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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte JILL HELMS, ROELAND NUSSE,
JAEBEOM KIM, and PHILIPP LEUCHT

Appeal 2011-010610
Application 12/074,766
Technology Center 1600

Before TONI R. SCHEINER, DEMETRA J. MILLS, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims directed to pharmaceutical formulations containing Wnt proteins, as well as processes of administering the formulations. The Examiner entered rejections for anticipation and obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

"Wnt proteins form a family of highly conserved secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis" (Spec. [0001]). "Wnt signaling is involved in numerous events in animal

development, including the proliferation of stem cells and the specification of the neural crest. Wnt proteins are therefore potentially important reagents in expanding specific cell types, and in treatment of conditions *in vivo*" (*id.* at [0004]).

The Specification explains that the inventors' initial attempts to deliver a Wnt protein, Wnt3a, to an injury site in vivo "were unsuccessful; neither purified protein by itself nor protein combined with a fibrin glue elicited any discernable [sic] effect in the wound environment. In sharp contrast, Wnt3a liposomes were highly efficacious at enhancing bone regeneration" (*id.* at [0096]).

To account for the difference in efficacy between liposomal delivery of the Wnt protein, and methods not using liposomes, the Specification posits:

> Wnt3a is modified by a palmitate residue, which is essential for its *in vivo* activity. The palmitate moiety itself has pronounced lipid affinity and during fabrication of the Wnt3a liposomes, it is probable that the palmitate associates with the liposome membrane. Consequently, Wnt3a may be effectively tethered to the liposome, which could prevent its clearance from the injury site.

(*Id.*)

Appellants' invention is thus directed to pharmaceutical compositions, "where the Wnt protein is inserted in the non-aqueous phase of a lipid structure, *e.g.* in the surface of a liposome, micelle, lipid raft, *etc*., in an emulsion, and the like" (*id.* at [0006]).

Claims 1, 3, 5-9, and 11-19 stand rejected and appealed (App. Br. 2). Claims 1, 7, and 11 illustrate the appealed subject matter and read as follows:

1. A method for the therapeutic delivery of a wnt protein to an animal, the method comprising:

administering to said animal an effective dose of a mammalian wnt protein comprising a lipid moiety, formulated in a liposome that comprises an outer liposome membrane, wherein active wnt protein is tethered to said outer liposome membrane.

7. A pharmaceutical formulation comprising an effective dose of a mammalian wnt protein comprising a lipid moiety, wherein the wnt protein is formulated in a lipid structure that comprises an outer liposome membrane, wherein active wnt protein is tethered to said outer liposome membrane; and a pharmaceutically acceptable excipient.

11. A method of accelerating bone repair in a mammal, the method comprising:

administering to a mammal having a bone injury an effective dose of a wnt protein comprising a lipid moiety, formulated in a lipid structure that comprises an outer liposome membrane, wherein active wnt protein is tethered to said outer liposome membrane.

The following rejections are before us for review:

(1) Claims 1 and 5-8, under 35 U.S.C. § 102(b) as anticipated by Matthews[1] (Ans. 3-4); and

(2) Claims 3, 8, 9, and 11-19, under 35 U.S.C. § 103(a) as obvious over Matthews, Shaughnessy,[2] Larsen,[3] Perreault,[4] and Weissig[5] (Ans. 4-6).

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[1] U.S. Patent No. 5,851,984 (issued December 22, 1998).
[2] U.S. Patent App. Pub. No. 2008/0193515 A1 (filed December 4, 2007).
[3] U.S. Patent App. Pub. No. 2005/0261189 A1 (published November 24, 2005).
[4] U.S. Patent App. Pub. No. 2006/0068494 A1 (published Mar. 30, 2006).
[5] Volkmar Weissig et al., *Accumulation of Protein-Loaded Long-Circulating Micelles and Liposomes in Subcutaneous Lewis Lung Carcinoma in Mice*, 15 PHARMACEUTICAL RESEARCH 1552-1556 (1998).

