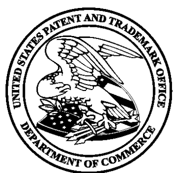

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte STEFAN BASSARAB, BARBARA ENENKEL, PATRICK GARIDEL, HEIDRUN SCHOTT, SANJAYA SINGH, and TOBIAS LITZENBURGER[1]

Appeal 2020-000370
Application 13/494,398
Technology Center 1600

Before ERIC B. GRIMES, LINDA M. GAUDETTE, and FRANCISCO C. PRATS, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to an antibody-containing pharmaceutical composition, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

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[1] Appellant identifies the real party in interest as ABGENOMICS COOPERATIEF U.A. Appeal Br. 3. We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42.

STATEMENT OF THE CASE

P-selectin glycoprotein ligand-1, or PSGL-1, "is likely to contribute to pathological leukocyte recruitment in many inflammatory disorders . . . , suggesting that inhibitors of PSGL-1, such as antibodies to PSGL-1, are potentially useful anti-inflammatory drugs." Spec. ¶ 4. One antibody to PSGL-1, known as h15A7, has been described in the prior art. *Id.* ¶ 163. "Antibody h15A7 is an IgG4 isotype antibody." *Id.* Appellant introduced a "$Ser^{228} \rightarrow Pro^{228}$ mutation . . . into the hinge region of h15A7. The resulting hinge mutant of h15A7 is called 15A7H herein. . . . The remaining protein sequence of 15A7H is identical to h15A7." *Id.* Antibody 15A7H includes all of the properties recited for the antibody in the claimed composition. *Id.* ¶¶ 20, 21.

"IgG4 antibodies are known to undergo a proccess [sic] called Fab arm exchange, also known as IgG4 shuffling, in which . . . the heavy chains . . . separate and randomly re-associate to produce a mixed population of IgG4 molecules with randomized heavy-chain and light-chain pairs." *Id.* ¶ 31. "It has been demonstrated that a Serine to Proline mutation . . . at position 228 using the EU index . . . in the hinge region of human IgG4 results in the reduction of IgG4 'half-antibody' molecules and reduced heterogeneity/shuffling of IgG4 molecules." *Id.* ¶ 32. The Specification discloses that, as a result of "the $Ser^{228} \rightarrow Pro^{228}$ mutation . . . [t]he amount of half antibody molecules was reduced from ~8–10% for h15A7 to below 1% for 15A7H." *Id.* ¶ 167.

Claims 7, 8, 10–12, and 22 are on appeal. Claim 7, reproduced below, is illustrative:

7. A pharmaceutical composition comprising

(i) a monoclonal antibody which immunospecifically binds to human PSGL-1 comprising:

(a) a variable light ("VL") chain region comprising the amino acid sequence of SEQ ID NO: 3;

(b) a heavy chain comprising variable heavy ("VH") chain region comprising the amino acid sequence of SEQ ID NO: 4; and

(c) a human IgG4 constant region which contains a Serine to Proline substitution at amino acid 228 of the heavy chain numbered according to the EU index; and

(ii) a pharmaceutically acceptable carrier,

wherein, the pharmaceutical composition comprises less than 1% half antibody molecules.

OPINION

Claims 7, 8, 10–12, and 22 stand rejected under 35 U.S.C. § 103(a) as obvious based on Lin,[2] Stubenrauch,[3] Mataraza,[4] Labrijn '366,[5] Osorio,[6] Graus,[7] and Demarest.[8] Final Action[9] 15. The Examiner finds that Lin teaches "anti-PSGL antibodies and compositions thereof, including the 15A7

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[2] Lin et al., US 2009/0191204 A1, published July 30, 2009.
[3] Kay Stubenrauch et al., "Impact of Molecular Processing in the Hinge Region of Therapeutic IgG4 Antibodies on Disposition Profiles in Cynomolgus Monkeys," Drug Metabolism and Disposition 38(1):84–91 (2010).
[4] Mataraza et al., US 2012/0183565 A1, published July 19, 2012.
[5] Labrijn et al., US 2011/0086366 A1, published Apr. 14, 2011.
[6] Osorio et al., US 2010/0233157 A1, published Sept. 16, 2010.
[7] Graus et al., US 7,563,441 B2, issued July 21, 2009.
[8] Demarest et al., US 2009/0092614 A1, published Apr. 9, 2009.
[9] Office Action mailed April 16, 2018.

antibody . . . for a variety of utilities." *Id*. at 16. The Examiner finds that Lin does not describe the serine-to-proline substitution (S228P) recited in Appellant's claims but finds that this substitution was known in the art based on Stubenrauch, Mataraza, Labrijn '366, Osorio, and Graus.

