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Paper 65
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CYANOTECH CORPORATION,
Petitioner,

v.

THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS,
Patent Owner.

Case IPR2013-00401[1]
Patent 5,527,533

Before SCOTT E. KAMHOLZ, SHERIDAN K. SNEDDEN, and GEORGIANNA W. BRADEN, *Administrative Patent Judges.*

SNEDDEN, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Consolidated with Case IPR2013-00404

I. INTRODUCTION

Cyanotech Corporation ("Cyanotech") filed corrected petitions in IPR2013-00401 (Paper 9, "Pet. '401") and IPR2013-00404 (IPR2013-00404, Paper 8, "Pet. '404") requesting *inter partes* review of claims 1–27 of U.S. Patent No. 5,527,533 ("the '533 patent"). The Board consolidated IPR2013-00401 and IPR2013-00404 and instituted trial for the challenged claims on the following grounds of unpatentability asserted by Cyanotech:

Reference(s)	**Basis**	**Claims challenged**
Grangaud[2]	§ 102	1, 3, 8–15, 21, 22, and 26
Grangaud and Dowling[3]	§ 103	1–15, 21, 22, and 26

Decision to Institute, 19 (Paper 17 ("Dec.")).

After institution and consolidation of both trials, the Board of Trustees of the University of Illinois ("the University"), filed its Patent Owner's Response ("Resp."). Paper 32.[4] Cyanotech filed a Reply (Paper 43, "Reply."). The University did not file a motion to amend claims.

Cyanotech relies upon declarations of Florian J. Schweigert (Ex. 1033) and C. Kathleen Dorey, Ph.D. (Ex. 1045) in support of its

[2] RENÉ GRANGAUD, RESEARCH ON ASTAXANTHIN, A NEW VITAMIN A FACTOR (1951) (unpublished doctorate dissertation, University of Lyon) (Ex. 1003, the English translation of which is Ex. 1002).

[3] J.E. Dowling & I.R. Gibbons, *The Effect of Vitamin A Deficiency on the Fine Structure of the Retina*, in THE STRUCTURE OF THE EYE 85-99 (1961) (Ex. 1026).

[4] This reference to "Paper" and all other references to "Paper" from this point forward in this Final Written Decision of consolidated proceedings IPR2013-00401 and IPR2013-00404 refer to paper numbers on record in IPR2013-00401.

Petition. The University relies upon a declaration of Shalesh Kaushal M.D., Ph.D. (Ex. 2015) in support of its Response.

Cyanotech filed a Motion to Exclude certain of the University's evidence. Paper 47. The University filed an Opposition (Paper 51), and Cyanotech filed a Reply (Paper 54).

Oral argument was conducted on July 16, 2014. A transcript is entered as Paper 64 ("Tr.").

This Final Written Decision addresses challenges to the patentability of claims 1–15, 21, 22, and 26.

Cyanotech has proved by a preponderance of the evidence that claims 1–14 and 26 of the '533 patent are unpatentable. Cyanotech has failed to prove the unpatentability of claims 15, 21, and 22.

A. The '533 Patent (Ex. 1001)

The retina of the eye, a component of the central nervous system, is important for sight. Ex. 1001, 1:49–52; *see also*, Ex. 1045, 6–12. Retinal structures important to vision include: a ganglion cell layer, which connects the retina to the brain; an inner nuclear layer containing neurons, such as bipolar cells; and an outer nuclear or photoreceptor cell layer. Ex. 1045, 6–12. Photoreceptor cells convert light into signals that are transmitted to the other neurons. Ex. 1001 at 1:57–60. The loss of a significant number of photoreceptor cells adversely affects visual function. *Id.* at 3:6–13.

The '533 patent discloses that eye diseases or injuries that can cause damage to the retinal tissue and neurons include age-related macular degeneration, photic injury, photoreceptor cell damage, ganglion cell damage, traumatic injury, ischemic insult-related diseases, and inflammatory

diseases. *Id.* at 1:9–14. Regarding photic injury, the ’533 patent discloses that excessive light energy reaching the retina can overwhelm the metabolic systems of photoreceptor cells causing damage to these neurons, either directly or indirectly. *Id.* at 1:65–67. The ’533 patent further discloses that free radical species can be generated by enzymatic processes or from the combination or continuous or excessive exposure to light and the relatively high concentration of oxygen in the eye. *Id.* at 2:1–5. The ’533 patent discloses that the free radical species lead to functional impairment of cell membranes and may cause temporary or permanent damage to retinal tissue. Ex. 1001, 2:13–21. According to the ’533 patent, however, the presence of antioxidant compounds counteracts the free radical species generated by light to protect the retina from damage. *Id.* at 2:29–32.

