UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CYANOTECH CORPORATION
Petitioner
v.
THE BOARD OF TRUSTEES OF THE UNIVERSITY OF ILLINOIS
Patent Owner

Case IPR2013-00401[1]

Patent 5,527,533

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

REPLY OF PETITIONER
CYANOTECH CORPORATION

Submitted: May 21, 2014

[1] Consolidated with Case IPR2013-00404

TABLE OF CONTENTS

I. Patent Owner cannot recast the bases of invalidity. 1

II. The photic and ischemic insults in the '533 patent initiate a chain of events that, like vitamin A deficiency ("VAD"), vitamin C deficiency, vitamin E deficiency, other types of photic insult, and most retinal genetic disorders, causes retinal damage, injury, and disease. 2

III. In administering astaxanthin to retard the progress of xerophthalmia, and in larger doses, to cure xerophthalmia, Grangaud necessarily treated the retinal damage, injury, and disease that are the sequelae of chronic VAD, as shown by Dowling. 5

IV. The oxidant to antioxidant ratio can be increased either (A) by increasing the concentration of reactive oxygen species compared to the concentration of antioxidants, or (B) by reducing the concentration of antioxidants compared to the concentration of oxidants; either means of increasing the oxidant to antioxidant ratio can be an "initiating event" of retinal damage and injury, and if the imbalance continues, of retinal disease. 6

V. The appearance of macrophages, as described and shown by Dr. Tso in Ex. 1062, and microglia in the retina and subretinal space means the innate immune system has been triggered to dispose of cellular debris (among other functions) through phagocytosis, which always means the appearance of more free radicals. 8

VI. At the time that Grangaud administered astaxanthin, the rats in both test and control groups, all of whom had been vitamin A deficient since weaning, were suffering from retinal injury and disease and under free radical attack. 10

VII. Reading and Hayes disclose that vitamin E deficiency leads to the same degenerative sequelae as vitamin A deficiency, vitamin C deficiency, photic or ischemic insult, and retinal genetic disorders: retinal damage, triggering of the innate immune response in the retina, and phagocytosis of photoreceptors. 11

IX. George Wald and René Grangaud were correct about the absorption

spectrogram of astaxanthin, and Grangaud was correct that his shrimp oil contained high concentrations of astaxanthin. 13

X. Grangaud's administering a therapeutically effect amount of astaxanthin to retard the progress of, and to cure, xerophthalmia anticipates claims 1-15, 21-22, and 26 of the '533 patent. 14

XI. Use of astaxanthin to treat retinal damage, injury, and disease from oxidative stress, including ARMD, was obvious. 15

Patent Owner cannot recast the bases of invalidity. In its Response ("Response"), the Patent Owner ("PO") attempts to recast the bases on which to determine unpatentability of instituted claims 1–15, 21, 22, and 26 of U.S. Patent No. 5,527,533 (the '533 patent) as whether "…Grangaud [or] Dowling mentions or suggests that *vitamin A* deficiency (to which each is directed) is at all related to free radical damage to a retina or central nervous system, or to any of the disorders or diseases to which the claims are directed." Paper 32 at 2:1-4 (emphasis added). PO's expert witness similarly argues that invalidation of the instituted claims requires Petitioner to demonstrate that "*vitamin A deficiency* and/or xerophthalmia involve … damage, injury, or disease caused by oxidative attack, free radical damage, or photic insult" and that Vitamin A "prevent[s] oxidative attack or free radical damage of the eye". Ex. 2015 at ¶28 (emphasis added) Only three claims (8, 13, and 21) out of 18 instituted claims contain the term, "free radical". Only dependent claim 15 contains the word "photic", and neither the specification nor the claims of the '533 patent contain the term "oxidative" (other than a bibcite to Kurashige et al., Ex. 1020).

Invalidation of the instituted claims requires Petitioner to show that Ex. 1002 (Grangaud, 1951), alone or in combination with Ex. 1026 (Dowling, 1961), discloses the administration of *astaxanthin* as "a method of treating" (an element of every instituted claim in the '533 patent) retinal damage, injury, or disease,

which "treating" *necessarily results from* such administration of astaxanthin. Petitioner has made such a showing. Chronic vitamin A deficiency ("VAD") causes retinal damage, injury, or disease, and administration of astaxanthin necessarily results in treating such retinal damage, injury, or disease. Dorey Decl. (Ex. 1045) at R¶¶28-32. "R¶" means "Rebuttal paragraph". Petitioner will explain (i) that VAD does involve free radical-induced damage of the retina, and (ii) how *astaxanthin* (since Grangaud and Tso administered astaxanthin, not vitamin A) "prevent[s] oxidative attack or free radical damage of the eye".

The photic and ischemic insults in the '533 patent initiate a chain of events that, like vitamin A, C, or E deficiency, other types of photic insult, and most retinal genetic disorders, causes retinal damage, injury, and disease. The initiating event, be it photic, ischemic (intraocular overpressure is subsumed within the term "ischemic insult" in the '533 patent), vitamin deficiency, or genetic, is merely the trigger; after the initiating event, retinal damage, injury, and disease progress over months and even years (e.g., retinitis pigmentosa, age-related macular degeneration ("ARMD")). The '533 patent is directed to treating retinal damage, injury, and disease, not to treating the initiating event, and the '533 patent specification and claims are not limited to treating instantaneous damage or injury. Ex. 1045 at R¶¶28-32, 46-59, 61-66, 68-70,73, 75-102, 112-115. The initiating event, or trigger, may vary, but the sequellae of the initiating event always include

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