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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte YOEL KLOOG, ELIZABETA AIZMAN, and JOAB CHAPMAN

Appeal 2015-005618
Application 13/521,637¹
Technology Center 1600

Before JEFFREY N. FREDMAN, RYAN H. FLAX and DAVID COTTA,
Administrative Patent Judges.

COTTA, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for treating a multiple sclerosis patient. The Examiner rejected the claims on appeal as obvious under 35 U.S.C. § 103(a).

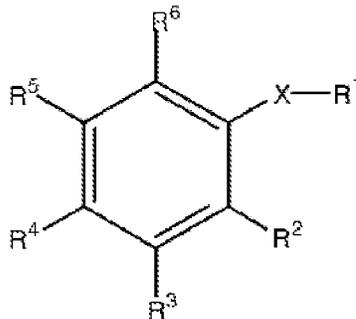
We affirm.

¹ According to Appellants, the Real Party in Interest is Kadmon Corporation.
App. Br. 4.

STATEMENT OF THE CASE

Claims 7–10, 12–17, and 19–22 are on appeal. Claim 7 is illustrative and reads as follows:

7. A method for treating a multiple sclerosis patient comprising co-administering to the patient therapeutically effective amounts of a Ras antagonist represented by the formula



wherein X represents S; wherein R¹ represents farnesyl, or geranyl-geranyl; R² is COOR⁷, CONR⁷R⁸, or COOCHR⁹OR¹⁰, wherein R⁷ and R⁸ are each independently hydrogen, alkyl, or alkenyl; wherein R⁹ represents H or alkyl; and wherein R¹⁰ represents alkyl; and wherein R³, R⁴, R⁵ and R⁶ are each independently hydrogen, alkyl, alkenyl, alkoxy, halo, trifluoromethyl, trifluoromethoxy, or alkylmercapto; and glatiramer acetate, wherein the glatiramer acetate is administered subcutaneously.

The Examiner rejected claims 7–10, 12–17, and 19–22 under 35 U.S.C. § 103(a) as unpatentable over the combination of Kloog,² Ávila Zaragoza,³ and Kreitman.⁴

² Kloog et al., WO 00/78303 A1, published Dec. 28, 2000 (“Kloog”).

³ Ávila Zaragoza et al., WO 2009/115634 A1, published Sept. 24, 2009 as evidenced by US Patent Publication No. 2011/0015132 A1 (“Ávila Zaragoza”).

⁴ Kreitman et al., WO 2006/089164 A1, published Aug. 24, 2006 (“Kreitman”).

FINDINGS OF FACT

1. Kloog discloses:

An aspect of the present invention is directed to a method for inhibiting Ras induced proliferation of cells associated with a non-malignant disease, disorder or pathological condition. The method entails administering to a patient (a human or other mammal) a Ras antagonist in an amount effective to inhibit the proliferation. The invention is particularly directed to autoimmune diseases characterized by a proliferation of T-cells (*e.g.*, normal T-cells) such as type 1 diabetes, lupus and multiple sclerosis.

Kloog p. 3, ll. 16–21.

2. Kloog discloses: “Preferred Ras antagonists include farnesyl thiosalicylic acid (FTS) and structurally related compounds or analogs thereof, which are believed to function by displacing or dislodging Ras from its membrane anchor.” *Id.* at p. 4, ll. 5–8.

3. Ávila Zaragoza discloses: “pathophysiology of MS is multifaceted and it may be necessary to combine different drugs with complementary mechanisms of action to obtain maximal clinical benefit in patients who do not respond to conventional monotherapies. The main clinical rationale for using drug combinations is obtaining additive or even synergistic therapeutic effects.” Ávila Zaragoza ¶ 4.

4. Ávila Zaragoza discloses: “It has been described that, due to its different mechanisms of action, glatiramer acetate may represent the ideal candidate to accompany other agents to achieve complementary and potentially synergistic therapeutic effects.” *Id.* ¶ 5.

5. Ávila Zaragoza discloses:

Due to its vaccine-type mechanism of action, in order to

be effective GA needs to induce an immune response against GA mediated by CD4+. Since MTA suppresses CD4+ activation, which is necessary for the generation of GA-specific T cell responses, it could be expected that the combination of MTA and GA could be neutral or even harmful.

Id. ¶ 9.