ANTICIPATION

The Examiner found that Matthews described therapeutic Wnt formulations that included liposomes and native forms of Wnt polypeptides "produced in mammalian cells" (Ans. 3). The Examiner cited Willert[6] as evidence that the therapeutically active Wnt proteins used in Matthews inherently comprised the lipid moiety "which would partition [the Wnt proteins] into the non-aqueous phase of a lipid structure" (*id.*), thus meeting the claims' requirement for the active Wnt protein to be tethered to the outer liposome membrane.

Appellants argue the claims subject to this rejection in two groups, the first group consisting of claims 1, 5, and 6, and the second group consisting of claims 7 and 8 (App. Br. 4). We select claim 1 as representative of the first group, and claim 7 as representative of the second group. *See* 37 C.F.R. § 41.37(c)(1)(vii).

Appellants argue, for a variety of reasons, that Matthews fails to describe or enable liposomal formulations that meet the claims' requirement for an effective dose of an active Wnt protein to be tethered to the outer liposome membrane (*see* App. Br. 5-8).

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

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[6] Karl Willert et al., *Wnt proteins are lipid-modified and can act as stem cell growth factors*, 423 NATURE 448-452 (2003).

Appellants' arguments do not persuade us that a preponderance of the evidence fails to support the Examiner's prima facie case of anticipation as to either claim 1 or claim 7.

Claim 1 recites a method for the therapeutic delivery of a Wnt protein to an animal. The claim's sole step requires the practitioner to administer to the animal an effective dose of an active mammalian Wnt protein that has a lipid moiety. Claim 1 requires the Wnt protein to be formulated in a liposome that has an outer liposome membrane, with the active Wnt protein being "tethered" to the outer liposome membrane (App. Br. 16 (claims 1 and 7)).

Claim 7 recites a pharmaceutical formulation that contains a pharmaceutically acceptable excipient, a lipid moiety, and an effective dose of a mammalian Wnt protein. Like claim 1, claim 7 requires the Wnt protein to be tethered to an outer liposome membrane.

As noted above, the Specification explains that the active mammalian Wnt protein Wnt3a has a palmitate residue that causes the protein to be tethered to the outer membrane of liposomes when the protein is formulated into liposome-containing compositions (*see* Spec. [0096]). The Specification also explains that liposomes according to Appellants' invention may be prepared by known prior art techniques (*see id.* at [0046] ("The liposomes may be prepared by a variety of techniques, such as those detailed in Szoka, F., Jr., et al., Ann. Rev. Biophys. Bioeng. 9:467 (1980).")).

Turning to the art, Matthews discloses that "Wnts can be used to stimulate proliferation and/or differentiation and/or maintenance of hematopoietic stem/progenitor cells either in vitro or in vivo (e.g., for

treating hematopoietic diseases or disorders)" (Matthews, col. 5, ll. 24-27). Matthews discloses that "native," i.e. naturally occurring, forms of Wnts are suitable for use in its methods (*id.* at col. 7, ll. 55-57), and that native polypeptides include Wnt3a (*id.* at col. 8, ll. 9-24).

Matthews discloses that a variety of administration routes and carriers can be used (*id.* at col. 36, ll. 24-51). As required by claim 1, Matthews discloses that "[f]or all administrations, conventional depot forms are suitably used. Such forms include, for example, microcapsules, nano-capsules, *liposomes*" (*id.* at col. 36, ll. 51-53 (emphasis added)).

Matthews later elaborates on the use of liposomes:

> Sustained-release Wnt polypeptide compositions also include liposomally entrapped polypeptides. Liposomes containing the Wnt polypeptide are prepared by methods known in the art, such as described in Eppstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688-3692 (1985); Hwang et al., *Proc. Nati.[sic] Acad. Sci. USA* 77:4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Ordinarily, the liposomes are the small (about 200-800 Angstroms) unilamelar [sic] type in which the lipid content is greater than about 30 mol.% cholesterol, the selected proportion being adjusted for the optimal Wnt polypeptide therapy. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556.

