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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BRUCE BLAZAR, JAKUB TOLAR, and
CATHERINE M. VERFAILLIE

Appeal 2019-001236
Application 11/919,901
Technology Center 1600

Before DEMETRA J. MILLS, ERIC B. GRIMES, and
RICHARD J. SMITH, *Administrative Patent Judges*.

SMITH, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 39–43, 46, 47, 49, 50, 52, and 54–57. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Regents of the University of Minnesota. Appeal Br. 3.

STATEMENT OF THE CASE

The Specification indicates that the field of cellular therapy includes "the use of stem cells, bone marrow transplants, and therapeutic cloning" to replace diseased or dysfunctional cells with healthy, functioning ones. Spec. 2, ll. 1–4. However, cellular therapy remains "limited by complications such as immune rejection and graft versus host disease (GVHD)." *Id.* at ll. 4–5. Thus, according to the Specification, "there is a need for methods to overcome the limitations of cellular therapies caused by the immunoreactivity of the host." *Id.* at ll. 8–9.

Claims on Appeal

Claims 39–43, 46, 47, 49, 50, 52, and 54–57 are on appeal. Claims Appendix.[2] Claim 39 is illustrative and reads as follows:

> 39. A method to increase persistence[3] of MHC-I[4] negative cells comprising administering the MHC-I negative cells and an effective amount of a pharmaceutical composition comprising an anti-natural killer (NK) cell[5] antibody, or an active fragment thereof, to a subject so that persistence of the MHC-I negative cells increases compared to the method without administration of the anti-NK cell antibody, or an active fragment thereof, wherein the cells are non-ES, non-EG, non-germ cells that can

[2] Submitted with Appellant's Response to Notice of Non-Compliant Appeal Brief (37 C.F.R. § 41.37), dated April 3, 2018, 3–5 ("Claims Appendix").
[3] "Persistence" is defined as "the ability of cells to resist rejection and remain and/or increase in number over time (e.g., days, weeks, months, years) *in vivo*." Spec. 11, ll. 16–17.
[4] MHC-I refers to "major histocompatibility complex (MHC) class I molecules." Spec. 4, ll. 8–9.
[5] The Specification states that "Natural Killer (NK) cells are characterized, in part, by cytolytic activity against cells which do not express significant [MHC-I] molecules." Spec. 4, ll. 7–9.

> differentiate into ectodermal, endodermal and mesodermal cell types and are CD45 negative and CD34 negative.

Id. at 3.

Examiner's Rejections[6]

1. Claims 39–41, 43, 46, 52, and 55–57 stand rejected under pre-AIA 35 U.S.C. § 103(a) as unpatentable over Chargui[7] or Cho[8] in view of Furcht,[9] as evidenced by Kasai.[10] Final Act. 7–8.[11]

2. Claims 39–41, 43, 47, 50, and 55–57 stand rejected under pre-AIA 35 U.S.C. § 103(a) as unpatentable over Chargui or Cho in view of Furcht and Zander,[12] as evidenced by Penack.[13] *Id.* at 8–10.

3. Claims 42, 49, and 51 stand rejected under pre-AIA 35 U.S.C.

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[6] The Examiner's rejections of claims 44, 45, and 48 under 35 U.S.C. § 112(a) or 35 U.S.C. § 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement, and claims 39–57 under 35 U.S.C. § 112(b) or 35 U.S.C. § 112 (pre-AIA), second paragraph, as being indefinite, are withdrawn. Ans. 3.

[7] J. Chargui et al., *Anti-NK antibodies injected into recipient mice enhance engraftment and chimerism after allogeneic transplantation of fetal liver stem cells*, Thymus 24(4), 233–46 (1997) ("Chargui").

[8] S.G. Cho et al., *Anti-NK cell treatment induces stable mixed chimerism in MHC-mismatched, T cell-depleted, nonmyeloablative bone marrow transplantation*, Experimental Hematology 32, 1246–54 (2004) ("Cho").

[9] Furcht et al., WO 01/11011 A2, published Feb. 15, 2001 ("Furcht").

[10] M. Kasai et al., *In vivo effect of anti-asialo GM1 antibody on natural killer activity*, Nature 291, 334–35 (1981) ("Kasai").

