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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/888,605	05/07/2013	David L. KAPLAN	166118.00183.T001422.CON2	3938

153544 7590 12/27/2019

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ART UNIT	PAPER NUMBER
1658	

NOTIFICATION DATE	DELIVERY MODE
12/27/2019	ELECTRONIC

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID L. KAPLAN and XIAOQIN WANG

Appeal 2019-004919
Application 13/888,605
Technology Center 1600

Before ERIC B. GRIMES, RACHEL H. TOWNSEND, and CYNTHIA M. HARDMAN, *Administrative Patent Judges.*

HARDMAN, *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 10–15, 17–22, 27, and 28. *See* Final Act. 2. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

[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 the Trustees of Tufts College. Appeal Br. 2.

CLAIMED SUBJECT MATTER

The claims are directed to a drug delivery composition comprising a therapeutic agent encapsulated in crosslinked silk fibroin microspheres. Claim 10, reproduced below, is illustrative of the claimed subject matter:

> 10. A drug delivery composition comprising a therapeutic agent encapsulated in crosslinked silk fibroin microspheres, wherein the microspheres comprise:
>
> lipid components in an amount no greater than 20% of the microspheres by weight and;
>
> silk fibroin, 50% or more of which is β-sheet form, wherein the lipid components are integrated with the silk fibroin.

Appeal Br. 14 (Claims Appendix).

REFERENCES

The Examiner relied on the following prior art:

Name	Reference	Date
Brown	US 2006/0024379 A1	Feb. 2, 2006
Masters	WO 2006/042310 A1	Apr. 20, 2006
Zhou et al., *Silk Fibroin: Structural Implications of a Remarkable Amino Acid Sequence*, 44 PROTEINS: Structure, Function, and Genetics 119–22 (2001) ("Zhou")		
Gobin et al., *Silk-fibroin-coated liposomes for long-term and targeted drug delivery*, 1(1) Int. J. Nanomedicine 81–87 (2006) ("Gobin")		

REJECTIONS

Claims 10–15, 18–20, and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Masters and Zhou. Final Act. 3.

Claims 10–15, 17–22, and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Masters and Gobin. Final Act. 7.

Claims 10–15, 18–20, 27, and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Masters and Brown. Final Act. 8.

Claims 10, 12, 14, 17–20, and 27 stand provisionally rejected for obviousness-type double patenting over claims 1, 3, 4, 6, 7, 9, and 13 of copending Application No. 14/390,351 in view of Masters. Final Act. 13.

OPINION

Obviousness over Masters and Zhou; Obviousness over Masters and Gobin; Obviousness over Masters and Brown

Because the same issue is dispositive of all three obviousness rejections, we address them together. Claim 10, the only independent claim at issue, recites in relevant part that 50% or more of the silk fibroin is in β-sheet form. Appeal Br. 14 (Claims Appendix). The Examiner finds that "[a]s evidenced by Zhou, silk fibroin has a pleated β-sheet structure (i.e. substantially 100%)." Final Act. 4. More specifically, the Examiner finds that Zhou "teaches that 94% of the silk fibroin sequence involves alternating layers of β-sheets" that pack on top of each other. Final Act. 12. The Examiner thus finds that Zhou "supports the finding that silk fibroin exhibits a predominantly (i.e., more than 50%) β-sheet structure under normal conditions, even if small parts of the fibroin polypeptide may adopt other secondary structures and/or if special conditions can be used to force the fibroin to adopt other secondary structures." Final Act. 12 (citing Zhou Abstract, 119, 121–22).

Appellant argues, among other things, that the Examiner has not met the "evidentiary burden to establish inherency," because "[a] skilled artisan would recognize that it is improper to assume that the secondary structure of a protein in a solid-state, crystalline form, as disclosed by Zhou, would retain the same secondary structure after exposure to a solvent, as disclosed by Masters." Appeal Br. 8.

