UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC. and AMNEAL PHARMACEUTICALS LLC

Petitioners

v.

YEDA RESEARCH AND DEVELOPMENT CO. LTD.

Patent Owner

Case IPR2015-00643 (Patent 8,232,250 B2)
Case IPR2015-00644 (Patent 8,399,413 B2)
Case IPR2015-00830 (Patent 8,969,302 B2)[1,2]

PATENT OWNER YEDA'S OBSERVATIONS ON CROSS-EXAMINATION OF PETITIONERS MYLAN AND AMNEAL'S REPLY WITNESSES

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[1] The word-for-word identical paper is filed in each proceeding identified in the caption.

[2] Cases IPR2015-01976, IPR2015-01980, and IPR2015-01981 have been joined with IPR2015-00643, IPR2015-00644, and IPR2015-00830, respectively.

Dr. Green's Reply Deposition Transcript (Ex. 1142)

1. In Ex. 1142 (224:3-5), Dr. Green testified that the Th1-Th2 shift theory of the mechanism of action of glatiramer acetate ("GA") was "one of the leading theories about one of the features of GA or how GA might contribute in terms of its therapeutic effect" in 2009. This testimony is relevant to Dr. Green's opinion that GA's effect on the balance of Th1/Th2 cells in the central nervous system was merely a "narrow" and "unproven" hypothesis regarding GA's therapeutic mechanism of action in ¶ 49 of Ex. 1085. This testimony is also relevant because it supports Dr. Ziemssen's testimony (Ex. 2135 at ¶ 58) and contradicts Dr. Green's assertion that a POSA would not rely on evidence regarding a Th1-Th2 shift to account for GA's therapeutic effect.

2. In Ex. 1142 (225:8-23), Dr. Green testified that the prior art he relied on to support his opinions states that "[m]ost investigations have attributed the immunomodulatory effect of GA to its capability to alter T-cell differentiation. Specifically, GA treatment is believed to promote development of Th2-polarized reactive . . . GA-reactive, CD4+ T-cells which may dampen neighboring inflammation within the central nervous system." This testimony is relevant for the same reasons identified above in ¶ 1.

3. In Ex. 1142 (228:15-25), Dr. Green testified that the prior art disclosed that "[t]he clinical effects of glatiramer acetate (GA), an approved therapy for multiple

sclerosis, are thought to be largely mediated by a T-helper 1 (Th1) to T-helper 2 (Th2) shift of GA-reactive T lymphocytes." This testimony is relevant for the same reasons identified above at ¶ 1.

4. In Ex. 1142 (278:6-18), Dr. Green testified that the prior art disclosed that, "[t]he GA-reactive T-cells are stimulated to secrete down-modulatory cytokines, like IL-4, which exert a bystander suppressive effect on other T-cells," and that these GA-reactive T-cells will enter into the central nervous system ("CNS") and secrete anti-inflammatory cytokines. This testimony is relevant for the same reasons identified above at ¶ 1.

5. In Ex. 1142 (241:23-242:7 and 280:7-11), Dr. Green testified that antigen specific T-cells secrete cytokines and proliferate in response to antigens and that the prior art disclosed that "[m]ost investigators of the human immune response to GA found that GA is not cross-reactive with MBP (myelin basic protein) at the level of proliferation." This testimony is relevant to Dr. Green's assertion that, based on Hickey 1991A (Ex. 2075), a POSA would believe that GA-specific Th2 cells that cross-react with MBP should persist in the CNS for beyond three days based upon Hickey's reference to antigen specific T-cells in ¶ 58 of Ex. 1085. This testimony clarifies that the portion of GA specific T-cells that cross react with MBP are not *specific* for MBP as described in Hickey 1991A and thus it contradicts Dr. Green's contention that a POSA would believe GA-specific T-cells

would persist for beyond three days by equating cross recognition of MBP with MBP specificity.

6. In Ex. 1142 (244:15-246:7), Dr. Green testified that he could not point to any evidence that a T-cell that cross-reacts with another antigen for which it is not specific will proliferate. This testimony is relevant for the same reasons described above in ¶ 5.

7. In Ex. 1142 (245:1-5), Dr. Green states that "this is not nor do I think I've ever presented myself to be an expert in the entire field of human immunology or mammalian immunology." This testimony is relevant to Dr. Green's expertise and ability to provide testimony in this matter.

8. In Ex. 1142 (253:21-254:2), Dr. Green testified that the prior art in the area of the immunological response to glatiramer acetate does draw distinctions between proliferation and cytokine secretion. This testimony is relevant for the same reasons described above in ¶ 5.

9. In Ex. 1142 (254:12-17), Dr. Green testified that in the section of Hickey 1991A (Ex. 2075) relied upon for T-cell lifetime in the CNS, that no mention is made of cross-reaction. This testimony is relevant to Dr. Green's hypothesis that a POSA would equate GA-activated Th2 cells (that cross-react) to MBP-specific T-cells (that specifically react) in ¶ 55 of Ex. 1085. This testimony is relevant

because it shows that Dr. Green's opinion regarding the effect of cross-reaction is not supported by the Hickey 1991A reference itself.

10. In Ex. 1142 (292:19-293:5), Dr. Green testified that it is "absolutely right" that it is unknown today how many Th2 reactive activated T-cells have to accumulate in the brain in order for GA therapy to be effective. This testimony is relevant to Dr. Green's assertion that a POSA would expect less frequent dosing to achieve a similar therapeutic effect to daily dosing in ¶ 59 of Ex. 1085. This testimony is relevant because it shows a POSA would have no mechanistic or pharmacokinetic basis upon which to form a reasonable expectation regarding whether GA would maintain its efficacy when used on a three times per week dosing regimen.

11. In Ex. 1142 (298:5-9), Dr. Green testified that the Flechter 2002A study was an open label study (*i.e.* it was unblinded). In Ex. 1142 (341:9-342:9), Dr. Green testified that "an un-blinded study is subject to greater bias than a blinded study" and that given the bias that is part of unblinded studies, the results reached by them are by no means unimpeachable. This testimony is relevant because it corroborates Dr. Ziemssen's opinion that "[t]he open-label nature of the [Flechter 2002A] study, coupled with its attempted cross-study comparison, makes it imprudent to draw any firm conclusions concerning the relative efficacy of alternate-day vs. daily administration." (Ex. 2135 at ¶155.)

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