[11] Office Action dated Feb. 10, 2017.

[12] A.R. Zander et al., *ATG as part of the conditioning regimen reduces transplant-related mortality (TRM) and improves overall survival after unrelated stem cell transplantation in patients with chronic myelogenous leukemia (CML)*, Bone Marrow Transplantation 32, 355–61 (2003) ("Zander").

[13] O. Penack et al., *The type of ATG matters — Natural Killer cells are influenced differentially by Thymoglobulin, Lymphoglobulin and ATG-Fresenius*, Transplant Immunology 18, 85–87 (2007) ("Penack").

§ 103(a) as unpatentable over Chargui or Cho in view of Furcht, as applied to claims 39–41, 43, 46, 52, and 55–57, and further in view of Tanaka.[14] *Id.* at 10–11.

4. Claims 42 and 49 stand rejected under pre-AIA 35 U.S.C. § 103(a) as unpatentable over Chargui or Cho in view of Furcht, as applied to claims 39–41, 43, 47, 50, and 55–57, and further in view of Liu.[15] *Id.* at 11–12.

5. Claims 49 and 54 stand rejected under pre-AIA 35 U.S.C. § 103(a) as unpatentable over Chargui or Cho in view of Furcht, as applied to claims 39–41, 43, 46, 52, and 55–57, and further in view of Pessino.[16] *Id.* at 12–13.

FINDINGS OF FACT

The following findings are included for emphasis and reference purposes.

FF 1. "Natural Killer (NK) cells are characterized, in part, by cytolytic activity against cells which do not express significant major histocompatibility complex (MHC) class I molecules, such as MAPCs[17] and embryonic stem (ES) cells." Spec. 4, ll. 7–9.

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[14] T. Tanaka et al., *Selective Long-Term Elimination of Natural Killer Cells In Vivo by an Anti-interleukin 2 Receptor β Chain Monoclonal Antibody in Mice*, J. Exp. Med. 178, 1103–07 (1993) ("Tanaka").

[15] Z-X Liu et al., *NK Cells Cause Liver Injury and Facilitate the Induction of T Cell-Mediated Immunity to a Viral Liver*, J. Immunology 164, 6480–86 (2000) ("Liu").

[16] A. Pessino et al., *Molecular Cloning of NKp46: A Novel Member of the Immunoglobulin Superfamily Involved in Triggering of Natural Cytotoxicity*, J. Exp. Med. 188 (5), 953–60 (1998) ("Pessino").

[17] "MAPCs" refers to multipotent adult progenitor cells and are a type of MHC-I negative cells. Spec. 1, ll. 28–29; 10, l. 3. The term "progenitor" as used in the acronym "MAPC" does not limit those cells to a particular lineage. *Id.* at 11, ll. 7–8.

FF 2. "There are several antibodies available in the art which inhibit NK cell function, including . . . anti-asialo-GM1." *Id.* at 23, l. 32–24, l. 2.

FF 3. Chargui teaches that "Natural killer (NK) cells have been shown to play a role in . . . resistance to transplantation of allogeneic stem cells," and describes an experiment in which anti-asialo GM1 rabbit antibodies (anti-NK) and fetal liver (ES) cells were injected into one group of mice (Group A). Chargui Abstract. Group A mice "demonstrated engraftment and chimerism," and stability of chimerism over time as compared to Group B mice which received injections of normal rabbit serum rather than anti-NK antibodies. *Id.* Chargui concludes that "[o]n the whole, anti-NK antibodies were able to improve engraftment, chimerism and stability of allogenic stem cell transplants." *Id.*; *see also* Final Act. 7.

FF 4. Furcht teaches multipotent adult stem cells (MASCs), and that to select the MASCs, "bone marrow mononuclear cells are derived from bone marrow aspirates, which can be obtained by standard means known to those of skill in the art." Furcht 22, ll. 9, 29–31.

FF 5. Furcht teaches that "[t]he cells of the present invention . . . may have the capacity to be induced to differentiate to form at least one differentiated cell type of mesodermal, ectodermal and endodermal origin." *Id.* at 9, ll. 4–6. Furcht also teaches that the multipotent stem cell of the invention is CD45 negative and CD34 negative. *Id.* at 106 (claims 1–4).