We determine that the Examiner has not established a *prima facie* case of obviousness, because there is insufficient evidence in the record to demonstrate that protein particles containing silk fibroin and lipid, as taught by Masters, would necessarily have more than 50% of the silk fibroin in β-sheet form. "[I]nherency may supply a missing claim limitation in an obviousness analysis," but is limited to situations where "the limitation at issue is the 'natural result' of the combination of prior art elements." *Par Pharm. Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014) (citing *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). Here, the Examiner has not established that the silk fibroin in particles made in accordance with Masters would necessarily have 50% or more of the silk fibroin in β-sheet form.

The Examiner focuses on the effect of residual solvent in solid silk fibroin particles. *See, e.g.*, Ans. 16 (asserting that because "[b]oth protein crystals used for x-ray crystallographic structure studies and the solid particles of Masters contain about the same amount of residual solvent," "Zhou stands as valid evidence that the structure of silk fibroin protein is predominantly (at least 94%) β-sheet structure"). This analysis overlooks the more pertinent question, which is the effect various processing conditions will have on the secondary structure of the resulting silk fibroin particles. That is, we understand Appellant to be arguing that a protein's secondary structure "depends on a multitude of factors, such as the solvent, the concentration of salts/ions, the pH, [and] the temperature" during processing. Appeal Br. 8; *see also* Kaplan Decl.[2] ¶ 8. Appellant argues that

[2] Aug. 15, 2017 Declaration under 37 C.F.R. § 1.132 of David Kaplan.

one cannot assume that a protein "would retain the same secondary structure after exposure to a solvent, as disclosed by Masters." Appeal Br. 8. Indeed, Appellant's declarant asserts that the percentage of β-sheet content in silk fibroin can vary based on processing conditions. *See* Kaplan Decl. ¶ 8 (citing Shang et al., *Accelerated in vitro Degradation of Optically Clear Low β-sheet Silk Films by Enzyme-Mediated Pretreatment*, 131(5) JAMA Ophthalmol. 676 (May 2013)). Thus, given the variability in β-sheet content that can follow from different processing conditions, the Examiner has not established that silk fibroin/lipid particles made in accordance with Masters' teachings would necessarily result in silk fibroin having 50% or more β-sheet form.

The Examiner acknowledges that there are processing conditions under which the β-sheet content of silk fibroin can be reduced. Ans. 20–21. The Examiner asserts, however, that "Masters suggests using the native silk fibroin prepared under normal conditions." Ans. 21. This argument is not persuasive, because it overlooks the claim requirement that the lipid components be "integrated" with the silk fibroin. The Examiner indicates that "the term 'integrated' is generally defined to mean 'with various parts or aspects linked or coordinated.'" Final Act. 4; Ans. 5. The Examiner additionally states, however, that "instant claims 21-22 encompass the lipid/protein/therapeutic agents being located in separate layers (note that uni- and multilamellar structures suggest a layer arrangement)." Ans. 5.

We disagree with the Examiner's suggestion that claims 21–22 permit an interpretation of "integrated" wherein the lipid and silk fibroin can be in wholly separate layers. Claim 21 does not address the relationship between the lipid and silk fibroin, but rather requires that *the therapeutic agent* and

the silk fibroin be "located in separate layers or domains." Thus, claim 21 sheds no light on the meaning of the term "integrated." Claim 22 speaks to the structure of the lipids only, and as such also does not have any bearing on the meaning of the term "integrated," which addresses the relationship between the lipid and silk fibroin. *See also* Spec. ¶¶ 28–29 (indicating that "silk fibroin solution and lipid composition ***should be mixed*** in a manner that ***integrates*** the silk fibroin and lipids," and that breaking "larger multilammelar lipid vesicles into smaller, unilamellar structures" can "promote[] mixing among the lipids, silk fibroin, and therapeutic agents, when present") (emphasis added). Thus, as indicated by the Examiner, "integrated" means that the lipid and silk fibroin must be "linked or coordinated" in some way, but wholly separate layers do not satisfy this requirement.