In particular, the Examiner finds that Stubenrauch "concluded that . . . IgG4 swapping in vivo was markedly attenuated by S228P mutation in efforts to stabilize therapeutic IgG4 antibodies with a reduced or eliminated of [sic] in vivo Fab arm exchange." *Id*. The Examiner also finds that Labrijn '366 teaches that "replacement of the core-hinge region resid[u]e Ser228 by Pro (S228P) results in partial stabilization of an IgG4 molecule in vitro and in vivo." *Id*.

The Examiner concludes that,

> [g]iven the availability of the anti-PSGL-1 antibody 15A7 taught by Lin . . . and the teachings . . . to reduce in vivo Fab arm exchange and stabilize therapeutic IgG4 antibodies, one of ordinary skill in the art at the time the invention was made would have been motivated to provide anti-PSGL-1 antibodies, including the 15A7 antibody, with the known modification of human therapeutic antibodies having the human IgG4 constant region which contains a serine to proline substitution at amino acid residue 228.

Id. at 17.

Appellant contends that

> a person of ordinary skill in the art would not have recognized that a pharmaceutical composition comprising a *specific* anti-PSGL-1 antibody (*e.g.*, 15A7) that includes an IgG4 heavy chain comprising the S228P mutation would predictably result in the composition having the *specific property* (*e.g.*, containing less than 1% half antibody molecules) recited in the claims on appeal.

Appeal Br. 6. Appellant cites references that, it contends, provide evidence that the effect of an S228P mutation on an antibody is unpredictable. *Id.* at 7–9. Appellant also contends that "[t]he extent of the reduction in Fab arm exchange exhibited by the claimed invention is unexpected, given the unpredictability in the art." *Id.* at 10.

We have considered the evidence cited by Appellant and by the Examiner and conclude that a preponderance of the evidence supports a conclusion of obviousness. Lin states that its "invention relates to antibodies and their derivatives that induce apoptosis upon binding to P-Selectin Glycoprotein Ligand-1 (PSGL-1) on activated T cells." Lin ¶ 3. Lin states that its antibodies are useful for treating subjects "having a condition related to an excessive or unwanted T cell-mediated immune response, e.g., patients suffering from autoimmune diseases, transplant rejection, allergic diseases, or T cell-derived cancers." *Id.* ¶ 25. Lin discloses therapeutic compositions comprising its antibodies and states that, "[g]enerally, the antibody is suspended in a pharmaceutically-acceptable carrier (e.g., physiological saline)." *Id.* ¶ 28.

One anti-PSGL-1 antibody disclosed by Lin is "a humanized 15A7 antibody." *Id.* ¶ 6. Appellant's Specification states that "[a]ntibody h15A7 contains the humanized 15A7 heavy and light chain variable regions." Spec. ¶ 163. The Specification also states that, other than the recited S228P mutation, "[t]he remaining protein sequence of 15A7H is identical to h15A7." *Id.* Appellant does not dispute that Lin's humanized 15A7 antibody comprises the SEQ ID NO: 3 and SEQ ID NO: 4 regions recited in claim 7. *See* Appeal Br. 6.

Rather, the critical issue in this case is whether the effect of mutating serine to proline at EU index position 228 (S228P) would have been predictable. More specifically, the issue is whether a person of ordinary skill in the art would have reasonably expected the S228P mutation to result in an antibody-containing pharmaceutical composition comprising less than 1% half antibody molecules, as required by claim 7.

On that issue, Stubenrauch addresses "whether stabilization of the core hinge of a therapeutic IgG4 antibody by mutation of Ser228 to Pro (S228P) would be sufficient to prevent in vivo Fab arm exchange." Stubenrauch 84, Abstract. "The results indicated that S228P mutation did not completely prevent Fab arm exchange in vitro in buffer under reducing conditions relative to IgG4 WT." *Id.* In the "[r]esults of the in vivo studies . . . [i]n contrast, serum from cynomolgus monkeys dosed with the IgG4 mutant was virtually free of swapped IgG4." *Id.* Stubenrauch concludes that "IgG4 swapping in vivo was markedly attenuated by S228P mutation." *Id.*

Stubenrauch's data address the effect of the S228P mutation on Fab arm exchange, which can result from the generation of half-antibodies. *See id.* at 84, right col. However, Stubenrauch does not disclose data regarding the effect of the S228 mutation on the presence of half-antibodies, specifically.