FF 6. Furcht teaches that "[u]sing cells from the developed individual, rather than an embryo, as a source of autologous or allogenic stem cells would overcome the problem of tissue incompatibility associated with the use of transplanted embryonic stem cells, as well as solve the ethical dilemma associated with embryonic stem cell research." *Id.* at 8, ll. 3–7.

DISCUSSION

Except as may otherwise be indicated, we adopt the Examiner's findings, analysis, and conclusions as our own, including with regard to the scope and content of, and motivation to combine, the prior art.

Issue

Whether a preponderance of evidence of record supports the Examiner's rejections under pre-AIA 35 U.S.C. § 103(a).

Analysis

1. Obviousness over Chargui or Cho in view of Furcht, as evidenced by Kasai (claims 39–41, 43, 46, 52, and 55–57)

We limit our consideration to claim 39 because claims 39–41, 43, 46, 52, and 55–57 were not argued separately. In addressing claim 39, we rely solely on the combined teachings of Chargui and Furcht. *See In re Bush*, 296 F.2d 491, 496 (CCPA 1961) (holding that the Board may rely on fewer references than relied upon by the Examiner without designating it as a new ground of rejection).

The Examiner finds that, due to the role of NK cells in resistance to transplantation of stem cells, Chargui teaches that anti-NK antibodies were given prior to fetal (liver) stem cell transplantation, thereby increasing the persistence and engraftment of the stem cells. Final Act. 7; FF 3. The Examiner also finds that Furcht teaches isolated multipotent adult mammalian stem cells that are CD45 negative and CD34 negative, and that "these stem cells have the capacity to differentiate to form cells of mesodermal, ectodermal and endodermal origin." Final Act. 7–8; FF 4, 5. The Examiner concludes that "[i]t would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the adult multipotent mammalian stem cell[s] taught by [Furcht] in the

method taught by Chargui;" namely, increasing persistence and engraftment of transplanted stem cells by also administering an anti-NK antibody. Final Act. 8.

Appellant's Arguments

Appellant argues that the Examiner erred in concluding that one of ordinary skill in the art would have been motivated to combine the cited references.[18] Appeal Br. 16–17. In particular, Appellant argues that "[t]he Examiner assumes that the cells of Furcht would have been easier to obtain simply because they are not derived from a fetal source," but that, in fact, the cells of Furcht are a rare population of cells that would have been overlooked by the skilled artisan "in favor of a more robust source of stem cells given the extremely low occurrence of the Furcht cells." *Id.* at 16.

The Examiner responds that Furcht teaches that "these MASCs cells are easily isolated from bone marrow using standard techniques and cultured *in vitro* using standard techniques to expand to appropriate numbers prior to administration." Ans. 12 (citing Furcht 22, l. 22–24, l. 2; 24, ll. 18–22). The Examiner also points to Furcht's teachings of the advantages of using MASCs and the disadvantages of using embryonic stem cells. *Id.* at 12–13 (citing Furcht 22, ll. 9–16; 7, l. 22–8, l. 2); FF 6.

We find that the Examiner has the better position because Furcht provides reasons why one of ordinary skill in the art would have used MASCs rather than embryonic stem cells in the technique of Chargui to

[18] Appellant advances this argument with respect to the combination of Chargui and Furcht and the combination of Cho and Furcht. Appeal Br. 16–17. Although we limit our consideration to the combination of Chargui and Furcht, we note that similar arguments are advanced by Appellant in connection with the combination of Cho and Furcht. *See id*.

arrive at the method of claim 39. In other words, the Examiner has provided a persuasive "reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Appellant does not persuasively address the Examiner's indicated motivation with factual evidence.

Appellant also argues that the Examiner fails to indicate that "there would have been a reasonable expectation that the claimed invention would have been achieved." Appeal Br. 17–18. Appellant specifically argues that

> the Examiner has failed to establish that, even if there was a sufficient motivation, one skilled in the art would have had a reasonable expectation that, more likely than not, administering an anti-NK cell antibody, or an active fragment thereof, with the recited cells as a pharmaceutical composition would increase persistence or engraftment of the recited cells.