The ’533 patent relates to methods of treating diseases and injuries to the central nervous system, especially the eyes, comprising administering a therapeutically-effective amount of astaxanthin. Ex. 1001, 1:9–19 and 6:54–62. The ’533 patent discloses that astaxanthin is a highly-effective antioxidant and ameliorates free radical-induced eye damage. *Id.* at 15:56–60. Astaxanthin is disclosed as particularly suited for treatment of the eye because, unlike other carotenoids such as β-carotene, astaxanthin can cross the blood-retinal brain barrier readily. *Id.* at 10:18–22. According to the ’533 patent, comparative studies with β-carotene demonstrate that astaxanthin is more effective than β-carotene at protecting rats from photic injury. *Id.* at 13:60 to 14:50.

B. Exemplary Claims

Independent claims 1, 13, 14, 21, and 26 are illustrative of the claims at issue in this *inter partes* review and recite as follows:

> 1. A method of treating an individual suffering from retinal damage or retinal disease, said method comprising administering a therapeutically effective amount of astaxanthin to the individual to improve the vision of the individual.
>
> 13. A method of treating an individual comprising administering a therapeutically effective amount of astaxanthin to the individual to protect neurons in a retina of the individual from free-radical induced retinal injury.
>
> 14. A method of treating an individual suffering from neuronal damage to a retina comprising administering a therapeutically-effective amount of astaxanthin to the individual to improve the condition of the retina.
>
> 21. A method of treating an individual suffering from a free radical-induced injury to a central nervous system, said method comprising administering a therapeutically-effective amount of astaxanthin to the individual to improve the condition of the central nervous system.
>
> 26. A method of treating an individual suffering from a degenerative retinal disease, said method comprising administering a therapeutically effective amount of astaxanthin to the individual to retard the progress of the disease.

II. DISCUSSION

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are interpreted according to their broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b);

Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,766 (Aug. 14, 2012). Claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

We expressly interpret below only those claim terms that require analysis to resolve arguments related to the patentability of the challenged claims.

1. Construction of the phrase "retinal damage or retinal disease"

We construed the phrase "retinal damage or retinal disease" recited in claims 1–12 in the alternative to refer to two classes of conditions: retinal damage and retinal disease. Dec. 9. The University argues for the construction of the terms "retinal damage" and "retinal disease" as a single concept such that both "retinal damage" and "retinal disease" refer to an identical class of medical conditions. Resp. 15–16. Specifically, the University contends that the specification confirms that free radical damage is associated with both injuries and disease. *Id.* (citing Ex. 1001, 15:23–27 ("The administration of astaxanthin to an individual suffering from an eye injury or disease, such as free radical induced injury, beneficiates the vision of the individual by rescuing further photoreceptor cells from damage destruction."); 15:57–60 ("the administration of astaxanthin also provides a method of treating free radical induced disease or injury to the central nervous system in general")).

As stated by the University, the specification discloses methods of treating damage caused by injury or disease (Resp. 14–15), however, the specification does not contain any indication that the patentee intended to act as his own lexicographer clearly defining "disease" and "damage" in the same manner. For example, the specification does not clearly convey the patentee's intent to appoint a special meaning to the phrase "retinal damage or retinal disease."

We must determine, therefore, the ordinary meaning of "disease" and "damage" as used in these claims to one of skill in the art in light of the specification and prosecution history. *In re Paulsen*, 30 F.3d at 1480. In this regard, the term "damage," as used in the specification, refers to damage resulting from injury or disease. Ex. 1001, 1:14–19. The specification does not equate damage and disease, but provides that damage may be caused by disease. *Id.* The meaning of the term disease, however, refers to conditions that may cause damage (such as degenerative eye disease), and are treatable themselves. *Id.* at 15:36–40. That is, the underlying cause of the damage is treatable, not just the damage alone. The University does not direct our attention to anything in the specification or prosecution that would clearly alter the ordinary meaning of "disease" and "damage." Resp. 14–16.

In view of the above, we do not construe "retinal damage" and "retinal disease" as a single concept. The evidence of record does not support a finding that the patentee acted as his own lexicographer by clearly defining the claim terms "damage" and "disease" in the same manner. In our Decision to Institute, we adopted the dictionary definition of "disease" and construed the term as "[a] morbid entity ordinarily characterized by two or more of the following criteria: recognized etiologic agent(s), identifiable

group of signs and symptoms, or consistent anatomic alterations." Dec. 8–9; *see*, Pet. '401 (citing Ex. 1040). We adopted the dictionary definition of "damage" and construed the term as "[h]arm, diminution, or destruction of an organ, body part, system, or function." *Id*. We maintain these constructions for "disease" and "damage" as they are consistent with the use of these terms in the Specification. "Retinal damage" refers to damage to the retina and "retinal disease" refers to disease of the retina. The phrase "retinal damage or retinal disease" refers to either retinal damage or retinal disease.