(*Id.* at col. 37, ll. 20-31.)

Thus, as required by claim 1, Matthews describes administering a liposome formulation containing an active Wnt protein to an animal. As required by claim 7, the Wnt protein is present in a therapeutically effective dosage. While Matthews discloses that its liposomes can be prepared using known prior art methods, Matthews does not explicitly state that the Wnt

protein in its liposome formulations is tethered to the outer liposome membrane, as claims 1 and 7 require.

However, as the Examiner points out, Willert discloses that active forms of Wnt proteins inherently contain a palmitate moiety, whereas inactive forms do not (*see* Willert 448 (abstract) ("By mass spectrometry, we found the proteins to be palmitoylated on a conserved cysteine. Enzymatic removal of the palmitate or site-directed and natural mutations of the modified cysteine result in loss of activity, and indicate that the lipid is important for signaling.")).

As the Examiner also points out, Appellants' Specification acknowledges that it is the presence of the palmitate moiety which causes the Wnt proteins to be tethered to the outer membranes when included in a liposome formulation (Spec. [0096]). Appellants' Specification also acknowledges that prior art techniques of preparing liposomes produce the tethered arrangement recited in claims 1 and 7 (*see id.* at [0046]-[0048]).

Thus, because Matthews describes its therapeutic liposomal Wnt formulations as being prepared using conventional prior art techniques, and because the active Wnt proteins in Matthews' formulations inherently contain the palmitate moiety that causes the Wnt proteins to be tethered to the outer liposomal membrane, we find that the Examiner had a reasonable evidentiary basis for finding that the liposomal formulations described by Matthews inherently included Wnt proteins tethered to the outer liposome membrane, as required by claims 1 and 7.

As our reviewing court has pointed out, "when the PTO shows sound basis for believing that the products of the applicant and the prior art are the

same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990).

We are not persuaded that Appellants have advanced evidence adequate to rebut the Examiner's prima facie case of anticipation as to claims 1 and 7.

Appellants argue that, as shown by the Helms Declaration,[7] liposome formulations typically consist of one or more lipid bilayers that enclose an aqueous core, with a drug or molecule of interest being disposed within the aqueous core from which it is delivered (App. Br. 5 (citing Banerjee[8] and Allen[9])). In contrast, Appellants argue, because the claimed formulations include active Wnt proteins tethered to the outer liposome membrane, whereas Wnt proteins entrapped within the aqueous core of liposomes are inactive, the claimed liposome formulations deliver the Wnt proteins in an unexpected manner (*see* App. Br. 5-6 (citing Morrell[10])).

As an initial matter, we note that evidence of unexpected results is not relevant to whether Matthews anticipates claims 1 and 7. *See In re Paulsen*, 30 F.3d 1475, 1482 n.11 (Fed. Cir. 1994) ("[E]vidence of nonobviousness is irrelevant for patentability purposes when an invention is anticipated under section 102.").

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[7] Declaration of Dr. Jill Helms under 37 C.F.R. § 1.132 (declaration executed April 8, 2010).
[8] R. Banerjee, *Liposomes: Applications in Medicine*, 16 JOURNAL OF BIOMATERIALS APPLICATIONS 3-21 (2001).
[9] Theresa M. Allen and Pieter R. Cullis, *Drug Delivery Systems: Entering the Mainstream*, 303 SCIENCE 1818-1822 (2004).
[10] Nathan T. Morrell et al., *Liposomal Packaging Generates Wnt Protein with In Vivo Biological Activity*, 3 PLOS ONE 1-9 (2008).

We also note that Matthews discloses compositions including "liposomally *entrapped* [Wnt] polypeptides" (Matthews, col. 37, l. 21 (emphasis added)). As noted above, however, Appellants' Specification supports the Examiner's finding that conventional liposome formation techniques inherently produce the claimed tethered arrangement (*see* Spec. [0046]-[0048]), and Matthews discloses that its liposome formulations are prepared using conventional prior art techniques (*see* Matthews, col. 37, ll. 21-31).

We note the disclosures in the Helms Declaration and Morrell, that actual entrapment of Wnt proteins within the liposomes' aqueous core yields a product with little or no activity (*see* Helms Declaration 1; Morrell 4). However, this inactivating entrapment of the Wnt proteins within the liposomes' aqueous core requires enzymatic trypsin digestion of the liposome preparation to remove the Wnt proteins that inherently become tethered to the outer liposomal membrane upon liposome formation (*see* Helms Declaration 2-4; Morrell 4).

Appellants point us to no clear or specific evidence of record suggesting that an ordinary artisan using conventional techniques to prepare liposomal Wnt formulations as taught by Matthews would have digested the liposomal formulations with trypsin after preparing them. Thus, a preponderance of the evidence supports the Examiner's finding that, when Matthews refers to liposomally entrapped therapeutically active Wnt formulations, Matthews is not referring to trypsin-digested formulations having no activity.

Appellants argue that Matthews does not enable preparing a liposomal preparation with active Wnt proteins as claimed, because,

although Matthews provides a laundry list of techniques for isolating Wnt proteins, "no specific methods or results are provided with respect to this goal" (App. Br. 6). However, as our reviewing court has explained, the fact that Matthews did not prepare a working example of its liposomes does not demonstrate that Matthews' disclosure is non-enabling:

> [F]ailures by those skilled in the art (having possession of the information disclosed by the publication) are strong evidence that the disclosure of the publication was nonenabling. *By contrast, the fact that the author of a publication did not attempt to make his disclosed invention does not indicate one way or the other whether the publication would have been enabling.*

In re Donohue, 766 F.2d 531, 533 (Fed. Cir. 1985) (emphasis added).

Appellants contend that the Austin reference, which Appellants assert is the "corresponding journal article" published by the inventors of the Matthews patent, demonstrates that the Wnt proteins of Matthews were not isolated using techniques that employed detergent to maintain the protein's solubility (App. Br. 6).

However, while Appellants assert that a copy of the Austin article was attached to the Appeal Brief (*id.*), the article does not appear to be cited in the Appeal Brief's Evidence Appendix, and our review of the application file does not show that the Austin article has been made of record. Nonetheless, it might be true, as Appellants assert (*id.* at 7), that Austin's purification methods do not use detergent, and that the affinity purified protein did not exhibit "increased biological activity" as compared to the pre-affinity-purified preparation.

As Appellants concede, however, the affinity purified Wnt protein described by Austin exhibited "biological activity" (*id.*). Thus, the fact that

the Wnt protein was active demonstrates that the protein possessed the activity-conferring palmitate moiety (*see* Willert), which is also responsible for the tethering arrangement recited in claims 1 and 7 (*see* Spec. [0096]).

Moreover, the test for public possession of subject matter described in an allegedly anticipating reference is whether "one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d. at 533.

As noted above, and as the Examiner points out, techniques of preparing active Wnt proteins that possessed the activity-conferring palmitate moiety were known in the art (*see* Willert *generally*). As it is the activity-conferring palmitate moiety which inherently produces the claimed tethered arrangement upon liposome formulation (*see* Spec. [0096]), we are not persuaded that Matthews' disclosure of therapeutically active Wnt-containing liposome formulations proteins failed to place into the hands of the public a formulation in which the Wnt protein inherently possessed the tethered arrangement required by claims 1 and 7.

Accordingly, as Appellants' arguments do not persuade us a preponderance of the evidence fails to support the Examiner's finding that Matthews anticipates claims 1 and 7, we affirm the Examiner's rejection of those claims over that reference. Claims 5, 6, and 8 fall with claim 1. *See* 37 C.F.R. § 41.37(c)(1)(vii).

OBVIOUSNESS

In rejecting claims 3, 8, 9, and 11-19 as obvious, the Examiner cited Matthews, Larsen, and Perreault, as evidence that liposomal Wnt protein formulations were known in art, but conceded that those references did not

describe administering the formulations to accelerate bone repair, as recited in claims 11-19 (Ans. 4).

To address that deficiency, the Examiner cited Shaughnessy as evidence that it was known in the art that Wnt proteins were useful for preventing or reducing bone destruction, and reasoned, therefore, that an ordinary artisan would have been "motivated and expect[ed] success in modifying the bone treatment method of Shaughnessy to include the use of liposomes, thereby arriving at the methods recited in claims 11-17" (*id.* at 5).

The Examiner also conceded that Matthews, Larsen, and Perreault, differed from claims 3, 8, 9, 18, and 19, in that those references did not describe using micelles as the lipid-based delivery vehicle for the Wnt proteins (*see id.* at 4). To address that deficiency, the Examiner cited Weissig for its disclosure that small sized micelles were more efficient than liposomes for in vivo delivery of a model protein having a lipid moiety (*id.* at 5). Based on these teachings, the Examiner found that

> one of skill in the art (1) would expect that a protein that comprises a lipid modification, such as a wnt protein, would readily incorporate into either liposomes or micelles, (2) would recognize liposomes and micelles as usable alternatives for *in vivo* administration of proteins and, (3) would have reason to expect that micelles may be advantageous over liposomes for particular applications. Thus, the substitution micelles for liposomes is at least a matter of substitution of one known element for another to obtain predictable results and possibly the use of a known technique to improve a similar method.

(*Id.*)

Appellants argue the claims subject to this ground of rejection in the following groupings: Group III (claim 3), Group IV (claim 8), Group V

(claim 9), Group VI (claims 11 and 16-19), and Group VII (claims 12-15) (*see* App. Br. 4-5).

We have carefully reviewed Appellants' arguments, but are not persuaded that a preponderance of the evidence fails to support the Examiner's conclusion of obviousness.

Regarding claim 3, Appellants initially reiterate their arguments that Matthews discloses Wnt proteins being entrapped in liposomes, which would result in an inactive formulation, and note that Larsen contains a similar disclosure regarding liposomal Wnt protein entrapment (App. Br. 8-9). As to claims 8 and 9, Appellants argue that "the cited art does not teach how to provide for an effective dose of a mammalian wnt protein, as the liposome compositions of the cited art would generate biologically inactive protein" (*id.* at 11).

For reasons similar to those discussed above, we do not find these arguments persuasive.

Thus, we again note Matthews' use of the term "entrapped" to describe its Wnt liposomal formulations (Matthews, col. 37, l. 20), as well as Larsen's use of the same term (Larsen, [0492]). We also note Perreault's disclosure that its Wnt protein "may be provided in the form of a purified protein, or in complex with another component such as a liposome or cell membrane to maintain its activity and/or increase its solubility" (Perreault [0013]).

However, both Matthews and Larsen disclose that their Wnt liposomal formulations should be prepared using conventional liposome preparation techniques (*see* Matthews, col. 37, l. 21-31; Larsen [0492]), whereas, as Appellants point out, actual inactivating entrapment of Wnt proteins within

liposomes requires the added step of digesting the liposome preparation with trypsin after the liposomes are formed (*see* Helms Declaration; *also* Morrell).

Appellants point to no clear or specific teaching in the cited references, or elsewhere in the record, suggesting that an ordinary artisan preparing Wnt liposomal preparations according to Matthews, Larsen, or Perreault would have treated the liposomes with trypsin before administering them for the therapeutic effects described in the references. We are therefore not persuaded that the prior art would have suggested preparing inactive Wnt formulations to an ordinary artisan.

Regarding the suitability of substituting the micelles recited in Appellants' claims 3, 8, and 9 for the liposomes of Matthews, Larsen, and Perreault, as the Examiner pointed out, Weissig discloses that both liposomes and micelles were recognized as lipid-based drug delivery vehicles (*see* Weissig 1552 ("[L]ong-circulating liposomes and micelles gain increasing recognition as drug carriers for intratumoral delivery . . . .")).