Id.

We are not persuaded by this argument. The reasonable expectation of success requirement "refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). Here, claim 39 is a method to increase persistence of MHC-I negative cells (as further defined in the "wherein" clause), and recites administering MHC-I negative cells and an effective amount of a pharmaceutical composition comprising an anti-natural killer (NK) cell antibody, or an active fragment thereof. Claims Appendix at 3. The claimed method is deemed satisfied when the "persistence of the MHC-I negative cells increases compared to the method without administration of the anti-NK cell antibody, or an active fragment thereof." *Id.*

Appellant acknowledges that natural killer (NK) cells are characterized by cytolytic activity against both MAPCs and embryonic stem cells. FF 1. Appellant further acknowledges that there are "several antibodies available in the art which inhibit NK cell function," including anti-asialo GM1, which is the same antibody used by Chargui. FF 2, 3. Thus, administering an anti-NK cell antibody would necessarily inhibit the cytolytic activity of NK cells against both MAPCs and embryonic stem cells. *See* Ans. 14.[19] A person of ordinary skill in the art would thus have had a reasonable expectation of success of inhibiting the cytolytic activity of NK cells (thereby increasing persistence) by administering MHC-I negative cells (as claimed), rather than embryonic stem cells, in connection with "an anti-natural killer (NK) cell antibody."

Accordingly, for the reasons of record and as set forth above, we affirm the rejection of claim 39 as obvious over Chargui and Furcht. Claims 40, 41, 43, 46, 52, and 55–57 were not argued separately and fall with claim 39.

2. Obviousness over Chargui or Cho in view of Furcht and Zander, as evidenced by Penack (claims 39–41, 43, 47, 50, and 55–57)

Appellant relies on the same arguments advanced in connection with Rejection No. 1 above. Appeal Br. 18. Accordingly, Rejection No. 2 is affirmed for the reasons of record and as set forth above in connection with Rejection No. 1.

[19] Appellant argues in its Reply Brief that the Examiner's response at page 14 of the Answer constitutes an undesignated new ground of rejection. Reply Br. 2–3. That is a matter for petition to the Director and not a matter properly before the Board. *See* 37 C.F.R. § 41.40(a).

3. Remaining Obviousness Rejections

Appellant does not contest Rejection Nos. 3, 4, and 5. Accordingly, those rejections are summarily affirmed.

CONCLUSION

Rejection No. 1: A preponderance of evidence of record supports the Examiner's rejection of claim 39 under pre-AIA 35 U.S.C. § 103(a). Claims 40, 41, 43, 46, 52, and 55–57 were not argued separately and fall with claim 39.

Rejection No. 2: A preponderance of evidence of record supports the Examiner's rejection of claim 39 under pre-AIA 35 U.S.C. § 103(a). Claims 40, 41, 43, 47, 50, and 55–57 were not argued separately and fall with claim 39.

Rejection Nos. 3–5: A preponderance of evidence of record supports the Examiner's rejection under pre-AIA 35 U.S.C. § 103(a) of claims 42, 49, and 51 (Rejection No. 3), claims 42 and 49 (Rejection No. 4), and claims 49 and 54 (Rejection No. 5).

SUMMARY

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
39–41, 43, 46, 52, 55–57	§ 103(a)	Chargui or Cho, Furcht, Kasai	39–41, 43, 46, 52, 55–57	
39–41, 43, 47, 50, 55–57	§ 103(a)	Chargui or Cho, Furcht, Zander, Penack	39–41, 43, 47, 50, 55–57	
42, 49, 51	§ 103(a)	Chargui or Cho, Furcht, Tanaka	42, 49, 51	

Claims Rejected	35 U.S.C. §	Basis	Affirmed	Reversed
42, 49	§ 103(a)	Chargui or Cho, Furcht, Liu	42, 49	
49, 54	§ 103(a)	Chargui or Cho, Furcht, Pessino	49, 54	
Overall Outcome			39–43, 46, 47, 49, 50, 52, 54–57	

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED