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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RUYING LU and RAPHAEL MANNINO

Appeal 2019-005186
Application 14/115,770
Technology Center 1600

Before DONALD E. ADAMS, FRANCISCO C. PRATS, and MICHAEL A. VALEK, *Administrative Patent Judges*.

VALEK, *Administrative Patent Judge.*

DECISION ON APPEAL

Appellant[1] submits this appeal under 35 U.S.C. § 134(a) involving claims to cochleate compositions and methods of making such compositions. 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(a). Appellant identifies Matinas Biopharma Nanotechnologies, Inc. and Rutgers, the State University of New Jersey, as the real parties in interest. Appeal Br. 4.

STATEMENT OF THE CASE

The Specification explains that

> [c]ochleates are anhydrous, stable, multi-layered lipid crystals which spontaneously form upon the interaction of phosphatidylserine and calcium. . . . Cochleate formulations remain intact in physiological fluids, including mucosal secretions, plasma and gastrointestinal fluid, thereby mediating the delivery of biologically active compounds by many routes of administration, including oral, mucosal and intravenous.

Spec. 1. According to the Specification, "[t]raditionally, such cochleate formulations have been restricted to the incorporation of hydrophobic active pharmaceutical ingredients (APIs)" and there is a "need in the art to provide compositions and methods for making and using cochleate compositions suitable for the stable and enhanced encochleation of hydrophilic APIs." *Id.*

Claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 are on appeal and can be found in the Claims Appendix of the Appeal Brief. Claim 1 is illustrative and reads as follows:

> 1. A cochleate composition comprising a population of cochleates, wherein the cochleates comprise:
>
> a) one or more negatively charged first lipids, wherein the one or more negatively charged first lipids comprise phosphatidylserine;
>
> b) a cation, wherein the cation is a divalent cation or a higher valency cation selected from the group consisting of calcium, zinc, barium, and magnesium cations;
>
> c) a neutral second lipid or group of neutral second lipids; and
>
> d) a hydrophilic biologically relevant molecule, wherein the hydrophilic biologically relevant molecule is a drug or an active pharmaceutical ingredient (API);
>
> wherein the ratio of the one or more negatively charged first lipids to the neutral second lipid or group of neutral second lipids is between 1:1 to 9:1; and

> wherein the neutral second lipid or group of neutral second lipids comprises phosphatidylcholine or a sphingomyelin.

Appeal. Br., Claims App. i. Appellant agrees that claims 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84 stand or fall with claim 1. *Id.* at 10.

Claims 22, 23, and 86 are argued separately. Claim 86 is similar to claim 1, but additionally specifies that "the biologically relevant molecule is an aminoglycoside." *Id.* at Claims App. v. Claim 22 indirectly depends from claim 1 and reads as follows:

> 22. The cochleate composition of claim 19, wherein the anti-infectious agent is an aminoglycoside selected from gentamicin, netilmicin, tobramycin, amikacin, kanamycin A, kanamycin B, neomycin, paromycin, neamine, streptomycin, dihydrostreptomycin, apramycin, ribostamycin, or spectinomycin.

Id. at ii. Claim 23 depends from claim 22 and recites that the "aminoglycoside is amikacin." *Id.*

Appellant seeks review of the following rejections:[2]

I. Claims 1, 6, 11, 12, 19, 31–34, 39, 47, 49, 81, 83, and 86 under 35 U.S.C. § 102 as anticipated by Balu-lyer.[3]

II. Claims 1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 under 35 U.S.C. § 103 as unpatentable over Balu-lyer.

[2] The obviousness-type double patenting rejection of claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 referred to Examiner's Answer (*see* Ans. 15) was withdrawn prior to the appeal in an Advisory Action mailed January 2, 2019.

[3] US 2007/0141135 A1, published June 21, 2007 ("Balu-lyer").

III. Claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 under 35 U.S.C. § 103 as unpatentable over Gould-Fogerite,[4] Tan,[5] Zarif '894,[6] and Zarif '473.[7]

IV. Claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 under 35 U.S.C. § 103 as unpatentable over Zarif '473 and Tan.

V. Claims 33, 34, 39, 42, 44, 47, 49, 80, 81, 83, and 84[8] under 35 U.S.C. § 103 as unpatentable over Gould-Fogerite, Zarif '894, Zarif '473, Tan, Daftary,[9] Onyuksel,[10] and Balu–lyer.

VI. Claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 under 35 U.S.C. § 103 as unpatentable over Zarif '894, Zarif '473, Tan, and Kessler.[11]

Findings of Fact

FF1. Balu-lyer discloses cochleate compositions "for reducing the immunogenicity and increasing the circulating half-life of therapeutic proteins such as Factor VIII." Balu-lyer, Abstr. These cochleate compositions comprise "a negatively charged lipid such as [phosphatidylserine]" and "may also comprise [phosphatidylcholine]," i.e.,

[4] US 5,994,318, issued Nov. 30, 1999 ("Gould-Fogerite").
[5] WO 03/082209 A2, published Oct. 9, 2003 ("Tan").
[6] US 6,592,894 B1, issued July 15, 2003 ("Zarif '894").
[7] US 2003/0219473 A1, published Nov. 27, 2003 ("Zarif '473").
[8] Both the Appeal Brief (at 9) and Final Action (at 10) list claims 82 and 85 in this rejection. Those claims, however, were cancelled prior to the Final Action and are not before us now. *See* Amdt filed May 2, 2018, 11.
[9] US 2005/0142178 A1, published June 30, 2005 ("Daftary").
[10] US 6,197,333 B1, issued Mar. 6, 2001 ("Onyuksel").
[11] US 2010/0310541 A1, published Dec. 9, 2010 ("Kessler").

an "amphipathic lipid." *Id.* ¶¶ 18, 21. Balu-lyer discloses that in some embodiments "cochleates may . . . comprise 100 mole % of [phosphatidylserine]," whereas in others "[u]p to 30 mole % of the [phosphatidylserine] may be replaced by [phosphatidylcholine]." *Id.* ¶ 29.

FF2. Balu-lyer teaches that "Factor VIII or other proteins or polypeptides can be associated with (i.e., surface absorbed) or be incorporated into these structures" because "the proteins associate with the negatively charged lipids." Balu-lyer ¶ 20.

FF3. Balu-lyer Example 4 "describes the preparation of [phosphatidylserine] containing cochleate structures or cylinders." Balu-lyer ¶ 48. According to this example, an "rFVIII-liposome complex was generated by incubating concentrated rFVIII solutions in the presence of liposomes" in a Ca^{2+} free buffer. *Id.* Balu-lyer teaches that "[t]he controlled growth of cochleates cylinders is [then] initiated by spiking Ca^{2+} ions in the solution." *Id.*

FF4. Gould-Fogerite discloses "cochleates comprising a) a biologically relevant molecule component b) a negatively charged lipid component, and c) a divalent cation component." Gould-Fogerite, Abstr. Gould-Fogerite teaches

> [t]o form cochleate precipitates, a majority of the lipid present should be negatively charged. One type of lipid can be used or a mixture of lipids can be used. Phosphatidylserine or phosphatidylglycerol generally have been used. . . . A substantial proportion of the lipid can, however, be neutral or positively charged. The instant inventors have included up to 40 mol % cholesterol based on total lipid present.

Id. at 6:62–7:3.

FF5. Gould-Fogerite teaches that suitable biologically relevant molecules for incorporation into such cochleates include polynucleotides as well as lipophilic drugs and peptides. Gould-Fogerite 2:4–9. According to Gould-Fogerite, "[b]ecause polynucleotides are hydrophilic molecules and cochleates are hydrophobic molecules that do not contain an internal aqueous space, it is surprising polynucleotides can be integrated into cochleates," (*id.* at 8:51–55) but "[a]s demonstrated herein, hydrophilic molecules can be 'cochleated', that is, can be made part of the cochleate structure, with little difficulty." *Id.* at 10:12–15.

FF6. Zarif '894 teaches

> [a] process for producing a small-sized, lipid-based cochleate. Cochleates are derived from liposomes which are suspended in an aqueous two-phase polymer solution. . . . The liposome-containing two-phase polymer solution, treated with positively charged molecules such as Ca_{2+} or Zn_{2+}, forms a cochleate precipitate of a particle size less than one micron. The process may be used to produce cochleates containing biologically relevant molecules.

Zarif '894, Abstr.

FF7. Zarif '894 teaches cochleate compositions comprise "a biologically relevant molecule," "a negatively charged lipid," "a cation component," and "may also include minor amounts of zwitterionic lipids, cationic lipids, polycationic lipids or neutral lipids capable of forming hydrogen bonds to a biologically relevant molecule." *Id.* at 2:33–41, 5:30–33. According to Zarif '894, the biologically relevant molecule incorporated into its cochleates may be "hydrophilic, amphiphilic, or hydrophobic in aqueous media" and may be an "anti-infectious" drug. *Id.* at 5:55–62.

FF8. Zarif ’473 describes cochleate compositions comprising “soy phosphatidylserine” and a “bioactive load.” Zarif ’473, Abstr.[12] According to Zarif ’473, “[t]he bioactive agent/drug (referred to as ‘load’ or drug) can be hydrophobic in aqueous media, hydrophilic or amphiphilic,” e.g., “a protein, a small peptide, bioactive polynucleotide,” or “an anti-infectious agent.” *Id.* ¶ 46.

FF9. Zarif ’473 teaches cochleates that “are made by using soy phosphatidylserine in an amount of at least 75% by weight of the lipid component of the cochleates.” Zarif ’473 ¶ 28. Zarif ’473 further teaches that these cochleates may include other phospholipids such as “phosphatidylcholine.” *Id.* ¶ 29. For example Zarif ’473 recites claims to a “lipid based cochleate” comprising “at least about 80% by mole soy phosphatidylserine,” “up to about 20% by mole of a mixture of one or more lipids other than phosphatidylserine,” selected from a group that includes “phosphatidylcholine,” and “a multivalent cation.” *Id.* claims 12, 16.

FF10. Zarif ’473 teaches that cochleates are made by preparing an aqueous solution of liposomes comprising “at least 75% by weight” soy phosphatidylserine and “a load of one or more bioactive compounds.” Zarif ’473 ¶¶ 33–34. A multivalent cation such as “Ca^{++}, Zn^{++} and Mg^{++}” is then added to form the cochleates. *Id.* ¶¶ 32, 35.

FF11. Onyuksel describes methods for preparing “biologically active liposome products comprising a biologically active amphipathic compound in

[12] Tan is related to the patent application published as Zarif ’473. Tan includes the same disclosure that we cite in Zarif ’473 for our findings and analysis here.

association with a liposome." Onyuksel, Abstr. Onyuksel teaches that the compounds in these liposomes are "peptides which are amphipathic, i.e., have both hydrophilic and hydrophobic portions." *Id.* at 1:9–12. According to methods taught in Onyuksel, "a combination of lipids" is mixed to form liposomes and then incubated with the biologically active compound "under conditions in which said compound becomes associated with said liposomes." *Id.* at 4:45–58.

FF12. Kessler describes "[c]ompositions and methods for reducing the toxic effect of certain peptide toxins by administering an agent that directly or indirectly reduces disulfide bonds that are important for maintaining the toxin in an active confirmation." Kessler, Abstr. Kessler teaches that these agents "can be administered via a nanochochleate or cochleate delivery vehicle." *Id.* ¶ 67.

FF13. Kessler teaches that "it can be useful to administer an antibiotic," including "[a]minoglycosides (e.g., Amikacin, Gentamicin, Kanamycin, Neomycin, Netilmicin, Streptomycin, Tobramycin, Paromornycin, Hygromycin, and Spectinomycin)," together with the "agent for promoting reduction of disulfide bonds." Kessler ¶ 34. Kessler teaches that this "[c]ombination therapy can be achieved by administering two or more agents, e.g., an agent for reducing toxicity described herein and antibiotic, each of which is formulated and administered separately, or by administering two or more agents in a single formulation." *Id.* ¶ 37.

Analysis

I. 102 Rejection: Balu-lyer

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's determination that Balu-lyer anticipates claims 1,

6, 11, 12, 19, 31–34, 39, 47, 49, 81, 83, and 86? Claim 1 is representative of rejected claims 6, 11, 12, 19, 31–34, 39, 47, 49, 81, and 83. We analyze claim 86 separately.

Claim 1

Examiner finds that Balu-lyer "teaches cochleate formulations containing an antigen," i.e., Factor VIII. Final Act. 2. According to Examiner, Factor VIII is a "hydrophilic biologically relevant molecule," as that term is recited in claim 1, because the "instant claims do not define the hydrophilicity in terms of the molecule having only hydrophilic domains or the degree of hydrophilicity" and "literature reference show that Factor VIII and recombinant Factor VIII is soluble in water and buffers." Final Act. 3. Examiner determines Balu-lyer discloses Factor VIII cochleate formulations with "up to 30 mole % of phosphatidylserine" lipid "replaced by phosphatidylcholine" lipid and, therefore, Balu-lyer discloses cochleates comprised of the recited negative and neutral lipids within the recited ratio range. *Id.* at 2–3; Ans. 10.

Appellant argues that Balu-lyer does not anticipate for two reasons. First, Appellant argues that it does not sufficiently disclose the invention as recited in claim 1 because "the only example in Balu-[l]yer of a cochleate composition is Example 4" and "there is no evidence that cochleates comprising recombinant Factor VIII were actually prepared." Appeal Br. 12. Appellant urges that Examiner's reliance on the "generic teaching" that "up to 30 mole % of the phosphatidylserine may be replace by phosphatidylcholine" is misplaced because there is "no specific embodiment preparing any such cochleate . . . much less a cochleate comprising a

hydrophilic biologically relevant molecule together with phosphatidylcholine." *Id.* at 13 (internal quotations omitted).

Second, Appellant contends that Balu-lyer "does not teach or suggest the incorporation of a hydrophilic drug or API into cochleate structures." *Id.* According to Appellant, "it is well-known in the art that most proteins, including Factor VIII, are not considered purely hydrophilic or hydrophobic structures." *Id.* at 14. Thus, Appellant urges that "even though Factor VIII does contain hydrophilic amino acids, the Examiner has failed to establish that Factor VIII is considered a hydrophilic biologically relevant molecule . . . as claimed herein." *Id.* at 15.

Based on the record before us, we determine the preponderance of the evidence supports Examiner's anticipation rejection of claim 1. *See* FF1–FF3. We agree with, and adopt, Examiner's findings and reasoning in support of the rejection of those claims. We are not persuaded by Appellant's arguments, which we address below.

We are unpersuaded by Appellant's argument that Example 4 and the "generic teaching" in Balu-lyer do not disclose a cochleate composition as recited in claim 1. *See* Appeal Br. 12–13. "Anticipation does not require the actual creation or reduction to practice of the prior art subject matter; anticipation requires only an enabling disclosure." *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003) (citing *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985)). Thus, it is "irrelevant" whether the cochleates in Example 4 (or any of the other cochleates described in Balu-lyer) were actually prepared. *Id.*

Nor is Balu-lyer's disclosure of cochleate compositions limited to the particular embodiment in Example 4. Balu-lyer also discloses cochleates

comprised of phosphatidylserine wherein "[u]p to 30 mole % of the phosphatidylserine may be replaced by phosphatidylcholine." FF2. Thus, Balu-Iyer describes cochleate compositions, "arranged or combined in the same way as recited in the claim," i.e., comprising a mixture of phosphatidylserine and phosphatidylcholine at a ratio within the recited range. *See Therasense, Inc. v. Becton, Dickinson & Co.*, 593 F.3d 1325, 1332 (Fed. Cir. 2010) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F. 3d 1359, 1371 (Fed. Cir. 2008)).

We are likewise unpersuaded by Appellant's argument that Factor VIII is not a "hydrophilic biologically relevant molecule," as recited in claim 1. *See* Appeal Br. 13–15. According to Appellant, "it is well-known in the art that most proteins, including Factor VIII, are not considered purely hydrophilic or hydrophobic" because they are made up of a multitude of "amino acids that may individually be considered hydrophilic or hydrophobic." Appeal Br. at 14. Thus, Appellant does not dispute Examiner's finding that portions of Factor VIII are hydrophilic, thereby allowing it to "associate with" water. *Id.*; *see also id.* at 15 (acknowledging that "Factor VIII does contain hydrophilic amino acids").

The issue then is whether, given its broadest reasonable interpretation, the claim term "hydrophilic biologically relevant molecule" encompasses a protein, like Factor VIII, that is not "purely" hydrophilic because it also contains hydrophobic portions; we conclude that it does. Claim 1 does not recite a "purely" hydrophilic molecule. It does not specify a particular degree of required hydrophilicity, nor does it otherwise exclude large molecules with both hydrophilic and hydrophobic domains. To the contrary, the Specification expressly names "peptides" and "protein" drugs as

examples of "biologically relevant molecules" that may be incorporated into cochleates. Spec. 14–15. Indeed, enhanced encochleation of "hydrophilic molecules *or large molecules with hydrophilic domains*" is repeatedly described as the inventors' purported discovery. *Id.* at 11, 93 (emphasis added). Accordingly, we agree with Examiner that the "instant claims do not define the hydrophilicity in terms of the molecule having only hydrophilic domains or the degree of hydrophilicity" (Final Act. e) and, therefore, that Balu-lyer discloses cochleates with a "hydrophilic biologically relevant molecule" as recited in claim 1.

For these reasons, we affirm the rejection of claim 1 as anticipated by Balu-lyer. We likewise affirm the rejection of claims 6, 11, 12, 19, 31–34, 39, 47, 49, 81, and 83, which Appellant agrees stand or fall with claim 1.

Claim 86

We reach a different conclusion for claim 86. Claim 86 limits the "hydrophilic biologically relevant molecule" to an "aminoglycoside." There is no evidence that Factor VIII is an aminoglycoside, nor does Examiner otherwise find that Balu-lyer discloses a "cochleate composition" comprising an "aminoglycoside" as recited in claim 86. Accordingly, we reverse the anticipation rejection of claim 86.

II. 103 Rejection: Balu-lyer

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that claims 1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 are obvious over Balu-lyer?

Claim 1

Examiner's findings for this rejection are substantially the same as those made for the anticipation rejection over the same reference. *See* Final

Act. 13. As before, Appellant argues that "Balu-lyer does not teach or suggest a hydrophilic drug or API." Appeal Br. 28.

Based on the record before us, we determine that the preponderance of the evidence supports Examiner's rejection of claim 1. *See* FF1–FF3. We agree with, and adopt, Examiner's findings and reasoning in support of that rejection. We likewise affirm the rejection of claims 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84, which Appellant agrees stand or fall with claim 1. We are not persuaded by Appellant's argument for the same reasons discussed above in our analysis of the anticipation rejection.

Claim 86

We reach a different conclusion for separately-argued claim 86. Examiner has not articulated a rationale to support a finding that the incorporation of an "aminoglycoside" into a cochleate compositions, as recited in claim 86, would have been obvious over the teachings in Balu-lyer. Accordingly, Examiner has failed to establish a prima facie case of unpatentability for claim 86.

III. 103 Rejection: Gould-Fogerite, Tan, Zarif '894, and Zarif '473

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 are obvious over the cited references? Claim 1 is representative of claims 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84. We analyze claims 22, 23, and 86 separately.

Claim 1

Examiner finds that Gould-Fogerite teaches cochleate compositions that meet all of the limitations of claim 1, including the "neutral second lipid," but does "not specifically disclose phosphatidylcholine" or

sphingomyelin as that neutral lipid. Final Act. 4. Examiner determines that Zarif '473 and Tan teach cochleates for the delivery of various biologically relevant molecules that are formed from phosphatidylserine "in an amount of at least 75% by weight" and that such compositions may further comprise "phosphatidylcholine." *Id.* at 5–6. Examiner concludes it would be obvious to use phosphatidylcholine as a neutral lipid to form cochleates taught by Zarif '473 and Tan. *Id.* at 6.

Appellant argues that Examiner has failed to establish a prima facie case of obviousness because the references fail to disclose a "neutral lipid" at the ratio recited in claim 1. *See* Appeal Br. 17–21. In addition, Appellant relies on Example 5 and Figure 14 of the Specification and the Declaration of Dr. Mannino, dated June 22, 2017 ("Mannino Decl."). *Id.* at 18–20. Appellant contends this evidence "demonstrates unexpectedly superior results using the claimed neutral second lipids, phosphatidylcholine and sphingomyelin, over the use of cholesterol, which is the only second lipid disclosed in Gould-Fogerite." *Id.* at 19.

Based on the record before us, we determine that the preponderance of the evidence supports Examiner's rejection of claim 1 over the cited references. *See* FF4–FF10. We agree with, and adopt, Examiner's findings and reasoning in support of that rejection. We are not persuaded by Appellant's arguments, which we address below.

We are unpersuaded by Appellant's argument that Examiner has failed to establish a prima facie case of obviousness. All four of the cited references disclose cochleates comprised of the recited negatively charged lipid, i.e., phosphatidylserine, and a bivalent cation. And all four references expressly teach that "hydrophilic" biologically relevant molecules can be

incorporated into such cochleates. *See* FF4–FF10. Moreover, Zarif '473 teaches cochleate compositions comprising a combination of phosphatidylserine and one of the recited neutral lipids, i.e., phosphatidylcholine, at ranges (i.e., 4:1 and 5:1 or greater)[13] that overlap with the "1:1 to 9:1" ratio in claim 1. FF9. This overlap is sufficient to establish a prima case of obviousness. *See In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) ("In cases involving overlapping ranges, we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie case* of obviousness.").

Appellant urges that "Zarif '473 and Tan teach a preferred embodiment that wholly excludes . . . neutral lipids." Appeal Br. 21. "But in a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered." *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)). Here, it is clear that Zarif '473 and Tan also teach embodiments comprising the recited lipids at ratios within the claimed range. FF9.

