DECLARATION OF FLORIAN J. SCHWEIGERT

Containing Claims Charts for Exhibits 1010 and 1014

I, Florian J. Schweigert, declare as follow:

1. I am a citizen of the Federal Republic of Germany, and resident of Berlin, Germany.
2. Since 1996 to the present, I have been employed by the University of Potsdam as (full) Professor of Physiology, and Chair of Physiology and Pathophysiology of Nutrition at the Institute of Nutritional Science, Faculty of Sciences, University of Potsdam, Potsdam, Germany.
3. From 1993 to 1996, I was employed as (full) Professor of Nutrition Physiology, Dept. of Physiology, University of Leipzig, Leipzig, Germany.
4. From 1988-1990, I was a Research Fellow in Medicine in the Channing Laboratories, Harvard Medical School, Boston, Mass.
5. From 1985 to 1993, I was employed in various research and teaching positions, as shown on Exhibit A, annexed hereto.
6. My graduate degree credentials are:

   1986 Ph.D. (Dr. med. vet.) in Nutritional Physiology is from the Veterinary Faculty, Department of Physiology, Biochemistry and Nutritional Physiology, Munich, Germany.

   1983 D.V.M., Veterinary Faculty, Munich, Germany.
7. Other degrees, honors, and fellowships are shown on Exhibit A, annexed hereto.
8. From 2004 until 2009, I was an Expert Member of the Working Group on Carotenoids of the European Food Safety Authority (colloquially known as the "F.D.A. of the E.U.").
9. Exhibit B annexed hereto recites 146 of my peer-reviewed publications (out of over 155) and 31 of my other publications in the fields of vitamin A and carotenoids; eye damage, injury, disease, and therapy; antioxidants and the eye, especially the retina; and other areas related to nutrition and disease.
10. I have made over 200 presentations in national and international conferences on vitamin A and carotenoids; free radicals; eye damage, injury, disease, and therapy; antioxidants and the eye, especially the retina; and other areas related to nutrition and disease.
11. I am being compensated at my normal consulting rate for my work. My compensation is not dependent on and in no way affects the substance of my statements in this Declaration.

12. I have no financial interest in Petitioner or the owner of the '533 patent.
13. I have reviewed and understand the specification, claims, and file history of U.S. Patent No. 5,527,533 (" '533 Patent"), including the Declarations filed in the '533 patent. I understand that '533 patent is considered to have been filed on 27 October 1994 ("Critical Date") for the purposes of determining whether a reference will qualify as prior art.
14. I have reviewed the following references, all of which were published before the Critical Date:

Berson, E., "Nutrition And Retinal Degenerations: Vitamin A, Taurine, Ornithine, and Phytanic Acid," Retina: Vol.2, Issue 4, pp 236-255 (Fall 1982)

Carter-Dawson, L., Kuwabara T., O'Brien P.J., and Bieri, J.G., "Structural and Biochemical Changes in Vitamin A-Deficient Rat Retinas". Invest. Ophthalmol. Vis. Sci. 18: 437-446, (1979).

Dowling, J.E. and Gibbons, I.R., "The effect of vitamin A deficiency on the fine structure of the retina", in The Structure of the Eye, Smelser C.K., editor. New York, Academic Press, Inc., p. 85-99 (1961).

Dowling, J.E. and Wald, G., "Vitamin A deficiency and night blindness". Proc Nat Acad Sci USA 44:648, (1958).

Dowling, J.E. and Wald, G., "The Biological Function of Vitamin A," Proc Nat Acad Sci USA, May; 46(5) 587–608 (1960).

Goto, H. Wu, G-S., Gritz, D.C., Atalia, L.R.A., and Rao, N.A., "Chemotactic activity of the peroxidized retinal membrane lipids in experimental autoimmune uveitis", Current Eye Res., Vo. 10, No. 11, 1009-1014 (1991).

Grangaud, René, "Astaxanthin Research, New Vitamin A Factor", 69 pp.(Éditions Desoer, Liège, 1951), English translation.

Grangaud, René, "Recherches sur l'Astaxanthine, Nouveau Facteur, Vitaminique A", 69 pp. (Éditions Desoer, Liège, 1951), in French.

Grangaud, René; Massonet, Renée; Conquy Thérèse; and Ridolfo, Jacqueline, "Transformation of Astaxanthin to Vitamin A in the Albino Rat: Neoformation in vivo and in vitro", Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, Vol. 252, pp. 1854-1856 (1961b), English translation.

Grangaud, René; Massonet, Renée; Conquy Thérèse; and Ridolfo, Jacqueline, "Transformation de l'astaxanthine en vitamine A chez le Rat albinos: néoformation in vivo et in vitro", Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, Vol. 252, pp. 1854-1856 (1961b), in French.

Grangaud, R., and Massonet, R., "Antixerophthalmic effect of the esters of astaxanthin", Comptes Rendus Hebdomadaires des seances de la Societe de biologie et de ses filiales, Vol. 148, pp. 1392-1394 (1954), English translation.

Grangaud, R., and Massonet, R., "Activité antixérophtalmique des esters de l'astaxanthine", Comptes Rendus Hebdomadaires des seances de la Societe de biologie et de ses filiales, Vol. 148, pp. 1392-1394 (1954), in French.

Grangaud, René, and Massonet, Renée, "Antixerophthalmic Activity of the Carotenoid Pigment of the Aristeomorpha foliacea (Penæidæ)", Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, Vol. 230, pp. 1319-1321 (March 27, 1950), English translation.

Grangaud, René, and Massonet, Renée, "Activité antixérophtalmique du pigment caroténoïde d'Aristeomorpha foliacea (Penæidæ)", Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, Vol. 230, pp. 1319-1321 (March 27, 1950) , in French.

Grangaud, René, and Massonet, Renée, "The Action of Shrimp Oil (Penaeus foliaceus) on the Vitamin A Deficient White Rat", Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, Vol. 227, pp. 568-570 (1948), English translation.

Grangaud, René, and Massonet, Renée, "Action de l'huile de Crevette (Penaeus foliaceus) sur le Rat blanc carence en vitamine A", Comptes Rendus Hebdomadaires des Seances de l'Academie des Sciences, Vol. 227, pp. 568-570 (1948), in French.

Hayes, K.C., "Retinal degeneration in monkeys induced by deficiencies of vitamin E or A," Invest. Ophthalmol. Vis. Sci., vol. 13 no. 7, 499-510 (July, 1974).

Herisset, Armand, "Antioxidant properties of carotenoids and their derivatives".Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences, v.253, pp. 47-49 (July – December) 1946, English translation.

Herisset, Armand, "Propriétés antioxygènes des carotènoïdes et de leurs derives".Comptes Rendus Hebdomadaires des Séances de l'Académie des Sciences, v.253, pp. 47-49 (July – Dcccmbcr) 1946, in Frcnch.

Kurashige, M. et al., "Inhibition of Oxidative Injury of Biological Membranes by Astaxanthin", Physiol. Chem. Phys. and Med. NMR, 22, pp. 27-38 (1990).

Massonet, Reneé, "Research into the Biochemistry of Astaxanthin", 146 pp.(F.Fontana, Algiers, 1960), English translation.

Massonet, Reneé, "Recherches sur la Biochemie de l'Astaxanthine,", 146 pp. (F.Fontana, Algiers, 1960, in French.

Massonet, R., Conquy, T., and Grangaud, R.R. "The Study of Astaxanthin Transformation into Vitamin A in the Albino Rat: in vitro Experiments", Ann. Nutrit. Alimentation, Vol. 19 pp. pages C655-C658 (1965)), English translation.

Massonet, R., Conquy, T., and Grangaud, R.R. "Étude de la transformation de l'astaxanthine en vitamine A chez le Rat albinos: Expériences 'in vitro'", Ann. Nutrit. Alimentation, Vol. 19 pp. pages C655-C658 (1965)), in French.

Massonet, R., Conquy, T., and Grangaud, R., "Transformation of astaxanthin to vitamin A by ocular tissue of the rat in vitro", Comptes Rendus Hebdomadaires des seances de la Societe de biologie et de ses filiales, Vol. 155, pp. 747-750 (1961a), English translation.

Massonet, R., Conquy, T., and Grangaud, R., "Transformation invitro de l'astaxanthine en vitamine A par le tissu oculaire du Rat", Comptes Rendus Hebdomadaires des seances de la Societe de biologie et de ses filiales, Vol. 155, pp. 747-750 (1961a) , in French.

Reading, V.M., Weale, R.A., Aberration, C., Malinow, M.R., "The Effect of Deficiency of Vitamins E And A on the Retina", Nutrition Reviews, Volume 38, Issue 11, pages 386–389 (Nov. 1980).

Schiedt et al., "Recent progress on carotenoid metabolism in animals", *Pure& Appl Chem*, Vol. 63, No. 1 pp 89-100 (1991).

U.S. Patent No. 5,310,764 ("Treatment of age related macular degeneration with β-carotene"), to Baranowitz, et al., issued 10 May 1994.

Zigler, J.S. and Hess H.H., "Cataracts in the Royal College of Surgeons Rat: Evidence for Initiation by Lipid Peroxidation Products", Exp. Eye. Res., 41:67-76 (1985).

15. I have reviewed and understand the Grangaud thesis in French and English (Ex. 1002 and 1003), the Massonet thesis in French and English (Ex.1004 and 1005), the six Massonet et al. journal articles in French and English (Exs. 1008-1019), the three Dowling et al. journal articles (Exs. 1024-1026), the file history of the '533 patent (Ex. 1006), and U.S. Patent No. ("USPAT") 5,310,764 (Ex. 1021), and the description of those publications in the Petition for *Inter Partes* Review and think each description set forth in Sections III(C), IV, and V accurately summarizes the disclosure of the relevant Exhibit.
16. I have reviewed and understand the claim charts in the Petition for *Inter Partes* Review, which claims charts are a condensed version of the claims charts in this Declaration. In my opinion, a person of ordinary skill in the art would agree that each chart identifies and discusses representative subject matter from the Exhibits cited in a given claims chart and (i) teaches each and every claim limitation of claims 1, 3, and 8-27 of the'533 patent as to the claims charts for Ground 1 in Cyan.IPR.One and in Cyan.IPR.Two (see Claims Charts for claims 25 and 27 for more detail on the absence of astaxanthin in the brain and spinal cord), and (ii) renders obvious each of claims 1-27 of the'533 patent as to the claims charts for Ground 2 in Cyan.IPR.One and in Cyan.IPR.Two.
17. "Cyan.IPR.One" refers to the Petition for *Inter Partes* Review filed by Cyanotech to challenge USPAT 5,527,533 and that cites Grangaud's thesis (Ex. 1002) as the base reference in Ground 1 thereof. "Cyan.IPR.Two" refers to the Petition for *Inter Partes* Review filed by Cyanotech to challenge USPAT 5,527,533 and that cites Massonet's thesis (Ex. 1004) as the base reference in Ground 1 thereof.
18. In my opinion, a person of ordinary skill in the art would find the Grangaud thesis, the Massonet thesis, the Massonet et al. journal articles, the Dowling et al. journal articles, and USPAT 5,310,764 recited in the Exhibits List of Cyan.IPR.One and of Cyan.IPR.Two to be enabling disclosures of the subject matter each discusses.
19. After searching on the terms "astaxanthin" or "vitamin A" in *Chemical Abstracts*, for instance, a diligent searcher would have easily been able to locate and retrieve the cited publications prior to the Critical Date, determine the author's name, and search on the authors' names to retrieve more prior art, e.g., Grangaud's thesis (Ex. 1002), Massonet's thesis (Ex. 1004), or any of the journal articles in the Exhibits List of Cyan.IPR.One or Cyan.IPR.Two.

20. The words "treating", "damage", "injury", and "disease" have commonly accepted meanings in the field of '533 patent (i.e., the pharmaceutical/medical arts) with regard to "treating an individual suffering from" damage, injury, or disease. Stedman's Medical Dictionary, 28th Edition (2006) (Philadelphia, Wolters Kluwer Health), attached as Ex. 1040, provides definitions appropriate for the '533 patent of the terms "treating", "damage", "injury", and "disease":

"Treating" means "To manage a disease by medicinal, surgical, or other measures; to care for a patient medically or surgically.".

"Damage" means "Harm, diminution, or destruction of an organ, body part, system, or function.".

"Injury" means "1. The damage or wound of trauma. 2. Lesion." .

"Disease" means a "1. An interruption, cessation, or disorder of a body, system, or organ structure or function. SYN: illness, morbus, sickness. 2. 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.". Substantially similar definitions for such terms are found in other medical dictionaries, such as Dorland's Medical Dictionary (Elsevier).

21. There are two classes of carotenoids: xanthophylls (e.g, lutein, zeaxanthin, canthaxanthin, and astaxanthin); and other carotenes (e.g., α-, β-, and γ-carotene). See attached Ex. 1032 (molecular skeletons of xanthophylls and β-carotene). Xanthophylls lutein, zeaxanthin, and astaxanthin are much stronger antioxidants than α-, β-, and γ-carotenes and other carotenes.

22. Before explaining in detail how Grangaud and Massonet performed and published the same methods as claimed in the '533 patent decades before the Critical Date, I first point out where the '533 patent is scientifically in error:

Today, almost two decades after the Critical Date, there is no evidence that astaxanthin is transported into, much less accumulates, in the brain and spinal cord, or in any part of the central nervous system other than the retina. If astaxanthin accumulated in the brain and spinal cord, those organs would be pigmented, just as the macula lutea in the human retina is pigmented by the xanthophylls lutein and zeaxanthin, and the corpus luteum in the human ovary is pigmented by the carotene β-carotene.

The statement in the '533 patent that "In addition, astaxanthin has a protective effect on

the central nervous system in general, especially damage to the brain and spinal cord caused by free radicals." (Ex. 1001, 14:60-62), has no support in the '533 patent (including the file history thereof) as to the brain and spinal cord, is scientifically erroneous, and cannot be supported even today (excluding damage to the retina; embryologically, the retina is an outgrowth of the developing brain, and is therefore is part of the central nervous system). Therefore, claims 25 and 27 of the '533 patent are scientifically erroneous.

23. Astaxanthin is one of the strongest antioxidants known; in addition to benefiting from the antioxidant properties of astaxanthin, in the rat retina astaxanthin is converted into vitamin A (Exs. 1008 and 1010), an essential vitamin.
24. Transport of astaxanthin from the bloodstream into a tissue requires specialized "binding proteins" that are present in the retina and a few other animal tissues. Suppression of free radicals necessarily occurs if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light. Irradiating the retina with bright light creates excited states of oxygen that characterize peroxyl radicals (ROO•) andsinglet oxygen ($^1O_2$) radicals.
25. Any administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. The only blood-based access to the eye in vertebrates is through the retinal and uveal capillary networks that service the retina (including the retinal pigment epithelium ("RPE")), and the iris and ciliary body, respectively. Retinal tissue contains binding proteins that preferentially transport *xanthophyll* carotenoids, like lutein, zeaxanthin, canthaxanthin, and astaxanthin, from the retinal capillary network into retinal tissue, but disfavor transport into retinal tissue of *carotene* carotenoids, like β-carotene. Transport of astaxanthin in the bloodstream requires specialized "binding proteins". Transport of astaxanthin from the bloodstream into a tissue, and accumulation of astaxanthin in a given type of tissue, requires specialized "binding proteins" that are present in some, but not all, animal tissue.
26. Astaxanthin's inherent mode of action in vertebrate tissue, including retinal tissue, is as a strong antioxidant and free radical scavenger. Suppression of free radicals, such as peroxyl and singlet oxygen radicals, and of free radical-induced damage necessarily occurs if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light.

27. Xerophthalmia ("dry eye disease") is the first plainly visible sign of vitamin A deficiency in rats (symptoms of "night blindness" precede visible signs of xerophthalmia). Xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage, injury, and disease from vitamin A deficiency occurs first (and causes night blindness), then xerophthalmia manifests at a later stage in the cornea and surrounding areas.
28. Xerophthalmia is caused by severe vitamin A deficiency. Rats and other vertebrates become diseased, go blind, and die from continued vitamin A deficiency. Infliction of vitamin A deficiency is an injury and causes stunted growth as well as retinal, corneal, and other injury and diseases.
29. The layered structure of the retina is shown in Ex. 1032. "Inner" retinal layers refer to layers closer to the center of the ocular globe. "Outer" retinal layers refer to layers closer to the sclera (outer surface) of the ocular globe. The retina is largely comprised of various types of neurons, e.g., ganglion, photoreceptor rods, and photoreceptor cones.
30. Although photoreceptor cells are one of the "bottom" or "outer" layers of the retina, photoreceptor cell membranes are especially vulnerable to oxidation, due to an unusual combination of conditions: a high concentration of oxygen and mitochondria, the presence of light energy, and a high proportion of polyunsaturated fatty acids ("PUFA") in their membranes. In general, the potential for free radical-induced cellular damage may be greater in the retina than in any other tissue because the transparency of ocular structures allows light-induced generation of free radicals (especially peroxyl radicals of PUFAs) in addition to free radicals produced by normal oxidative metabolism.
31. All oxygen-consuming tissues produce small amounts of highly reactive free radicals by univalent reduction of oxygen, an alternative pathway of oxygen reduction through the cytochrome system. The high density of mitochondria (which use oxygen in synthesizing ATP, but create free radicals when oxygen is prematurely reduced) in the photoreceptor cells increases the production of free radicals. Free radical production increases dramatically when bright light strikes the photoreceptor cell membranes. Aerobic cells (which use mitochondria for glycolysis and ATP production) have evolved many "free radical scavengers". A vitamin A-deficient retina, with inadequate amounts of endogenous free radical scavengers, such as retinol (the alcohol form of vitamin A), cannot neutralize

even normal amounts of free radicals produced in retinal tissue, much less free radicals produced by photic insult, ischemia, or high intraocular pressure.