We also maintain our constructions of "disease" and "damage" with respect to claims 8–12, which recite particular types of retinal damage, and thus, further limit "retinal damage" recited in claim 1. Claims 8–12, however, do not limit further "retinal disease," as recited in claim 1. Thus, for example, claim 12 encompasses a method of treating an individual suffering from damage caused by age-related macular degeneration or suffering from any retinal disease.

B. The Prior Art

1. Summary of Grangaud

Grangaud discloses the results of experiments conducted on rats fed a vitamin A-deficient diet. Ex. 1002, 43. The animals developed complications of vitamin A deficiency that included xerophthalmia ("dry eye") and death. Visible signs of xerophthalmia were described as ocular lesions. *See e.g.*, *id.* at 44, 49. The restoration of vitamin A or astaxanthin to the vitamin A-deficient diet was sufficient to heal the ocular lesions. *Id*. Grangaud concluded that astaxanthin has vitamin A activity. *Id*. at 56.

Grangaud further noted that the antioxidant strength of astaxanthin is comparable to that of vitamin A, and that astaxanthin shares the antixerophthalmic activity of vitamin A. *Id*.

Grangaud is silent as to the mechanism of the disease pathogenesis for vitamin A deficiency. Grangaud provides no evidence tending to establish that the vitamin A-deficient rats exhibited retinal damage.

2. Summary of Dowling

Dowling discloses the results of a study showing the effect of vitamin A deficiency on the fine structure of the retina. Ex 1026. Dowling used an albino rat model kept on a vitamin A-free diet, supplemented with vitamin A acid. *Id.* at 85. The vitamin A acid kept the rats healthy and growing, but did not support the visual cycle and thus the rats gradually become night-blind. *Id.* Dowling discloses that the visual cells (photoreceptor cells) of animals fed such a diet degenerated after 2 months on the diet. *Id.* at 87–88. Other retinal cells, such as bipolar and ganglion cells, however, appeared normal, even after 6 months on the diet. *Id.* Dowling also discloses that the damage to the retinal cells is reversible by giving vitamin A to the deficient animals. *Id.* at 94.

C. Patentability of Original Claims

To prevail in its challenges to the patentability of claims, the petitioner must establish facts supporting its challenges by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

1. Anticipation of Claims 1, 3, 8–15, 21, 22, and 26 by Grangaud

The Court of Appeals for the Federal Circuit summarized the analytical framework for determining whether prior art anticipates a claim as follows:

> If the claimed invention was "described in a printed publication" either before the date of invention, 35 U.S.C. § 102(a), or more than one year before the U.S. patent application was filed, 35 U.S.C. § 102(b), then that prior art anticipates the patent. Although § 102 refers to "the invention" generally, the anticipation inquiry proceeds on a claim-by-claim basis. *See Hakim v. Cannon Avent Group, PLC*, 479 F.3d 1313, 1319 (Fed. Cir. 2007). To anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation. *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998). But disclosure of each element is not quite enough—this court has long held that "[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention *arranged as in the claim*." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (citing *Soundscriber Corp. v. United States*, [] 360 F.2d 954, 960 (1966) (emphasis added)).

Finisar Corp. v. DirecTV Grp., Inc., 523 F.3d 1323, 1334–35 (Fed. Cir. 2008). We must analyze prior art references as a skilled artisan would. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (to anticipate, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention").

To establish inherent disclosure, the evidence must show that a feature necessarily is described in the reference, and that it would be recognized by persons of ordinary skill. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999); *cf. EMI Grp. N. Am., Inc. v. Cypress Semiconductor Corp.*, 268 F.3d

1342, 1351 (Fed. Cir. 2001) ("Theoretical mechanisms or rules of natural law that are recited in a claim, that themselves are not patentable, however, do not need to be recognized by one of ordinary skill in the art for a finding of inherency."). The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993). Inherency may not be established by probabilities or possibilities. *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981).