Labrijn '366 also discusses half-antibody (or "half-molecule") formation and Fab arm exchange in IgG4 antibodies. Labrijn '366 ¶ 3. Labrijn '366 states that "[n]atalizumab . . . and gemtuzumab . . . are two humanized IgG4 antibodies currently approved for human use." *Id.* ¶ 4.

Labrijn '366 discloses results based on commercial formulations of the two antibodies. *Id*. ¶ 107.

Specifically, "[t]o determine the type of core-hinge[,] samples . . . of natalizumab and gemtuzumab were analyzed" and compared to three antibodies (IgG1, IgG4 (i.e., WT) and IgG4S228P) directed against EGFR and an IgG4 (WT) antibody directed against CD20. *Id*. ¶ 128. Labrijn '366 discloses that "the IgG4 molecules revealed substantial amounts of half-molecules in addition to intact antibodies." *Id*. However, "[t]he S228P mutation (IgG4S228P) stabilized the IgG4 molecule as demonstrated by the loss of half-molecules." *Id*.

Labrijn '366 states that "[a]nalysis of natalizumab revealed the presence of half-molecules indicative of a wild-type IgG4 core-hinge. Gemtuzumab, however, showed no half-molecules, indicating a stabilized core-hinge." *Id*. Labrijn '366 also discloses "the hinge region amino acid sequences for natalizumab and gemtuzumab." *Id*. The disclosed sequences are reproduced below (differing amino acid emphasized):

Natalizumab: YGPPCP**S**CPAPEFLGGPSVFLFPPKPK
Gemtuzumab: YGPPCP**P**CPAPEFLGGPSVFLFPPKPK

The only amino acid difference, thus, is an S (serine) in natalizumab (WT core-hinge) versus a P (proline) in gemtuzumab (stabilized core-hinge).

In summary, Labrijn '366 discloses that gemtuzumab, with a stabilized core-hinge having the same S228P mutation as IgG4S228P, "showed no half-molecules" in the pharmaceutical composition obtained from the manufacturer.

Labrijn '366 also discloses further data "suggesting that IgG4 core-hinge stabilization prevents Fab-arm exchange in vitro." *Id*. ¶ 129. Finally,

Labrijn ’366 discloses that its data showed that, for “hinge-stabilized IgG4 (IgG4S228P-EGFR and gemtuzumab) . . . core-hinge stabilization prevented IgG4 Fab-arm exchange in vivo, although we can not rule out that low-level exchange below the level of detection (<0.5% in 72 hrs) of hinge-stabilized IgG4 does occur.” *Id.* ¶ 130.[10]

Labrijn ’366 thus provides evidence that the S228P mutation eliminated half-antibody generation in compositions comprising IgG4S228P-EGFR (“the loss of half-molecules”) or gemtuzumab (“no half-molecules”). This disclosure would have provided a person of ordinary skill in the art with a reasonable expectation that half-antibody generation would be eliminated by modifying the humanized 15A7 antibody disclosed by Lin to include the S228P mutation, and suspending the modified antibody in physiological saline (Lin ¶ 28).

Lin and Labrijn ’366 provide a reason to modify Lin’s humanized 15A7 to include the S228P mutation, because Lin discloses that pharmaceutical compositions comprising its antibody are useful in treating diseases (Lin ¶¶ 25–28) and Labrijn ’366 teaches that the Fab arm exchange resulting from half-antibody formation can cause adverse effects when antibodies are used therapeutically (Labrijn ’366 ¶¶ 3, 6–7). Thus, it would

[10] The Examiner also cites Mataraza, Osorio, and Graus with respect to the S228P mutation. Final Action 16–17. These references discuss the S228P mutation in general terms, but they do not shed light on its effect on half-antibody generation. *See* Mataraza ¶ 396; Osorio ¶ 161; Graus 11:16–23. Therefore, they do not add any disclosure that is material to the rejection on appeal.

have been obvious to modify humanized 15A7 to include the S228P mutation to avoid the adverse effects discussed by Labrijn '366.

However, Appellant argues that "[a]t the time of the claimed invention, there was unpredictability in the art with regard to antibody stabilization in pharmaceutical compositions." Appeal Br. 7. Appellant cites Wang[11] as teaching that "[a]lthough antibodies share certain structural similarities, development of commercially viable antibody pharmaceuticals has not been straightforward because of their unique and somewhat unpredictable solution behavior." *Id.* (citing Wang 1, abstract). Appellant argues that, based on this disclosure, a skilled artisan "would have understood that certain modifications that were sufficient to stabilize one antibody *were not* necessarily sufficient to stabilize another antibody having a different amino acid sequence." *Id.*

Appellant has not, however, pointed to any disclosure in Wang that addresses the specific issue relevant to this appeal: the effect of the S228P mutation on half-antibody generation in a pharmaceutical composition. Wang therefore carries no weight as evidence on the dispositive issue here.

Appellant argues, though, that "[t]here was also unpredictability in the art with respect to the effects of the S228P mutation on antibody stability." Appeal Br. 7. Appellant points to the statement in Labrijn (2009)[12] that "[t]hus, core-hinge stabilization alone prevents IgG4 Fab-arm exchange *in*

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[11] Wang et al., "Antibody Structure, Instability, and Formulation," J. Pharm. Sci. 96:1–26 (2007).
[12] Labrijn et al., "Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 *in vivo*," Nature Biotechnol. 27:767–771 (2009).

vivo, although we cannot eliminate the possibility of low-level exchange of hinge-stabilized IgG4 below the level of detection (<8.3% in 72 h; Supplementary Fig. 2).” *Id*. (citing Labrijn (2009) at 768, right col.). In contrast, Appellant argues, Schuurman[13] “discloses ‘half molecule exchange occurs between an IgG4 molecule containing an IgG1 hinge [e.g., having the S228P mutation] and IgG4 wt molecules.’” *Id*. (citing Schuurman 63:6–9, bracketed material in original). Appellant argues that a skilled artisan would understand “arm exchange,” as used by Schuurman, to mean “half-molecule exchange in excess of 5%.” *Id*. (citing Schuurman 63:9–10).

Appellant concludes that

> [i]n view of the conflicting teachings of Labrijn (2009) and Shuurman [sic], a person of ordinary skill in the art at the time the claimed invention was made would not have been able to reasonably predict whether the IgG4 S228P mutation, or any other mutation, would result in reduction of half-antibody molecules to an amount below 1% in a pharmaceutical composition comprising *any* antibody, let alone the *specific* anti-PSGL-1 antibody of the claimed pharmaceutical compositions.

Id. at 8.

We do not find the cited disclosures to be persuasive evidence of a lack of predictability with respect to the relevant issue: whether a *pharmaceutical composition* comprising the antibody recited in claim 7 would comprise less than 1% *half antibody molecules*. The disclosure in Schuurman that Appellant points to reports results obtained “under [certain] in vitro conditions (0.1 mM GSH).” Schuurman 63:4. “GSH” is reduced glutathione. *Id*. at 54:11–12. Schuurman states that the GSH was added to

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[13] WO 2008/119353 A1, published October 9, 2008.

"restore" (i.e., promote) "exchange activity." *See id*. at 55:12–17. These conditions reflect Schuurman's goal: to provide "reducing conditions" so that "two IgG4-or IgG4-like antibodies having different antigen-binding specificities can perform highly efficient half-molecule exchange and thus form bispecific antibodies." *Id*. at 2:11–13. Appellant has not shown that the conditions of the cited experiment represent those of a "pharmaceutical composition" comprising an antibody and a "pharmaceutically acceptable carrier," as claimed.

Similarly, the disclosure in Labrijn (2009) that Appellant points to does not represent results from a pharmaceutical composition. Rather, those results were found after antibody compositions were "injected . . . into severe combined immunodeficient (SCID) mice[,] [b]lood samples were drawn at different times and bispecific antibodies were quantified." Labrijn (2009) at 768, right col.

In addition, the disclosures cited by Appellant in both Schuurman and Labrijn (2009) do not include data that quantify the amount of *half-antibodies*, but rather the amount of *arm exchange* that happens under in vitro or in vivo conditions. As Appellant's Specification explains, in IgG4 antibodies, "susceptibility of native IgG4 hinge disulfide bonds to reduction allows the heavy chains to separate." Spec. ¶ 31. The result of this separation of an IgG4 antibody is two half-antibodies. Claim 7 recites that the claimed composition comprises no more than 1% half-antibodies.

Half-antibodies from different original antibodies can "randomly re-associate to produce a mixed population of IgG4 molecules with randomized heavy-chain and light-chain pairs." Spec. ¶ 31. This process is "called Fab

arm exchange." *Id*. Thus, the levels of arm exchange that Appellant points to in Schuurman and Labrijn (2009) are evidence that half-antibodies have recombined (under the in vitro or in vivo conditions used) but the amount of the resulting mixed (bispecific) antibodies is not the same as the amount of half-antibodies present.

In fact, when Labrijn (2009) addresses the quantity of half-antibodies (or half-molecules) in a commercial composition of gemtuzumab, it reports the same results as Labrijn '366: "gemtuzumab showed no half-molecules (indicating a stabilized core-hinge)." Labrijn (2009) at 767, right col. *See also id*. at "ONLINE METHODS" (gemtuzumab obtained from manufacturer).

In summary, we do not find Appellant's evidence—relating to quantification of a different compound than recited in claim 7, in compositions other than a pharmaceutical composition—to be persuasive of a lack of expectation of success based on the references cited by the Examiner.

Appellant also argues that van de Winkel[14] "discloses that mutations within the CH3 domain in human IgG4 could prevent Fab arm exchange, and thus stabilize IgG4, even in the absence of the Ser to Pro mutation of the core hinge region sequence." Appeal Br. 9 (citing van de Winkel ¶ 11).[15] Appellant argues that "[b]ased upon these teachings, a person of ordinary

[14] US 2010/0267934 A1, published October 21, 2010.
[15] Appellant also points to van de Winkel's paragraph 228 and the accompanying table (Appeal Br. 9), but the disclosures therein are identical to those cited by Appellant in Schuurman, which have already been discussed.

skill in the art would understand that more than one antibody-stabilizing mutation exists and that such mutations do not always result in inhibition of Fab arm exchange." *Id*.

We do not agree with Appellant's reasoning. The fact that other mutations also have the effect of stabilizing an IgG4 antibody (i.e., reducing or preventing half-antibody formation) is not evidence that the S228P mutation does not have that effect. Thus, van de Winkel does not cast doubt on the evidence of record stating that a pharmaceutical composition of gemtuzumab—with an S228P mutation—"showed no half-molecules." Labrijn '366 ¶ 128.

Finally, Appellant asserts that it "has provided evidence in the form of experimental data indicating that the claimed pharmaceutical compositions comprise less than 1% half antibody molecules, retain PSGL-1 binding activity, and are effective *in vivo*." Appeal Br. 10 (citing Spec. ¶¶ 167, 177, 189; Table 7). Appellant argues that "[t]he extent of the reduction in Fab arm exchange exhibited by the claimed invention is unexpected, given the unpredictability in the art." *Id*.

We have considered the cited evidence, but do not find it persuasive of nonobviousness. Appellant points to evidence that h15A7 (with a wild-type hinge) and 15A7H (with an S228P mutation) "demonstrated comparable binding to activated T cells)." Spec. ¶ 177. Appellant also points to evidence that "both h15A7 and 15A7H inhibited the *trans vivo* DTH in a dose dependent manner." *Id*. ¶ 189. "DTH" is delayed-type hypersensitivity. *Id*. ¶ 178. Appellant has not explained how either of these results support the allegedly unexpected reduction in Fab arm exchange.

Appellant also points to the Specification's statement that "the $Ser^{228} \rightarrow Pro^{228}$ mutation significantly lowered the formation of the intra-chain disulfide bond in the hinge region. The amount of half antibody molecules was reduced from ~8–10% for h15A7 to below 1% for 15A7H." Spec. ¶ 167.

While this evidence does relate to Appellant's assertion of unexpected results, Appellant has not adequately shown that it would, in fact, have been unexpected by a person of ordinary skill in the art. The prior art of record shows that a pharmaceutical composition of a different antibody having the same $Ser^{228} \rightarrow Pro^{228}$ mutation "showed no half-molecules." Labrijn '366 ¶ 128. In view of that knowledge in the art, Appellant has not persuasively shown that the Specification's evidence of less than 1% half antibody molecules for the 15A7H antibody, also with the $Ser^{228} \rightarrow Pro^{228}$ mutation, would not have been expected.

In summary, a preponderance of the evidence of record supports a conclusion of obviousness with respect to claim 7. The rejection of claim 7 under 35 U.S.C. § 103(a) is affirmed. Claims 8, 10–12, and 22 were not argued separately and therefore fall with claim 7. 37 C.F.R. § 41.37(c)(1)(iv).

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
7, 8, 10–12, 22	103(a)	Lin, Stubenrauch, Mataraza, Labrijn '366, Osorio, Graus, Demarest	7, 8, 10–12, 22	

TIME PERIOD FOR RESPONSE

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

AFFIRMED