Appellant's argument that Zarif '893 "teaches away" from the claimed range because it describes the use of "*minor* amounts" of neutral lipids and "only exemplifies a ratio of 100:1" is not persuasive. *See* Appeal Br. 18. Zarif '893 does not provide a numerical range for the "minor

[13] Zarif '473 discloses an amount of phosphatidylserine in terms of both weight (i.e., "at least 75% by weight of the lipid component") and moles (i.e., "at least about 80% by mole") and teaches that the remainder may be phosphatidylcholine. FF9. These amounts equate to a ratio of phosphatidylserine to phosphatidylcholine of 4:1 and 5:1 respectively.

amounts" of neutral lipids it teaches. *See* FF6. The 100:1 ratio that Appellant cites in the Appeal Brief is from one of the examples in Zarif '893. There is nothing in Zarif '893 that suggests the ratio in that example is an upper limit on the amount of neutral lipid, nor does Zarif '893 otherwise discourage the use an amount of neutral lipid within the claimed ratio range. Accordingly, Zarif '893 does not teach away from claim 1 because it does not "criticize, discredit, or otherwise discourage investigation into" a ratio of neutral to negatively charged lipid within the recited range. *See Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)).

Appellant's evidence of purported unexpected results is insufficient to overcome Examiner's prima facie showing of obviousness. The results in Example 5 report "encapsulation efficiencies" at "99.9% pure PS" and "50% soy PS" for only two hydrophilic biologically relevant molecules, i.e., amikacin and gentamicin. Spec. 94. Figure 14 shows data over a wider range of ratios, but just for amikacin. Appellant has not demonstrated that these results are commensurate with the much broader scope of claim 1, which encompasses any "hydrophilic biologically relevant molecule."[14] *See In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) (Evidence of alleged unexpected results must be "commensurate in scope with the degree of protection sought by the claims" to demonstrate non-obviousness.). In addition, Figure 14 shows that the "Percent of Amikacin Encochleated" at

[14] The Mannino Declaration refers to Example 5 and Figure 14; it does not provide any additional data to support Appellant's unexpected results argument.

10% DOPC (dioleoylphosphatidylcholine) is roughly the same as that for 100% DOPS (dioleoylphosphatidylserine). Thus, even if the data were commensurate with the scope of claim 1, it does not evidence any increase in encapsulation efficiency at a 9:1 ratio of one of the two recited neutral lipids—phosphatidylcholine. As such, Appellant has not shown unexpected results for the entire claimed range. *See Peterson*, 315 F.3d at 1330–31 (affirming that the prima facie case was not overcome where unexpected results had not been shown "for the entire claimed range").

When considered in context of the record as a whole, Appellant's evidence does not overcome Examiner's strong prima facie showing. Accordingly, we affirm the rejection of claim 1. We likewise affirm the rejection of claims 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84, which Appellant agrees stand or fall with claim 1.

Claims 22, 23, and 86

Examiner states in the Answer that "Zarif teaches aminoglycosides such as amphotericin B and nystatin," as recited in claims 22, 23, and 86. Ans. 12. However, Examiner does not identify any evidence in the record to support this finding. Moreover, as Appellant points out, this finding is new in Examiner's Answer and contradicted by Examiner's prior determination that these references do not teach aminoglycosides as active agents. Reply Br. 3; *see, e.g.*, Final Act. 12 ("What is lacking in [Zarif '894 and Zarif '473] is the teaching of aminoglycosides as the active agents."). Accordingly, Examiner has failed to establish a prima facie case of obviousness for claims 22, 23, and 86. We, therefore, reverse the rejection of these claims.

IV. 103 Rejection: Zarif '473 and Tan

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 are obvious over the cited references? Claim 1 is representative of claims 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84. We analyze claims 22, 23, and 86 separately.

Claim 1

This rejection is similar to the preceding obviousness rejection. As before, we determine that the preponderance of the evidence supports Examiner's rejection of claim 1 over the cited references. *See* FF8–FF10. We agree with, and adopt, Examiner's findings and reasoning in support of that rejection. *See* Final Act. 8–10. We are not persuaded by Appellant's arguments, which we address below.

Appellant argues that "read as a whole" Zarif '473 and Tan "advocate for the use of hydrophobic material over a hydrophilic one." Appeal Br. 23. We disagree. As explained above, these references expressly teach that the biologically active agent may be "hydrophilic." FF8.