Cyanotech contends that Grangaud's disclosure of the administration of dietary astaxanthin to cure xerophthalmia ("dry eye") in vitamin A-deficient rats anticipates claims 1, 3, 8–15, 21, 22, and 26, which are directed to a method of administering a therapeutically effective amount of astaxanthin to improve the vision of an individual suffering from retinal damage or retinal disease. Pet. 15–17. For the reasons expressed below, we conclude that Cyanotech has demonstrated by a preponderance of evidence that Grangaud anticipates claims 1, 3, 8–14 and 26. Cyanotech has failed to establish by a preponderance of evidence that Grangaud anticipates claims 15, 21, and 22.

a. Claims 1, 3, and 10

Claim 1 encompasses a method of treating an individual suffering from retinal damage with the administration of astaxanthin in an amount sufficient to improve the vision of the individual. Claims 3 and 10 depend directly from claim 1. Claim 3 requires astaxanthin to be administered orally. Claim 10 specifies that the retinal damage may be photoreceptor cell retinal damage.

Although Grangaud discloses the administration of astaxanthin to cure ocular lesions (Ex. 1002, 43, 44, 49), Cyanotech concedes that Grangaud does not discuss whether or not vitamin A-deficient rats exhibit retinal damage. Pet. 18–19. Cyanotech contends, however, that animals developing xerophthalmia due to vitamin A-deficiency inherently suffer retinal damage. *Id.* For support of this assertion, Cyanotech relies on the Declaration of Florian J. Schweigert ("Schweigert declaration") (Ex. 1033) to establish that vitamin A-deficient rats exhibiting dry eye necessarily have retinal damage and, more specifically, photoreceptor cell retinal damage.

With reference to Dowling (Ex. 1026), Dr. Schweigert testifies that severe vitamin A deficiency causes degeneration in the retina that precedes dry eye. Ex. 1033 ¶¶ 27, 36, and 39–43. Dowling reported that albino rats experienced degeneration of visual cells (photoreceptor cells) after about 2 months of vitamin A deficiency. Ex. 1026, 87-88. Such retinal damage could be reversed upon restoring vitamin A to rats' diets. *Id.* at 94. The other retinal cells (bipolar and ganglion cells), however, appeared normal with vitamin A deficiency. *Id.* at 87-88. According to Schweigert, the astaxanthin administration by Grangaud necessarily treats retinal damage, because astaxanthin is converted in rat retina into vitamin A, which is then used to reconstruct the retina. Ex. 1033 ¶¶ 23 and 43; *see* Ex. 1045, 59, 60, and 160.

The University argues that at the time of invention it was accepted scientific fact that astaxanthin did not have any Vitamin A activity. Resp. 30–31 and 35–36 (citing Ex. 2015 ¶¶ 97–102; Ex. 2010, 2483). The University adds that the work of Grangaud was rejected as unreliable to establish that astaxanthin exhibited Vitamin A activity. *Id.* at 30–31. These

arguments are unpersuasive to controvert the evidence presented by Cyanotech that, during Vitamin A deficiency, astaxanthin is converted to Vitamin A by the rat. Ex. 1002, 44; Ex. 1033 ¶¶ 42–43 and 51; Ex. 1045, 59–60, 73, 160, 163–164. That is, while astaxanthin itself is without Vitamin A-like activity, a biological pathway exist in rats that is capable of metabolically converting astaxanthin to Vitamin A, whereby Vitamin A may present its own activity.

In view of the above, we conclude that the preponderance of the evidence presented by Cyanotech demonstrates that retinal damage is inherent to the condition of vitamin A deficiency-induced xerophthalmia. Grangaud's animals were kept on a vitamin A-deficient diet for about 2 months (Ex. 1002, 43), and Dowling supports a conclusion that animals kept on such a diet would have suffered retinal damage. Ex. 1026, 88–89. Dowling also supports a finding that restoration of vitamin A to the diet could reverse the damage caused by a vitamin A deficiency. *Id.* at 94–96. Grangaud did not administer vitamin A itself, but rather administered astaxanthin. Astaxanthin, however, is capable of being converted to vitamin A in rats, which then would be available to correct the retinal damage caused by a vitamin A-deficient diet, as well as treat ocular lesions resulting from xerophthalmia, thereby improving the vision of the rats. Pet., 14-16; Ex. 1002, 44; Ex. 1033 ¶¶ 42–43 and 51; Ex. 1045, 60 and 160. As such, the inherent action of astaxanthin would have resulted in improved vision in Grangaud's animal model.

The University argues that it is unclear whether Grangaud isolated astaxanthin. *Id.* at 27–31. The University contends that Grangaud's spectrographic analysis of the *Aristoeomorpha foliacea* (krill) oil

administered to the xeropthalmic rats was insufficient to identify the active compound in the oil as astaxanthin because the peaks observed by Grangaud were "broad" and different from the peak for free astaxanthin referenced in the literature (492 nm). Resp. 28 (citing Ex. 2015 at ¶¶ 86–90). That is, the University argues that it is unclear whether Grangaud isolated astaxanthin or whether Grangaud correctly identified astaxanthin as the compound that gave rise to the observed vitamin A activity. *Id.* at 27–31.