6. Ávila Zaragoza discloses: “Despite what could be expected, it has now been surprisingly found that the combined administration of MTA and GA to an MS animal model gives rise to a more potent immunomodulatory activity compared to the administration of each of the drugs separately.” *Id.* ¶ 10.

7. Ávila Zaragoza discloses: “Boggild [Boggild. J Neural (2006), 253 (Suppl 6):VI/45-VI/51] and Ramtahal et al. [Ramtahal et al. J Neural (2006); 253:1160-1164] used mitoxantrone as an induction therapy followed by maintenance therapy with GA in a series of non-random, uncontrolled observational cases, and observed a 90% reduction in the relapse rate among patients.” *Id.* ¶ 5.

8. Ávila Zaragoza discloses: “WO2005009333 describes that Copolymer 1 (GA)-related heteropolymers or peptides in combination with other immunosuppressive drugs induce an unexpected synergistic effect, and thus improve the efficacy of the current immunosuppressive regimens.” *Id.*

9. Kreitman discloses:

Glatiramer acetate (GA), also known as Copolymer-1, has been shown to be effective in treating multiple sclerosis (MS) Daily subcutaneous injections of glatiramer acetate (20 mg/injection) reduce relapse rates, progression of disability, appearance of new lesions by magnetic resonance imaging (MRI), . . . and appearance of “black holes” . . . Glatiramer acetate reduces the

proportion of MS lesions evolving into black holes.

Kreitman p. 3, ll. 15–29.

10. Kreitman discloses:

The subject invention provides a method of treating a subject afflicted with a form of multiple sclerosis comprising periodically administering to the subject an amount of glatiramer acetate and an amount of rasagiline or a pharmaceutically acceptable salt thereof, wherein the amounts when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject.

Id. at p. 9, ll. 1–10.

11. The only experimental data provided in the Specification is data relying on “experimental autoimmune encephalomyelitis (EAE),” an “animal model widely found useful for multiple sclerosis research.” Specification ¶ 55; Examples I–III.

ANALYSIS

Appellants argue claims 7–10, 12–17, and 19–22 as a group. We designate claim 7 as representative for claims 7–10, 12–17, and 19–22.

The Examiner found that Kloog disclosed administration of farnesylthiosalicylic acid (FTS) to treat multiple sclerosis, but did not teach co-administration with glatiramer acetate (GA). Final Rej. 7.

The Examiner found that Ávila Zaragoza disclosed that multiple sclerosis has a multifaceted pathophysiology, potentially making it a necessary to combine therapies for treatment. *Id.* at 8. The Examiner found that Ávila Zaragoza disclosed that GA is “an ideal candidate” for combination therapy and that multiple sclerosis could be treated with the

combination of GA and 5'-methylthioadenosine (MTA). *Id.* Ávila Zaragoza further teaches that the combined administration of GA and MTA provides a benefit over the administration of either alone. *Id.*

The Examiner found that Kreitman disclosed that treating multiple sclerosis with the combination of GA and rasigiline (a monoamine oxidase inhibitor) provides benefits over administration of either alone. *Id.* at 8–9.

Based on the combined disclosures of Kloog, Ávila Zaragoza, and Kreitman, the Examiner concluded:

It would have been obvious to a person of ordinary skill in the art at the time of invention to combine the teachings of Kloog and Avila Zaragoza along with the example of Kreitman to co-administer a Ras antagonist with glatiramer acetate because prior teaching has indicated that coadministering any drug that treats multiple sclerosis with glatiramer acetate should predictably have added benefit. The Applicant has utilized an alternative combination to address the same problem that exists in the art.

Id. at 9. In response to Appellants' arguments during prosecution, the Examiner also cited Herges,⁵ Stüve,⁶ Soos⁷ and Costello⁸ as providing

⁵ Herges et al., *Neuroprotective Effect of Combination Therapy of Glatiramer Acetate and Epigallocatechin-3-Gallate in Neuroinflammation*, 6(10) PLoS ONE 1–9 (2011) (“Herges”).

⁶ Stüve et al., *Immunomodulatory Synergy by Combination of Atorvastatin and Glatiramer Acetate in Treatment of CNS Autoimmunity*, 116(4) JOURNAL OF CLINICAL INVESTIGATION 1037–1044 (2006) (“Stüve”).

⁷ Soos et al., *Cutting Edge: Oral Type I IFN- τ Promotes a Th2 Bias and Enhances Suppression of Autoimmune Encephalomyelitis by Oral Glatiramer Acetate*, 169 JOURNAL OF IMMUNOLOGY 2231–2235 (2002) (“Soos”).