We are also unpersuaded by Appellant's argument that Zarif '473 and Tan "teach away" from the claimed cochleates because they express a "preference for 100% phosphatidylserine." Appeal Br. 23. It is well-settled that "'[a] reference does not teach away . . . if it merely expresses a general preference for an alternative invention.'" *Galderma*, 737 F.3d at 738 (quoting *DePuy*, 567 F.3d at 1327). That Zarif '473 and Tan disclose preferred embodiments outside the scope of claim 1, does not negate the fact that it also teaches cochleate compositions as recited in claim 1. *See* FF8–FF9; *see also Merck* 874 F.2d at 807 (explaining that a reference's

disclosure of "a multitude of effective combinations does not render any particular formulation less obvious"). Thus, there is a prima facie showing that claim 1 is obvious over Zarif '473 and Tan.

For the same reasons discussed above (*see supra* § III), Appellant's evidence in Example 5 and Figure 14 of the Specification, and in the Mannino Declaration, is insufficient to overcome Examiner's prima facie showing. Accordingly, we affirm the rejection of claim 1. We likewise affirm the rejection of claims 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84, which Appellant agrees stand or fall with claim 1.

Claims 22, 23, and 86

For the same reasons discussed in our analysis of claims 22, 23, and 86 for the ground above (*supra* § III) Examiner has not established a prima facie showing of obviousness. Thus, we reverse the rejection of these claims.

V. 103 Rejection: Gould-Fogerite, Zarif '894, Zarif '473, Tan, Daftary, Onyuksel, and Balu–Iyer

The issue for this rejection is: Does the preponderance of evidence of record support Examiner's conclusion that claims 33, 34, 39, 42, 44, 47, 49, 80, 81, 83 and 84 are obvious over the cited references? Claim 33 is directed to a "method of making the cochleate composition of claim 1" involving "mixing a hydrophlilic biologically relevant molecule with a liposome comprising" the recited lipids and adding a divalent cation "to make the cochleate composition." Appeal Br., Claims App. iii. Claim 33 is representative of claims 34, 39, 42, 44, 47, 49, 80, 81, 83 and 84.

Examiner finds that "Daftary [and] Onyuksel each teach the addition of [an] active agent to the preformed liposomes to load the active agent."

Final Act. 11. Examiner determines it would have been obvious in light of the cited references "to mix the active agent with preformed liposomes to load the active agent and then add calcium ions to prepare the cochleates encapsulating the active agent" as recited in claim 33. *Id.*

Based on the record before us, we determine that the preponderance of the evidence supports Examiner's rejection of claim 1 over the cited references. *See* FF1–FF11. We agree with, and adopt, Examiner's findings and reasoning in support of that rejection. To the extent Appellant repeats arguments from the other obviousness rejections, we are not persuaded by those arguments for the reasons discussed above. We address Appellant's additional arguments concerning Onyuksel and Daftary below.

Appellant argues that Onyuksel fails "to teach mixing a hydrophilic biologically relevant molecule with a liposome, which is an express" limitation of claim 33. Appeal Br. 25. We disagree. Onyuksel teaches the preparation of liposomes that encapsulate "amphipathic molecules," including peptides with both hydrophilic and hydrophobic portions. FF11. As explained above (*supra* § I), the broadest reasonable interpretation of the term "hydrophilic biologically relevant molecule," as in Appellant's claims, includes "large molecules [e.g., peptides] with hydrophilic domains." *See* Spec. 11, 93. Thus, we agree with Examiner that Onyuksel teaches the preparation of liposomes with a hydrophilic biologically relevant molecule, as recited in claim 33. *See* Ans. 14 ("Onyuksel teaches water soluble peptides and instant claim does not exclude amphipathic peptides which are also hydrophilic.").

Moreover, even if Onyuksel did not teach this limitation, the other references in the cited combination do. Gould-Fogerite, Zarif '894, Zarif

’473 each teach the incorporation of “hydrophilic” molecules into cochleate compositions. *See* FF5, FF7, and FF8. Moreover, both Zarif ’473 and Balu-lyer teach the preparation of cochleates by adding a divalent cation to a solution of liposomes comprising the recited lipids and a hydrophilic biologically relevant molecule.[15] FF3, FF9–10. Appellant cannot overcome the rejection “by attacking [Onyuksel and Daftary] individually” because “the rejection is based upon the teachings of a combination of references” that includes Zarif ’473 and Balu-lyer. *See Soft Gel Techs., Inc. v. Jarrow Formulas, Inc.*, 864 F.3d 1334, 1341 (Fed. Cir. 2017) (quoting *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986)).

For these reasons, we affirm the rejection of claim 33. We likewise affirm the rejection of claims 34, 39, 42, 44, 47, 49, 80, 81, 83 and 84, which are not argued separately. *See* 37 C.F.R. § 41.37 (c)(1)(iv).