We are not persuaded by the University's argument. Even if we were to agree with the University that Grangaud's krill oil contained other carotenoids, the University does not dispute that Grangaud's krill oil contained astaxanthin, which, upon administration to vitamin A-deficient rats, is converted to vitamin A for use in the retina. Ex. 1002, 50:31–51:20; Ex. 1033 ¶¶ 23, 42, 43, 51.

The University's also argues that neither Grangaud nor Dowling suggests that vitamin A deficiency (to which each is directed) is related, in any way, to either free radical damage to a retina or central nervous system, or to any of the disorders or diseases to which the claims are directed. This argument is unpersuasive as the evidence shows that astaxanthin is converted in vivo to vitamin A, which is then available to treat vitamin A deficiency-induced xerophthalmia. Ex. 1002, 50:31–51:20; Ex. 1033 ¶¶ 23, 42, 43, 51

In view of the above, we find that Grangaud's disclosure of a method of feeding astaxanthin to rats suffering vitamin A deficiency-induced xerophthalmia meets all elements of the methods recited in claims 1, 3, and 10. Accordingly, we conclude that Grangaud anticipates claims 1, 3, and 10.

b. Claims 8–9 and 11–12

Claims 8–9 and 11–12 depend directly from claim 1 and further limit the retinal damage element of claim 1. Claim 8 requires the retinal damage to include free radical-induced retinal damage. Claim 9 requires the retinal damage to include light-induced retinal damage. Claim 10 requires the retinal damage to include ganglion cell retinal damage. Claim 11 requires the retinal damage to include age-related macular degeneration.

The evidence of record shows that vitamin A functions as a precursor to the structural protein rhodopsin, found in the retina. Ex. 2105 ¶ 84. Dowling discloses that the loss of this structural protein in vitamin-A deficiency causes photoreceptor cell loss and night-blindness, which may be corrected by adding vitamin A back to the diet. Ex. 1026; *see* Ex. 1045, 29–30 and Ex. 2015 ¶ 46. In view of the above, we find that the preponderance of the evidence presented by Cyanotech supports a finding that Grangaud's animals were suffering from vitamin A deficiency that necessarily resulted in retinal damage.

The preponderance of the evidence presented by Cyanotech, however, fails to demonstrate that Grangaud's animals were suffering necessarily from free radical-induced retinal damage (claim 8) or light-induced retinal damage[5] (claim 9). Certain forms of vitamin A may have antioxidant properties, and thus, be capable of protecting the retina from free radical-induced retinal damage (Ex. 1033 ¶ 37), however, vitamin A is not the only antioxidant that plays a role in the retina—at least both vitamin C and E also

[5] Light generates free radicals in the retina, and thus, light-induced retinal damage is a specific form of free radical-induced retinal damage. Ex. 2015, ¶ 60; *see* Ex. 1001, 2:1-4.

play an antioxidant role in the retina. Ex. 1029 and Ex. 1045, 18–19. Grangaud's animals were suffering from vitamin A deficiency, but the retinal damage seen with this condition may be explained by the lack of rhodopsin. Ex. 2015 ¶ 50 and Ex. 1045, 86–88. There is insufficient evidence on this record to conclude that the absence of vitamin A alone would create conditions that resulted necessarily in free radical-induced retinal damage. Accordingly, we are not able to conclude that Grangaud's animals were suffering necessarily from free radical-induced retinal damage, as required by claims 8 and 9.

Regarding claim 11, Dowling teaches that animals suffering from vitamin A deficiency have normal ganglion cells. Ex. 1026, 88. Thus, the evidence does not support a finding that Grangaud's animals were experiencing ganglion cell retinal damage. Ex. 1026. Regarding claim 12, Grangaud does not disclose the treatment of an animal suffering from age-related macular degeneration. Accordingly, we are not able to conclude that Grangaud's animals were necessarily suffering from the conditions required by claims 11 and 12.

However, as discussed previously, we do not construe the phrase "retinal damage or retinal disease" as a single concept. As such, claims 8–9 and 11–12 do not limit further the concept of disease in the preamble of claim 1, from which claims 8–9 and 11–12 depend. We also construed the term "disease" to refer to conditions in which the underlying cause of damage is treatable. In this regard, Grangaud discloses a method of treating an individual suffering from retinal disease—that is, xerophthalmia. Xerophthalmia is a nutritional disorder that may be treated by replacement of vitamin A, and thus, meets the element of retinal disease recited in the

claims. Ex. 2015 ¶ 56. Accordingly, we conclude that Grangaud anticipates claims 8–9 and 11–12.

c. Claim 13

Claim 13 recites a method comprising administering a therapeutically-effective amount of astaxanthin to protect neurons in a retina from free-radical induced retinal injury. Cyanotech presents evidence that astaxanthin is an antioxidant that is capable of being transported into the retina, and argues that the biological role of astaxanthin obtained from the diet inherently involves protecting neurons in a retina from free-radical induced retinal injury. Pet. 14–15, 22 and 59 (citing Ex. 1002 and Ex. 1033 ¶¶ 24–25 and 43–45).