Turning back to the Examiner's statement that "Masters suggests using the native silk fibroin prepared under normal conditions," the silk fibroin that is part of Masters' protein particles is clearly not native, because to meet the claims, the silk fibroin must be integrated with lipid components. Thus, even if Masters were limited to use of "native" silk fibroin as the starting material (which the Examiner has not established), in order to meet the claims, the silk fibroin has to be processed in some way such that it is integrated with the lipid components. The Examiner has not established that such processing will necessarily retain the β-sheet form of naturally-occurring silk fibroin.

The Examiner further asserts that "Masters cautions the artisan NOT to disrupt the natural secondary and/or tertiary structure of the proteins used in the invention." Ans. 19 (citing Masters 22:6–10). This argument is also

not persuasive, because it takes the cited statement from Masters out of context. Masters states: "[C]are should be taken to not irreversibly denature the proteins ***of the cohesive body*** during preparation through various actions on the composition that will disrupt the secondary and/or tertiary structure of the protein(s) such as application of excessive heat or strong alkaline solution, which may cause coagulation/gelation." Masters 22:6–10 (emphasis added).

Masters teaches that the cohesive body can be formed in two ways, either by first forming a coated film (or coatable composition) prepared from the proteins, solvent, and any additives (such as lipids) (*see* Masters 21:13–16, 21–25), or without first preparing the film (Masters 22:10–12). In context, the statement in Masters relied upon by the Examiner appears to refer to maintaining the structure of the proteins in the cohesive body formed after making a film, because the preceding discussion relates to forming the film. Accordingly, the statement does not speak to maintaining the "natural" secondary structure of the native protein, because the film already contains the protein integrated with any additives such as lipid. Thus, in context, the statement in Masters is directed to maintaining whatever secondary structure was adopted by the protein/integrated lipid in the film.

Even if Masters were referring to the secondary structure of the starting material, the Examiner incorrectly assumes that a person of ordinary skill in the art would have started with silk fibroin having 50% or more β-sheet form. As noted above, the Examiner has not established that Masters is limited to use of "native" silk fibroin as the starting material, and on the present record, nothing demonstrates that a person of ordinary skill in the art

would have necessarily started with silk fibroin that has the required amount of β-sheet content.

Accordingly, for the reasons discussed above, we determine that the Examiner has not established a *prima facie* case of obviousness, and thus we reverse the obviousness rejections.

Obviousness-Type Double Patenting

The Examiner provisionally rejected claims 10, 12, 14, 17–20, and 27 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, 7, 9, and 13 of copending Application No. 14/390,351 in view of Masters. Final Act. 13.

As of the writing of this opinion, the co-pending application has not issued as a patent. Thus, we decline to reach the rejection, as the issue is not ripe for decision. *Ex parte Moncla*, 95 USPQ2d 1884, 1885 (BPAI 2010) (precedential).

CONCLUSION

We reverse the rejection of claims 10–15, 18–20, and 28 under 35 U.S.C. § 103(a) as being unpatentable over Masters and Zhou.

We reverse the rejection of claims 10–15, 17–22, and 28 under 35 U.S.C. § 103(a) as being unpatentable over Masters and Gobin.

We reverse the rejection of claims 10–15, 18–20, 27, and 28 under 35 U.S.C. § 103(a) as being unpatentable over Masters and Brown.

We do not reach the provisional rejection of claims 10, 12, 14, 17–20, and 27 for obviousness-type double patenting over claims 1, 3, 4, 6, 7, 9, and 13 of copending Application No. 14/390,351 in view of Masters.

DECISION SUMMARY

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
10–15, 18–20, 28	103	Masters, Zhou		10–15, 18–20, 28
10–15, 17–22, 28	103	Masters, Gobin		10–15, 17–22, 28
10–15, 18–20, 27, 28	103	Masters, Brown		10–15, 18–20, 27, 28
10, 12, 14, 17–20, 27		Provisional Obviousness-type Double Patenting[3]		
Overall Outcome:				10–15, 17–22, 27, 28

REVERSED

[3] As explained above, we do not reach this rejection per *Ex parte Moncla*, 95 USPQ2d 1884, 1885 (BPAI 2010) (precedential).