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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MARCEL MERSEL and CLOVIS RAKOTOARIVELO

Appeal 2021-005459
Application 15/298,757
Technology Center 1600

Before RICHARD M. LEBOVITZ, RYAN H. FLAX, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134(a) involving claims to a method of restoring a normal heavy chain (HC)/β2-microglobulin (β2m) molar ratio within the membrane of major histocompatibility complexes (MHC-I). Appellant[1] appeals the Examiner's rejection of claims 35–49 under 35 U.S.C. § 112(a).[2] We have jurisdiction under 35 U.S.C. § 6(b).

We reverse.

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[1] "Appellant" herein refers to the "applicant" as defined by 37 C.F.R. § 1.42. Appellant identifies "Beta Innov" as the real party-in-interest. Appeal Br. 2.

[2] *See* Final Office Action, dated October 16, 2020 ("Final Action"). Also, Oral argument was heard on February 10, 2022; a transcript of the hearing (Hr'g Tr.) is a part of the record.

STATEMENT OF THE CASE

The Specification states that β2m is a known protein of 99 amino acids, which forms a part of the major histocompatibility complex (MHC-I), which plays a central role in the recognition of "self" and "not-self" by the immune system and is present on the surface of most human cells other than erythrocytes. Spec. 1:14–22. "The MHC I complexes are composed of a glycosylated heavy chain (HC), of approximately 44kDa, and of a light chain, [and] the β2m, which associates non-covalently with the extracellular domain of the heavy chain." *Id.* at 1:26–28. The Specification describes that β2m plays an important role in the structure of the heavy chain of the MHC-I, contributing to the stability of the complex. *Id.* at 2:2–7.

The Specification describes that an imbalance in the HC/β2m ratio, as measured by analyzing β2m in serum, is suspected to play a role in some autoimmune diseases because "a local β2m deficit in the membrane MHC-I complexes . . . is liable to alter the presentation of the antigens to the T cells (CD8)." *Id.* at 10:10–12. In view of this theory, "[a]ccording to the invention, the β2m is more particularly used for its capacity to restore a normal HC/β2m ratio within the membrane MHC-I complexes in a patient." *Id.* at 15:14–16.

Independent claim 35 is representative and states:

> 35. A method of restoring a normal heavy chain (HC) / β2-microglobulin (β2m) molar ratio within the membrane in the membrane major histocompatibility complexes (MHC-I), comprising administering to a subject having a deficit of membrane β2m bound to HC in MHC-I present at the surface of cells of the subject, wherein the HC/β2m ratio is greater than 1, an effective amount of β2 microglobulin.

Appeal Br. 30 (Claims App'x).

The following rejections are on appeal:

Claims 35–49 stand rejected in the Final Office Action under 35 U.S.C. § 112(a) as not enabled by the application's disclosure. Final Action 2–3.

Claims 36, 37, 39, 40, 42, 43, 45, 46, and 49 stand rejected in the Final Office Action under 35 U.S.C. § 112(a) as not supported by a written description of the claimed invention. *Id.* at 7.

DISCUSSION

"[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. [Once] . . . that burden is met, the burden of coming forward with evidence or argument shifts to the applicant." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). We review the appealed rejections for Examiner error based upon the issues identified by Appellant and in light of Appellant's arguments and evidence. *Ex parte Frye*, 94 USPQ2d 1072, 1075 (BPAI 2010) (precedential). Arguments made by Appellant in the Appeal Brief and properly presented in the Reply Brief have been considered. *See* 37 C.F.R. § 41.37(c)(1)(iv) (2020); *see also Ex parte Borden*, 93 USPQ2d 1473, 1474 (BPAI 2010) (informative) ("Any bases for asserting error, whether factual or legal, that are not raised in the principal brief are waived.").

Regarding the statutory enablement requirement, "to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993); *see also In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (explains factors to be considered in determining whether a disclosure would require undue

experimentation to practice the claimed invention). "Enablement does not require an inventor to meet lofty standards for success in the commercial marketplace. Title 35 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

Regarding the written description requirement, "the test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

With these standards in mind, we address the Examiner's rejections and Appellant's arguments there-over.

The Examiner's first rejection is for lack of enablement. The Examiner determines that the Specification provides insufficient evidence that the method of the instant claims would function as claimed because there is no evidence to support the theory that administering β2m to a patient may treat an autoimmune disease, such as Crohn's disease, or that administering β2m to a Crohn's disease patient would result in the β2m winding up in cell surface MHC class I complexes. Final Action 2–5 (the Examiner states that "[w]hile the claims may not now be explicitly drawn to a method of treating Crohn's disease, it is clearly the intent."). The Examiner determines that the ordinarily skilled artisan would, instead, expect administered β2m to simply be degraded. *Id.* at 5 (citing Miltiadis

Zissis, M.D., et al., *B2 Microglobulin: Is It a Reliable Marker of Activity in Inflammatory Bowel Disease?*, 96(7) AM. J. GASTROENTEROLOGY 2177 (2001) ("Zissis")).[3]

Appellant argues that "[t]he examiner improperly construes the claims as requiring therapeutic or treatment efficacy with respect to some disease, when in fact the claims do not require therapeutic efficacy." Appeal Br. 5. Appellant argues that "[i]t is true that the Specification contemplates the use of the claimed method in treating autoimmune diseases such as Crohn's disease, but practicing the claim does not require a therapeutically effective result for this or any other disease." *Id.* at 6.

Appellant is correct. Claim 35 says noting about treating any disease. It is directed to "restoring a normal heavy chain (HC)/β2-microglobulin (β2m) molar ratio." *See supra* recitation of claim language. Contrary to the Examiner's position, the only requirement for claim 35 is that the Specification enable the claimed restoration method, not treating a disease.

Appellant also argues that "the Examiner err[s] by reading Applicant's claims to require administration of free β2m and/or by reading into applicant's claims a negative limitation that excludes administering . . . the β2m with a liposome carrier." Appeal Br. 17. This argument relates to the Examiner's determination that the ordinarily skilled artisan would have expected administered β2m to simply degrade upon administration, rather than integrate with cell membranes.

On this point we also agree with Appellant. The Specification explains in detail how β2m is to be administered to a patient in liposomes

[3] The record includes the first page of Zissis. This page does not discuss β2m protein administered in liposomes, but rather free β2m in serum.

and explains that such loaded liposomes protect the β2m from "proteolytic attacks" and "enables the [peptide] to be delivered in a targeted manner to the MHC-I complexes, in particular by fusion of the liposome with the phospholipids, which constitute the cell membranes." Spec. 17:3–11. The Specification provides an explanation of how to fabricate and administer such liposomes at its Example 2. *Id.* at 20:19–31:21. This same Example also explains how the liposomes are shown to protect the β2m and deliver it to cell membranes, and how the β2m becomes associated with the membranes by the process. *Id.*; *see also id.* at Figs. 1, 10. There appears to be ample explanation and data in the Specification from which an ordinarily skilled artisan could make and use the invention as claimed.

Because the Examiner has premised the rejection on subject matter not claimed, but rather on subject matter merely appearing in the embodiments of the Specification, and has overlooked the Specification's detailed description and actual example of practicing the method recited by the claim, we reverse the enablement rejection.

Turning to the second of the two rejections, the Examiner determined that the HC/β2m ratios (in the treated subject) of greater than 1.2 and 2 recited by claims 36 and 37, respectively are not supported by the Specification, which merely discloses a "patient suffering from autoimmune diseases." Final Action 8.

Appellant argues that the HC/β2m ratios of 1.2 and 2, and greater, are disclosed in the Specification at pages 15–16 (bridging paragraph), and at page 9 (Table 1). Appeal Br. 27–28. We agree.

At page 9, the Specification provides the following disclosure:

Table 1:

Determination of the different forms of β2m
in patients suffering from autoimmune diseases

Patients	Serum β2m (a)	HC/β2m proteins (b)	HC/β2m membranes (c)
P1	1.9	1.3	1.8
P2	1.8	1.1	1.7
P3	1.1	1.6	1.5
P4	1.1	1.2	2.1

HC: heavy chains of the MHC I

(a) Concentration of β2m in mg/l;

(b) HC/β2m calculated from the total lymphocyte proteins.

(c) HC/β2m calculated on the plasma membranes isolated from a purified lymphocyte fraction.

The results of table 1 above show an imbalance in the HC/β2m ratio. These results have revealed an unexpected situation, whereby the MHC-I membrane complexes present in those four patients is apparently significantly deficient in β2m relative to the HC concentration, without this increasing the concentration of free β2m in the blood.

These observations are to be compared to the controls in good health, who show a HC/β2m ratio in the neighborhood of 1.

Spec. 9:6–23. At pages 15–16, the Specification states:

The inventors have been able to determine that a deficit of intracellular or membrane β2m could give rise to a HC/β2m ratio greater than 1 or even 2 in certain patients suffering from autoimmune diseases. The invention is thus directed to

> returning said HC/β2m to a value close to physiological values i.e. preferably less than 2, more preferably less than 1.5 and still more preferably less than 1.2.

Id. at 15:29–16:2.

The above quoted and reproduced portions of the Specification disclose (to-be-treated) patients having an imbalance in their membrane HC/β2m ratio of greater than 1.2 and greater than 2, as claimed and indicates that 2 and 1.2 are physiological end point values to which the invention aims to lower the ratio of HC/β2m below. It is not clear why the Examiner discounts such disclosure, but we find it to be sufficient written description for the subject matter of the rejected claims and, therefore, we reverse the rejection.

CONCLUSION

In summary, the Examiner's rejections are each reversed.

DECISION SUMMARY

In summary:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
35–49	112	Enablement		35–49
36, 37, 39, 40, 42, 43, 45, 46, 49	112	Written Description		36, 37, 39, 40, 42, 43, 45, 46, 49
Overall Outcome				35–49

REVERSED