As discussed above, Grangaud discloses the results of experiments conducted on albino rats fed a vitamin A-deficient diet. Ex. 1002, 43. The University does not dispute that astaxanthin obtained from the diet is capable of crossing the blood-retinal barrier to protect neurons in a retina from free-radical induced damage. Resp. 4–8. Rather, the University argues that evidence of record does not demonstrate that vitamin A protects the retina from free-radical attack and that the vitamin A-deficient rats in Grangaud do not suffer retinal damage from free radicals necessarily. *Id.* at 12 and 19–24.

The language of claim 13, however, does not require the administration of vitamin A nor does it require an individual to suffer from free-radical damage. Claim 13 requires the administration of astaxanthin to an individual and, as summarized above, both parties agree that astaxanthin's biological role involves antioxidant activities in the retina. Paper 64, 18:10–13; Resp. 5. Thus, the necessary result of such

administration would be protection of neurons in a retina from free-radical induced retinal injury. Accordingly, we conclude that Grangaud anticipates claim 13.

d. Claim 14

Claim 14 recites a method of treating an individual suffering from neuronal damage to a retina comprising administering a therapeutically-effective amount of astaxanthin to the individual to improve the condition of the retina. As discussed above with regard to claims 1 and 10, the preponderance of evidence of record demonstrates that neuronal damage to a retina is inherent to the condition of vitamin A deficiency-induced xerophthalmia. Furthermore, as discussed above, the inherent action of astaxanthin involves conversion to vitamin A, which is then available to repair the retina, thereby improving vision in Grangaud's animal model. Accordingly, Grangaud's method of feeding astaxanthin to rats suffering vitamin A deficiency-induced xerophthalmia meets all elements of claim 14.

e. Claim 15

Claim 15 depends from claim 14 and specifies that the neuronal damage may be caused by photic injury to the retina. Cyanotech contends that damage resulting from photo injury is caused by free radicals created by photic energy. Pet. 23.

As discussed above with regard to claim 8, the preponderance of evidence of record does not support a conclusion that Grangaud's animals were suffering necessarily from free radical-induced retinal damage caused by photic injury. Certain forms of vitamin A may have antioxidant properties, and thus, be capable of protecting the retina from free radical-

induced retinal damage (Ex. 1033 ¶ 37), however, vitamin A is not the only antioxidant that plays a role in the retina—at least both vitamin C and E also play an antioxidant role in the retina. Ex. 1029 and Ex. 1045, 18–19. Grangaud's animals were suffering from vitamin A deficiency, but the retinal damage seen with this condition may be explained by the lack of rhodopsin. Ex. 2015 ¶ 50 and Ex. 1045, 86–88. There is insufficient evidence to conclude that the absence of vitamin A alone would create conditions that resulted necessarily in free radical-induced retinal damage. Accordingly, we are not persuaded that the preponderance of evidence shows that Grangaud's animals were necessarily suffering from photic injury, as required by claim 15.

f. Claims 21 and 22

Claim 21 recites a method of treating an individual suffering from a free radical-induced injury to a central nervous system. Claim 22 depends from claim 22 and specifies that the central nervous system may be the retina. As discussed above with regard to claim 15, the preponderance of evidence of record does not support a conclusion that Grangaud's animals were necessarily suffering from free radical-induced retinal damage. Accordingly, we are not able to conclude that the preponderance of evidence shows that Grangaud's animals were necessarily suffering from free radical-induced injury as required by claims 21 and 22.

g. Claim 26

Claim 26 recites a method comprising administering a therapeutically effective amount of astaxanthin to retard the progress of a degenerative retinal disease. The specification identifies age-related macular

degeneration as one such degenerative retinal disease. Ex. 1001, 15:36–40. The specification also discloses that degenerative retinal diseases result in injury to the photoreceptor cells. *Id.* at 7:50–59.

Grangaud discloses the administration of astaxanthin to rats suffering from xerophthalmia due to being kept on a vitamin A-deficient diet. Ex. 1002, 43. Vitamin A deficiency inherently results in the loss of photoreceptor cells. Ex. 1033 ¶¶ 27, 36, and 39–43; *see* Ex. 1026, 87–88. Due to this loss of photoreceptor cells, we consider vitamin A deficiency a degenerative retinal disease encompassed by claim 26. Grangaud's administration of astaxanthin to vitamin A deficient rats necessarily retarded the progress of retinal damage caused by vitamin A deficiency—astaxanthin is converted in rat retina into vitamin A, which then is used to reconstruct the retina. Ex. 1033 ¶¶ 23 and 43; *see* Ex. 1045, 59, 60, and 160. Accordingly, Grangaud's method of feeding astaxanthin to rats suffering vitamin A deficiency-induced xerophthalmia meets all elements of the method recited in claim 26. We conclude that Grangaud anticipates claim 26.

2. Obviousness

"Section 103 [of 35 U.S.C.] forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007)(quoting 35 U.S.C. §103). To establish obviousness of a claimed invention, all the claim limitations must be taught or suggested by

the prior art. *See CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

To establish inherent disclosure, the evidence must show that a feature is necessarily described in the reference, and that it would be so recognized by persons of ordinary skill. *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

Cyanotech contends that the combination of Grangaud and Dowling renders claims 1–15, 21, 22, and 26 obvious. For the reasons expressed below, we conclude that Cyanotech has demonstrated by a preponderance of evidence that the combination of Grangaud and Dowling would have rendered claims 1–14 and 26 obvious. Cyanotech has failed, however, to establish by a preponderance of evidence that claims 15, 21, and 22 would have been obvious.

a. Obviousness of Claims 1–15, 21, 22, and 26 over Grangaud and Dowling

(1) Claims 1–14 and 26

Cyanotech challenges claims 1–14 and 26 as obvious over Grangaud and Dowling. Cyanotech presents substantially the same evidence for both their anticipation and obviousness challenges of claims 1, 3, 8–14, and 26. Pet. 29–44. With regard to claims 2 and 4–7, we determined in our Decision to Institute that the evidence presented Cyanotech's Petition reasonably supported a finding that the administration routes and dosages encompassed by claims 2 and 4–7 would have been a predictable variation of the teachings of Grangaud that could have been implemented by one of ordinary skill in the art. Dec. 15–16, (citing *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 417 (2007) ("If a person of ordinary skill can implement a predictable variation,

§ 103 likely bars its patentability.")).

In its Response, the University argues separately for the nonobviousness of claims 8, 9 and 11–13. Resp. 33–40. The University further argues that several lines of objective evidence (or "secondary considerations") demonstrate the non-obviousness of claims 1–14 and 26. *Id.* at 45–51. In particular, the University argues praise (*id.* at 46–48), commercial success (*id.* at 49), commercial acquiescence (*id.*), copying (*id.* at 50), unexpected results (*id*. at 50–51), and long-felt but unmet need (*id.* at 51). The University does not argue separately for the nonobviousness of the elements recited in claims 1–7, 10, 14 and 26.

In making our decision on the obviousness of the University's claims over prior art, the entirety of the evidence submitted, including the evidence based on the applied prior art and the evidence of nonobviousness based on secondary consideration factors, has been considered as a whole.

Regarding the University's arguments addressing the specific elements of claims 8, 9, 11, and 12, we agree that Grangaud fails to disclose retinal damage comprising free radical-induced retinal damage (claim 8), light-induced retinal damage (claim 9), ganglion cell retinal damage (claim 11), and age-related macular degeneration (claim 12). We do not find claims 8, 9, 11, and 12 to be so limited, however, due to the recitation of "retinal disease" in independent claim 1. None of dependent claims 8, 9, 11, or 12 further limits the "retinal disease" recited in claim 1. Rather, we find that Grangaud discloses the treatment of xerophthalmia, which is a nutritional disorder that may be treated by replacement of vitamin A, and thus meets the element of retinal disease recited in these claims. Ex. 2015 ¶ 56.

As to secondary considerations, we note that factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17 (1966). Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the University's invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471-1472 (Fed. Cir. 1984). However, such a conclusion requires the finding of a nexus to establish that the evidence relied upon traces its basis to a novel element in the claim and not to something in the prior art. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). All types of objective evidence of nonobviousness must be shown to have nexus. *In re GPAC Inc*., 57 F.3d at 1580 (nexus generally); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *In re Antor Media Corp*., 689 F.3d 1282, 1293 (Fed. Cir. 2012) (licensing); *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364 (Fed. Cir. 2012) (copying); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); and *In re Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) (unexpected results).