As the Examiner also pointed out, Weissig found that micelles were superior to liposomes at delivering a model therapeutic protein having a hydrophobic moiety to experimental tumors in mice (*see id.* (abstract) ("Small-sized long-circulating delivery systems, such as PEG-lipid micelles, are more efficient in the delivery of protein to Lewis lung carcinoma than larger long-circulating liposomes.")).

We note, as Appellants argue, that Weissig's study was directed to evaluating suitable vehicles for delivery of therapeutic proteins to lung carcinoma cells (*see id.* ("The purpose of our work was to compare the biodistribution and tumor accumulation of a liposome- or micelle-

incorporated protein in mice bearing subcutaneously-established Lewis lung carcinoma.”)).

As the Supreme Court has pointed out, however, “the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). Thus, a “person of ordinary skill is . . . a person of ordinary creativity, not an automaton.” *Id.* at 421.

Here, given the teachings in Matthews, Larsen, and Perreault of the suitability of liposomes as vehicles for Wnt protein delivery, we agree with the Examiner that an ordinary artisan, further advised by Weissig of the suitability of micelles as delivery vehicles for a therapeutic protein having a hydrophobic moiety, would have reasonably inferred that micelles would be a suitable alternative to liposomes for delivering other therapeutic proteins, such as Wnt, having hydrophobic residues, and therefore would have been prompted to substitute micelles, such as those described in Weissig, for the liposomal carriers of Wnt proteins described in Matthews, Larsen, and Perreault.

As the Supreme Court also advised in *KSR*, “when a patent claims a structure already known in the prior art that is altered by mere substitution of one element for another known in the field, the combination must do more than yield a predictable result.” *KSR*, 550 U.S. at 417.

Thus, as we agree with the Examiner that an ordinary artisan would have been prompted to substitute micelles for the liposomes described in Matthews, Larsen, and Perreault as the lipid-based delivery vehicle for

therapeutic administration of Wnt proteins, and as Appellants do not argue that the methods and compositions recited in claim 3, 8, and 9 produce unexpected results, we affirm the Examiner's obviousness rejection of claims 3, 8, and 9.

As to claim 11, contrary to Appellants' arguments (*see* App. Br. 12; Reply Br. 3), we are not persuaded that Shaughnessy fails to suggest administering Wnt proteins for the purpose of accelerating bone repair:

> Additionally, it is also contemplated that the method can be used to promote more rapid effective healing of bone fractures in the elderly. Furthermore, although the present invention demonstrated repairing the lytic lesions with Wnt-3a protein, it is contemplated that other canonical Wnt ligands such as Wnt-l, Wnt-2 or Wnt-10b will be equally effective. The Wnt-3a protein may be directly administered at the site of a lytic lesion to promote osteoblast differentiation and spontaneous healing.

(Shaughnessy [0030].)

In addition to describing administering at the site of injury as recited in Appellants' claim 12, Shaughnessy explicitly discloses the pulsed administration technique Appellants urge is described in their examples (*see* App. Br. 11; Reply Br. 2):

> [T]here may be a reluctance to use Wnt-3a systemically because of its putative tumor promoting effects. This possibility may be eliminated by local use, ex-vivo exposure of osteoblasts precursors and/or pulsing the compound for short periods of time to avoid chronic exposure. Thus, pulsing Wnt-3a for short periods of time in-vivo might eliminate the unwanted pro-growth effects this molecule may have on cell types sensitive to Wnt signaling perturbation in cancers.

(Shaughnessy [0030].)

We note the Specification's disclosure that administration to a bone injury site of either purified Wnt3a protein or Wnt3a incorporated into fibrin glue did not improve rates of bone regeneration (*see* Spec. [0087], [0096]). We also note the Specification's disclosure regarding the significant difference in bone regeneration rates between control liposomes containing only PBS and liposomes containing Wnt3a:

> [I]njury sites that received a single injection of Wnt3a liposomes were completely filled with mature bony trabeculae (n=7; Fig. 5c). This dramatic effect was achieved in 72h, since liposomes were injected on post-surgical d3 and histological evaluations were carried out on post-surgical d6. Histomorphometric analyses showed that injury sites treated with Wnt3a liposomes had 350% more bone than control injury sites (average number of pixels representing bone in Wnt3a treated samples = 78146; PBS samples = 20615; Fig. 5d,e).