32. Membrane lipid peroxidation is one of the most prominent forms of cellular damage induced by conditions of oxidative stress (e.g., free radical barrage). The retina contains several enzymatic free radical scavengers (e.g., superoxide dismutase, and catalase) for neutralizing free radicals as well as a host of endogenous antioxidant compounds, including (among others) vitamin E, ascorbate, taurine, glutathione, various vitamin A compounds, and various carotenoids.
33. Astaxanthin suppresses free radicals, such as peroxyl radicals (ROO•) and singlet oxygen ($^1O_2$) radicals, and thereby suppresses free radical-induced damage in tissues into which astaxanthin is transported and accumulates.
34. Light impinging on the retina penetrates the "inner" layers of the retina (some of which is called the inner retinal thickness or "IRT" in the '533 patent), the middle layer (including the outer nuclear layer, or "ONL" in the '533 patent) of the retina, and passes through the photoreceptor cell membrane (made primarily of PUFAs) to excite rhodopsin in the rods (monochrome vision) and photopsins in the cones (color vision) of photoreceptor cells. Rhodopsin consists of the protein moiety opsin and a reversibly covalently bound cofactor, retinal (the aldehyde form of vitamin A).
35. PUFAs exposed to light energy readily form peroxyl radicals that attack and destroy photoreceptor cell membranes and other membranes and structures in the retina unless the peroxyl radicals are neutralized by a free radical scavenger, such as an antioxidant. In the absence of effective free radical scavenging, a barrage of peroxyl radicals is released from the photoreceptor layer that can travel through the eye causing damage, injury, and disease in the middle and inner layers of the retina, and even travel across the vitreous humor to the anterior parts of the eye. For instance, peroxyl radicals from degenerated retina are a primary or contributing cause of cataracts (Zigler, 1985) and of uveitis (Goto, 1991).
36. The role of vitamin A in the chemistry of vision was elucidated by George Wald in the period from the mid-1930s to the mid-1960s, which led to his Nobel Prize in 1967. Wald, John Dowling, and I.R. Gibbons published in the late 1950s and early 1960s the results of their extensive research on degeneration of the retina caused by vitamin A deficiency (Dowling and Wald (1958); Dowling and Wald (1960); Dowling and Gibbons (1961).

Those publications (Ex. 1024, 1025, and 1026, respectively) contain numerous micrographs showing the reduction of the ONL and IRT, and graphs of the reduction of rhodopsin levels, in photoreceptor cells lacking adequate vitamin A. See, e.g., Fig. 1 of Ex. 1024 (Dowling and Wald, 1958) (reduction of rhodopsin levels); Figs. 2, 13, and 15 of Ex. 1025 (Dowling and Wald, 1960) (reduction of ONL and IRT); Figs. 2 and 10 of Ex. 1026 (Dowling and Gibbons, 1961) (reduction of ONL and IRT). Later publications (Reading (1980), Zigler (1985)) explained that the degeneration of the photoreceptor cell membranes, reduction in thickness of the retina, and reduced rhodopsin levels were due to attack by free radicals, especially attack by peroxidized lipids emitted from disintegrating outer segments of photoreceptor rods.

37. Vitamin A has three molecular forms relevant to this discussion: an acid form, "retinoic acid", required for normal growth, but not active in the chemistry of vision; an aldehyde form, "retinal", that combines with opsin to create rhodopsin; and an alcohol form, "retinol", which is an antioxidant. Retinal and retinol are enzymatically interconvertible, but the enzymatic conversion to retinoic acid is irreversible.
38. The absence of vitamin A in the retina of a vitamin A deficient rat would necessarily result in the absence of vitamin A as an antioxidant and as a component of rhodopsin, rendering the retina vulnerable to free radical attack, e.g., during photic insult and during reperfusion following retinal ischemia or high intraocular pressure (the experiments conducted in the '533 patent), and causing collapse of the rods in the photoreceptor cell layer by the inability to synthesize rhodopsin (which is vital to rod structure).
39. In Fig. 15 of Ex. 1025 (Dowling and Wald, 1960), a retina (middle micrograph and electroretinogram ("ERG")), degenerated by 6.5 months of vitamin A deficiency with severe damage to the photoreceptor cell layer, was restored to normal structure and function (Fig. 15, right micrograph and ERG) by administration of vitamin A.
40. Figs. 2a to 2d, and 10a to 10c, of Ex. 1026 (Dowling and Gibbons, 1961) also irrefutably establish the protective, and therapeutic, effects of vitamin A (as both an antioxidant and as a component of rhodopsin). Again, the retinal degeneration, including the ONL and IRT, as shown in Figs. 2d and 10b, is far more severe than reported in the '533 patent. As in Ex. 1025 (Dowling and Wald, 1960), in Ex. 1026 (Dowling and Gibbons, 1961), vitamin A protected the eye from retinal degeneration (group receiving vitamin A, Figs 2a and 10a)

and healed the degeneration and resultant disease when administered therapeutically (Figs. 2d and 10c) after free radical-induced retinal injury in a different group.

41. If adequate vitamin A is available and photoreceptor cells are undamaged, rhodopsin levels are normal. The reduction of ONL, IRT, and rhodopsin levels in the '533 patent reflect the free radical scavenging mechanisms being temporarily overwhelmed by a free radical barrage and consequent damage to the photoreceptor cells. The much more pronounced reduction of rhodopsin levels in Ex. 1025 (p. 588, Dowling and Wald, 1960) and Fig. 10 of Ex. 1026 (Dowling and Gibbons, 1961), compared with the minor, short term, drop in rhodopsin levels in the '533 patent, reflect the combination of vitamin A deficiency and more severe photoreceptor cell damage in the Dowling et al. references.
42. Fig. 15 of Ex. 1025 (Dowling and Wald, 1960) and Fig. 10 of Ex. 1026 (Dowling and Gibbons, 1961) are notable for showing not only the retinal degeneration (including reduction of ONL and IRT) in rat retina caused by vitamin A deficiency, but prevention of such degeneration by vitamin A, and reconstruction of degenerated rat retinal layers by administration of vitamin A after retinal injury (in different test groups). This protection against retinal degeneration (in the control group that received vitamin A) and "treating" of retinal degeneration in the vitamin A deficient group that subsequently received vitamin A, is biochemically, prophylactically (in the case of prevention) and therapeutically (in the case of damage, injury, and disease) equivalent to the administration of astaxanthin to rats (since astaxanthin is an antioxidant and is also converted in rat retina to vitamin A (Massonet et al. (Ex. 1008, (1965) and Ex. 1010 (1961b)).
43. Therefore, if astaxanthin is administered before an event that would otherwise cause a free radical barrage (e.g., vitamin A deficiency, photic insult, reperfusion after ischemia or high intraocular pressure), astaxanthin is necessarily transported to the retina and scavenges (neutralizes) free radicals before they can cause damage. If astaxanthin is administered after free radical-induced injury of the retina, astaxanthin is converted in rat retina into vitamin A, which is then used to reconstruct the retina (explained in Dowling et al., 1958, 1960, and 1961), assuming that irreversible damage of the cornea (from xerophthalmia) and retina has not occurred.
44. Whether the retinal degeneration arises from vitamin A deficiency or from photic insult or reperfusion following ischemia or high intraocular pressure, the biochemical, histological,

and pathological mechanism is the same: if the photoreceptor cell membranes (particularly the rod outer segments) are exposed to light energy without adequate free radical scavenging, the result is a free radical barrage of peroxidized fatty acids and singlet oxygen that cause retinal degeneration and reduction of ONL, IRT, and rhodopsin levels. Even in rats with normal vitamin A levels, intense photic energy or reperfusion (after ischemia or high intraocular pressure) depletes available free radical scavengers, thereby enabling peroxidation of lipids in the photoreceptor membranes, which unleashes a free radical barrage and resultant damage, injury, and (if vitamin A deficiency ensues) disease.

45. Vitamin A deficiency inherently produces the same types of retinal damage and injury that the experiments in the '533 patent produced. Grangaud et al. (in Ex. 1014) and Massonet et al. (in Ex. 1010) administered to vitamin A-deficient rats astaxanthin to prevent, and to treat, one type of eye damage, injury, and disease (xerophthalmia) caused by vitamin A deficiency or by lack of antioxidant, but **necessarily (inherently) treated** other types of eye damage and injury caused by vitamin A deficiency or by lack of antioxidant, including the type of damage and injury that the experiments in the '533 patent produced.

46. The preceding discussion of biochemical, histological, and pathological mechanisms of free radical-induced retinal degeneration was confirmed in other animal models before the Critical Date. I quote from these other studies:

Berson, Eliot., "Nutrition And Retinal Degenerations: Vitamin A, Taurine, Ornithine, and Phytanic Acid," Retina: Fall 1982 - Volume 2 - Issue 4 – pp 236-255. (Ex. 1028)

Bersonp.240, left col., top. (emphasis added) "In contrast, rats raised on a vitamin A-free diet supplemented with retinoic acid show changes in the outer segments at about two months (Fig. 6B) and loss of outer segments, inner segments, and about half the photoreceptor nuclei at about six months (Fig. 6C). At ten months (Fig. 6D) the photoreceptors have disappeared except for one row of nuclei. … In fact, reversal of function and structure can be achieved with refeeding vitamin A in early stages. Figure 7 illustrates the retina of a control rat (A), that of a vitamin A-deficient rat at six months with loss of outer segments and half the photoreceptors (B), and the retina of a rat depleted for about six months and then given vitamin A for 16 days (C). No increase in the thickness of the outer nuclear layer occurs (Fig. 7C compared with

Fig. 7B), but new outer segments (Fig. 7C) with normal length and width regenerate within 16 days."

L. Carter-Dawson, T. Kuwabara, P.J. O'Brien and J.G. Bieri: Structural and Biochemical Changes in Vitamin A-Deficient Rat Retinas. Invest. Ophthalmol. Vis. Sci. 18: 437-446, 1979. (Ex. 1030)

See Fig. 2 showing reduction of rhodopsin levels, and Figs. 7 and 8 showing reduced thickness of ONL in vitamin A-deficient rats, and pages 444-445 discussing recovery of normal rhodopsin levels and ONL by administration of vitamin A.

Hayes, K.C., "Retinal degeneration in monkeys induced by deficiencies of vitamin E or A," Invest. Ophthalmol. Vis. Sci.July 1974 vol. 13 no. 7 499-510. (Emphasis added). (Ex. 1027)

Fig. 1 caption. "On the other hand, both peripheral retina (C) and macula (D) in the vitamin-A deficient monkey have degenerated outer segments, the latter appearing much worse than the former. **Thinning of the ONL has also occurred in the macula**."

p. 505 bottom, rt. col. In a vitamin A deficient monkey, "**The ONL was reduced in thickness** and contained degenerating nuclei corresponding to the degree of OS [outer segment] degeneration (Fig. 1)."

p. 508 bottom to left col. top of page 509. "protracted vitamin A depletion in adult monkeys produced classical signs of deficiency including **xerophthalmia** and keratomalacia. Rupture of the cornea resulted in destructive panophthalmitis in one monkey. … Both rods and cones appeared damaged in the macula and in the surrounding retina of the more advanced lesion. **Degeneration of the ONL** and numerous lipid-laden lysosomes in the pigment epithelium were the only other changes observed."

Kurashige, M. et al., "Inhibition of Oxidative Injury of Biological Membranes by Astaxanthin", Physiol. Chem. Phys. and Med. NMR, 22, pp. 27-38 (1990). (Ex. 1020)

Kurashige, p. 27 (Abstract) (emphasis added). "The value of astaxanthin, a carotenoid pigment, in the treatment of oxidative injury is assessed.Astaxanthin protects the mitochondria of vitamin E-deficient rats from damage by Fe2+-catalyzed lipid

peroxidation both *in vivo and in vitro*. **The inhibitory effect of astaxanthin on mitochondrial lipid peroxidation is stronger than that of α-tocopherol**."

Reading, V.M., Weale, R.A., Aberration, C., Malinow, M.R., "The Effect of Deficiency of Vitamins E And A on the Retina", Nutrition Reviews, Volume 38, Issue 11, pages 386–389 (Nov. 1980).(Ex. 1029)

Reading, p. 387, left col middle of page. "The reason for considering marginal vitamin A in conjunction with vitamin E deficiency is that vitamin A depletion is known to result in deterioration of the ROS [rod outer segment] disk structure, due to loss of rhodopsin."

Reading, p. 387, right col top of page. "Surprisingly, there was a 46 percent loss of rod nuclei in the –E-A group, whereas the –E+A group lost none, compared to controls. Therefore, the normal level of dietary vitamin A was essential for preserving the number of rod cells. … The decline in vitamin A level in the RPE and the ROS may be such as to mimick the effect of a frank vitamin A deficiency in the whole animal, and thus disrupt the ROS disk structure."

Reading, p. 388, left col bottom of page. "With regard to the structure of the retina, the vitamin E deficiency alone (-E+ A), after 35 weeks, caused a disruption of the disk membranes and a 20 percent loss of photoreceptor cells. A vitamin A deficiency superimposed on the vitamin E deficiency (-E-A) led to almost complete destruction of the ROS membranes and loss of more than 90 percent of the photo-receptor cells. As one would expect, vitamin A deficiency alone (+E-A) led to a greatly shortened ROS and an intermediate loss of cells (34 percent). Thus, a -E-A diet produced a greatly accelerated degeneration of the photoreceptor cells compared to a + E-A diet."

Schiedt et al., "Recent progress on carotenoid metabolism in animals", *Pure& Appl Chem*, Vol. 63, No. 1 pp 89-100 (1991) (emphasis added). (Ex. 1031)

Schiedt, p. 89 (Abstract). "The influence of dietary astaxanthin, canthaxanthin and zeaxanthinon the carotenoid content and composition of the oil droplets in chicken retinawas investigated. **From a "racemic" astaxanthin mixture, the (3S,3'S)-isomer was deposited almost selectively in the retina.** Both oxidative and reductivemetabolic pathways were followed by all three carotenoids. Astaxanthin,

themain carotenoid in avian oil droplets, was obviously formed from both dietaryzeaxanthin and canthaxanthin."

Grangaud and Massonet: Astaxanthin shown to be an antioxidant and a pro-vitamin A.

47. In 1946, the French scientist, Armand Herisset, published a journal article (Ex. 1022) that announced the discovery of the antioxidant properties of astaxanthin (which Herisset called "hematochrome" in French), a bright red xanthophyll pigment extracted from certain organs in shrimp. Herisset wrote (Ex. 1022, 49:10), "Astaxanthin and vitamin A are powerful anti-oxidants; the carotene used was a little less active."
48. René Grangaud's doctoral thesis (Ex. 1002) demonstrated and explained the effect of administration of astaxanthin in curing vitamin A deficiency-induced injury and diseases in rats, particularly the cure of xerophthalmia. Grangaud wrote (Ex. 1002, 106:14-18) "In astaxanthin, the double-bond of the enediol group is conjugated with the entire polyenic system and this favorable position, if it truly explains the fragility of the molecular structure, might also explain the vitamin activity of the bio-catalyzer. This idea is supported by experimental data in the recent work by Herisset on the comparative antioxidant strength of carotene, vitamin A and astaxanthin: clearly greater than that of carotene, the antioxidant strength of astaxanthin is on the same order as that of vitamin A itself." (footnotes omitted)
49. Grangaud published his doctoral thesis in 1951, and described in great detail the collection of astaxanthin by dissection of shrimp, the oral administration of various doses of astaxanthin to vitamin A-deficient rats, and the preventive and therapeutic effect of astaxanthin on eye injury and diseases.
50. Grangaud wrote in his doctoral thesis (Ex. 1002, 60:24-27), "Xerophthalmia is, in fact, considered to be a secondary manifestation of the general infestation of epitheliums which is completely comparable to infectious processes such as the formation of abscesses which are so frequent with vitamin A deficiency." (footnotes omitted)
51. Grangaud's published thesis (Ex. 1002) and Massonet's published thesis (Ex. 1004) established that (i) astaxanthin is a powerful antioxidant, (ii) orally administered astaxanthin was transported to, and accumulated in, the retina, and (iii) one of the effects of orally administered astaxanthin is the cure of xerophthalmia and other symptoms of vitamin A

deficiency, such as stunted growth (Ex. 1002, p.57). We now know that astaxanthin is a much stronger antioxidant than retinol, the alcohol form of vitamin A that also acts as an antioxidant in the retina. Massonet et al. later proved (Exs. 1008 and 1010) that astaxanthin is converted to vitamin A in the rat retina.

52. Vitamin A deficiency-induced free radical barrage and retinal degeneration in Grangaud's and Massonet's rat models (Exs. 1014 and 1010) is necessarily the same as the vitamin A deficiency-induced free radical barrage and retinal degeneration in Dowling et al.'s rat models (Exs. 1024, 1025, and 1026).
53. Grangaud's and Massonet's *prevention*, by administration of astaxanthin, of free radical-induced damage and retinal degeneration in Grangaud's and Massonet's rat models is necessarily the same as Dowling et al.'s prevention, by administration of vitamin A, of free radical-induced damage and retinal degeneration in Dowling et al.'s rat models, since astaxanthin functions as a strong antioxidant, and is also converted into vitamin A.
54. Grangaud's and Massonet's *treating*, by administration of astaxanthin, free radical-induced retinal damage, injury, and disease in Grangaud's and Massonet's rat models is necessarily the same as Dowling et al.'s treating, by administration of vitamin A, free radical-induced retinal damage, injury, and disease in Dowling et al.'s rat model, since astaxanthin is a strong antioxidant, and is also converted into vitamin A.
55. Grangaud's and Massonet's *prevention*, by administration of astaxanthin, of free radical-induced damage and retinal degeneration in Grangaud's and Massonet's rat models is necessarily the same as prevention, by administration of astaxanthin, of free radical-induced damage and retinal degeneration in the rat model in the '533 patent, since (as proven by Dowling et al.) free radical-induced damage and retinal degeneration necessarily resultsfrom vitamin A deficiency : Grangaud's and Massonet's rat models were vitamin A deficient in the control group, but the test group received astaxanthin and retained ocular health.
56. Grangaud's and Massonet's *treating*, by administration of astaxanthin, of free radical-induced retinal damage, injury, and disease in Grangaud's and Massonet's rat models is necessarily the same as treating, by administration of astaxanthin, of free radical-induced retinal damage, injury, and disease in the rat model of the '533 patent, since (as proven by Dowling et al.) curing of free radical-induced damage and retinal degeneration, which was not reported or shown in the '533 patent but which Grangaud, Massonet, and Dowling et al.

did conclusively establish, necessarily results from administration of vitamin A, and astaxanthin is converted in the rat retina into vitamin A.

57. Decades before the Critical Date, René Grangaud (Ex. 1014) and Renée Massonet (Ex. 1010) administered astaxanthin to rats and achieved the results disclosed in the '533 patent. As explained in more detail herein, by preventing, and curing, xerophthalmia (in different experiments) through the administration of astaxanthin, Grangaud and Massonet necessarily prevented, and cured (in different experiments), the retinal degeneration (i.e., retinal damage and injury) reported in the '533 patent.
58. Scavenging of free radicals necessarily occurs when astaxanthin is present in the retina. In curing xerophthalmia in rats, Grangaud and Massonet necessarily treated the type of retinal degeneration caused by the experiments described in the '533 patent.
59. Grangaud reported in 1951 (Ex.1002, 51:19-20 ("It should be noted that the examination of the enucleated eyes show that only the retinal area is pigmented [by astaxanthin in the shrimp oil]")), and Massonet reported in 1960 (Ex. 1004, 102:31-34 ("For astaxanthin, localization is without doubt most apparent in the eye; upon dissection, the rat retinas having received the pigment showed most often a salmon color that already reveals the presence of the carotenoid [astaxanthin] before any extraction…"), that after administration of astaxanthin and enucleation, astaxanthin is detected in rat retina by visual inspection.
60. Massonet reported in 1960 (Ex. 1004, Table XX on p.105 and Table XXI on p.107) that astaxanthin is not detected in the brain or spinal cord (denoted as "encephalon" in French). "Encephalon" is a medical term (in French and English) of Greek origin, the broad meaning of which is the central nervous system other than the retina, and the narrowest meaning is the brain and spinal cord. Massonet's observations have not been disproven.
61. The "central nervous system" consists essentially of the brain, spinal cord, and retina.
62. The group receiving vitamin A in Ex. 1025 (Dowling and Wald, 1960) and Ex. 1026 (Dowling and Gibbons, 1961) maintained healthy retinas, since they maintained adequate vitamin A, which functions as an antioxidant (retinol form) and as a component of rhodopsin (retinal form).
63. The test groups in Ex. 1014 (Grangaud) and Ex. 1010 (Massonet) maintained healthy retinas, since they received astaxanthin, which functions as an antioxidant similar to retinol

and as a precursor of retinal, and is converted in the rat retina into the retinal and retinol forms of vitamin A.

64. The test group in the '533 patent had less damage after photic insult or reperfusion, since they received astaxanthin, which functions as an antioxidant similar to retinol and as a precursor of retinal, and is converted in the rat retina into the retinal and retinol forms of vitamin A.
65. Fig. 15 of Ex. 1025 (Dowling and Wald, 1960) and Fig. 10c of Ex. 1026 (Dowling and Gibbons, 1961), and by inherency, Ex. 1014 (Grangaud) and Ex. 1010 (Massonet), show something that the '533 patent does not show… successful treatment of retinal degeneration by administration of vitamin A (Dowling et al.) or astaxanthin (Grangaud, and Massonet).
66. The ONL, IRT, and rhodopsin reduction in the Grangaud thesis or the Massonet thesis would have been similar to the over 75% reduction shown in Dowling et al. (1960 and 1961), and more severe than in the '533 patent, since the vitamin A deficiencies in the Grangaud and Massonet rat models were "life-long" deficiencies; in contrast, the depletion of antioxidants in the experiments in the '533 patent were temporary.
67. Grangaud and Massonet, in preventing and curing xerophthalmia (in different experiments), necessarily prevented and cured (in different experiments), by administration of astaxanthin, the retinal degeneration reported in the '533 patent.
68. The Grangaud, Massonet, and Dowling et al. publications teach that one can prevent retinal damage and injury, and cure retinal disease, caused by oxidative stress by administering an antioxidant that is transported into retinal tissue.

The '533 Patent

69. I have reviewed and understand the overview of the '533 patent set forth in Sections III(A)-III(B) of the Petition for *Inter Partes* Review. In my opinion, the overview accurately describes that the claims of the '533 patent are directed to administration of astaxanthin as an antioxidant to "treat" free radical-induced injury.
70. The experimental design used in the '533 patent would only yield data about the **preventive** effect of astaxanthin. In the '533 patent, (i) astaxanthin was administered to rats before various types of retinal injury were inflicted, (ii) the rat retinas were injured by light, ischemia, or intraocular pressure, (iii) the rat retinas were harvested, and (iv) the retinal

outer nuclear layer ("ONL") thickness and inner retinal thickness ("IRT"), and rhodopsin levels, of rats receiving astaxanthin were compared with the ONL, IRT, and rhodopsin levels of a control group that did not receive astaxanthin.

71. The '533 patent (including the Declarations in the file history) reiterates that "we have found that astaxanthin has the unpredictable and unexpected ability to cross the blood-retinal brain barrier", or equivalent statements asserting non-obviousness. (e.g., Ex. 1001, 8:21-28; 8:33-39; 10:10:54-61; 11:12-16. Ex. 1006, para 15, pdf pp 37-38; para. 17, pdf p.38) Those abilities of astaxanthin were first published in 1951 (Exhibit 1002), 43 years before the Critical Date. Astaxanthin's *inability* to cross into the brain and spinal cord (i.e., into the central nervous system other than the retina) was first published in 1960 (Exhibit 1004), 34 years before the Critical Date.
72. The '533 patent contains no data on the therapeutic use of astaxanthin, i.e., **treating** damage, injury, or disease by administering astaxanthin *after* infliction of such damage or injury, or onset of disease.
73. Antioxidants in the retina, such as commonly present lutein and zeaxanthin, and administered astaxanthin, protect photoreceptor cells from degeneration during photic or other free radical insult. The reduction in ONL, IRT, and rhodopsin levels are a result of degeneration of the photoreceptor cell (aka "rods and cones") layer. The photoreceptor cell layer lies immediately "below" or "outside" the ONL and is also outside the IRT (see Ex. 1032, which shows the layers of the retina). Photoreceptor cell layer damage is the root cause (i.e., the origin of the free radical barrage) of the injury actually measured in the '533 patent, as explained above.
74. The '533 patent discloses "methods of treating individuals suffering from central nervous system injury or disease … [or] eye injury or disease, and … methods of retarding a degenerative disease of the eye" by administration of astaxanthin. Ex. 1001, 6:48-53. (emphasis added)
75. The '533 patent discloses reducing retinal injury by administration of astaxanthin before injury by insult or reperfusion (following ischemia or high intraocular pressure), and asserts that prevention of retinal injury also establishes prevention of brain, spinal cord, and central nervous system injury and disease.

76. The damage or injury in the '533 patent is reduction, in a rat retina, (i) of the "thickness of the outer nuclear layer", and (ii) of the "distance between the internal limiting membrane to the interface of the outer plexiform layer and the outer nuclear layer". Ex. 1001, 11:52-56, 12:37-43, and Figs. 1-4. The relationship of such injury to health or disease in rats or humans, or how astaxanthin "treated" such injury, is not disclosed in the '533 patent.
77. The '533 patent contains no data that confirm the accumulation of astaxanthin in any organ of the body other than the retina, and discloses only the effect on retinal ONL, IRT, and rhodopsin levels of administration of astaxanthin before injury.
78. All damage, injury, and disease, e.g., various inflammatory diseases, various ischemias, macular degeneration, degeneration from stroke or trauma, etc., disclosed in the '533 patent are asserted to result from the action of free radicals. The '533 patent further asserts that suppression of such free radicals by the action of astaxanthin ameliorates such free radical-induced damage, injury, and disease. Incidentally, the rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for human retina.
79. The only support for the claims in the '533 patent is the effect on retinal ONL, IRT, and rhodopsin levels of administration of astaxanthin before injury. The ONL and IRT measurements are morphological data, obtained by measuring micrographs of rat retina. ("The measurements were made with an image processing system wherein the stained retinal sections were projected onto a digitizing pad coupled to a microcomputer." Ex. 1001, 11:57-59). The measurement of ONL and IRT in the '533 patent uses the method described J. Michon et al., Invest. Ophthalmol. Vis. Sci., 32, pp. 280-84 (1991). The measurement of rhodopsin levels in the '533 patent uses the method described in Z. Li et al., Current Eye Res., 10, pp. 133-44 (1991).

Technical Basis Underlying the Grounds of Rejections Set Forth in the Petition for *Inter Partes* Review

80. I understand that claims 1–27 of the '533 patent are being challenged in the above-referenced *Inter Partes* Review.

81. I supplement the references applied in the grounds of rejections set forth in Section IV of the Petition for *Inter Partes* Review by explaining why Exs. 1014 and 1010 are printed publications before the Critical Date that anticipate or render obvious all claims in the '533 patent.

82. For ease of reference, the four claims charts below will be used when referring to portions of claims 1–27 the '533 patent.

GROUND 1. '533 PATENT CLAIMS ANTICIPATED BY CYAN EXHIBIT 1010 (Massonet (1961b)). '533 claim language in left column and prior art Description and my comments in right column.	
Claim 1. A method of treating an individual suffering from retinal damage or retinal disease, said method comprisingadministering a therapeutically effective amount of astaxanthin to the individual to improve the vision of the individual.	Irradiating the retina with bright light, or other oxidative stress, such as reperfusion, creates peroxyl, singlet oxygen, and other free radicals(Zigler, 1985; Goto, 1991). Grangaud (Ex. 1002) discovered and published that dietary astaxanthin was transported into the retina and cured xerophthalmia when administered to vitamin A-deficient rats. Massonet (Exs. 1004) confirmed the results of Grangaud.The only cause of retinal damage, injury, or disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. *Any* administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Retinal tissue contains binding proteins that preferentially transport *xanthophyll* carotenoids, like lutein, zeaxanthin, canthaxanthin, and astaxanthin, from the retinal capillary network into retinal tissue, but disfavor transport into retinal tissue of *carotene* carotenoids like β-carotene. Astaxanthin is transported in the bloodstream, and from the bloodstream into the retina, by specialized "binding proteins". Suppression of free radicals **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light or other oxidative stress. Astaxanthin's inherent mode of action in vertebrate tissue,

	including retinal tissue, is as a strong antioxidant. Suppression of free radicals, such as peroxyl and singlet oxygen radicals, and free radical-induced damage **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light. Xerophthalmia ("dry eye disease")is *secondary* to retinal damage, injury, and disease (Grangaud, (1951); Massonet (1960); Dowling (1958); in other words, photoreceptor cell membrane attack by a barrage of free radicals, photoreceptor cell degeneration, and reduction of the ONL, IRT, and rhodopsin levels occur first, then xerophthalmia manifests at a later stage in the cornea and surrounding areas. Rats and other vertebrates become diseased, go blind, and die from continued vitamin A deficiency. Infliction of vitamin A deficiency is an injury and causes retinal, corneal, and other injury and diseases (Dowling (1958); Dowling (1960); Dowling (1961)). The free radical-induced damage from photic insult or reperfusion following retinal ischemia or high intraocular pressure in the '533 patent causes the same free radical-induced damage as caused by severe vitamin A deficiency in Ex.1008. The rats in the '533 patent and Ex.1010 suffered from retinal damage and injuryinduced by free radicals (no disease was reported in the data of the '533 patent). If astaxanthin is in the retina (preferentially transported into the retina from the bloodstream), a **necessary and inherent result** is (i) suppression by astaxanthin of free radicals, such as peroxyl and singlet oxygen radicals, (ii) prevention of initial or further free radical damage and injury, and (iii) prevention of resultant free radical-induced disease. Massonet, in Ex. 1010, administered astaxanthin to treat ocular damage, injury, and disease, to slow the progress of ocular damage, injury, and disease in low doses, and to cure ocular damage, injury, and disease in higher doses and established that astaxanthin is

	converted into vitamin A in rat retina. Blood-based transport of astaxanthin into the rat retina in Ex.1010 is a **necessary and inherent result** just as it is in the '533 patent. The suppression of free radicals and free radical-induced damage, injury, and disease by astaxanthin in the rat retina in Ex.1010 is a **necessary and inherent result** just as it is in rat retina in the '533 patent. In short, if there was xerophthalmia, there was already major retinal damage from free radicals, and the method disclosed in Ex.1010 put astaxanthin into the rat retina, necessarily "treating" free radical retinal damage, injury, or disease of whatever origin (photic, ischemic, inflammatory, degeneration from stroke or trauma, ocular pressure-related, etc.) and in all tissuesinto which astaxanthin is transported. Therefore, Ex.1010 anticipates every element in all independent claims (except claim 27) and most dependent claims of the '533 patent. Claims 25 and 27, which are directed to the brain or spinal cord, are scientifically in error, as explained above; astaxanthin does not accumulate in the brain or spinal cord. A therapeutically effective amount of a bioactive agent is essentially an amount that achieves the intended therapeutic effect when administered. A therapeutically effective amount is determined by dose/response experiments. Ex.1010 shows that the therapeutically effective amount of astaxanthin require to treat ocular disease is a fraction of the amount administered in the '533 patent. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this

	experiment, 2.1µg is equal to 0.066 mg/kg of body wt].”); 1856:1-2 (“Thus, in the experimental conditions described, ***in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**”);
Claim 3. The method of claim 1 wherein the astaxanthin is administered **orally**.	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Ex.1010 expressly discloses oral administration of astaxanthin(as a dietary supplement). Therefore, Ex.1010 anticipates every element in claim 3. §102: EXHIBIT 1010. 1855:12-14 (“**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt].”);
Claim 8. The method of claim 1 wherein the retinal damage comprises **free radical-induced** retinal damage.	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Moreover, *any* administration of astaxanthin (other than topical) results in blood-based transport of astaxanthin to the retina. Astaxanthin’s inherent mode of action in vertebrate tissue, including the retina, is suppression of free radicals and free radical-induced retinal damage. “Treating” of free radical-induced retinal damage necessarily occurs by administration of astaxanthin in Ex.1010. Therefore, Ex.1010anticipates every element in claim 8. CYAN EX. 1010. 1854:15-17 (“**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**”); 1854:23 (“ability, **in the eye**, of **converting astaxanthin into vitamin A**”); 1855:12-14 (“**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt].”); 1856:1-2

	("Thus, in the experimental conditions described, ***in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 9. The method of claim 1 wherein the retinal damagecomprises **light-induced** retinal damage.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult) retinal damage in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as light-induced peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radicalretinal damage. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 9. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Claim 10. The method of claim 1 wherein the retinal damage comprises **photoreceptor cell retinal damage** or **damage to neurons of inner retinal layers.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Photoreceptor cells and neurons of the inner retinal layer are layers in the retina serviced by the retinal capillary network. Damage of the photoreceptor cells and neurons of the inner retinal layer in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radicaldamage to photoreceptor cells or neurons of inner retinal layers. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 10. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1above.
Claim 11. The method	**Summary.** The Summary and prior description/citations

of claim 1 wherein the retinal damage comprises **ganglion cell retinal damage.**	regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Retinal ganglion cells are near the inner surface of the retina and are serviced by the retinal capillary network. Damage of the ganglion cells in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage of retinal ganglion cells. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 11. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 12: The method of claim 1 wherein the retinal damage comprises **age-related macular degeneration.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored

	by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 12. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); Note: The rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for human retina.

Claim 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.**	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. The only cause of retinal injury disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. Any administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue is suppression of free radicals. If astaxanthin is in the retina, it inherently suppresses free radicals, and thereby protects neurons in a retina from free radical-induced retinal injury. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 13. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 14. A method of treating an individual suffering from neuronal damage to a retina comprising	**Summary**: The Summary and prior description/citations regarding claims 1 and 13 in this Chart are incorporated in this cell by reference. The only cause of neuronal damage to a retina disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. Any administration of astaxanthin (other than

administering a therapeutically-effective amount of astaxanthin to the individual **to improve the condition of the retina.**	topical) results in (i) transport of astaxanthin by blood to the retina, (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage to neurons in the retina, and (iii) support for visual phototransduction (astaxanthin is converted into vitamin A in the rat retina; vitamin A is essential for visual phototransduction). Administered astaxanthin thereby inherently improves the condition of the retina.Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 12. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 15. The method of claim 14 wherein the neuronal damage comprises **photic injury to the retina**, **ischemic insult** to the retina, or intraocular **pressure-related insult to the retina.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult), ischemic, and intraocular pressure-related retinal damage in the '533 patent are all caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin

	of free radicals, such as peroxyl, and singlet oxygen, and prevention of initial or further photic injury to the retina, ischemic insult to the retina, or intraocular pressure-related insult to the retina.Therefore, Ex.1010 anticipates every element in claim 15. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 16. A method of treating an individual suffering from age-related macular degeneration comprising administering a therapeutically-effective amount of astaxanthin to the individual to retard the progress of **age-related macular degeneration**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and

	singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 16. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); Note: The rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for human retina. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 17. A method of treating an individual suffering from an ischemic or intraocular pressure-related disease of a retina comprising	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Ischemic and intraocular pressure-related retinal disease in the '533 patent is caused by free radicals

administering a therapeutically-effective amount of astaxanthin to the individual to **improve thecondition of the retina and to prevent further damage to the retina.**	(e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, 1021 to treat anindividual suffering from an ischemic or intraocular pressure-related disease of a retina to improve the condition of the retina and to prevent further damage to the retina. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 17. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 18. The method of claim 17 wherein the ischemic retinal diseaseis selected from the group consisting of **diabetic retinopathy, cystoid macular**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause of ischemic retinal disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals; therefore, diabetic retinopathy,

edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma.	cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucomain the '533 patent are all caused by free radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and thereby to treat anindividual suffering diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 18. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 19. A method of treating an individual suffering from an **inflammatory disease of a retina** comprising administering a therapeutically effective	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause ofinflammatory disease of a retinadisclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. If astaxanthin is

amount of astaxanthin to the individual to **improve the condition of the retina** and to **prevent further damage to the retina.**	in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals,and thereby to treat anindividual suffering an inflammatory disease of a retina, improve the condition of the retina, and prevent further damage to the retina.Ex.1010 discloses administration of astaxanthin. The only damage disclosed in the '533 patent, whether from inflammation or other causes, is from free radical-induced damage.Therefore, Ex.1010 anticipates every element in claim 19. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 20. The method of claim 19 wherein the inflammatory disease is selected from the group consisting of **retinitis, uveitis, iritis, keratitis, and scleritis**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause ofinflammatory disease of a retinadisclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen,

	radicals,and thereby to treat anindividual suffering an inflammatory disease of a retina, such as retinitis, uveitis, iritis, keratitis, and scleritis.Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 20. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 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	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii)

system.	suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 21 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 21 other than the brain and spinal cord, since astaxanthin does not accumulate in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 22. The method of claim 21 wherein the central nervous system comprises **a brain, a**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals).

spinal cord and a retina.	If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 22 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 22 other than the brain and spinal cord, since astaxanthin does not accumulate in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A:**

	traces; lot B: 1 µg; lot C: 2.1 µg [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt].”); 1856:1-2 (“Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**”);
Claim 23. The method of claim 22 wherein the free radical-induced injury comprises a **traumatic injury** or an **ischemic injury**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the ‘533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-inducedtraumatic or ischemic injury in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 23 of the ‘533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 23 other than the brain and spinal cord, since astaxanthin does not accumulate in the brain or

	spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 24. The method of claim 23 wherein the ischemic injury comprises a **stroke**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-inducedstroke in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on

	p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 24 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 24 other than the brain or spinal cord, since astaxanthin does not accumulate in the brain. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 25. The method of claim 23 wherein the traumatic injury comprises **a spinal cord injury.**	**Summary.**Ex. 1010 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 25 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord.

	The Summary and prior description/citations regarding claims 1 and 21-24 in this Chart are incorporated in this cell by reference. Administered astaxanthin in Ex. 1010 would have treated a spinal cord injury if astaxanthin accumulated in the spinal cord, which is does not. Therefore, Ex. 1010 anticipates claim 25. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**").
Claim 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.**	**Summary**: The Summary and prior description/citations regarding claims 1, 13, 14 and 19 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, and (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage, injury, and degenerative retinal disease. Administered astaxanthin thereby inherently retards the progress of degenerative retinal disease by suppression of free radicals.The only retinal disease disclosed in the '533 patent, whether degenerative or not, is from free radical-induced damage. Ex.1010 discloses administration of astaxanthin. Therefore, Ex.1010 anticipates every element in claim 26. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene)

	manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 27. A method of treating an individual suffering from a **degenerative central nervous system disease of a brain or spinal cord,** said method comprising administering a therapeutically effective amount of astaxanthin to the individual to retard the progress of the disease.	**Summary.**Ex. 1010 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 27 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord. The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Administered astaxanthin in Ex. 1010 would have treated degenerative central nervous system disease of a brain or spinal cord if astaxanthin accumulated in the brain or spinal cord, which is does not. Therefore, Ex. 1010 anticipates claim 27. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin**

	into vitamin A"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Grounds of Invalidity for Challenged Claims 1, 3, 8-27based on anticipation by Massonet (1961b) (Ex. 1010) as a Primary Reference

83. I have reviewed and understand Massonet (1961b) (Ex. 1010) and Grangaud (1954) (Ex. 1014). In my opinion, a person of ordinary skill in the art would find Exs. 1014 and 1010 each to be an enabling disclosure of the subject matter it discusses.
84. The treatment, improvement, or cure of all diseases, injuries, or conditions disclosed in the '533 patent depends solely on the presence of astaxanthin in a given tissue in a therapeutically effective amount. "The pathogenesis of photic injury, of age-related macular degeneration, of ischemia/reperfusion damage, of traumatic injury and of inflammations of the eye and central nervous system have been attributed to singlet oxygen and free radical generation, and subsequent free radical-initiated reactions." (Ex. 1001 3:23-31). Claims 1-27 all survive or fall on the premise that astaxanthin, as a strong antioxidant, by its mere presence in a tissue, treats free-radical induced damage, injury, or disease.
85. The only active ingredient administered in the '533 patent was astaxanthin, and the only action of astaxanthin disclosed in the '533 patent was its antioxidant action, i.e., suppression of free radicals and free radical-induced damage.
86. As I explained in paragraphs 24-46 above, whether retinal degeneration arises from vitamin A deficiency or from photic insultor reperfusion following ischemia or high intraocular pressure, the biochemical, histological, and pathological mechanism is the same: if the photoreceptor cell membranes (particularly the rod outer segments) are exposed to light

energy without adequate free radical scavenging, the result is a free radical barrage of peroxidized fatty acids and singlet oxygen that cause retinal degeneration and reduction of ONL, IRT, and rhodopsin levels.

87. Even in rats with normal vitamin A levels, intense photic energy or reperfusion (after ischemia or high intraocular pressure) depletes all available free radical scavengers, thereby enabling peroxidation of lipids in the photoreceptor membranes, which unleashes a free radical barrage and resultant damage, injury, and disease.

88. Vitamin A deficiency inherently produces the same types of retinal damage and injury that the experiments in the '533 patent produced. Grangaud (Ex. 1014) and Massonet (Ex. 1010) each administered to vitamin A-deficient rats astaxanthin to prevent, and to treat, one type of eye damage and injury (xerophthalmia) caused by vitamin A deficiency but **necessarily (inherently) treated** other types of eye damage and injury caused by vitamin A deficiency, including the free radical-induced damage and injury that the experiments in the '533 patent produced.

89. If astaxanthin is in the retina (preferentially transported into the retina from the bloodstream), a necessary and inherent result is (i) suppression by astaxanthin of free radicals, such as peroxyl radicals, especially peroxidized PUFAs, (ii) prevention of initial or further free radical damage and injury(including reduction of ONL, IRT, and rhodopsin levels), and (iii) prevention of resultant free radical-induced disease.

90. The rats in Ex. 1014 (Grangaud) and in Ex. 1010 (Massonet) suffered from retinal damage, injury, and disease induced by free radicals and chronic vitamin A deficiency, including the same free radical-induced retinal degeneration disclosed in the '533 patent and in Dowling (1960) (Ex. 1026). The rats in the '533 patent suffered from retinal damage, injury, and disease induced by free radicals following photic insult or reperfusion (after retinal ischemia or high intraocular pressure), but the retinal degeneration in the '533 patent arose from inadequate free radical scavenging, just as in Exs.1010, 1014, and 1026.

91. In 1958, Dowling et al. wrote: PNAS 1958, p.656-657 (Ex. 1024):

"Our supposition that, when opsin goes, **the outer segments of the rods should deteriorate structurally has proved to be correct.** By this time, however, the animal is deteriorating generally. Not only are other retinal tissues affected as just described, but the superficial structures of the eye now begin to display the classic signs of vitamin A deficiency:

corneal clouding, **xerophthalmia**, and secretion of a sticky red exudate about the eyes." (emphasis added)

92. Inspection of Figs. 2, 13, and 15 of Ex. 1025 (Dowling and Wald, 1960) and Figs. 2 and 10 of Ex. 1026 (Dowling and Gibbons, 1961) shows that the degeneration of the retina of a vitamin A deficient rat to be far more severe than the retinal degeneration reported in the '533 patent (see Figs. 1-2 and 4 of the '533 patent).
93. Figs. 1 and 4 of the '533 patent report a maximum ONL reduction (Fig. 1, temporal quadrant) of about 38% and an average ONL reduction of about 23% (Fig. 1, rightmost column) and about 17% (Fig. 4). Based on measurements of the ONL, as defined in the '533 patent, measurement of the ONL in Figs. 2, 13, and 15 of Ex. 1025 (Dowling and Wald, 1960) and Figs. 2 and 10 of Ex. 1026 (Dowling and Gibbons, 1961) shows reduction of the ONL of over 75%.
94. Fig. 2 of the '533 patent reports an average IRT reduction of about 12%. Based on measurement of the IRT, as defined in the '533 patent, measurement of the IRT in Figs. 2, 13, and 15 of Ex. 1025 (Dowling and Wald, 1960) and Figs. 2 and 10 of Ex. 1026 (Dowling and Gibbons, 1961) shows reduction of the IRT of over 30%.
95. Fig. 3 of the '533 patent reports a rhodopsin reduction of about 38% (at 6 days after insult). Fig. 9 of Ex. 1025 (Dowling and Wald, 1960) reports a rhodopsin reduction of up to 99% (PNAS 1960. p.588, penultimate para. "Rhodopsin could be extracted from the retinas of animals in this [vitamin A deficient] condition in only 1-5 percent of normal amounts."). Dowling et al. report a rhodopsin loss of 96% to 98% in Ex. 1026, 1:28-30. (Dowling and Gibbons, 1961).
96. The suppression of free radicals and free radical-induced damage, injury, and disease by administration of astaxanthin in the rat retina in each of Ex. 1010and Ex. 1014 is a necessary and inherent result just as it is in rat retina in the '533 patent. In short, if there was xerophthalmia, there was already major retinal damage (degeneration) from free radicals, and the method disclosed in each of Ex. 1010and Ex. 1014 put astaxanthin into the rat retina, necessarily "treating" free radical retinal damage of whatever origin.
97. As far as a therapeutically effective dose, Exhibit 1010and Ex. 1014 each establishes that a dose of slightly less than 1mg , up to 2 mg, of astaxanthin per kg of body mass was therapeutically effective in prevention and treatment of ocular disease and injury, and by

extension, of free-radical induced disease or injury in tissues into which astaxanthin is transported.

98. Therefore, Grangaud, and Massonet, by administration of astaxanthin, treated and cured far worse free radical-induced retinal degeneration than that reported in the '533 patent, using far lower doses of astaxanthin.

99. Given that oral administration of astaxanthin necessarily results in suppression of free radicals in the retina, and that claims of the '533 patent each recite variations of "administrating astaxanthin to suppress free radicals and free radical-induced damage and injury", Ex. 1010and Ex. 1014 *each* expressly discloses at least claims 1, 3, 8-27 of the '533 patent.

GROUND 2. '533 PATENT CLAIMS OBVIOUS OVER CYAN EXHIBIT 1010 (Massonet 1961b) IN VIEW OF CYAN EXHIBIT 1021 (USPAT 5,310,764) OR CYAN EXHIBIT 1026 (DOWLING ET AL. 1961). '533 claim language in left column and prior art Description and my comments in right column.	
Claim 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	Irradiating the retina with bright light, or other oxidative stress, such as reperfusion, creates peroxyl, singlet oxygen, and other free radicals(Zigler, 1985; Goto, 1991). Grangaud (Ex. 1002) discovered and published that dietary astaxanthin was transported into the retina and cured xerophthalmia when administered to vitamin A-deficient rats. The only cause of retinal damage, injury, or disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. *Any* administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Retinal tissue contains binding proteins that preferentially transport *xanthophyll* carotenoids, like lutein, zeaxanthin, canthaxanthin, and astaxanthin, from the retinal capillary network into retinal tissue, but disfavor transport into retinal tissue of *carotene* carotenoids like β-carotene. Astaxanthin is

improve the vision of the individual.	transported in the bloodstream, and from the bloodstream into the retina, by specialized "binding proteins". Suppression of free radicals **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light or other oxidative stress. Astaxanthin's inherent mode of action in vertebrate tissue, including retinal tissue, is as a strong antioxidant. Suppression of free radicals, such as peroxyl and singlet oxygen radicals, and free radical-induced damage **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light. Xerophthalmia ("dry eye disease")is *secondary* to retinal damage, injury, and disease (Massonet, (1951); Massonet (1960); Dowling (1958); in other words, photoreceptor cell membrane attack by a barrage of free radicals, photoreceptor cell degeneration, and reduction of the ONL, IRT, and rhodopsin levels occur first, then xerophthalmia manifests at a later stage in the cornea and surrounding areas. Rats and other vertebrates become diseased, go blind, and die from continued vitamin A deficiency. Infliction of vitamin A deficiency is an injury and causes retinal, corneal, and other injury and diseases (Dowling (1958); Dowling (1960); Dowling (1961)). The free radical-induced damage from photic insult or reperfusion following retinal ischemia or high intraocular pressurein the '533 patent causes the same free radical-induced damage as caused by severe vitamin A deficiency in Ex.1010. If astaxanthin is in the retina (preferentially transported into the retina from the bloodstream), a **necessary and inherent result** is (i) suppression by astaxanthin of free radicals, such as peroxyl and singlet oxygen radicals, (ii) prevention of initial or further free radical damage and injury, and (iii) prevention of resultant free radical-induced disease. The rats in the '533 patent, Ex.1010, and Ex. 1026 (Dowling 1961) suffered from retinal damage and injuryinduced by free radicals (no disease was reported in the data of the '533 patent). Massonet, in Ex.1010, administered astaxanthin to treat ocular

	damage, injury, and disease, to slow the progress of ocular damage, injury, and disease in low doses, and to cure ocular damage, injury, and disease in higher doses. Blood-based transport of astaxanthin into the rat retina in Ex.1010 is a **necessary and inherent result** just as it is in the '533 patent. The suppression of free radicals and free radical-induced damage, injury, and disease by astaxanthin in the rat retina in Ex.1010 is a **necessary and inherent result** just as it is in rat retina in the '533 patent. In short, if there was xerophthalmia, there was already major retinal damage from free radicals, and the method disclosed in Ex.1010 put astaxanthin into the rat retina, necessarily "treating" free radical retinal damage, injury, or disease of whatever origin (photic, ischemic, inflammatory, degeneration from stroke or trauma, ocular pressure-related, etc.) and in all tissues into which astaxanthin is transported. Ex.1010 discloses administration of astaxanthin to treat ocular damage, injury, and disease. Ex. 1026 discloses administration of vitamin A to treat retinal damage, injury, and disease, and Ex. 1021 discloses administration of β-carotene to treat retinal damage, injury, and disease. Astaxanthin and vitamin A were known to POSA as an effective retinal antioxidants,and astaxanthin and vitamin A were known accumulate in the retina; it would have been obvious to POSA to substitute astaxanthin for β-carotene in the method of Ex. 1021 or to substitute astaxanthin for vitamin A in the method of Ex. 1026.Therefore, claim 1 is obvious over Ex.1010in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg

	of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:9-10, 3:12-17, and 5:48-54 ("the major carotenoids in the retina were lutea and zeaxanthin, use of retinal carotenoids to confer antioxidant protection. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a mediator of light damage in the retina *** by increasing the availability of carotinoids [*sic*] … to the retinal pigment epithelium, function can be normalized."); 4:27-29 and 6:20-23 ("administration of appropriate amounts of beta-carotene can successfully treat ARMD [age-related macular degeneration] *** Therapeutically effective amounts of beta-carotene are those amounts sufficient to stabilize the progression of the disease or to resolve the symptoms of ARMD". CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). Figures show prevention and cure of retinal degeneration by administration of vitamin A in different groups.
Claim 2. The method of claim 1 wherein the astaxanthin is administered **parenterally**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. "Systemic administration" includes oral, parenteral, intravenous, and other routes of administration of a composition to treat a subject's disease or injury. Parenteral administration is administration of a composition to a subject's body other than in the mouth and alimentary canal, i.e., by injection or placement of a composition in a subject. Baranowitz (Ex. 1021) systemically administered an antioxidant carotenoid, β-carotene, to prevent and treat a retinal disease, age-related macular degeneration ("AMD"), through by β-carotene's suppression of free radicals and of free radical-induced damage, injury, and disease. The base reference (Ex. 1010) discloses only oral (dietary) administration of astaxanthin, but Ex. 1021 discloses systemic administration, curing the possible deficiency in claim 2. Oral and parenteral administration is well known to POSA, and the choice

	of parenteral instead of oral would have been obvious to POSA. Therefore, claim 2 is obvious over Ex.1010in view of Ex. 1021. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); EXHIBIT 1021, 5:55-56 ("In all of the embodiments of the present invention, β-carotene is preferably **administered systemically**.")
Claim 3. The method of claim 1 wherein the astaxanthin is administered **orally**.	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Ex.1010 discloses oral administration of astaxanthin (as a dietary supplement), Ex. 1026 discloses oral administration of vitamin A, and Ex. 1021 discloses oral administration of a different anti-oxidant,β-carotene (as a dietary supplement) to treat ocular damage, injury, and disease. Therefore, claim 3 is obvious over Ex.1010 in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**,**

	in vivoas well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX.1021,5:57-58 ("Systemic administration most preferably is by the **oral route**."). CYAN EX.1026, 86 (last sentence on page). ("Groups of albino, weanling rats were raised on Standard D.S.P.vitamin A-test diets supplemented orally with 50 µg/day of vitamin A acid, dissolved in vegetable oil.")
Claim 4. The method of claim 1 wherein the astaxanthin is administered **topically directly to the eye**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. The pigmented, residual oil prepared by Massonet was mixed with rat feed, but it could just as easily been applied topically, e.g., to rat cornea, to treat the corneal lesions. The base reference (Ex. 1010) discloses a preparation of astaxanthin, and Ex. 1026 discloses oral administration of vitamin A acid dissolved in oil. Topical administration is well known to POSA, particularly for ophthalmic administration of a composition. The choice of topical instead of oral would have been obvious to POSA as of the filing date of the '533 patent. Therefore, claim 4 is obvious over Ex.1010in view of Ex. 1021. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a dccidcdly antixcrophthalmic activity. In fact, thc daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX.1026, 86 (last sentence on page). ("Groups of albino,

	weanling rats were raised on Standard D.S.P.vitamin A-test diets supplemented orally with 50 µg/day of vitamin A acid, dissolved in vegetable oil.")
Claim 5. The method of claim 1 wherein the astaxanthin is administered in the amount of about **5 to about 500 milligrams per kilogram** of body weight.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Although the doses administered in Exhibit 1010(0.066 mg/kg) and in Exhibit 1021 (.063mg/kg to 4.4mg/kg) were a fraction of the doses disclosed in the '533 patent (5mg/kg to 500 mg/kg), the doses disclosed in Exhibits 1010, 0121, and 1026(5mg/kg of vit. A) were therapeutically effective, e.g., the lower doses in Ex. 1010 healed ocular lesions and the higher doses healed ocular lesions and restored normal growth, and the doses in Ex. 1026 healed retinal degeneration. If a lower dose of astaxanthin is therapeutically effective, it would have been obvious to POSA that a higher dose of astaxanthin would be effective. Therefore, claim 5 is obvious over Ex.1010in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021. 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient **to stabilize the progression of the**

	disease or to resolve the symptoms"; 6:30-33 and 8:10-12 ("Typically for a human being, that amount will be **at least about 50 mg/day** [.0625mg/kg in an 80 kg human] of β-carotene. Most preferably, that amount will range from about **60 mg/day to about 350 mg/day** [.063mg/kg to 4.4mg/kg in an 80 kg human] *** The patient was placed on a regimen of **180 mg/day** [2.25mg/kg in an 80 kg human] of β-carotene."). CYAN EX. 1026, 94:15-19 ("The control animal was fed vitamin Athroughout the experiment, while the other two animals were fed vitaminA acid. The recovery animal was fed a large dose of vitamin A (500 μg)and then periodically fed further vitamin A for 16 days.") 500 μg of vitamin A/day/100g rat = 5mg/kg/day; 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 6. The method of claim 1 wherein the astaxanthin is administered in the amount of about **10 to about 200 milligrams per kilogram** of body weight.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Although the doses administered in Exhibit 1010(0.066 mg/kg) and in Exhibit 1021 (.063mg/kg to 4.4mg/kg) were a fraction of the doses disclosed in the '533 patent (5mg/kg to 500 mg/kg), the doses disclosed in Exhibits 1010, 0121, and 1026(5mg/kg of vit. A) were therapeutically effective, e.g., the lower doses in Ex. 1010 healed ocular lesions and the higher doses healed ocular lesions and restored normal growth, and the doses in Ex. 1026 healed retinal degeneration.If a lower dose of astaxanthin is therapeutically effective, it would have been obvious to POSA that a higher dose of astaxanthin would be effective. Therefore, claim 6 is obvious over Ex.1010in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 μg of pigment heals ocular lesions rapidly**"); 1854:23

	("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021. 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient **to stabilize the progression of the disease or to resolve the symptoms**"; 6:30-33 and 8:10-12 ("Typically for a human being, that amount will be **at least about 50 mg/day** [.0625mg/kg in an 80 kg human] of β-carotene. Most preferably, that amount will range from about **60 mg/day to about 350 mg/day** [.063mg/kg to 4.4mg/kg in an 80 kg human] *** The patient was placed on a regimen of **180 mg/day**[2.25mg/kg in an 80 kg human] of β-carotene.") CYAN EX. 1026, 94:15-19 ("The control animal was fed vitamin Athroughout the experiment, while the other two animals were fed vitaminA acid. The recovery animal was fed a large dose of vitamin A (500 µg)and then periodically fed further vitamin A for 16 days.") 500 µg of vitamin A/day/100g rat = 5mg/kg/day; 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 7. The method of claim 1 wherein the astaxanthin is administered in the amount of about **25 to about 150 milligrams per kilogram** of body weight.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Although the doses administered in Exhibit 1010(0.066 mg/kg) and in Exhibit 1021 (.063mg/kg to 4.4mg/kg) were a fraction of the doses disclosed in the '533 patent (5mg/kg to 500 mg/kg), the doses disclosed in Exhibits 1010, 0121, and 1026(5mg/kg of vit. A) were therapeutically effective, e.g., the lower doses in Ex. 1010 healed ocular lesions and the higher doses healed ocular lesions and restored normal growth, and the doses in Ex. 1026 healed retinal degeneration.If a lower dose of astaxanthin is therapeutically effective, it would have been obvious to POSA that a higher dose of astaxanthin would

	be effective. Therefore, claim 7 is obvious over Ex.1010in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021. 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient **to stabilize the progression of the disease or to resolve the symptoms**"; 6:30-33 and 8:10-12 ("Typically for a human being, that amount will be **at least about 50 mg/day** [.0625mg/kg in an 80 kg human] of β-carotene. Most preferably, that amount will range from about **60 mg/day to about 350 mg/day** [.063mg/kg to 4.4mg/kg in an 80 kg human] *** The patient was placed on a regimen of **180 mg/day** [2.25mg/kg in an 80 kg human] of β-carotene.") CYAN EX. 1026, 94:15-19 ("The control animal was fed vitamin Athroughout the experiment, while the other two animals were fed vitaminA acid. The recovery animal was fed a large dose of vitamin A (500 µg)and then periodically fed further vitamin A for 16 days.") 500 µg of vitamin A/day/100g rat = 5mg/kg/day; 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 8. The	**Summary**: The Summary and prior description/citations regarding

method of claim 1 wherein the retinal damage comprises **free radical-induced** retinal damage.	claim 1 in this Chart are incorporated in this cell by reference. Moreover, *any* administration of astaxanthin (other than topical) results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue, including the retina, is suppression of free radicals and free radical-induced retinal damage. Ex.1010 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. One form of vitamin A administered in Ex. 1026 is an antioxidant (retinol), with an inherent mode of action in vertebrate tissue, including the retina, of suppression of free radicals and free radical-induced retinal damage. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage.Vitamin A was known to POSA as an effective retinal antioxidant,and astaxanthin was known accumulate in the retina; it would have been obvious to POSA to substitute astaxanthin for vitamin A. Therefore, claim 8 is obvious over Ex.1010 in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal

	pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1.
Claim 9. The method of claim 1 wherein the retinal damagecomprises **light-induced** retinal damage.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult) retinal damage in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as light-induced peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease. Ex.1010 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by light energy ("light-induced retinal damage"). Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat light-induced retinal damage. Therefore, claim 9 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a**

	decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 10. The method of claim 1 wherein the retinal damage comprises **photoreceptor cell retinal damage** or **damage to neurons of inner retinal layers.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Photoreceptor cells and neurons of the inner retinal layer are layers in the retina serviced by the retinal capillary network. Damage of the photoreceptor cells and neurons of the inner retinal layer in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage to photoreceptor cells or neurons of inner retinal layers. Ex.1010 discloses administration of astaxanthin and Ex. 1026 discloses

	administration of vitamin A to treat ocular injury and disease. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, in particular in the RPE [retinal pigment epithelium] and photoreceptor cells. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat retinal damage comprising photoreceptor cell retinal damage or damage to neurons of inner retinal layers. Therefore, claim 10 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 2:37-40 ("Vision loss can occur when **RPE** [retinal pigment epithelium] **and photoreceptor cells** over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing

	the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 11. The method of claim 1 wherein the retinal damage comprises **ganglion cell retinal damage.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Retinal ganglion cells are near the inner surface of the retina and are serviced by the retinal capillary network. Damage of the ganglion cells in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical-induced damage of retinal ganglion cells. Ex.1010 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex. 1021, 5:49-51) retinal damage caused by free radicals, such as ganglion cell damage. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ganglion cells damage. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration**

	of 10 to 15 µg of pigment heals ocular lesions rapidly"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 12: The method of claim 1 wherein the retinal damage comprises **age-related macular degeneration.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and

	injury, and resultant free radical-induced disease, such as ARMD. Ex.1010 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. The primary focus of Ex. 1021 is prevention and treatment of ARMD by administration of the carotenoid β-carotene. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ARMD. Therefore, claim 12 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain"); 3:12-17 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective

	agents against highly reactive singlet oxygen"); 4:27-29 ("administration of appropriate amounts of β-carotene **can successfully treat ARMD**"); 5:49-51 ("by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."); 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient to stabilize the progression of the disease or **to resolve the symptoms of ARMD**"; 9:30-31(" **the successful treatment of ARMD due to β-carotene administration")**. Note: The rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for human retina.
Claim 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.**	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. The only cause of retinal injury disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. Any administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue is suppression of free radicals. If astaxanthin is in the retina, it inherently suppresses free radicals, and thereby protects neurons in a retina from free radical-induced retinal injury.Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. The prevention and treatment of ARMD protect the neurons of the retina. Ex. 1021 discloses that (i) carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen, and (ii) the administration of β-carotene to protect the retina of the individual from free radical-induced retinal injury. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to useastaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not

	preferentially transported into the retina, in the method of Ex. 1021 toprotect neurons in a retina of the individual from free radical-induced retinal injury. Therefore, claim 14 is obvious over Ex.1010 in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Claim 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.**	**Summary**: The Summary and prior description/citations regarding claims 1 and 13 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage to neurons in the retina, and (iii) support for visual phototransduction (astaxanthin is converted into vitamin A in the rat retina; vitamin A is essential for visual phototransduction). Administered astaxanthin thereby inherently improves the condition of the retina.Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. The prevention and treatment of ARMD is an improvement of the condition of the retina. Ex. 1021 discloses that (i) carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen, and (ii) the administration of β-carotene to improve the condition of the retina (by treating ARMD, a retinal disease). Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to useastaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 toprotect neurons in a retina of the individual from free radical-induced retinal injury. Therefore, claim 14 is obvious over Ex.1010 in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg

	of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 15. The method of claim 14 wherein the neuronal damage comprises **photic injury to the retina**, **ischemic insult** to the retina, or intraocular **pressure-related insult to the retina.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult), ischemic, and intraocular pressure-related retinal damage in the '533 patent are all caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and prevention of initial or further photic injury to the retina, ischemic insult to the retina, or intraocular pressure-related insult to the retina.Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by light energy or other free radical action (e.g., by ischemia or intraocular pressure). Accordingly,

	it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat light-induced, ischemic, and intraocular pressure-related retinal damage. Therefore, claim 15 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 16. A method of treating an individual	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and

suffering from age-related macular degeneration comprising administering a therapeutically-effective amount of astaxanthin to the individual to retard the progress of **age-related macular degeneration**.	disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. The primary focus of Ex. 1021 is prevention and treatment of ARMD by administration of the carotenoid β-carotene. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ARMD. Therefore, claim 16 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**");

	1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17 ("use of **retinal carotenoids to confer antioxidant protection**"). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 17. A method of treating an individual suffering from an ischemic or intraocular pressure-related disease of a retina comprising administering a therapeutically-effective amount of astaxanthin to the individual to **improve thecondition of the retina and to prevent further damage to the retina.**	**Summary.Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Ischemic and intraocular pressure-related retinal disease in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, thereby treating anindividual suffering from an ischemic or intraocular pressure-related disease of a retina to improve the condition of the retina and to prevent further damage to the retina. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by light energy or other free radical action (e.g., by ischemia or intraocular pressure). Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat anindividual suffering from an ischemic or intraocular pressure-related disease of a retina to improve the

	condition of the retina and to prevent further damage to the retina. Therefore, claim 17 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 18. The method of claim 17 wherein the ischemic retinal diseaseis selected from the group consisting of	**Summary** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause of ischemic retinal disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals; therefore, diabetic retinopathy, cystoid macular edema, central retinal arterial

diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma.	occlusion, central retinal venous occlusion, and glaucomain the '533 patent are all caused by free radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and thereby treating anindividual suffering diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage or disease, such as that caused by ischemia. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ischemic retinal disease, such as diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Therefore, claim 18 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the**

	eye can only be due to astaxanthin transformation."); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 19. A method of treating an individual suffering from an **inflammatory disease of a retina** comprising administering a therapeutically effective amount of astaxanthin to the individual to **improve the condition of the retina** and to **prevent further damage to the retina.**	**Summary**: The Summary and prior description/citations regarding claims 1, 13 and 14 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, (ii) suppression by astaxanthin of free radicals in the retina and of free radical-inducedinflammation and inflammatory disease, and (iii) support for visual phototransduction (astaxanthin is converted into vitamin A in the rat retina; vitamin A is essential for visual phototransduction). The only damage disclosed in the '533 patent, whether from inflammation or other causes, is from free radical-induced damage.Administered astaxanthin thereby inherently treats free radical-induced inflammatory disease, improves the condition of the retina, and prevents further damage to the retina.Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage or disease, such as that caused by ischemia. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat inflammatory retinal disease, such as diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion,

	central retinal venous occlusion, and glaucoma. Therefore, claim 19 is obvious over Ex.1010 in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 20. The method of claim 19 wherein the inflammatory disease is selected from the group consisting of **retinitis, uveitis,**	**Summary.** The Summary and prior description/citations regarding claim 1 and 19 in this Chart are incorporated in this cell by reference. Inflammatory disease of the retina in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage, such as that caused by inflammatory disease.

iritis, keratitis, and scleritis.	Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat inflammatory disease of the retina, such as retinitis, uveitis, iritis, keratitis, and scleritis. Therefore, claim 20 is obvious over Ex.1010 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).

Claim 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.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treat free radical-induced injury to treat free radical-induced injury of the retina. Therefore, claim 21 is obvious over Ex.1010 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not* present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 21 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord.

	For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 22. The method of claim 21 wherein the central nervous system comprises **a brain, a spinal cord and a retina**.	**Summary.** The Summary and prior description/citations regarding claims 1 and 21 in this Chart are incorporated in this cell by reference. Injury of the central nervous system, including the brain, spinal cord, and retina in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **nccessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1010discloses accumulation of astaxanthin in rat retina, and Ex.1026 discloses

	accumulation of vitamin A in rat retina, but neither addresses the brain or spinal cord. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treat free radical-induced injury to the retina. Therefore, claim 22 is obvious over Ex.1010 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 22 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");

	CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 23. The method of claim 22 wherein the free radical-induced injury comprises a **traumatic injury** or an **ischemic injury**.	**Summary.** The Summary and prior description/citations regarding claims 1 and 21 in this Chart are incorporated in this cell by reference. Traumatic or ischemic injury of the central nervous system, including the brain, spinal cord, and retina in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treat free radical-induced traumatic or ischemic injury of the retina. Therefore, claim 23 is obvious over Ex.1010 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or

	spinal cord, it cannot be chemically active. Therefore, claim 23 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 24. The method of claim 23 wherein the ischemic injury comprises a **stroke**.	**Summary.** The Summary and prior description/citations regarding claims 1 and 21 in this Chart are incorporated in this cell by reference. A stroke in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the brain. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by

	blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treata free radical-induced stroke other than in brain or spinal cord tissue. Therefore, claim 24 is obvious over Ex.1010 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 24 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described,

	in vivoas well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 25. The method of claim 23 wherein the traumatic injury comprises **a spinal cord injury.**	**Summary.**Ex. 1010 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 25 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord. The Summary and prior description/citations regarding claims 1 and 21-24 in this Chart are incorporated in this cell by reference. It would have been obvious at the time of the invention to have tried to treat a spinal cord injury with astaxanthin. Therefore, Ex. 1010 renders claim 25 obvious. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**");
Claim 26. A method of treating an individual	**Summary**: The Summary and prior description/citations regarding claims 1, 13, 14 and 19 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical)

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.**	results in (i) transport of astaxanthin by blood to the retina, and (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage, injury, and degenerative retinal disease. Administered astaxanthin thereby inherently retards the progress of degenerative retinal disease by suppression of free radicals.The only retinal disease disclosed in the '533 patent, whether degenerative or not, is from free radical-induced damage. Ex.1010 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Therefore, claim 16 is obvious over Ex.1010 in view of Exs. 1021 or 1026. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described**, *in vivo*** as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 27. A method of treating an individual suffering from a **degenerative central nervous**	**Summary.**Ex. 1010 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 27 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous

system disease of a brain or spinal cord, said method comprising administering a therapeutically effective amount of astaxanthin to the individual to retard the progress of the disease.	regarding the activity of astaxanthin in the brain or spinal cord. The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. It would have been obvious at the time of the invention to have tried to treat a degenerative central nervous system disease of a brain or spinal cord with astaxanthin. Therefore, Ex. 1010 renders claim 27 obvious. CYAN EX. 1010. 1854:15-17 ("**In vitamin A deficient albino rats, astaxanthin** (3,3'-dihydroxy-4,4'-diketo-β-carotene) **manifests a decidedly antixerophthalmic activity. In fact, the daily administration of 10 to 15 µg of pigment heals ocular lesions rapidly**"); 1854:23 ("ability, **in the eye**, of **converting astaxanthin into vitamin A**"); 1855:12-14 ("**the animals** were divided into 3 lots which **received the following daily doses [of astaxanthin]: Lot A: traces; lot B: 1 µg; lot C: 2.1 µg** [in a 32g rat used in this experiment, 2.1µg is equal to 0.066 mg/kg of body wt]."); 1856:1-2 ("Thus, in the experimental conditions described, ***in vivo***as well as for *in vitro*, **neoformed and detected vitamin A in the eye can only be due to astaxanthin transformation.**"); For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Grounds of Invalidity for Challenged Claims 1-27 as obvious over Massonet (Ex. 1010) in view or USPAT 5,527,533 (Ex. 1021) or Dowling (1961) (Ex. 1025)

100. I have reviewed and understand Massonet (1961b) (Ex. 1010) and Grangaud (1954) (Ex. 1014). In my opinion, a person of ordinary skill in the art would find Exs. 1014 and 1010 each to be an enabling disclosure of the subject matter it discusses.In my opinion, a person of ordinary skill in the art would find Grangaud (Ex. 1014), Massonet (Ex. 1010), USPAT 5,527,533 (Ex. 1021), Dowling (1961) (Ex. 1026) each to be an enabling disclosure of the subject matter each discusses.

101. The treatment, improvement, or cure of all diseases, injuries, or conditions disclosed in the '533 patent depends solely on the presence of astaxanthin in a given tissue in a

therapeutically effective amount. Claims 1-27 all survive or fall on the premise that astaxanthin, as a strong antioxidant, by its mere presence in a tissue, treats free-radical induced damage, injury, or disease.

102. The only active ingredient administered in the '533 patent was astaxanthin, and the only action of astaxanthin disclosed in the '533 patent was its antioxidant action, i.e., suppression of free radicals and free radical-induced damage.

103. As I explained in paragraphs 24-46 above, whether retinal degeneration arises from vitamin A deficiency or from photic insultor reperfusion following ischemia or high intraocular pressure, the biochemical, histological, and pathological mechanism is the same: if the photoreceptor cell membranes (particularly the rod outer segments) are exposed to light energy without adequate free radical scavenging, the result is a free radical barrage of peroxidized fatty acids and singlet oxygen that cause retinal degeneration and reduction of ONL, IRT, and rhodopsin levels.

104. Even in rats with normal vitamin A levels, intense photic energy or reperfusion (after ischemia or high intraocular pressure) depletes all available free radical scavengers, thereby enabling peroxidation of lipids in the photoreceptor membranes, which unleashes a free radical barrage and resultant damage, injury, and disease.

105. Vitamin A deficiency inherently produces the same types of retinal damage and injury that the experiments in the '533 patent produced. Grangaud (Ex. 1014) and Massonet (Ex. 1014) each administered to vitamin A-deficient rats astaxanthin to prevent, and to treat, one type of eye damage and injury (xerophthalmia) caused by vitamin A deficiency but **necessarily (inherently) treated** other types of eye damage and injury caused by vitamin A deficiency, including the free radical-induced damage and injury that the experiments in the '533 patent produced.

106. If astaxanthin is in the retina (preferentially transported into the retina from the bloodstream), a necessary and inherent result is (i) suppression by astaxanthin of free radicals, such as peroxyl radicals, especially the formation of peroxidized PUFAs, (ii) prevention of initial or further free radical damage and injury, and (iii) prevention of resultant free radical-induced disease following the formation of peroxidized PUFAs.

107. The rats in Ex. 1014 (Grangaud) and in Ex. 1010 (Massonet) suffered from retinal damage, injury, and disease induced by free radicals and chronic vitamin A deficiency,

including the same free radical-induced retinal degeneration disclosed in the ‘533 patent and in Dowling (1960) (Ex. 1026). The rats in the '533 patent suffered from retinal damage, injury, and disease induced by free radicals following photic insult or reperfusion (after retinal ischemia or high intraocular pressure), but the retinal degeneration in the ‘533 patent arose from inadequate free radical scavenging, just as in Exs.1010, 1014, and 1026.

108. The suppression of free radicals and free radical-induced damage, injury, and disease by administration of astaxanthin in the rat retina in each of Ex. 1010and Ex. 1014 is a necessary and inherent result just as it is in rat retina in the ‘533 patent. In short, if there was xerophthalmia, there was already major retinal damage (degeneration) from free radicals, and the method disclosed in each of Ex. 1010and Ex. 1014 put astaxanthin into the rat retina, necessarily "treating" free radical retinal damage of whatever origin.

109. As far as a therapeutically effective dose, Ex.1010 and Ex. 1014 each establishes that a dose of slightly less than 1 mg, up to 2 mg, of astaxanthin per kg of body mass was therapeutically effective in prevention and treatment of ocular disease and injury, and by extension, of free-radical induced disease or injury in tissues into which astaxanthin is transported.

110. It is obvious that if a dose of slightly less than 1 mg, up to 2 mg, of astaxanthin per kg of body mass was therapeutically effective, a higher dose (e.g., 5 mg to 500 mg per kg of body mass, as claimed in the ‘533 patent) would be effective.

111. The ‘533 patent recites that xanthophylls like lutein, zeaxanthin, and canthaxanthin were transported into the retina, and reports the problem of canthaxanthin retinopathy (crystals of canthaxanthin forming in the retina). Ex. 1001, 4:30-38; 6:13-24; 8:59-67; 10:11-22.

112. Even without knowing about Exs. 1010, 1014, 1021, or 1026, it would be well within routine creativity of a person of ordinary skill in the art, who would know that the molecular structures of canthaxanthinand astaxanthin differonly by the presence of an additional hydroxyl unit on the two terminal rings of astaxanthin (see Ex. 1032), to combine two or more of the references quoted in paragraph 45 above (e.g., “The inhibitory effect of astaxanthin on mitochondrial lipid peroxidation is stronger than that of α-tocopherol” (Kurashige (1990), Ex. 1020) to arrive at the basic invention and all embodiments claimed in the ‘533 patent.

113. I agree with the following statements in the '533 patent about the state of the art of the use of antioxidants to prevent retinal injury as of the filing date (27 October 1994, or "Critical Date") of the '533 patent:

> "The pathogenesis of photic injury, of age-related macular degeneration, of ischemia/reperfusion damage, of traumatic injury and of inflammations of the eye … have been attributed to singlet oxygen and free radical generation, and subsequent free radical-initiated reactions."
>
> "Therefore, antioxidants which inhibit free radical formation, or which quench singlet oxygen and scavenge for free radical species, can decrease lipid peroxidation … These and other antioxidants are effective quenchers and scavengers for singlet oxygen and free radicals. In particular, the carotenoids, as a class of compounds, are very effective singlet oxygen quenchers and free radical scavengers. However, individual carotenoids differ in their ability to quench singlet oxygen and scavenge for free radical species."
>
> "It has been theorized that zeaxanthin and lutein are concentrated in the retina because of their ability to quench singlet oxygen and scavenge free radicals, and thereby limit or prevent photic damage to the retina."
>
> "It also is known that another carotenoid, canthaxanthin, can cross the blood-retinal brain barrier and reach the retina."
>
> "… several carotenoids, including astaxanthin, are strong antioxidants compared to .beta.-carotene, ascorbic acid and other widely used antioxidants."
>
> "astaxanthin is a strong antioxidant".

114. It would be well within routine creativity of a person of ordinary skill in the art, who would know what is quoted in the statements in the preceding paragraph (especially, "It also is known that another carotenoid, canthaxanthin, can cross the blood-retinal brain barrier and reach the retina"), to combine either Ex. 1010 or Ex. 1014 with either Ex. 1021 or Ex. 1026 to arrive at the claimed invention in the '533 patent.

115. Even without the knowledge of what is quoted in paragraphs 46 or 113, the application of either Ex. 1021 (USPAT 5,527,533) or Ex. 1026 (Dowling 1961) to Ex. 1014 (Grangaud) or to Ex. 1014 (Massonet) would constitute the application of a known method (administration of antioxidants) using aknown material (astaxanthin, a stronger *xanthophyll* antioxidant, differing only by two hydroxyls from canthaxanthin), ready for improvement, to yield

predictable results, and therefore it would have been obvious to a person of ordinary skill in the art.

116. The '533 patent recites that xanthophylls like lutein, zeaxanthin, canthaxanthin were transported into the retina, and report the problem of canthaxanthin retinopathy (crystals of canthaxanthin forming in the retina). Ex. 1001, 4:30-38; 6:13-24; 8:59-67; 10:11-22. Therefore, a person skilled in the art would have expected astaxanthin, as a xanthophyll differing from canthaxanthin by an additional hydroxyl unit on each of astaxanthin's two terminal rings, to be transported into the retina… even without knowledge of Exs. 1010 or 1014.

117. Given that oral administration of astaxanthin necessarily results in suppression of free radicals in the retina, and that the claims of the '533 patent each recite variations of "administrating astaxanthin to suppress free radicals and free radical-induced damage and injury", combining either Ex. 1010 or Ex. 1014 with either Ex. 1021 or Ex. 1026 to arrive at claims 1-27 of the '533 patent would have been obvious to one of ordinary skill in the art.

GROUND 3. '533 PATENT CLAIMS ANTICIPATED BY CYAN EXHIBIT 1014 (Grangaud (1954)). '533 claim language in left column and prior art Description and my comments in right column.	
Claim 1. A method of treating an individual suffering from retinal damage or retinal disease, said method comprisingadministering a therapeutically effective amount of astaxanthin to the individual to improve the vision of the	Irradiating the retina with bright light, or other oxidative stress, such as reperfusion, creates peroxyl, singlet oxygen, and other free radicals(Zigler, 1985; Goto, 1991). Grangaud (Ex. 1002) discovered and published that dietary astaxanthin was transported into the retina and cured xerophthalmia when administered to vitamin A-deficient rats. Massonet (Exs. 1004) confirmed the results of Grangaud. The only cause of retinal damage, injury, or disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. *Any* administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the

individual.	retina. Retinal tissue contains binding proteins that preferentially transport *xanthophyll* carotenoids, like lutein, zeaxanthin, canthaxanthin, and astaxanthin, from the retinal capillary network into retinal tissue, but disfavor transport into retinal tissue of *carotene* carotenoids like β-carotene. Astaxanthin is transported in the bloodstream, and from the bloodstream into the retina, by specialized "binding proteins". Suppression of free radicals **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light or other oxidative stress. Astaxanthin's inherent mode of action in vertebrate tissue, including retinal tissue, is as a strong antioxidant. Suppression of free radicals, such as peroxyl and singlet oxygen radicals, and free radical-induced damage **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light. Xerophthalmia ("dry eye disease")is *secondary* to retinal damage, injury, and disease (Grangaud, (1951); Massonet (1960); Dowling (1958); in other words, photoreceptor cell membrane attack by a barrage of free radicals, photoreceptor cell degeneration, and reduction of the ONL, IRT, and rhodopsin levels occur first, then xerophthalmia manifests at a later stage in the cornea and surrounding areas. Rats and other vertebrates become diseased, go blind, and die from continued vitamin A deficiency. Infliction of vitamin A deficiency is an injury and causes retinal, corneal, and other injury and diseases (Dowling (1958); Dowling (1960); Dowling (1961)). The free radical-induced damage from photic insult or reperfusion following retinal ischemia or high intraocular pressure in the '533 patent causes the same free radical-induced damage as caused by severe vitamin A deficiency in Ex.1014. The rats in the '533 patent and Ex.1014suffered from retinal damage and injuryinduced by free radicals (no disease was reported in the data of the '533 patent).

	If astaxanthin is in the retina (preferentially transported into the retina from the bloodstream), a **necessary and inherent result** is (i) suppression by astaxanthin of free radicals, such as peroxyl and singlet oxygen radicals, (ii) prevention of initial or further free radical damage and injury, and (iii) prevention of resultant free radical-induced disease. Massonet, in Ex. 1014, administered astaxanthin to treat ocular damage, injury, and disease, to slow the progress of ocular damage, injury, and disease in low doses, and to cure ocular damage, injury, and disease in higher doses and established that astaxanthin is converted into vitamin A in rat retina. Blood-based transport of astaxanthin into the rat retina in Ex.1014 is a **necessary and inherent result** just as it is in the '533 patent. The suppression of free radicals and free radical-induced damage, injury, and disease by astaxanthin in the rat retina in Ex.1014 is a **necessary and inherent result** just as it is in rat retina in the '533 patent. In short, if there was xerophthalmia, there was already major retinal damage from free radicals, and the method disclosed in Ex.1014 put astaxanthin into the rat retina, necessarily "treating" free radical retinal damage, injury, or disease of whatever origin (photic, ischemic, inflammatory, degeneration from stroke or trauma, ocular pressure-related, etc.) and in all tissuesinto which astaxanthin is transported. Therefore, Ex.1014 anticipates every element in all independent claims (except claim 27) and most dependent claims of the '533 patent. Claims 25 and 27, which are directed to the brain or spinal cord, are scientifically in error, as explained above; astaxanthin does not accumulate in the brain or spinal cord. A therapeutically effective amount of a bioactive agent is essentially an amount that achieves the intended therapeutic effect when administered. A therapeutically effective amount is determined by dose/response experiments. Ex.1014 shows that the

	therapeutically effective amount of astaxanthin require to treat ocular disease is a fraction of the amount administered in the '533 patent. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 3. The method of claim 1 wherein the astaxanthin is administered **orally**.	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Ex.1014 expressly discloses oral administration of astaxanthin(as a dietary supplement). Therefore, Ex.1014 anticipates every element in claim 3. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th**

	day of treatment."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 8. The method of claim 1 wherein the retinal damage comprises **free radical-induced** retinal damage.	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Moreover, *any* administration of astaxanthin (other than topical) results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue, including the retina, is suppression of free radicals and free radical-induced retinal damage. "Treating" of free radical-induced retinal damage necessarily occurs by administration of astaxanthin in Ex.1014. Therefore, Ex.1014anticipates every element in claim 8. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 9. The method of claim 1 wherein the	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by

retinal damagecomprises **light-induced** retinal damage.	reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult) retinal damage in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as light-induced peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radicalretinal damage. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 9. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 10. The method of claim 1 wherein the retinal damage comprises **photoreceptor cell**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Photoreceptor cells and neurons of

retinal damage or **damage to neurons of inner retinal layers.**	the inner retinal layer are layers in the retina serviced by the retinal capillary network. Damage of the photoreceptor cells and neurons of the inner retinal layer in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage to photoreceptor cells or neurons of inner retinal layers. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 10. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1above.
Claim 11. The method of claim 1 wherein the retinal damage comprises **ganglion cell**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first,

retinal damage.	then xerophthalmia manifests. Retinal ganglion cells are near the inner surface of the retina and are serviced by the retinal capillary network. Damage of the ganglion cells in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage of retinal ganglion cells. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 11. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 12: The method of claim 1 wherein the retinal damage comprises **age-related macular degeneration.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)*

	of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 12. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). Note: The rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for

	human retina.
Claim 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.**	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. The only cause of retinal injury disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. Any administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue is suppression of free radicals. If astaxanthin is in the retina, it inherently suppresses free radicals, and thereby protects neurons in a retina from free radical-induced retinal injury. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 13. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Claim 14. A method of treating an individual suffering from neuronal damageto a retina comprising administering a therapeutically-effective amount of astaxanthin to the individual **to improve the condition of the retina.**	**Summary**: The Summary and prior description/citations regarding claims 1 and 13 in this Chart are incorporated in this cell by reference. The only cause of neuronal damage to a retina disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage to neurons in the retina, and (iii) support for visual phototransduction (astaxanthin is converted into vitamin A in the rat retina; vitamin A is essential for visual phototransduction). Administered astaxanthin thereby inherently improves the condition of the retina.Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 12. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Claim 15. The method of claim 14 wherein the neuronal damage comprises **photic injury to the retina**, **ischemic insult** to the retina, or intraocular **pressure-related insult to the retina.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult), ischemic, and intraocular pressure-related retinal damage in the '533 patent are all caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and prevention of initial or further photic injury to the retina, ischemic insult to the retina, or intraocular pressure-related insult to the retina.Therefore, Ex.1014 anticipates every element in claim 15. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").

Claim 16. A method of treating an individual suffering from age-related macular degeneration comprising administering a therapeutically-effective amount of astaxanthin to the individual to retard the progress of **age-related macular degeneration**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 16. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia,

	the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions"). Note: The rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for human retina. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 17. A method of treating an individual suffering from an ischemic or intraocular pressure-related disease of a retina comprising administering a therapeutically-effective amount of astaxanthin to the individual to **improve thecondition of the retina and to prevent further damage to the retina.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Ischemic and intraocular pressure-related retinal disease in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, 1021 to treat anindividual suffering from an ischemic or intraocular pressure-related disease of a retina to improve the condition of the retina and to prevent further damage to the retina. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 17. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg

	of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 18. The method of claim 17 wherein the ischemic retinal diseaseis selected from the group consisting of **diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause of ischemic retinal disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals; therefore, diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucomain the '533 patent are all caused by free radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and thereby to treat anindividual suffering diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 18. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4

	("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 19. A method of treating an individual suffering from an **inflammatory disease of a retina** comprising administering a therapeutically effective amount of astaxanthin to the individual to **improve the condition of thc rctina** and to **prevent further damage to the retina.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause ofinflammatory disease of a retinadisclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals,and thereby to treat anindividual suffering an inflammatory disease of a retina, improve the condition of the retina, and prevent further damage to the retina.Ex.1014 discloses administration of astaxanthin. The only damage disclosed in the '533 patent, whether from inflammation or other causes, is from free radical-induced damage.Therefore, Ex.1014 anticipates every element in claim 19. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient**

	regime, 80 mg of oily solution of astaxanthin esters [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 20. The method of claim 19 wherein the inflammatory disease is selected from the group consisting of **retinitis, uveitis, iritis, keratitis, and scleritis**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause ofinflammatory disease of a retinadisclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals,and thereby to treat anindividual suffering an inflammatory disease of a retina, such as retinitis, uveitis, iritis, keratitis, and scleritis.Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 20. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient**

	regime, 80 mg of oily solution of astaxanthin esters [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 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.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not* present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 21 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord.

	Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 21 other than the brain and spinal cord, since astaxanthin does not accumulate in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 22. The method of claim 21 wherein the central nervous system comprises **a brain, a spinal cord and a retina**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the

	brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 22 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 22 other than the brain and spinal cord, since astaxanthin does not accumulate in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").;

Claim 23. The method of claim 22 wherein the free radical-induced injury comprises a **traumatic injury** or an **ischemic injury**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-inducedtraumatic or ischemic injury in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 23 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 23 other than the brain and spinal cord, since astaxanthin does not accumulate in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

	CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 24. The method of claim 23 wherein the ischemic injury comprises a **stroke**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-inducedstroke in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal

	cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 24 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014 anticipates every element in claim 24 other than the brain or spinal cord, since astaxanthin does not accumulate in the brain. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 25. The method of claim 23 wherein the traumatic injury comprises **a spinal cord injury.**	**Summary.**Ex. 1014 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 25 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the

	brain or spinal cord. The Summary and prior description/citations regarding claims 1 and 21-24 in this Chart are incorporated in this cell by reference. Administered astaxanthin in Ex. 1014 would have treated a spinal cord injury if astaxanthin accumulated in the spinal cord, which is does not. Therefore, Ex. 1014 anticipates claim 25. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime,** 80 mg of oily solution of astaxanthin esters [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").
Claim 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**	**Summary**: The Summary and prior description/citations regarding claims 1, 13, 14 and 19 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, and (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage, injury, and degenerative retinal disease. Administered astaxanthin thereby inherently retards the progress of degenerative retinal disease by suppression of free radicals.The only retinal disease disclosed in the '533 patent, whether degenerative or not, is from free radical-induced damage. Ex.1014 discloses administration of astaxanthin. Therefore, Ex.1014

disease.	anticipates every element in claim 26. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 27. A method of treating an individual suffering from a **degenerative central nervous system disease of a brain or spinal cord,** said method comprising administering a therapeutically effective amount of astaxanthin to the individual to retard the progress of the disease.	**Summary.**Ex. 1014 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 27 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord. The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Administered astaxanthin in Ex. 1014 would have treated degenerative central nervous system disease of a brain or spinal cord if astaxanthin accumulated in the brain or spinal cord, which is does not. Therefore, Ex. 1014 anticipates claim 27.

	CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.**]"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Grounds of Invalidity for Challenged Claims 1, 3, 8-27based on Grangaud (1954) (Ex. 1014) as a Primary Reference

118. See paragraphs 83-99 above, following the Claims Chart for Ground 1, which paragraphs 83-99 apply with equal force to the Claims Chart for Ground 3 immediately above.

GROUND 4. '533 PATENT CLAIMS OBVIOUS OVER CYAN EXHIBIT 1014 (Grangaud 1954) IN VIEW OF CYAN EXHIBIT 1021 (USPAT 5,310,764) OR CYAN EXHIBIT 1026 (DOWLING ET AL. 1961). '533 claim language in left column and prior art Description and my comments in right column.	
Claim 1. A method of treating an individual	Irradiating the retina with bright light, or other oxidative stress, such as reperfusion, creates peroxyl, singlet oxygen, and other free radicals(Zigler, 1985; Goto, 1991). Grangaud (Ex. 1002) discovered and

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.	published that dietary astaxanthin was transported into the retina and cured xerophthalmia when administered to vitamin A-deficient rats. The only cause of retinal damage, injury, or disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. *Any* administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Retinal tissue contains binding proteins that preferentially transport *xanthophyll* carotenoids, like lutein, zeaxanthin, canthaxanthin, and astaxanthin, from the retinal capillary network into retinal tissue, but disfavor transport into retinal tissue of *carotene* carotenoids like β-carotene. Astaxanthin is transported in the bloodstream, and from the bloodstream into the retina, by specialized "binding proteins". Suppression of free radicals **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light or other oxidative stress. Astaxanthin's inherent mode of action in vertebrate tissue, including retinal tissue, is as a strong antioxidant. Suppression of free radicals, such as peroxyl and singlet oxygen radicals, and free radical-induced damage **necessarily occurs** if astaxanthin is present in animal tissue that contains free radicals, such as retinal tissue exposed to bright light. Xerophthalmia ("dry eye disease")is *secondary* to retinal damage, injury, and disease (Massonet, (1951); Massonet (1960); Dowling (1958); in other words, photoreceptor cell membrane attack by a barrage of free radicals, photoreceptor cell degeneration, and reduction of the ONL, IRT, and rhodopsin levels occur first, then xerophthalmia manifests at a later stage in the cornea and surrounding areas. Rats and other vertebrates become diseased, go blind, and die from continued vitamin A deficiency. Infliction of vitamin A deficiency is an injury and causes retinal, corneal, and other injury and diseases (Dowling (1958); Dowling (1960); Dowling (1961)). The free radical-induced damage from photic insult or reperfusion following retinal ischemia or high intraocular pressurein the '533 patent causes the same free radical-induced damage as caused by severe vitamin A

	deficiency in Ex.1014. If astaxanthin is in the retina (preferentially transported into the retina from the bloodstream), a **necessary and inherent result** is (i) suppression by astaxanthin of free radicals, such as peroxyl and singlet oxygen radicals, (ii) prevention of initial or further free radical damage and injury, and (iii) prevention of resultant free radical-induced disease. The rats in the '533 patent, Ex.1014, and Ex. 1026 (Dowling 1961) suffered from retinal damage and injuryinduced by free radicals (no disease was reported in the data of the '533 patent). Grangaud, in Ex.1014, administered astaxanthin to treat ocular damage, injury, and disease, to slow the progress of ocular damage, injury, and disease in low doses, and to cure ocular damage, injury, and disease in higher doses. Blood-based transport of astaxanthin into the rat retina in Ex.1014 is a **necessary and inherent result** just as it is in the '533 patent. The suppression of free radicals and free radical-induced damage, injury, and disease by astaxanthin in the rat retina in Ex.1014 is a **necessary and inherent result** just as it is in rat retina in the '533 patent. In short, if there was xerophthalmia, there was already major retinal damage from free radicals, and the method disclosed in Ex.1014 put astaxanthin into the rat retina, necessarily "treating" free radical retinal damage, injury, or disease of whatever origin (photic, ischemic, inflammatory, degeneration from stroke or trauma, ocular pressure-related, etc.) and in all tissues into which astaxanthin is transported. Ex.1014 discloses administration of astaxanthin to treat ocular damage, injury, and disease. Ex. 1026 discloses administration of vitamin A to treat retinal damage, injury, and disease, and Ex. 1021 discloses administration of β-carotene to treat retinal damage, injury, and disease. Astaxanthin and vitamin A were known to POSA as an effective retinal antioxidants,and astaxanthin and vitamin A were known accumulate in the retina; it would have been obvious to POSA to substitute astaxanthin for β-carotene in the method of Ex. 1021 or to substitute astaxanthin for

	vitamin A in the method of Ex. 1026.Therefore, claim 1 is obvious over Ex.1014in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:9-10, 3:12-17, and 5:48-54 ("the major carotenoids in the retina were lutea and zeaxanthin, use of retinal carotenoids to confer antioxidant protection. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a mediator of light damage in the retina *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."); 4:27-29 and 6:20-23 ("administration of appropriate amounts of beta-carotene can successfully treat ARMD [age-related macular degeneration] *** Therapeutically effective amounts of beta-carotene are those amounts sufficient to stabilize the progression of the disease or to resolve the symptoms of ARMD". CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). Figures show prevention and cure of retinal degeneration by administration of vitamin A in different groups.
Claim 2. The method of claim 1	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. "Systemic

wherein the astaxanthin is administered **parenterally**.	administration" includes oral, parenteral, intravenous, and other routes of administration of a composition to treat a subject's disease or injury. Parenteral administration is administration of a composition to a subject's body other than in the mouth and alimentary canal, i.e., by injection or placement of a composition in a subject. Baranowitz (Ex. 1021) systemically administered an antioxidant carotenoid, β-carotene, to prevent and treat a retinal disease, age-related macular degeneration ("AMD"), through by β-carotene's suppression of free radicals and of free radical-induced damage, injury, and disease. The base reference (Ex. 1014)discloses only oral (dietary) administration of astaxanthin, but Ex. 1021 discloses systemic administration, curing the possible deficiency in claim 2. Oral and parenteral administration is well known to POSA, and the choice of parenteral instead of oral would have been obvious to POSA. Therefore, claim 2 is obvious over Ex.1014in view of Ex. 1021. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). EXHIBIT 1021, 5:55-56 ("In all of the embodiments of the present invention, β-carotene is preferably **administered systemically**.")
Claim 3. The method of claim 1	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Ex.1014

wherein the astaxanthin is administered **orally**.	discloses oral administration of astaxanthin (as a dietary supplement), Ex. 1026 discloses oral administration of vitamin A, and Ex. 1021 discloses oral administration of a different anti-oxidant,β-carotene (as a dietary supplement) to treat ocular damage, injury, and disease. Therefore, claim 3 is obvious over Ex.1014 in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX.1021,5:57-58 ("Systemic administration most preferably is by the **oral route**."). CYAN EX.1026, 86 (last sentence on page). ("Groups of albino, weanling rats were raised on Standard D.S.P.vitamin A-test diets supplemented orally with 50 μg/day of vitamin A acid, dissolved in vegetable oil.")
Claim 4. The method of claim 1 wherein the astaxanthin is administered **topically directly to the eye**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. The pigmented, residual oil prepared by Grangaud was mixed with rat feed, but it could just as easily been applied topically, e.g., to rat cornea, to treat the corneal lesions. The base reference (Ex. 1014) discloses a preparation of astaxanthin, and Ex. 1026 discloses oral administration of vitamin A acid dissolved in oil. Topical administration is well known to POSA,

	particularly for ophthalmic administration of a composition. The choice of topical instead of oral would have been obvious to POSA as of the filing date of the '533 patent. Therefore, claim 4 is obvious over Ex.1014in view of Ex. 1021. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX.1026, 86 (last sentence on page). ("Groups of albino, weanling rats were raised on Standard D.S.P.vitamin A-test diets supplemented orally with 50 μg/day of vitamin A acid, dissolved in vegetable oil.")
Claim 5. The method of claim 1 wherein the astaxanthin is administered in the amount of about **5 to about 500 milligrams per kilogram** of body weight.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Although the doses administered in Exhibit 1014 (4mg/kg) and in Exhibit 1021 (.063mg/kg to 4.4mg/kg) were a fraction of the doses disclosed in the '533 patent (5mg/kg to 500 mg/kg), the doses disclosed in Exhibits 1014, 0121, and 1026(5mg/kg of vit. A) were therapeutically effective, e.g., the lower doses in Ex. 1014 healed ocular lesions and the higher doses healed ocular lesions and restored normal growth, and the doses in Ex. 1026 healed retinal degeneration. If a lower dose of astaxanthin is therapeutically effective, it would have been obvious to POSA that a higher dose of astaxanthin would

	be effective. Therefore, claim 5 is obvious over Ex.1014in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021. 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient **to stabilize the progression of the disease or to resolve the symptoms**"; 6:30-33 and 8:10-12 ("Typically for a human being, that amount will be **at least about 50 mg/day** [.0625mg/kg in an 80 kg human] of β-carotene. Most preferably, that amount will range from about **60 mg/day to about 350 mg/day** [.063mg/kg to 4.4mg/kg in an 80 kg human] *** The patient was placed on a regimen of **180 mg/day** [2.25mg/kg in an 80 kg human] of β-carotene."). CYAN EX. 1026, 94:15-19 ("The control animal was fed vitamin Athroughout the experiment, while the other two animals were fed vitaminA acid. The recovery animal was fed a large dose of vitamin A (500 μg)and then periodically fed further vitamin A for 16 days.") 500 μg of vitamin A/day/100g rat = 5mg/kg/day; 89:Figs. 2a-2d (captions on p.88);

	95:Figs. 10a-10c(captions on p.94).
Claim 6. The method of claim 1 wherein the astaxanthin is administered in the amount of about **10 to about 200 milligrams per kilogram** of body weight.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Although the doses administered in Exhibit 1014 (4mg/kg) and in Exhibit 1021 (.063mg/kg to 4.4mg/kg) were a fraction of the doses disclosed in the '533 patent (5mg/kg to 500 mg/kg), the doses disclosed in Exhibits 1014, 0121, and 1026(5mg/kg of vit. A) were therapeutically effective, e.g., the lower doses in Ex. 1014 healed ocular lesions and the higher doses healed ocular lesions and restored normal growth, and the doses in Ex. 1026 healed retinal degeneration.If a lower dose of astaxanthin is therapeutically effective, it would have been obvious to POSA that a higher dose of astaxanthin would be effective. Therefore, claim 6 is obvious over Ex.1014in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021. 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient **to stabilize the progression of the**

	disease or to resolve the symptoms"; 6:30-33 and 8:10-12 ("Typically for a human being, that amount will be **at least about 50 mg/day** [.0625mg/kg in an 80 kg human] of β-carotene. Most preferably, that amount will range from about **60 mg/day to about 350 mg/day** [.063mg/kg to 4.4mg/kg in an 80 kg human] *** The patient was placed on a regimen of **180 mg/day** [2.25mg/kg in an 80 kg human] of β-carotene.") CYAN EX. 1026, 94:15-19 ("The control animal was fed vitamin Athroughout the experiment, while the other two animals were fed vitaminA acid. The recovery animal was fed a large dose of vitamin A (500 μg)and then periodically fed further vitamin A for 16 days.") 500 μg of vitamin A/day/100g rat = 5mg/kg/day; 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 7. The method of claim 1 wherein the astaxanthin is administered in the amount of about **25 to about 150 milligrams per kilogram** of body weight.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Although the doses administered in Exhibit 1014 (4mg/kg) and in Exhibit 1021 (.063mg/kg to 4.4mg/kg) were a fraction of the doses disclosed in the '533 patent (5mg/kg to 500 mg/kg), the doses disclosed in Exhibits 1014, 0121, and 1026(5mg/kg of vit. A) were therapeutically effective, e.g., the lower doses in Ex. 1014 healed ocular lesions and the higher doses healed ocular lesions and restored normal growth, and the doses in Ex. 1026 healed retinal degeneration.If a lower dose of astaxanthin is therapeutically effective, it would have been obvious to POSA that a higher dose of astaxanthin would be effective. Therefore, claim 7 is obvious over Ex.1014in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per**

	day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021. 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient **to stabilize the progression of the disease or to resolve the symptoms**"; 6:30-33 and 8:10-12 ("Typically for a human being, that amount will be **at least about 50 mg/day** [.0625mg/kg in an 80 kg human] of β-carotene. Most preferably, that amount will range from about **60 mg/day to about 350 mg/day** [.063mg/kg to 4.4mg/kg in an 80 kg human] *** The patient was placed on a regimen of **180 mg/day** [2.25mg/kg in an 80 kg human] of β-carotene.") CYAN EX. 1026, 94:15-19 ("The control animal was fed vitamin Athroughout the experiment, while the other two animals were fed vitaminA acid. The recovery animal was fed a large dose of vitamin A (500 μg)and then periodically fed further vitamin A for 16 days.") 500 μg of vitamin A/day/100g rat = 5mg/kg/day; 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 8. The method of claim 1 wherein the retinal damage comprises **free radical-induced** retinal damage.	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Moreover, *any* administration of astaxanthin (other than topical) results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue, including the retina, is suppression of free radicals and free radical-induced retinal damage. Ex.1014 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. One form of vitamin A administered in Ex. 1026 is an antioxidant (retinol), with an

	inherent mode of action in vertebrate tissue, including the retina, of suppression of free radicals and free radical-induced retinal damage. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage.Vitamin A was known to POSA as an effective retinal antioxidant,and astaxanthin was known accumulate in the retina; it would have been obvious to POSA to substitute astaxanthin for vitamin A. Therefore, claim 8 is obvious over Ex.1014 in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the

	Claims Chart for Ground 1.
Claim 9. The method of claim 1 wherein the retinal damagecomprises **light-induced** retinal damage.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult) retinal damage in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as light-induced peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease. Ex.1014 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by light energy ("light-induced retinal damage"). Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat light-induced retinal damage. Therefore, claim 9 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the**

	treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 10. The method of claim 1 wherein the retinal damage comprises **photoreceptor cell retinal damage** or **damage to neurons of inner retinal layers.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Photoreceptor cells and neurons of the inner retinal layer are layers in the retina serviced by the retinal capillary network. Damage of the photoreceptor cells and neurons of the inner retinal layer in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage to photoreceptor cells or neurons of inner retinal layers. Ex.1014 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A to treat ocular injury and disease. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, in

	particular in the RPE [retinal pigment epithelium] and photoreceptor cells. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat retinal damage comprising photoreceptor cell retinal damage or damage to neurons of inner retinal layers. Therefore, claim 10 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 2:37-40 ("Vision loss can occur when **RPE** [retinal pigment epithelium] **and photoreceptor cells** over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium,

	function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 11. The method of claim 1 wherein the retinal damage comprises **ganglion cell retinal damage.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Retinal ganglion cells are near the inner surface of the retina and are serviced by the retinal capillary network. Damage of the ganglion cells in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical-induced damage of retinal ganglion cells. Ex.1014 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex. 1021, 5:49-51) retinal damage caused by free radicals, such as ganglion cell damage. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ganglion cells damage. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per**

	day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 12: The method of claim 1 wherein the retinal damage comprises **age-related macular degeneration.**	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet

	oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1014 discloses administration of astaxanthin and Ex. 1026 discloses administration of vitamin A. The primary focus of Ex. 1021 is prevention and treatment of ARMD by administration of the carotenoid β-carotene. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ARMD. Therefore, claim 12 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen

	degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain"); 3:12-17 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen"); 4:27-29 ("administration of appropriate amounts of β-carotene **can successfully treat ARMD**"); 5:49-51 ("by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."); 6:20-23 ("Therapeutically effective amounts of β-carotene are those amounts sufficient to stabilize the progression of the disease or **to resolve the symptoms of ARMD**"; 9:30-31(" **the successful treatment of ARMD due to β-carotene administration"**). Note: The rat retina does not have a macula, but as of the filing date of the '533 patent, the rat retina model was still accepted by some researchers as a surrogate for human retina; since the mid-1990s, the rat retina model is no longer accepted as a surrogate for human retina.
Claim 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.**	**Summary**: The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. The only cause of retinal injury disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals. Any administration of astaxanthin (other than topical) necessarily results in blood-based transport of astaxanthin to the retina. Astaxanthin's inherent mode of action in vertebrate tissue is suppression of free radicals. If astaxanthin is in the retina, it inherently suppresses free radicals, and thereby protects neurons in a retina from free radical-induced retinal injury.Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. The prevention and treatment of ARMD protect the neurons of the retina. Ex. 1021 discloses that (i) carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen, and (ii) the administration of β-carotene to protect the retina of the individual from free radical-induced retinal injury. Accordingly, it

	would have been obvious to POSA as of the filing date of the '533 patent to useastaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 toprotect neurons in a retina of the individual from free radical-induced retinal injury. Therefore, claim 14 is obvious over Ex.1014 in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see

	the prior art description/citations regarding claim 1 above.
Claim 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.**	**Summary**: The Summary and prior description/citations regarding claims 1 and 13 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage to neurons in the retina, and (iii) support for visual phototransduction (astaxanthin is converted into vitamin A in the rat retina; vitamin A is essential for visual phototransduction). Administered astaxanthin thereby inherently improves the condition of the retina.Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. The prevention and treatment of ARMD is an improvement of the condition of the retina. Ex. 1021 discloses that (i) carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen, and (ii) the administration of β-carotene to improve the condition of the retina (by treating ARMD, a retinal disease). Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to useastaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 toprotect neurons in a retina of the individual from free radical-induced retinal injury. Therefore, claim 14 is obvious over Ex.1014 in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered**

	orally to vitamin A deficient rats."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 2:37-40 ("Vision loss can occur when RPE [retinal pigment epithelium] and photoreceptor cells over the drusen degenerate and debris accumulates. Although the drusen fade and ultimately disappear, areas of atrophy remain."); 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 15. The method of claim 14 wherein the neuronal damage comprises **photic injury to the retina**, **ischemic insult** to the	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Light-induced (photic insult), ischemic, and intraocular pressure-related retinal damage in the '533 patent are all caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals) created by photic energy. If astaxanthin is in the retina, a **necessary and inherent result** is suppression

retina, or intraocular **pressure-related insult to the retina.**	by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and prevention of initial or further photic injury to the retina, ischemic insult to the retina, or intraocular pressure-related insult to the retina.Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by light energy or other free radical action (e.g., by ischemia or intraocular pressure). Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat light-induced, ischemic, and intraocular pressure-related retinal damage. Therefore, claim 15 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal**

	carotenoids to confer antioxidant protection. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 16. A method of treating an individual suffering from age-related macular degeneration comprising administering a therapeutically-effective amount of astaxanthin to the individual to retard the progress of **age-related macular degeneration**.	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The macula is a yellow spot (colored by high xanthophyll concentration) on the inner surface (*fundus oculi)* of the retina and is serviced by the choriocappilarias (part of the retinal capillary network). Age-related macular degeneration ("ARMD") in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Astaxanthin is preferentially transported from the retinal capillary network into retinal tissue. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease, such as ARMD. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. The primary focus of Ex. 1021 is prevention and treatment of ARMD by administration of the carotenoid β-carotene. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by free radicals, particularly singlet oxygen. Accordingly, it would have been obvious to POSA as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the

	method of Ex. 1021 to treat ARMD. Therefore, claim 16 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17 ("use of **retinal carotenoids to confer antioxidant protection**"). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 17. A method of treating an individual suffering from an ischemic or intraocular pressure-related disease of a retina comprising	**Summary.Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. Ischemic and intraocular pressure-related retinal disease in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, thereby treating anindividual suffering from an ischemic or intraocular pressure-

administering a therapeutically-effective amount of astaxanthin to the individual to **improve thecondition of the retina and to prevent further damage to the retina.**	related disease of a retina to improve the condition of the retina and to prevent further damage to the retina. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage caused by light energy or other free radical action (e.g., by ischemia or intraocular pressure). Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat anindividual suffering from an ischemic or intraocular pressure-related disease of a retina to improve the condition of the retina and to prevent further damage to the retina. Therefore, claim 17 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal**

	carotenoids to confer antioxidant protection. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 18. The method of claim 17 wherein the ischemic retinal diseaseis selected from the group consisting of **diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma.**	**Summary** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. In vitamin A deficiency, xerophthalmia is secondary to retinal damage, injury, and disease, i.e., retinal damage occurs first, then xerophthalmia manifests. The only cause of ischemic retinal disease disclosed in the '533 patent is the action of free radicals, e.g., peroxyl, and singlet oxygen, radicals; therefore, diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucomain the '533 patent are all caused by free radicals. If astaxanthin is in the retina, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, and thereby treating anindividual suffering diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin Λ to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage or disease, such as that caused by ischemia. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat ischemic retinal disease, such as diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Therefore, claim 18 is

	obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 19. A method of treating an individual suffering from an **inflammatory disease of a**	**Summary**: The Summary and prior description/citations regarding claims 1, 13 and 14 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced inflammation and inflammatory disease, and (iii) support for visual

retina comprising administering a therapeutically effective amount of astaxanthin to the individual to **improve the condition of the retina** and to **prevent further damage to the retina.**	phototransduction (astaxanthin is converted into vitamin A in the rat retina; vitamin A is essential for visual phototransduction). The only damage disclosed in the '533 patent, whether from inflammation or other causes, is from free radical-induced damage.Administered astaxanthin thereby inherently treats free radical-induced inflammatory disease, improves the condition of the retina, and prevents further damage to the retina.Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage or disease, such as that caused by ischemia. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat inflammatory retinal disease, such as diabetic retinopathy, cystoid macular edema, central retinal arterial occlusion, central retinal venous occlusion, and glaucoma. Therefore, claim 19 is obvious over Ex.1014 in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**").

	CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.
Claim 20. The method of claim 19 wherein the inflammatory disease is selected from the group consisting of **retinitis, uveitis, iritis, keratitis, and scleritis**.	**Summary.** The Summary and prior description/citations regarding claim 1 and 19 in this Chart are incorporated in this cell by reference. Inflammatory disease of the retina in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) retinal damage, such as that caused by inflammatory disease. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into the retina, rather than β-carotene, a weaker antioxidant that is not preferentially transported into the retina, in the method of Ex. 1021 to treat inflammatory disease of the retina, such as retinitis, uveitis, iritis, keratitis, and scleritis. Therefore, claim 20 is obvious over Ex.1014 in view of Exs. 1021 or 1026. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were

	distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51 ("use of **retinal carotenoids to confer antioxidant protection**. … carotenoids as protective agents against highly reactive singlet oxygen and proposed that singlet oxygen-induced liquid peroxidation was a **mediator of light damage in the retina** *** by increasing the availability of carotinoids [*sic*] ... to the retinal pigment epithelium, function can be normalized."). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 21. A method of treating an individual suffering from a free radical-induced injury to a **central nervous system**, said method comprising administering a	**Summary.** The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. Injury of the central nervous system in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i)

therapeutically-effective amount of astaxanthin to the individual to improve the condition of the central nervous system.	transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treat free radical-induced injury to treat free radical-induced injury of the retina. Therefore, claim 21 is obvious over Ex.1014 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 21 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were**

	becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 22. The method of claim 21 wherein the central nervous system comprises **a brain, a spinal cord and a retina**.	**Summary.** The Summary and prior description/citations regarding claims 1 and 21 in this Chart are incorporated in this cell by reference. Injury of the central nervous system, including the brain, spinal cord, and retina in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1014discloses accumulation of astaxanthin in rat retina, and Ex.1026 discloses accumulation of vitamin A in rat retina, but neither addresses the brain or spinal cord. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treat free radical-induced injury to the retina. Therefore, claim 22 is obvious over Ex.1014 in view of Exs.

	1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 22 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5µg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 23. The method of claim 22 wherein the free radical-	**Summary.** The Summary and prior description/citations regarding claims 1 and 21 in this Chart are incorporated in this cell by reference. Traumatic or ischemic injury of the central nervous system, including the brain, spinal cord, and retina in the '533 patent is caused by free radicals

induced injury comprises a **traumatic injury** or an **ischemic injury**.	(e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the other parts of the central nervous system, such as the brain and spinal cord. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treat free radical-induced traumatic or ischemic injury of the retina. Therefore, claim 23 is obvious over Ex.1014 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 23 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1.

	CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 24. The method of claim 23 wherein the ischemic injury comprises a **stroke**.	**Summary.** The Summary and prior description/citations regarding claims 1 and 21 in this Chart are incorporated in this cell by reference. A stroke in the '533 patent is caused by free radicals (e.g., peroxyl, and singlet oxygen, radicals). If astaxanthin is in the bloodstream, a **necessary and inherent result** is suppression by astaxanthin of free radicals, such as peroxyl, and singlet oxygen, radicals, and prevention of initial or further free radical damage and injury, and resultant free radical-induced disease in tissue into which astaxanthin is transported. Astaxanthin is preferentially transported into the retina, but not into the brain. Any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood, and (ii) suppression by astaxanthin of free radicals and of free radical-induced disease in tissue into which astaxanthin is transported. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Ex. 1021 discloses that carotenoids are "protective agents against singlet oxygen-

	induced" (Ex, 1021, 5:49-51) damage. Accordingly, it would have been obvious as of the filing date of the '533 patent to use astaxanthin, a stronger antioxidant that is preferentially transported into tissue with xanthophyll binding proteins, rather than β-carotene, a weaker antioxidant that is not preferentially transported into such tissue, in the method of Ex. 1021 to treata free radical-induced stroke other than in brain or spinal cord tissue. Therefore, claim 24 is obvious over Ex.1014 in view of Exs. 1021 or 1026. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not*present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 24 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneousregarding the activity of astaxanthin in the brain or spinal cord. For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above or claim 1 in the Claims Chart for Ground 1. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51.

	CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).
Claim 25. The method of claim 23 wherein the traumatic injury comprises **a spinal cord injury.**	**Summary.**Ex. 1014 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 25 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord. The Summary and prior description/citations regarding claims 1 and 21-24 in this Chart are incorporated in this cell by reference. It would have been obvious at the time of the invention to have tried to treat a spinal cord injury with astaxanthin. Therefore, Ex. 1014 renders claim 25 obvious. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94).

Claim 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.**	**Summary**: The Summary and prior description/citations regarding claims 1, 13, 14 and 19 in this Chart are incorporated in this cell by reference. Moreover, any administration of astaxanthin (other than topical) results in (i) transport of astaxanthin by blood to the retina, and (ii) suppression by astaxanthin of free radicals in the retina and of free radical-induced damage, injury, and degenerative retinal disease. Administered astaxanthin thereby inherently retards the progress of degenerative retinal disease by suppression of free radicals.The only retinal disease disclosed in the '533 patent, whether degenerative or not, is from free radical-induced damage. Ex.1014 discloses administration of astaxanthin to protect the eye, and Ex. 1026 discloses administration of vitamin A to protect the retina. Therefore, claim 16 is obvious over Ex.1014 in view of Exs. 1021 or 1026. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Claim 27. A method of treating an individual suffering from a **degenerative central nervous system disease of a brain or spinal cord,** said method comprising administering a therapeutically effective amount of astaxanthin to the individual to retard the progress of the disease.	**Summary.**Ex. 1014 discloses administration of astaxanthin. Massonet looked carefully for administered astaxanthin in the brain and spinal cord, but found none there. (Ex. 1004, Table XX on p.105 and Table XXI on p.107). If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claim 27 of the '533 patent was speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord. The Summary and prior description/citations regarding claim 1 in this Chart are incorporated in this cell by reference. It would have been obvious at the time of the invention to have tried to treat a degenerative central nervous system disease of a brain or spinal cord with astaxanthin. Therefore, Ex. 1014 renders claim 27 obvious. CYAN EX. 1014. 1393:12-13 ("We used all of these properties to prepare an oily **solution of astaxanthin esters which we administered orally to vitamin A deficient rats**."); 1394:3-4 ("**the animals** were distributed into 2 lots: seven of them (2 males and 5 females), **received per day in addition to the deficient regime, 80 mg of oily solution of astaxanthin esters** [80*1.5μg/mg of oil (Ex. 1002 data) per 30g rat = **4mg astaxanthin/kg body wt.]**"); 1394:10-11 ("At the same time, **among the treated animals, the ocular lesions were regressing, the cornea were becoming perfectly healthy, healing was achieved between the 12th and 15th day of treatment**."); 1394:16-18 ("in the vitamin A deficient white rat, with a stable weight curve and a fully-developing xerophthalmia, **the administration of an oily solution of astaxanthin esters led, within a few days, to the complete healing of the ocular lesions**"). CYAN EX. 1021, 3:12-17, and 5:49-51. CYAN EX.1026, 89:Figs. 2a-2d (captions on p.88); 95:Figs. 10a-10c(captions on p.94). For quotations omitted in a plain page:line citation in this cell, see the prior art description/citations regarding claim 1 above.

Grounds of Invalidity for Challenged Claims 1-27 as obvious over Grangaud (Ex. 1014) in view or USPAT 5,527,533 (Ex. 1021) or Dowling (1961) (Ex. 1025)

119. See paragraphs 100-117 above, following the Claims Chart for Ground 2, which paragraphs 100-117 apply with equal force to the Claims Chart for Ground 4 immediately above.

Conclusion

120. Massonet (Ex. 1004, Table XX on p.105 and Table XXI on p.107) showed that astaxanthin is *not* present in the brain or spinal cord after administration of astaxanthin. If astaxanthin is not present in the brain or spinal cord, it cannot be chemically active. Therefore, claims 25 and 27 of the '533 patent were speculative (not supported by any data) and, in fact, scientifically erroneous regarding the activity of astaxanthin in the brain or spinal cord.

121. The presence and therapeutic efficacy in rat retina of administered astaxanthin is conclusively demonstrated in Ex. 1014 (Grangaud) and Ex. 1010 (Massonet) by the complete cure of xerophthalmia and by the prevention of xerophthalmia in vitamin A-deficient rats. As explained above, such prevention and cure of xerophthalmia as reported in those publications can only arise from blood-borne delivery of astaxanthin to the eye through the retinal and uveal capillary networks, which in turn necessarily results in accumulation of astaxanthin in retinal tissue. Such accumulation in retinal tissue necessarily results in suppression of peroxyl, singlet oxygen, and other free radicals by astaxanthin's inherent antioxidant properties, which properties necessarily include "treating" (more accurately, reducing or partially preventing) free radical-induced damage and injury reported and claimed in the '533 patent.

122. The methods disclosed in Ex. 1010 and in Ex. 1014 necessarily results in the accumulation of astaxanthin in the rat retina, and treats free radical retinal damage, injury, or disease of whatever origin (photic, ischemic, inflammatory, degeneration from stroke or trauma, ocular pressure-related, etc.) and in all tissues into which astaxanthin is transported. The suppression of free radicals and free radical-induced damage and injury by astaxanthin in the rat retina in Ex. 1010 and in Ex. 1014 is a necessary and inherent result just as it is in rat retina in the '533 patent. The preventive and therapeutic effects on free radical-induced

retinal damage, injury, and disease of administering astaxanthin would necessarily be the same as the preventive and therapeutic effects of administering vitamin A, as shown in Ex. 1026 (Dowling 1961), as explained above. Accumulation of astaxanthin in the retina cures free radical-induced retinal disease if astaxanthin is administered before permanent damage to retinal tissue (although treating disease was not shown or reported in the '533 patent since astaxanthin was not administered after damage or injury).

123. The rats in the '533 patent, Ex. 1014 (Grangaud),Ex. 1010(Massonet), and Ex. 1026 (Dowling (1961)) suffered from the same free radical-induced retinal damage and injury. The rats in the '533 patent, Ex. 1014 (Grangaud), and Ex. 1010 (Massonet)responded to the same treatment, administration of astaxanthin.

124. A person of skill in the art would realize that the lower doses of astaxanthin administered in Exs. 1010or 1014, compared to the doses administered in the '533 patent, were prophylactically and therapeutically effective.

125. Based on the above analysis, I state without qualification that each claimed method and materialin the '533 patent was fully disclosed in each of Grangaud (Ex. 1014) and Massonet(Ex. 1014) before the Critical Date, and consequently, all claims of the '533 patent were anticipated by Grangaud (Ex. 1014) and Massonet (Ex. 1014)and/or obvious over either Ex. 1010 or Ex. 1014 in view of Ex. 1021 or Ex. 1026.

Cross-examination

126. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear forcross examination within the United States during the time allotted for cross examination.

Right to Supplement

127. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner raises and to take into account new information as it becomes available to me.

Jurat

128. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 27 June 2013

FLORIAN J. SCHWEIGERT

CURRICULUM VITAE

FLORIAN J. SCHWEIGERT born March, 8. 1958 in München, Germany

Education:

1978-1983 Veterinary Medicine at the Veterinary FacuLty in München
DVM in 1984;
1983-1986 DoctoraL-Thesis in Nutrition PhysioLogy at the Veterinary FacuLty (Department of PhysioLogy, Biochemistry and NutritionaL PhysioLogy) in München
Dr. med. vet. (PhD) in 1986
Mentor: Professor Dr. H. Zucker "summa cum Laude"
1990 "HabiLitation" (Dr. med. vet. habiL.) for PhysioLogy and PhysioLogicaL
Chemistry at the Veterinary FacuLty in München
1991 Fachtierarzt (SpeciaLisation) for PhysioLogy

Honours and Fellowships:

1984-1985	Hanns-SeideL-Stiftung FeLLowship (PhD)
1986	Dr. med. vet. "summa cum Laude" (PhD)
1987	Study traveL supported by the Deutschen Forschungsgemeinschaft (DFG) to the USA (Boston)
1988-1990	Deutsche Forschungsgemeinschaft Post-DoctoraL-Research FeLLowship
1989	Research award: "Preis zur Förderung von Nachwuchswissen-schaftLern" der Deutschen Veterinärmedizinischen GeseLLschaft

Employment Experience:

1985-1986	Research Associate (voLLbeschäftigte wissenschaftLiche HiLfskraft) at the Department of PhysioLogy, PhysioLogicaL Chemistry and Nutrition PhysioLogy, Veterinary FacuLty, Munich, Germany
1986-1988	PostdoctoraL Research Associate (Akademischer Rat a.Z.) at the Department of PhysioLogy, PhysioLogicaL Chemistry and Nutrition PhysioLogy, Veterinary FacuLty, Munich, Germany
1988	PostdoctoraL Research Associate in the Department of Biochemistry, Tufts University, SchooL of Medicine, and Research FeLLow in Medicine in the Channing Laboratories, Harvard MedicaL SchooL, both Boston, USA
1988-1990	Research FeLLow in Medicine in the Center for BiochemicaL and BiophysicaL Sciences and Medicine, Harvard MedicaL SchooL, Boston, MA, USA
1990-1992	comparabLe to Assistant Professor (voLLbeschäftiger WissenschaftLicher AngesteLLter) at the Department of

	Reproduction and Lactation PhysioLogy at the TechnicaL University of München
1993-1996	FuLL Professor (C3) for Nutrition PhysioLogy (Department of PhysioLogy) at the Veterinary FacuLty, University Leipzig
1996-present	FuLL Professor (C4), Chair of PhysioLogy and PathophysioLogy of Nutrition at the Institute of NutritionaL Science, FacuLty of Sciences, University of Potsdam
1998 - 2002	Director of the Institut of NutritionaL Science
1999- present	Founder, Owner and Managing Director of BioAnaLyt GmbH in TeLtow Germany

Activities in the Administration of the University and Professional Politic:

University of Leipzig

- Member of the board of the FacuLty of Veterinary Medicine (FakuLtätsrat) from 1993 to 1994 and in 1996)
- Member of Commissions for SeLection of AppLicants for fuLL professorship (Berufungskommision), for HabiLitations and of the PhD Commity
- Member and Head of the Commission for technicaL equipment of the facuLty and Member of the Commission for students affairs (teaching evaLuation, coordination and evaLuation of the curricuLum)
- Member of the CounciL of the University of Leipzig (1994-1996)
- Member of the Commission for foreign Languages at the University of Leipzig (1994-1996)

University of Potsdam

- Member of the Commission for FinanciaL- and PersonaL Affairs (Head of this section) (EntwickLungs- und PLanungskommission) since 1997
- Member of the board of the FacuLty of NaturaL Science (FakuLtätsrat) from 1996 to 2004)
- Member of the Ethic comity (2002-present)

Others

- Member of the Board (1994-present) and Vice-president (1994-1997) of the ALumni Organisation (Freundeskreises Tiermedizin der Veterinärmedizinischen FakuLtät Leipzig e.V.)
- DeLegate of the Veterinary Association in Saxonia (1994-1997)
- Member of the Board and vice-president (2013-present) of the ALumni Organisation (Potsdamer UniversitätsgeseLLschaft e.V. (1997-present)
- Member of the Board of the German Nutrition Association (Deutschen GeseLLschaft für Ernährung e.V. (1997-present)
- Leader of the regionaL group (Vertrauensdozent) of the Hanns-SeideL-Foundation e.V. for BerLin und Brandenburg (1997-2010)
- Member of the Board of the Danone Research Institute (2000-present)
- Member and president (2006-2012) of the board of the Society for AppLied Vitamin Research e.V. (2002-present)

Research Projects:
Research of the Last 15 years can be summarized under the four headings

a) Carotenoids and retinoids - metaboLism and function
b) NutritionaL Proteomic
c) InternationaL Nutrition
d) Vitamins in animaL nutrition

(www.nutriproteomics.de)

Publications and Oral Presentations
ResuLts of the different projects have been presented in over 200 oraL presentations on nationaL and internationaL meetings.
Most pubLication has been pubLished in EngLish. The totaL of more than 200 pubLications consist of approx 155 originaL refereed papers, more than 30 invited reviews and contributions to text books and more than 250 abstracts.

LIST OF PUBLICATIONS -FLORIAN J. SCHWEIGERT

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