As discussed above, we conclude that claims 1, 3, and 8–12 are anticipated by Grangaud, as evidenced by Dowling. Because anticipation is the epitome of obviousness, a disclosure that anticipates under 35 U.S.C. § 102 also renders the claim unpatentable under 35 U.S.C. § 103. *See In re Fracalossi*, 681 F.2d 792, 794 (CCPA 1982) ("[E]vidence establishing lack

of all novelty in the claimed invention necessarily evidences obviousness."); *In re Meyer*, 599 F.2d 1026, 1031 (CCPA 1979); *In re Pearson*, 494 F.2d 1399, 1402 (CCPA 1974). Here, Cyanotech presents substantially the same evidence for both their anticipation and obviousness challenges of claims 1, 3, 8–14, and 26. As such, and for the same reasons set forth in our anticipation analysis above, we hold that claims 1, 3, 8–14, and 26 are rendered obvious by Grangaud, alone or in combination with Dowling. Because we have determined that claims 1, 3, and 8–12 lack a novel feature with which to establish a nexus with secondary considerations, Cyanotech, as a matter of law, cannot establish a nexus. *In re Kao*, 639 F.3d at 1068 (Objective evidence that results from something that is not "both claimed and novel in the claim" lacks a nexus to the merits of the invention.).

As to claims 2 and 4–7, the University has not directed any arguments to these claims specifically and has not made any attempts to establish a nexus between the presented objective evidence of nonobviousness and these claims. Thus, we maintain our unopposed determination that the specific doses and routes of administration recited in these claims are predictable variations within the technical grasp of a person of ordinary skill in the art, and are not persuaded by the objective evidence that claims 2 and 4–7 are nonobvious.

In view of the above, we conclude that Cyanotech has demonstrated the unpatentability of claims 1–14 and 26 by a preponderance of the evidence.

(2) Claim 15

Claim 15 depends from claim 14. As discussed above, we conclude

that the preponderance of evidence of record demonstrates that neuronal damage to a retina is inherent to the condition of vitamin A deficiency-induced xerophthalmia.

The question before us with regard to claim 15, however, is whether such neuronal damage is due to photic injury, ischemic insult, or intraocular pressure-related insult to the retina, each of which, as argued by Cyanotech, causes damage via a release of free radicals. *See* Pet. 16. We find that the preponderance of evidence of record does not support a finding that neuronal damage to a retina observed in the condition of vitamin A deficiency-induced xerophthalmia is necessarily caused by any of these insult occurrences. Rather, the preponderance of evidence of record suggests that the inherent contribution of astaxanthin to the effective treatment of vitamin A deficiency-induced xerophthalmia involves the conversion of astaxanthin to vitamin A, where vitamin A is then available to repair and improve the condition of the retina. As such, the treatment of neuronal damage comprising photic injury to the retina, ischemic insult to the retina, or intraocular pressure-related insult to the retina is not suggested by the combination of references cited by Cyanotech. *In re Dillon*, 919 F.2d 688, 718 (Fed. Cir. 1990) ("Arguments based on 'inherent' properties cannot stand when there is no supporting teaching in the prior art. Inherency and obviousness are distinct concepts.")(*citing In re Spormann*, 363 F.2d 444, 448 (CCPA 1966)).

Accordingly, we conclude that Cyanotech has not met its burden to prove claim 15 obvious by a preponderance of evidence.

(3) Claim 21 and 22

Claim 21 recites a method of treating an individual suffering from a free radical-induced injury to a central nervous system. Claim 22 depends from claim 21 and specifies that the central nervous system may be the retina. As discussed above with regard to claim 15, the preponderance of evidence of record does not support a conclusion that the retinal damage Grangaud's animals necessarily were suffering was induced by free radicals. Accordingly, we conclude that Cyanotech has not met its burden to prove claims 21 and 22 obvious by a preponderance of evidence.

III. CYANOTECH'S MOTION TO EXCLUDE

Cyanotech seeks to exclude Exhibits 2033–2036. Paper 47, 1. As discussed above, however, we have determined that Cyanotech, as a matter of law, cannot establish a nexus because the challenged claims lack a novel feature for with which to establish a nexus with secondary considerations. Because we do not rely on any of exhibits 2033–2036 to reach the final decision, we dismiss Cyanotech's motion as *moot*.

IV. CONCLUSION

Cyanotech has shown, by a preponderance of the evidence, that claims 1–14 and 26 of the '533 patent are unpatentable. Cyanotech, however, has failed to meet its burden of proof regarding the unpatentability of claims 15, 21, and 22.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–14 and 26 of the ’533 patent are determined to be unpatentable;

FURTHER ORDERED that Cyanotech’s request for cancellation of claims 15, 21, and 22 is *denied*;

FURTHER ORDERED that Cyanotech’s Motion to Exclude is dismissed as moot; and

FURTHER ORDERED that because this is a final written decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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