VI. 103 Rejection: Zarif ’894, Zarif ’473, Tan, and Kessler

The issue for this rejection is: Does the preponderance of evidence of record support Examiner’s conclusion that claims 1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, and 86 are obvious over the cited references? Claim 1 is representative of claims 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84. We analyze claims 22, 23, and 86 separately.

[15] As explained above, the biologically relevant molecule taught in Balu-lyer, Factor VIII is within the broadest reasonable interpretation of “hydrophilic biologically relevant molecule” as recited in Appellant’s claims. *See supra* § I.

Claim 1

We affirm the rejection of claims 1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, and 84 for the same reasons we affirm the rejection of those claims as obvious over Zarif '473 and Tan. *See supra* § IV.

Claims 22, 23, and 86

Examiner finds "Kessler teaches that drugs such as aminoglycosides can be encapsulated in cochleates" and therefore it would be obvious to include an aminoglycoside, as taught in Kessler, in the cochleate compositions taught in the other references. *See* Final Act. 12.

Appellant argues that Kessler does not teach that aminoglycosides can be administered in a cochleate. *See* Appeal Br. 26–27. According to Appellant, Kessler references the recited aminoglycosides "only as part of an exhaustive list of potential antibiotics" that may be used "*in combination therapy*" with a different agent, i.e., an "agent for reducing disulfide bonds." *Id.* at 27. Appellant contends there is no teaching "that the antibiotic for use in [this] combination therapy would or could be encapsulated together with the agent for reducing disulfide bonds inside of a cochleate structure." *Id.*

Based on the record before us, we determine the preponderance of the evidence supports Examiner's rejection of claims 22, 23, and 86 as obvious over the combination of Zarif '894, Zarif '473, Tan, and Kessler. *See* FF6–FF10, FF12–13. We agree with, and adopt, Examiner's findings and reasoning in support of the rejection of these claims. We are not persuaded by Appellant's arguments, which we address below.

We are not persuaded by Appellant's interpretation of Kessler. Appellant interprets Kessler's teaching that "the agent can be administered via a nanocochleate or cochleate delivery vehicle" in paragraph 67 to mean

that only the agent for reducing disulfide bonds may be "encochleated." Appeal Br. 27. But Kessler specifically teaches that antibiotics, including the aminoglycosides recited in claims 22, 23, and 86, may be together with that agent "in a single formulation." FF12. Thus, in addition to teaching recited aminoglycosides, Kessler reasonably suggests those molecules may be encapsulated in a cochleate. Kessler's teachings regarding the particular antibiotics recited in claims 22, 23, and 86, together with Zarif '473's general teaching that hydrophilic, anti-infectious drugs can be enclosed within the cochleate compositions it describes (*see* FF8), are sufficient to establish a prima facie case of obviousness. Accordingly, we agree Examiner has met the burden to establish a prima facie case that claims 22, 23, and 86 are obvious over the combination of Zarif '894, Zarif '473, and Tan with Kessler.

Appellant does not present an unexpected results argument, or other evidence of objective indicia, for this rejection.[16] *See* Appeal Br. 27–28; Reply Br. 4. Accordingly, we affirm the rejection of claims 22, 23, and 86 based on Examiner's prima facie showing.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 6, 11, 12, 19, 31–34, 39, 47, 49,	102	Balu-lyer	1, 6, 11, 12, 19, 31–34, 39, 47, 49,	86

[16] We do not consider arguments outside the Appeal Brief. *See* 37 C.F.R. 41.37(c)(iv). However, we note that the evidence in Example 5, Figure 14, and the Mannino Declaration does not show unexpected results for the full range of the ratio recited in claims 22, 23, and 86. *See supra* § III.

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
81, 83, 86			81, 83	
1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, 86	103	Balu-lyer	1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84	86
1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, 86	103	Gould-Fogerite, Tan, Zarif ’894, Zarif ’473	1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84	22, 23, 86
1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, 86	103	Zarif ’473, Tan	1, 6, 11, 12, 19, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84	22, 23, 86
33, 34, 39, 42, 44, 47, 49, 80, 81, 83, 84	103	Gould-Fogerite, Zarif ’894, Zarif ’473, Tan, Daftary, Onyuksel	33, 34, 39, 42, 44, 47, 49, 80, 81, 83, 84	
1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, 86	103	Zarif ’894, Zarif ’473, Tan, Kessler	1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, 86	
Overall Outcome			1, 6, 11, 12, 19, 22, 23, 30–34, 39, 42, 44, 47, 49, 80, 81, 83, 84, 86	

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED