very first step [in the method] has already limited the cell pool to MSCs. In other words, the claimed method does not isolate cells from a pool of unsorted cells, but from heterogeneous MSCs that have a broad and variable range of proliferation potentials." *Id.* at 12.

The issue is whether the preponderance of evidence of record supports Examiner's conclusion that NG2 positive mesenchymal stem cells would inherently meet the colony forming efficiency and ABC values as claimed?

A. Findings of Fact (FF)

FF1. Crisan teaches analyzing and sorting "perivascular cells by using multicolor fluorescence-activated cell sorting (FACS). . . . Perivascular cells were identified and sorted by high CD146 expression and lack of CD34, the latter in order to

ascertain the absence of endothelial cells within sorted cells." Crisan 302.

FF2. Crisan teaches that "CD146+ perivascular cells are also positive for NG2 expression." *Id.* Crisan teaches that "[a]fter either 4, 8, or 14 passages, muscle derived perivascular cells stably expressed NG2, CD146, and α-SMA, but not CD31, CD34, CD45, or CD144, excluding the growth of contaminating endothelial or hematopoietic cells." *Id.* at 304–05.

FF3. Kozanoglu teaches flow cytometry on expanded adherent human mesenchymal stromal cells (MSC) derived from bone marrow (BM). Kozanoglu 528–29. Kozanoglu teaches staining cells with NG2-PE. *Id.* at 528. Kozanoglu teaches that "human BM MSC express NG2. . . . [suggesting] that NG2 may be used as a marker to identify MSC." *Id.* at 532.

FF4. Stallcup teaches that "NG2 with extracellular and intracellular ligands regulates signaling events that are important for both cell proliferation and cell migration." Stallcup, Abstract.

B. Analysis

Crisan teaches that cell surface markers can be used to collect cells using fluorescent-activated cell sorting (FACS). FF1. Crisan teaches using perivascular cells in their methods. *Id*. These cells are different from the claimed mesenchymal stem cells. Crisan's method uses CD146 as a marker for sorting cells. *Id*. Crisan also teaches that the CD146 sorted perivascular cells are positive for the NG2 marker. FF2. Kozanoglu teaches that NG2 can

be used as a marker for identifying mesenchymal stem cells from bone marrow using flow cytometry but does not teach cell sorting by FACS as does Crisan. FF4.

Based on the teaching of Crisan and Kozanoglu, we agree with Examiner it would have been obvious to one of ordinary skill in the art at the time the invention was made to use NG2 as the marker for collecting human bone marrow derived mesenchymal stem cells. Thus, the combination of Crisan and Kozanoglu teaches steps [1] and [2] of claim 6. However, what is missing from the Examiner's analysis is a reason to perform step [3] of claim 6. Specifically, Examiner has not provided evidence that an artisan would have a reason for "selecting the mesenchymal stem cells having high antibody binding capacity (ABC) of anti-NG2 antibodies of at least 100,000 molecules of anti-NG2 antibodies per mesenchymal stem cell." *See KSR Int'l Co. v. Teleflex Inc*., 550 U.S at 418 (obviousness rejections require "some articulated reasoning with some rational underpinning").

Antibody binding capacity (ABC) is a way of measuring the number of antigens present on a cell surface. *See* Spec. ¶¶ 30, 31. We agree with Appellant that none of the cited references disclose selecting cells among a population of mesenchymal stem cells. *See* Appeal Br. 14; Reply Br. 3. The combined references provide a reason to use NG2 as a marker for cell sorting but do not provide a reason to select a particular population of among the NG2 positive cells having the recited high antibody binding capacity. Even knowing that NG2 is involved in cell proliferation (*see* FF4) the Examiner has not provided an articulated reason why one of skill in the art at the time the invention was made would have selected a population of NG2

positive cells that has an ABC value of 100,000 antibody molecules or more per stem cell.

We agree with Appellant that the limitation "having high antibody binding capacity (ABC) of anti-NG2 antibodies of at least 100,000 molecules of anti-NG2 antibodies per mesenchymal stem cell" is not an inherent property of all NG2 positive mesenchymal stem cells. Appeal Br. 6. The art explains that it is only after culture expansion that mesynchymal stem cells begin to express NG2. Kozanoglu 529. Kozanoglu further teaches that "viability of the cells was preserved [over passage 1 to passage 9] by MSC markers CD73, CD105 and CD166, NG2 expression decreased with passages. This may be because of changing differentiation and growth characteristics of MSC throughout passages." Kozanoglu 532. From Kozanoglu, we know that NG2 levels in cell population changes over time. There is nothing in the cited art that informs us how many NG2 molecules are found on the cell surface of any MSC expressing NG2 molecules. Even knowing that NG2 may be involved in cell proliferation as suggested by Stallcup (*see* FF4; Ans. 4), without more, there is no reason to select a particular group of cells having an ABC cut off value for sorting cells that bind 100,000 anti-NG2 antibodies on their cell surface.

C. Conclusion

We conclude that the preponderance of the evidence of record does not support the Examiner's conclusion that the combination of Crisan, Kozanoglu, and Stallcup teaches a method having all limitations of independent claim 6. Specifically, the step [3] limitation of "isolating . . . by selecting the mesenchymal stem cells having high antibody binding capacity (ABC) of anti-NG2 antibodies of at least 100,000 molecules of anti-NG2

antibodies per mesenchymal stem cell" is missing from the references. Appellant's other independent claims recite the same limitation. We thus reverse all of Examiner's rejections because all of those rejections are premised on the same combination of Crisan, Kozanoglu, and Stallcup.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
6, 9, 21, 22, 24, 25	103(a)	Crisan, Kozanoglu, Stallcup		6, 9, 21, 22, 24, 25
9, 11, 14, 26, 27, 29, 30	103(a)	Crisan, Kozanoglu, Stallcup, Silva Meirelles		9, 11, 14, 26, 27, 29, 30
8	103(a)	Crisan, Kozanoglu, Stallcup, Shiels		8
13	103(a)	Crisan, Kozanoglu, Stallcup, Silva Meirelles, Shiels		13
23	103(a)	Crisan, Kozanoglu, Stallcup, Lin		23
28	103(a)	Crisan, Kozanoglu, Stallcup, Silva Meirelles, Lin		28
Overall Outcome				6, 8, 9, 11, 13, 14, 21-30

REVERSED