⁸ Costello et al., *Combination Therapies for Multiple Sclerosis: Scientific Rationale, Clinical Trials, and Clinical Practice*, 20 CURRENT OPINION IN NEUROLOGY 281–285 (2007) (“Costello”).

further evidence of the use of GA “as a co-administered agent to produce synergistic therapy for MS.” Final Act. 5. The teachings of these references are summarized in the Final Action. *Id.*

We adopt the Examiner’s findings of fact and reasoning regarding the scope and content of the prior art (Ans. 3–13; Final Act. 4–11) and agree that the claims are obvious over Kloog, Ávila Zaragoza, and Kreitman. We address Appellants’ arguments below.

Appellants contend that the person of ordinary skill would not have been able to predict the synergy achieved by the claimed drug combination. As support, Appellants cite Ávila Zaragoza’s teaching of “drawbacks” deriving from GA therapy, App. Br. 13–14, Kreitman’s teaching that the administration of two drugs to treat the same condition is unpredictable, *id.* at 13, and the following passage from Conway⁹:

Disease-modifying therapies have also been used in combination with drugs approved for other indications, such as corticosteroids, methotrexate, azathioprine, and cyclophosphamide. Many preliminary studies have provided favourable results for various combination regimens. However, several subsequent large, randomized, controlled trials have had negative or conflicting results. *Therefore, the usefulness of combination therapy in MS remains uncertain.*

Id. at 15. We are not persuaded.

Ávila Zaragoza expressly teaches that the pathophysiology of multiple sclerosis may require a combination of different drugs to obtain maximal clinical benefit and that “glatiramer acetate [GA] may represent the ideal

⁹ Conway et al., *Combination Therapy in Multiple Sclerosis*, 9(3) LANCET NEURO. 299–308 (2010) (“Conway”). Conway was excerpted in the December 13, 2013 Declaration of the inventor Joab Chapman.

candidate to accompany other agents to achieve complementary and potentially synergistic therapeutic effects.” FF3 and FF4. Further, both Ávila Zaragoza and Kreitman provide examples where GA was used successfully in combination other drugs, specifically, MTA and rasagiline. FF6 and FF10; *see also* FF7 and FF8 (discussing GA combination therapy with mitoxantrone and with “other immunosuppressive drugs”). These teachings provide a reasonable expectation that combination therapy with GA would be effective. The general teaching of Kreitman that combination therapy is unpredictable and Ávila Zaragoza’s discussion of the drawbacks of GA therapy do not diminish this expectation of success, particularly as both Kreitman and Ávila Zaragoza provide examples of successful GA combination therapy.

Conway’s discussion of the uncertainty of combination therapy in multiple sclerosis patients likewise does not diminish the expectation of success. The uncertainty taught by Conway is in the context of human trials and, indeed, Conway notes that preliminary animal studies of combination therapy provided favorable results. Conway Abstract. This vitiates Appellants’ argument because Appellants rely on data only from animal studies. *See* FF11. We agree with the Examiner that “Appellants can’t now argue that while [the] art demonstrates synergy in EAE models but not in human trials, [] the instant combination demonstrating synergy in EAE models with no human trials is now unexpected.” *See* Ans. 9–10.

Appellants argue that the skepticism of the inventor, Dr. Joab Chapman,¹⁰ reflects the nonobviousness of the claimed combination. App. Br. 16–19. Dr. Chapman states “[a]t the inception of the project, and before

¹⁰ Declaration of Joab Chapman, dated Dec. 31, 2013 (“Chapman Decl.”).

any experiments were initiated, my personal belief was that the combination of FTS and glatiramer acetate (GA) would not be beneficial in the treatment of multiple sclerosis.” Chapman Decl. 2. Dr. Chapman explains:

My belief was based on the knowledge that GA is an immunomodulator and is dependent on the immune system being stimulated whereas FTS is a suppressor of the immune system. Thus, I believed that the use of FTS had the potential of counteracting the stimulatory effects of GA. I did not [at] all expect the results that we achieved.

Id. We acknowledge Dr. Chapman’s initial skepticism, but are not persuaded that it renders the claimed invention nonobvious.

We have broad discretion as to the weight to give to declarations offered in the course of prosecution. *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1368 (Fed Cir. 2004). Here, we agree with the Examiner that Dr. Chapman’s skepticism mirrors that expressed in *Ávila Zaragoza*. *See* Ans. 10. Both Dr. Chapman and *Ávila Zaragoza* expressed skepticism about the effectiveness of combination therapy with GA and an immunomodulator. *Compare* FF5 and FF6 *with* Chapman Decl. 2. Both explained that they expected that an immunosuppressant (MTA in the case of *Ávila Zaragoza* and FTS in Chapman’s case) would counteract the effects of GA, which acts by stimulating the immune system. *Id.* *Ávila Zaragoza* teaches that this skepticism is misplaced and that an immunosuppressant may indeed exhibit synergistic effects when used with GA. FF6.

Appellants argue that *Ávila Zaragoza*’s teaching that the combination of MTA and GA exhibits synergism would not have caused one to expect that FTS would exhibit synergism with GA because of the differences between MTA and FTS with respect to structure, cellular mode of action and

immunological effects. App. Br. at 19. As support, Appellants cite the Chapman Declaration, which states:

The differences between the FTS and MTA are substantial. They are structurally distinct, have a completely different cellular mode of action, and exert different immunological effects. 5'-Methylthioadenosine (MTA) is a naturally occurring sulfur-containing nucleoside present in all mammalian tissues. MTA is produced from S-adenosylmethionine mainly through the polyamine biosynthetic pathway, where it behaves as a powerful inhibitory product. FTS is a synthetic compound which is analogous to the farnesylated signaling proteins such as Ras and inhibits their activity by competing with their membrane binding sites. Another important difference is how the two agents exert their immunological effect. As described in Avila Zaragoza, MTA acts on CD4 cells. As reported in Aizman et *al.*, 2010 and in earlier literature, . . . [i]nhibition of Ras attenuates the course of experimental autoimmune neuritis. . . . FTS acts by inhibiting both CD4 and CD8 cells. Based on these differences, my professional opinion is that the results reported in Avila Zaragoza would not have suggested that the combination of FTS and GA is synergistic.

Chapman Decl. 5–6 (internal citations omitted). We are not persuaded.

Both MTA and FTS are immunosuppressants used to treat multiple sclerosis. The principal difference between MTA and FTS, as explained by Dr. Chapman, is that MTA acts on CD4 cells while FTS acts on both CD4 and CD8 cells. While Dr. Chapman provides his professional opinion with respect to the cumulative effects of the differences between MTA and FTS, Appellants do not provide persuasive evidence that FTS's additional action through CD8 cells would distinguish it from MTA with respect to its potential to act synergistically with GA. Accordingly, we agree with the Examiner that "Appellants have not clearly shown how the initial skepticism

that was solved by Avila [Zaragozá] is different from the instant skepticism provided by the expert's declaration." Ans. 10.

Appellants contend that the additional evidence of synergistic GA combination therapy relied upon by the Examiner – i.e., Herges, Stüve, Soos, and Costello – is “not probative of obviousness.” App. Br. 20. Appellants argue that Herges, Stüve, and Soos do not support obviousness based on considerations derived from testing in humans. *Id.* at 21. We are not persuaded at least because, as the Examiner explained “[e]ach disclosure explicitly teaches that synergistic benefit is achieved when combining GA to a plurality of therapeutic agents in an EAE animal model.” Ans. 11. As discussed above, Appellants rely solely on data from an EAE animal model. *See supra* p. 8–9; *see also* FF11.

Appellants contend that Costello does not support a finding of obviousness based on Dr. Chapman's disagreement with Costello's statement that GA is “the ideal candidate to partner with other agents to achieve complementary and potentially synergistic effects.” App. Br. 22; Costello 283. The reasons for Dr. Chapman's disagreement with Costello are similar to the reasons Dr. Chapman provided for not expecting the combination of FTS and glatiramer acetate (GA) to be effective when he initiated his project. For the reasons already discussed in connection with that argument, we are not persuaded. *See supra* p. 9–10.

Accordingly, we affirm the Examiner's decision to reject claim 7 as obvious over the combination of Kloog, Ávila Zaragozá, and Kreitman. Because they were not argued separately, 8–10, 12–17, and 19–22 fall with claim 7.

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SUMMARY

For these reasons and those set forth in the Examiner's Answer, the Examiner's final decision to reject claims 7–10, 12–17, and 19–22 is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1).

AFFIRMED