(*Id.* at [0091].)

As the Federal Circuit has pointed out, however, "any superior property must be *unexpected* to be considered as evidence of non-obviousness." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007).

Here, because Shaughnessy teaches that Wnt proteins enhance bone repair rates, an ordinary artisan might have considered it unexpected that purified Wnt3a protein and fibrin glue-incorporated Wnt3a protein did not elicit improvement in bone repair in Appellants' tests. However, in view of Shaughnessy's express disclosure that Wnt proteins "promote more rapid effective healing of bone fractures in the elderly" (Shaughnessy [0030]), we are not persuaded that the results Appellants obtained using liposomal formulations would have been considered unexpected.

Moreover, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

Also, "[m]ere improvement in properties does not always suffice to show unexpected results. . . . [W]hen an applicant demonstrates *substantially* improved results . . . and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary." *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995).

Here, Shaughnessy describes obtaining significant results in a bone tumor model using a non-liposomal Wnt formulation (*see* Shaughnessy [0061] (Example 14)). In contrast, the Specification does not explain the specific conditions of the experiments which produced negative results using purified and fibrin glue-incorporated Wnt3a proteins (*see* Spec. [0087], [0096]). Thus, we are not persuaded that Appellants have demonstrated that Shaughnessy's methods do not work, as Appellants argue.

Moreover, given that Shaughnessy's non-liposomal preparations were active, whereas Appellants' non-liposomal preparations were not, it does not appear that Appellants compared the liposomal compositions used in claim 11 to the closest functional non-liposomal compositions from the prior art. Absent such a comparison, we are not persuaded that Appellants have adequately demonstrated a substantial improvement over the prior art. *See In re Baxter Travenol Labs.*, 952 F.2d at 392.

Moreover, while Appellants' briefs assert that the results obtained using liposomal formulations show "a surprising effect [which] could not have been predicted from the teachings of the cited art" (App. Br. 11; Reply

Br 3), other than the briefs, Appellants point to no such assertion in the Specification, or elsewhere in the record. It is well settled that argument by counsel is no substitute for actual evidence of non-obviousness. *See In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

In sum, for the reasons discussed, Appellants' arguments do not persuade us that the Examiner erred in finding that an ordinary artisan would have been prompted to accelerate bone repair in a mammal by administering a Wnt liposomal formulation encompassed by claim 11. As we are also not persuaded, for the reasons discussed, that Appellants have advanced evidence of unexpected results sufficient to outweigh the evidence of prima facie obviousness advanced by the Examiner, we affirm the Examiner's rejection of claim 11. As they were argued in the same group as claim 11 (App. Br. 5), claims 16-19 fall with claim 11.

As also discussed above, given Shaughnessy's express disclosure that "Wnt-3a protein may be directly administered at the site of a lytic lesion to promote osteoblast differentiation and spontaneous healing" (Shaughnessy [0030]), Appellants' arguments do not persuade us that the Examiner erred in finding that an ordinary artisan would have been prompted to administer liposomal Wnt3a formulations, such as taught or suggested by Matthews, Larsen, and Perreault, directly to the site of a bone injury, as recited in claim 12. We therefore affirm the Examiner's obviousness rejection of that claim, as well as claims 13-15, which were argued in the same claim grouping (*see* App. Br. 5).

SUMMARY

We affirm the Examiner's anticipation rejection of claims 1 and 5-8 over Matthews.

We also affirm the Examiner's obviousness rejection of claims 3, 8, 9, and 11-19 over Matthews, Shaughnessy, Larsen, Perreault, and Weissig.

TIME PERIOD

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

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