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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte WOUTER VAN'T HOF

Appeal 2019-004787
Application 14/070,075
Technology Center 1600

Before ERIC B. GRIMES, JOHN G. NEW, and
JAMIE T. WISZ, *Administrative Patent Judges*.

WISZ, *Administrative Patent Judge*.

DECISION ON APPEAL

STATEMENT OF THE CASE

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 29–37. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

CLAIMED SUBJECT MATTER

According to the instant Specification, "[t]he process of acute inflammation is initiated by the blood vessels local to the injured tissue, which alter to allow the exudation of plasma proteins and leukocytes into the surrounding tissue." Spec. ¶ 2. The Specification describes the invention as being directed to "cell banks that can be used to provide cells for administration to a subject, the banks comprising cells having a desired potency with respect to downregulating expression of cellular adhesion molecules in leukocytes and reducing leukocyte adhesion and extravasation." Spec. ¶ 1. Claim 29, the only independent claim, is illustrative of the claimed subject matter and is reproduced below:

> 29. A method to construct a cell bank, the method comprising expanding and storing cells (I), and further comprising detecting in vitro the effect of the cells (I) on (1) leukocyte extravasation, (2) leukocyte adhesion to vascular endothelium or to isolated endothelial cells, (3) Fut-7 expression on a leukocyte or (4) expression of CD15s on a leukocyte, by contacting cells (I) with a leukocyte and detecting the level of one or more of (1)-(4), the cells (I) being non-embryonic, non-germ cells that have one or more of oct4 expression, telomerase expression, rex-1 expression, rox-1 expression or can

[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 ABT Holding Company. Appeal Br. 3.

> differentiate into cell types of at least two of endodermal, ectodermal, and mesodermal germ layers.

Appeal Br. 19 (Claims App.).

REJECTIONS

The Examiner rejected claims 29–31 and 33–37 under 35 U.S.C. § 103(a) as being obvious over Maziarz[2] as evidenced by Korngold.[3]

The Examiner rejected claim 32 under 35 U.S.C. § 103(a) as being obvious over Maziarz (as evidenced by Korngold), further in view of Nguyen.[4]

The Examiner provisionally rejected claims 29–37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23–30 of co-pending Application No. 14/051,164.

The Examiner provisionally rejected claims 29–31 and 33–37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28–30 of co-pending Application No. 13/071,801 in view of Maziarz as evidenced by Korngold.

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[2] Maziarz et al., US 2006/0263337 A1, published Nov. 23, 2006 ("Maziarz").
[3] Robert Korngold, et al., *Role of Tumor Necrosis Factor-α in Graft-versus-Host Disease and Graft-versus-Leukemia Responses*, Biology of Blood and Marrow Transplantation 9:292–303 (2003) ("Korngold").
[4] Xuan Duc Nguyen, et al., *Flow cytometric analysis of T cell proliferation in a mixed lymphocyte reaction with dendritic cells*, Journal of Immunological Methods, 275, 57–68 (2003) ("Nguyen").

ISSUES AND ANALYSIS

Rejection of claims 29–31 and 33–37 under 35 U.S.C. § 103(a) as being obvious over Maziarz as evidenced by Korngold

The Examiner finds that Maziarz teaches a method of constructing a cell bank where the cells are expanded and stored. Final Act. 3 (citing Maziarz ¶¶ 43, 47, 200, 277, 337, 338, 340, and 384). The Examiner also finds that Maziarz teaches that the expanded and stored cells are "multipotent adult progenitor cells" (MAPCs). *Id.* (citing Maziarz ¶¶ 40, 47). According to the Examiner, Maziarz teaches that the MAPCs have the limitations recited in claim 29 as shown in the chart below:

Claim 29 limitations of the cell:	**Maziarz (paragraph(s)):**
the cells (i.e., "the" cells or "any" cells) being:	
non-embryonic and non-germ cells;	**42, 168, 171 and 177**
the cells that have one or more of:	
Oct4 expression	**41, 59, 177, 178, claim 4;**
Telomerase expression	**41, 58, 177, 178, claim 3;**
Rex-1 expression	**41, 177, 333;**
Rox-1 expression	**41, 177, 333;**
or can differentiate into cell types of at least two of	
endodermal,	**39, 40, 177 191; Claims 1-2;**
ectodermal and	**39, 40, 177 191; Claims 1-2;**
mesodermal germ layers	**39, 40, 177 191; Claims 1-2;**

Id. 5. Overall, the Examiner finds that "Maziarz teaches the same cells (MAPCs) that express the same markers for the same purpose and uses the same expansion and storage methods as Applicant." *Id.* at 4–5 (citing Maziarz ¶¶ 43, 47, 48, 49, 60, 213, 313, 317, 318, 337, 338, claims 5, 8–10; Spec. ¶¶ 98, 99).

With regard to the *in vitro* assay recited in the claims, the Examiner finds that the assay is not defined in the claims or the Specification such that it would provide any definitive meaning as to how the generic cell *in vitro* assay that detects the claimed effects is to be interpreted. Final Act. 2; Ans.

30. Therefore, the claim terms are given their broadest reasonable interpretation, "where detection can be any physical wet lab assay known in the art that is able to assay any functional or physical properties of cells related to one of the four recited properties." Ans. 30. The Examiner further finds that the claims encompass detection that can be a direct or an indirect effect (and are not limited to positive, negative, or neutral effect). *Id.* at 30–31.

The Examiner finds that Example 6 of Maziarz teaches an assay in which ConA (a T-cell activator), responder T-cells (prepared from lymph nodes) and MAPCs were added to microtiter plate wells (e.g., MAPCs are in contact with lymphocytes-leukocytes). Final Act. 5 (citing Maziarz ¶¶ 405–409). The plates were incubated for 4–5 days, pulsed with ^{3}H-thymidine, and then the cells were harvested and thymidine uptake was quantified in a micro-plate scintillation counter (i.e., detecting an effect of the cells on leukocytes). *Id.* at 5–6 (citing Maziarz ¶ 409). The results showed that MAPCs inhibited proliferation of ConA-activated T-cells and the amount of inhibition depended on the dose of MAPCs. *Id.* (citing Maziarz ¶ 412, Fig. 4).

Furthermore, according to the Examiner:

> Maziarz teaches in regard to Example 7 that the addition of increasing doses of syngeneic Lewis MAPCs and non-matched (allogeneic) third-party Sprague-Dawley MAPCs resulted in a significant and dose-dependent inhibition of T-cell activation, where maximal levels of inhibition were ~80% and even at the lowest doses of MAPCs, there was 40-50% inhibition.

Ans. 29 (citing Maziarz ¶ 421).

The Examiner admits that Maziarz does not teach that MAPCs' suppression of proliferation of activated T-cells has an effect on leukocyte extravasation or adhesion to vascular endothelium; however, the Examiner finds that Korngold cures this deficiency. Final Act. 8. Specifically, the Examiner finds that Korngold provides evidence that when leukocytes are activated, they produce inflammatory cytokines, such as TNF-α, IFN-γ, and IL-2, and these inflammatory cytokines cause leukocyte extravasation and adhesion. *Id.* at 8–9 (citing Korngold 292–293). The Examiner further finds that if MAPCs suppress activation of leukocytes, then they suppress production of these inflammatory cytokines and, therefore, MAPCs suppress leukocyte extravasation and adhesion. *Id.* at 9. The Examiner concludes that, "where Maziarz teaches an *in vitro* assay of observing [] the effect of leukocyte activation, that assay is inherently a detection of the effect of MAPCs on leukocyte extravasation or leukocyte adhesion to vascular endothelium (MPEP § 2112 (II))." *Id.*

The Examiner concludes that

> A person of ordinary skill in the art knows both Maziarz and Korngold and would look at the results from the Maziarz assays and even though Maziarz does not explicitly explain all the consequences that follow from the results, a person of ordinary skill in the art would have understood those consequential results since they would understand the pleiotropic functions of MAPCs, and from the evidence provided by Korngold that suppressing T-cell activation means that there is suppressed leukocyte extravasation. As noted above, the only thing that's missing from Maziarz is the meaning of the results, and such meaning, in conjunction with the evidence provided by Korngold is inherent within Maziarz (MPEP § 2112 (II)).

Ans. 28.

Appellant does not appear to contest that the MAPCs disclosed in Maziarz meet the limitations of the "cells (I)" recited in the claims, nor that Maziarz teaches a method of constructing a cell bank by expanding and storing such cells as recited in the claims. Appellant's main argument is that "the only conclusion that can be drawn from Maziarz is that MAPCs suppress T cell proliferation" and that "the mechanisms underlying suppression of T cell proliferation is not inherently biologically linked" to leukocyte extravasation or adhesion "because the factors (e.g., cytokines, signaling molecules and cellular components) involved in T cell proliferation and leukocyte extravasation are distinct." Appeal Br. 11. Appellant also cites to the Declaration of Dr. Busch as support for this argument. *Id.* at 12 ("[T]here is no data provided by Maziarz that suggests identifying a factor (or factors) or a biological effect directly related to leukocyte extravasation, adhesion to vascular endothelium or to isolated endothelial cells, Fut-7 expression, or expression of CD15s on a leukocyte." Busch Decl. 3.))

Appellant further asserts that Maziarz fails to teach that MAPCs inherently affect T cell activation. Appeal Br. 13. Specifically, Appellant argues that, in the MLR (mixed lymphocyte reaction) assay described in Maziarz, responder T cells were stimulated with ConA and contacted with MAPCs to assess the effect of MAPCs on the *proliferation* of stimulated T cells but it is the presence of ConA in the MLR, and not the MAPCs, that affects T cell *activation* because ConA is a known T cell mitogen. *Id.* Appellant concludes that the Examiner incorrectly assumes that there is an inherent association between the ability of MAPCs to suppress T cell

activation and leukocyte extravasation or adhesion because it is not the MAPCs that are affecting T cell activation. *Id.*

With regard to the statement in Example 7 of Maziarz that MAPCs inhibited T-cell activation, Appellant responds by contending that it is not clear what the term "T-cell activation" means in this context at the time of the claimed invention and, furthermore, the Declaration of Dr. Busch indicates that the skilled artisan would have only understood from Maziarz that MAPCs suppress T cell proliferation. Reply 2–3.

Appellant also asserts that Korngold does not remedy the deficiencies of Maziarz because it does not say anything about the action of MAPCs in inflammation. *Id.*

We find that the Examiner has the better position. We begin with claim interpretation because before a claim is properly interpreted, its scope cannot be compared to the prior art. "[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000). We agree with the Examiner that, under the broadest reasonable interpretation, the "detecting *in vitro*" limitation can be any physical or wet lab assay known in the art that is able to assay one of the four recited properties. We also agree that this limitation encompasses detection that is direct or indirect and can be positive, negative, or neutral. Therefore, the assays disclosed in Maziarz, which detect the effect of MAPCs on T-cell proliferation and/or activation, indirectly detect the effect of MAPCs on leukocyte extravasation and adhesion as evidenced by Korngold. *See* Korngold 292–293.

Appellant argues that the Declaration of Dr. Busch establishes that the skilled artisan would have understood from Maziarz only that MAPCs

suppress T cell proliferation (Appeal Br. 12, Reply 2–3); however, we do not find this contention to be supported by the Busch Declaration. The Busch Declaration does not include such a broad statement nor does it specifically address the results of Example 7 from Maziarz, which found that addition of increasing doses of syngeneic Lewis MAPCs and non-matched (allogenic) MAPCs "resulted in a significant and dose-dependent inhibition of T-cell *activation*." Maziarz ¶ 421 (emphasis added). As discussed in Korngold, T-cell activation leads to a cascade of cytokines, which ultimately leads to leukocyte extravasation and leukocyte adhesion on vascular endothelium. Korngold 292–293.

Furthermore, we agree with the Examiner that Maziarz teaches that MAPCs were known to have pleiotropic functions, not limited to a narrow subset of functions. *See, e.g.*, Maziarz ¶¶ 205–210. Therefore, by contacting MAPCs with a leukocyte, as disclosed in Maziarz (and as claimed), one is inherently detecting *in vitro* the effect of the cells on, e.g., leukocyte extravasation and/or leukocyte adhesion.

Therefore, we affirm the Examiner's rejection of claim 29 as obvious over Maziarz in view of Korngold. Claims 30, 31, and 33–37 are not argued separately apart from the independent claims, and, therefore, fall with claim 36. *See* 37 C.F.R. § 41.37(c)(1)(iv).

Rejection of claim 32 under 35 U.S.C. § 103(a) as being obvious over Maziarz (as evidenced by Korngold), further in view of Nguyen

The Examiner's findings with respect to Maziarz in view of Korngold are discussed *supra*. With regard to claim 32, the Examiner concedes that Maziarz and Korngold do not explicitly teach that the lymphocytes are $CD4^+$ or $CD8^+$ but that this deficiency is cured by Nguyen. Final Act. 24 (citing

Nguyen, Abstract, 59). The Examiner finds that Nguyen teaches an assay in which "$CD3^+/CD4^+$ or $CD3^+/CD8^+$ antibodies were used separately to distinguish [T helper] cells or [cytotoxic T lymphocytes] from other cell populations." *Id*. (citing Nguyen 59). The Examiner concludes that "[a] person of ordinary skill in the art would have been motivated to utilize a subset of T-cells within a MLR assay using the techniques in Nguyen so that all non T -cell populations are depleted for more accurate cell proliferation assays." *Id.*

Appellant asserts that claim 32 is patentable for at least the reasons that claim 29 is patentable over Maziarz as evidenced by Korngold. Appeal Br. 17.

For the reasons discussed *supra* with respect to Maziarz and Korngold, we affirm the Examiner's obviousness rejection of claim 32.

Provisional Obviousness-type Double Patenting of Claims 29–37

We decline to reach these undisputed provisional rejections. *See Ex parte Moncla*, Appeal No. 2009-006448 (PTAB June 22, 2010) (precedential). The rejections are provisional and Application Nos. 14/051,164 and 13/071,801 remain copending and not allowed; accordingly, the issues are not ripe for decision.

CONCLUSION

For the reasons described herein and those already of record, we affirm the Examiner's rejection of claims 29–37.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
29–31, 33–37	103	Maziarz, Korngold	29–31, 33–37	
32	103	Maziarz, Korngold, Nguyen	32	
29–37		Provisional Obviousness-type Double Patenting[5]		
29–31, 33–37		Provisional Obviousness-type Double Patenting[6]		
Overall Outcome			29–37	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

[5] As explained above, we do not reach this rejection per *Ex parte Moncla*, Appeal No. 2009-006448 (PTAB June 22, 2010) (holding that it is premature to address a provisional rejection) (designated precedential).
[6] As explained above, we do not reach this rejection per *Ex parte Moncla*, Appeal No. 2009-006448 (PTAB June 22, 2010) (holding that it is premature to address a provisional rejection) (designated precedential).