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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STALEY A. BROD[1]

Appeal 2019-004711
Application 15/063,822
Technology Center 1600

Before ERIC B. GRIMES, JOHN G. NEW, and JAMIE T. WISZ, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method of treating multiple sclerosis, which have been rejected as anticipated or obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM but designate the affirmance a new ground of rejection.

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[1] Appellant does not identify a real party in interest in the Appeal Brief, so we assume that the named inventor is the real party in interest. 37 C.F.R. § 41.37(c)(1)(i). We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42.

STATEMENT OF THE CASE

The Specification states that "B cell depletion in MS [multiple sclerosis] using a mAb to CD20 (rituximab) has shown promising results and leads to amelioration of disease." Spec. 2:7–8 (reference citation omitted). "Additionally, recent clinical trials have established B cell depletion by the anti-CD20 chimeric antibody Rituximab as a beneficial therapy for patients with relapsing-remitting multiple sclerosis (MS)." *Id.* at 2:10–13. "[T]he present invention relates to uses of ingested (orally administered) anti-CD20 antibody in the treatment of autoimmune diseases," including multiple sclerosis. *Id.* at 1:9–10, 16:7–8.

Claims 1–3, 5–11, and 13–15 are on appeal. Claims 1 and 9, reproduced below, are the independent claims:

> Claim 1: A method for treating or delaying the onset of multiple sclerosis in a human subject comprising orally administering to the subject an effective dose of an anti-CD20 monoclonal antibody.
>
> Claim 9: A method of decreasing IL-17, IL-12, TNF-α and IFN-γ in a human subject with multiple sclerosis comprising:
>
> orally administering to the subject an effective dose of dose of an anti-CD20 monoclonal antibody.

The claims stand rejected as follows:

Claims 1–3, 5–7, 9–11, 13, and 14 under 35 U.S.C. § 102(a)(1) as anticipated by Smith[2] (Ans. 3) and

Claims 1–3, 5–11, and 13–15 under 35 U.S.C. § 103 as obvious based on Smith and Brod[3] (Ans. 4).

[2] US 2008/0089885 A1, published Apr. 17, 2008.
[3] WO 2008/049011 A2, published Apr. 24, 2008.

OPINION

Anticipation

The Examiner has rejected claims 1–3, 5–7, 9–11, 13, and 14 as anticipated by Smith. The Examiner finds that Smith teaches "oral administration of fully humanized monoclonal antiCD20 antibody for the treatment of autoimmune disease such as MS (aka multiple sclerosis) (see, e.g., [0011], [0097], [0242], [0247], [0270], [0272], [0273], [0281], Example 1, claim 18)." Ans. 3. The Examiner also finds that the functions recited in claim 9 "are inherently found in the method of Smith et al. because said claims recite use of the same antibody orally administered to the same autoimmune disease." *Id.*

Appellant argues that "claims 1 and 9 recite oral administration of an anti-CD20 monoclonal antibody in distinct contrast to Smith's disclosure of intravenous administration of the optimized anti-CD20 antibody (Example 5)." Appeal Br. 5. Appellant argues that Smith's disclosure of oral administration "is boilerplate language that Smith's antibodies may be administered by any route and method known in the world, including oral administration, at the time of the invention." *Id.*

We agree with Appellant that the Examiner has not shown that Smith anticipates the claimed method. Smith discloses "[c]ompositions and methods . . . for treating diseases associated with CD20, including lymphomas, autoimmune diseases, and transplant rejections. Compositions include anti-CD20 antibodies." Smith ¶ 8. "Particular autoimmune diseases contemplated for treatment using the methods of the invention include systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn's disease,

psoriasis, autoimmune thrombocytopenic purpura, multiple sclerosis," etc. *Id.* ¶ 11.

Smith states that "[m]ethods of preparing and administering the anti-CD20 antibodies . . . of the invention to a subject in need thereof are well known to or are readily determined by those skilled in the art." *Id.* ¶ 273. "The route of administration of the anti-CD20 antibody . . . may be, for example, oral, parenteral, by inhalation or topical." *Id.* Smith provides a working example in which an anti-CD20 monoclonal antibody is intravenously administered to mice that had been injected with human lymphoma cells. *Id.* ¶¶ 375–376.

"[U]nless a reference discloses within the four corners of the document not only all of the limitations claimed but also all of the limitations arranged or combined in the same way as recited in the claim, it cannot be said to prove prior invention of the thing claimed and, thus, cannot anticipate under 35 U.S.C. § 102." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). "[I]t is not enough that the prior art reference . . . includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Id.* "Such picking and choosing may be entirely proper in the making of a 103, obviousness rejection . . . but it has no place in the making of a 102, anticipation rejection." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972).

Here, Smith lists multiple sclerosis as one of the autoimmune diseases contemplated for treatment using its methods, and it lists oral administration as one of the routes by which anti-CD20 antibodies could be administered. However, it does not provide any teachings that link the treatment of multiple sclerosis, specifically, with oral administration, specifically, of

Smith's anti-CD20 antibodies. Because Smith does not disclose "all of the limitations arranged or combined in the same way as recited in the claim[s]," *Net MoneyIN*, 545 F.3d at 1371, it does not anticipate them. We reverse the rejection under 35 U.S.C. § 102(a)(1).

Obviousness

The Examiner has rejected all of the claims as obvious based on Smith and Brod. The Examiner relies on Smith for the same findings discussed above with regard to anticipation. The Examiner finds that Smith does not teach administration of one of the compounds recited in claims 8 and 15, such as α-MSH, in its method. Ans. 4.

The Examiner finds that "Brod teaches use of alpha MSH to treat autoimmune disease including SLE." *Id.* The Examiner finds that both Smith and Brod teach that their methods can be combined with another treatment. *Id.* The Examiner concludes that it would have been obvious

> to create the claimed invention because Smith et al. teach oral administration of fully humanized anti-CD20 antibody for the treatment of autoimmune disease such as SLE whilst Brod teaches use of alpha MSH to treat autoimmune disease including SLE and both references disclose that their treatments can be combined with any art known therapy for the autoimmune disease.

Id. at 5.

We agree with the Examiner that the claimed methods would have been obvious based on Smith and Brod. Because we rely on findings and reasoning in addition to those presented by the Examiner, however, we designate our affirmance a new ground of rejection in order to give Appellant a full and fair opportunity to respond.

As discussed above, Smith discloses methods of treating autoimmune diseases with anti-CD20 antibodies. Smith ¶ 8. Smith states that "[p]articular autoimmune diseases contemplated for treatment using [its] methods" include multiple sclerosis. *Id.* ¶ 11. Smith discloses monoclonal antibodies that are useful in its methods. *Id.* ¶¶ 103–104.

Smith discloses that anti-CD20 antibodies can be administered orally, parenterally, by inhalation, or topically. *Id.* ¶ 273. *See also id.* ¶ 281 ("Certain pharmaceutical compositions used in this invention may be orally administered in an acceptable dosage form including, e.g., capsules, tablets, aqueous suspensions or solutions.").

Smith discloses that effective dosages for multiple sclerosis, and other diseases, will vary and "[t]reatment dosages may be titrated using routine methods known to those of skill in the art to optimize safety and efficacy." *Id.* ¶ 284. Smith describes factors that may influence the mode of administration and amount of anti-CD20 antibody administered, and provides exemplary dosages and dosage ranges. *Id.* ¶ 285.

Based on Smith's teachings, it would have been obvious to treat a human subject having multiple sclerosis by orally administering an anti-CD20 monoclonal antibody (mAb). Smith discloses that effective doses can be determined by those skilled in the art using routine methods.

Smith does not describe the effect of an anti-CD20 mAb on IL-17, IL-12, TNF-α, and IFN-γ, as recited in claims 7 and 9. However, as the Examiner pointed out (Ans. 3), administration of the same antibody, by the same route, to the same patient, would reasonably be expected to have the same effects. It is therefore reasonable to shift the burden to Appellant to show that carrying out the method suggested by Smith would not result in

decreasing the levels of IL-17, IL-12, TNF-α, and IFN-γ, as recited in the claims. *See In re Best*, 562 F.2d 1252, 1254–55 (CCPA 1977) ("[W]here the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.").

Thus, Smith supports a prima facie case of obviousness with respect to independent claims 1 and 9, and dependent claim 7. With regard to claims 2 and 10, Smith suggests using a fully humanized mAb in its methods. *See* Smith ¶¶ 88–91. With regard to claims 3 and 11, Smith discloses that rituximab was a commercially available anti-CD20 mAb. *Id.* ¶ 104. Thus, it would have been obvious to use rituximab in Smith's method, because it was commercially available. With regard to claims 5 and 13, Smith describes a broad range of dosages that depend on a patient's weight but encompass the claimed doses for most, if not all, human patients. *Id.* ¶ 285.[4] With regard to claims 6 and 14, Smith suggests solid and liquid formulations. *Id.* ¶ 281.

With regard to claims 8 and 15, Smith discloses that "[t]he anti-CD20 antibodies of [its] invention can be used in combination with any known therapies for autoimmune and inflammatory diseases." *Id.* ¶ 263. Smith does not, however, specifically suggest combining its anti-CD20 antibody treatment with a SIRS peptide, α-MSH, ACTH, or SST.

[4] Smith suggests specific dosages of, for example, 0.02 mg/kg and 0.5 mg/kg. *Id*. For a patient weighing 75 kg (165 pounds), these dosages correspond to doses of 1.5 mg and 37.5 mg.

Brod states that "[a]lpha-melanocyte stimulating hormone (MSH) is a short amino acid hormone." Brod ¶ 4. Brod discloses "a method for treating or delaying the onset of an autoimmune disease in a subject comprising administering to the subject an effective dose of an alpha-MSH monomer." *Id.* ¶ 6. "In preferred embodiment, an alpha-MSH monomer is administered to a subject orally." *Id.*

Brod also discloses that "[i]n some preferred aspects, the invention provides methods for treating or delaying the onset of an autoimmune disease in a human subject." *Id.* ¶ 13. "In some particularly preferred aspects, a subject for treatment by methods of the invention has, or is a [sic] at risk for developing, multiple sclerosis. As used herein, a 'subject' may be human or animal." *Id.*

Based on these teachings, it would have been obvious to a person of ordinary skill in the art to modify Smith's method of treating multiple sclerosis with an anti-CD20 mAb to include further administering α-MSH, because Smith suggests combining its method with any known therapy for autoimmune diseases and Brod discloses administration of α-MSH for treatment of autoimmune diseases, especially multiple sclerosis, in humans.

Appellant argues that Smith's disclosure does not "provide a person of ordinary skill in this art with a reasonable expectation that oral administration of an anti-CD20 antibody would actually work." Appeal Br. 5. Appellant cites Wang[5] as evidence that "it is very well recognized in the art that oral administration of antibodies is limited by degradation in the gastrointestinal

[5] Wang et al., Monoclonal Antibody Pharmacokinetics and Pharmacodynamics, *Clinical Pharmacology & Therapeutics*, 84:548–58 (2008).

tract and by inefficient diffusion through the gastrointestinal epithelium and thus oral administration is not desirable." *Id.* at 6. Appellant argues that "**Wang** et al. describes the state of this art at the time of **Smith** et al. which reference was publically available." *Id.* at 7.

In response, the Examiner cites Weisbart[6] as showing that "oral administration of antibody can be done and has been done." Ans. 6. With regard to Appellant's argument that Weisbart's composition contained polyclonal antibodies, not monoclonal antibodies as in the claims (Appeal Br. 9), the Examiner finds that "Weisbart's polyclonal antibod[ies] from human serum were fractionated, precipitated *and reconstituted in water* which makes them no different than a formulation comprising monoclonal antibodies." *Id.*, citing Weisbart's Examples 1 and 2. The Examiner concludes that "[t]he reason Weisbart's antibody can be orally administered is not because they are polyclonal but because Weisbart took into consideration of protecting the antibody against degradation in the oral formulation by using enteric coating with capsules or tablets." *Id.*, citing Weisbart ¶¶ 36–38.

"[A] prior art printed publication cited by an examiner is presumptively enabling barring any showing to the contrary by a patent applicant." *In re Antor Media Corp.*, 689 F.3d 1282, 1288 (Fed. Cir. 2012). "The applicant, however, can then overcome [a] rejection by proving that the relevant disclosures of the prior art patent are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003).

[6] Weisbart et al., US 2002/0098182 A1, published July 25, 2002.

Thus, Smith is presumed to enable what it discloses, and the burden is on Appellant to prove that it is not enabling. More to the point, though, the affirmed rejection is for obviousness, not anticipation, and "[u]nder § 103, a reference need not be enabled; it qualifies as prior art, regardless, for whatever is disclosed therein." *Id.* at 1357. The relevant question is whether the cited prior art would have provided a skilled artisan with a reasonable expectation of success in carrying out the oral administration suggested by Smith.

Appellant cites Wang as evidence that Smith does not teach successful oral administration of anti-CD20 antibodies. Appeal Br. 7. Wang provides an overview of antibody pharmacokinetics and pharmacodynamics, and states that "many antibody drugs demonstrate attributes that complicate drug development, including very poor oral bioavailability." Wang 548, Abstract. Wang also states that "oral absorption of antibody is limited by presystemic degradation in the gastrointestinal tract and by inefficient diffusion or convection through the gastrointestinal epithelium." *Id.* at 550, left col.

Appellant also cites Renukuntla[7] and Shaji[8] as evidence that "many projects focusing on oral delivery of peptides and proteins have ended in failure." Appeal Br. 8. Renukuntla states that "[o]ral delivery of peptide and protein drugs faces immense challenge partially due to the gastrointestinal (GI) environment. . . . Upon oral administration, gastrointestinal epithelium acts as a physical and biochemical barrier for absorption of proteins resulting

[7] Jwala Renukuntla et al., Approaches for Enhancing Oral Bioavailability of Peptides and Proteins, *Int. J. Pharm.* 447:75–93 (2013).
[8] Jessy Shaji & V. Patole, Protein and Peptide Drug Delivery: Oral Approaches, *Indian J. Pharm. Sci.*, 70:269–77 (2008).

in low bioavailability." Renukuntla, Abstract. Shaji states that "[d]elivering proteins and peptides by the oral route is extremely challenging. . . . The low bioavailability of drugs remains to be an active area of research. Several sites in the [GI tract] have been investigated by researchers, but no major breakthrough with broad applicability to diverse proteins and peptides has been achieved." Shaji, Conclusion.

On the other hand, the Examiner cites Weisbart as evidence of successful oral administration of antibodies. Ans. 6. Weisbart discloses "a method for treating an immune-mediated disease by orally administering a composition constituting a human plasma fraction enriched in human immunoglobulin G." Weisbart ¶ 15. Weisbart provides working examples that describe precipitating desired antibody fractions from human plasma, freeze drying the product, and redissolving the purified antibodies in water. *Id.* ¶¶ 46–54. With regard to oral administration, Weisbart states:

> In order to administer the disclosed compositions orally, such compositions can be coated by, or administered with, a material to prevent inactivation. For example, an enteric coated composition can be specifically designed to transport [antibody fractions] to the gastrointestinal tract. Enteric coating technology is conventional in the art of pharmaceutical preparation and is readily practiced in accordance with the present invention with the knowledge of the ordinarily skilled artisan.

Id. ¶ 36.

In addition, Appellant's Specification itself states: "*Ingested proteins* such as type I IFN . . . SIRS peptide 1–21 . . . a-MSH . . . ACTH . . . and SST . . . inhibit attacks and inflammation in acute EAE." Spec. 1:21–22 (emphasis added). Experimental autoimmune encephalomyelitis (EAE) "is a T cell mediated inflammatory autoimmune process of the CNS that

resembles the human demyelinating disease multiple sclerosis (MS) . . . and provides a useful animal model for the evaluation of potential therapies for cellular mediated autoimmune diseases." *Id.* at 1:18–21.

Thus, Appellant's Specification itself provides evidence that, at the time the instant application was filed, five proteins had been shown to alleviate symptoms in an animal model of multiple sclerosis when administered by ingestion; i.e., orally.

In summary, Appellant's evidence shows that oral administration of antibodies and other proteins generally resulted in low bioavailability. But Weisbart describes oral administration of antibodies in combination with, for example, a conventional enteric coating for delivery to the GI tract, and Appellant's Specification itself provides evidence that other proteins had been orally administered in an animal model of multiple sclerosis and shown to alleviate symptoms. And both Smith and Brod expressly suggest oral administration of their proteinaceous active agents.

We conclude that, on balance, the evidence supports the Examiner's position that a person of ordinary skill in the art would have had a reasonable expectation of successfully carrying out Smith's method of treating multiple sclerosis by administering an anti-CD20 monoclonal antibody by oral administration. While success in doing so might not have been assured, "[o]nly a reasonable expectation of success, not absolute predictability, is necessary for a conclusion of obviousness." *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985) (citation omitted).

CONCLUSION

We reverse the rejection of claims 1–3, 5–7, 9–11, 13, and 14 as anticipated by Smith.

We affirm the rejection of claims 1–3, 5–11, and 13–15 as obvious based on Smith and Brod but, because our findings and rationale differ substantively from the Examiner's, we designate the affirmance a new ground of rejection. *See In re Kronig*, 539 F.2d 1300, 1302–03 (CCPA 1976).

DECISION SUMMARY

In summary:

Claims Rejected	**35 U.S.C. §**	**Reference(s)/ Basis**	**Affirmed**	**Reversed**	**New Ground**
1–3, 5–7, 9–11, 13, 14	102(a)(1)	Smith		1–3, 5–7, 9–11, 13, 14	
1–3, 5–11, 13–15	103	Smith, Brod	1–3, 5–11, 13–15		1–3, 5–11, 13–15
Overall Outcome			1–3, 5–11, 13–15		1–3, 5–11, 13–15

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). Section 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review." Section 41.50(b) also provides:

> When the Board enters such a non-final decision, the appellant, within two months from the date of the decision, must exercise

> one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:
>
> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

AFFIRMED; 37 C.F.R. § 41.50(b)