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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte DAVID M. GOLDENBERG and HANS J. HANSEN

Appeal 2014-006809
Application 13/214,767
Technology Center 1600

Before ERIC B. GRIMES, MELANIE L. McCOLLUM, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal¹ under 35 U.S.C. § 134 involving claims to a method for treating an autoimmune disease in a subject who has failed methotrexate therapy. The Examiner rejected the claims as failing to comply with the written description requirement and as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm the rejections based on obviousness.

¹ Appellants identify the Real Party in Interest as Immunomedics, Inc. (*See* App. Br. 2).

Statement of the Case

Background

“[T]his invention is directed to methods for treating autoimmune disorders by administering antibodies that bind to a B-cell antigen, such as the CD22, CD20, CD19, and CD74 or HLA-DR antigen” (Spec. 1, ll. 15–17).

The Claims

Claims 1–6, 11–23, and 25 are on appeal.² Claim 1 is representative and reads as follows:

1. A method of treating an autoimmune disease in a subject comprising administering a human, humanized, chimeric or murine anti-CD20 antibody which binds human CD20 and an anti-TNF α antagonist or anti-IL-1 antagonist, wherein said subject is a subject that has failed therapy with methotrexate.

The Issues

A. The Examiner rejected claims 1, 2, 5, 6, 11–13, 16–20, 22, and 25 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement (Ans. 2–4).

B. The Examiner rejected claims 1–6, 11–22, and 25 under 35 U.S.C. § 103(a) as obvious over FDA³ and Feldmann⁴ (Ans. 5–6).

² Claim 25 is not included in the Claims Appendix, but there is no indication that claim 25 was cancelled during prosecution and both the Examiner and Appellants include claim 25 in the rejections, so we treat claim 25 as pending and rejected.

³ FDA Approves Enbrel for Rheumatoid Arthritis, <http://www.pslgroup.com/dg/BC0DA.htm>, dated Nov. 3, 1998 (“FDA”).

⁴ Feldmann et al., WO 95/09652 A1, published Apr. 13, 1995 (“Feldmann”).

C. The Examiner rejected claims 1–6, 11–15, 20–22, and 25 under 35 U.S.C. § 103(a) as obvious over FDA and Curd⁵ (Ans. 6–7).

D. The Examiner rejected claims 16–19 under 35 U.S.C. § 103(a) as obvious over FDA, Curd, and Feldmann (Ans. 7–8).

E. The Examiner rejected claims 1–6, 11–23, and 25 under 35 U.S.C. § 103(a) as obvious over Le,⁶ Feldmann, and FDA (Ans. 8–10).

F. The Examiner rejected claims 1–6, 11–15, 20–23, and 25 under 35 U.S.C. § 103(a) as obvious over Le, Curd, and FDA (Ans. 10–11).

A. 35 U.S.C. § 112, first paragraph

The issue with respect to this rejection is: Does the evidence of record support the Examiner’s conclusion that the phrase “IL-1 antagonist” lacks descriptive support in the Specification?

Findings of Fact

1. The Specification teaches:

Cytokine agonists and antagonists may also be used in multimodal therapies according to the present invention. Tumor necrosis factor alpha (TNF α) and interleukin-1 (IL-1) are important in mediating inflammation in rheumatoid arthritis. Accordingly, anti-TNF α reagents, such as Infiximab [sic, infliximab] and Etanercept (Embrel [sic, Enbrel]), are useful in multimodal therapy according to the invention, as well as anti-IL-1 reagents.

(Spec. 17:15–20).

⁵ Curd et al., US 7,820,161 B1, issued Oct. 26, 2010 (“Curd”).

⁶ Le et al., US 7,192,584 B2, issued Mar. 20, 2007 (“Le”).

2. Feldmann teaches “[r]epresentative inflammatory mediators include agents which block, diminish, inhibit, or interfere with IL-1 activity, synthesis, or receptor signalling, such as anti-IL-1 antibody, soluble IL-1R, IL-1 receptor antagonist, or other appropriate peptides and small molecules” (Feldman 7:18–23).

3. Le teaches that after treatment with anti-TNF antibody “IL-1 production was abolished” (Le 38:65).

4. Marinova-Mutafchieva⁷ teaches the availability of “hamster anti-interleukin-1 β (anti-IL-1 β) mAb (B122; Genzyme, West Malling, UK)” (Marinova-Mutafchieva 639, col. 2).

Principles of Law

“[I]t is the specification itself that must demonstrate possession. And while the description requirement does not demand any particular form of disclosure . . . or that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy the requirement.” *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010)(citations omitted).

Analysis

The Examiner finds:

The term IL-1 antagonist encompasses a potentially vast array of molecules which can function as antagonists of IL-1 wherein said molecules are not disclosed in the specification or known in the prior art (such as small organic molecules, peptide

⁷ Marinova-Mutafchieva et al., *A comparative study into the mechanisms of action of anti-tumor necrosis factor α , anti-CD4, and combined anti-tumor necrosis factor α /anti-CD4 treatment in early collagen-induced arthritis*, 43 *Arthritis & Rheumatism* 638-644 (2000).

mimetics, nonprotein inhibitors, etc.) and wherein the structure of said molecules is unpredictable. The claims encompass use of antibodies which bind IL-1, wherein said antibodies can bind IL-1 from any animal species, whilst human or murine IL-1 were known in the art, IL-1 from other mammalian species were not apparently known in the art. The identity of IL-1 from undescribed animal species is unpredictable. Thus, the written description provided in the specification is not commensurate with the scope of the claimed inventions.

(Ans. 3).

Appellants contend that “a quick online search reveals an abundance of commercially available IL-1 antibodies, and first page printouts are of record. In summary, all of the sequences needed to prepare a chimeric, or humanized anti-IL-1 monoclonal antibody were published in 1995” (App. Br. 4).

We find that Appellants have the better position. Claim 1, as interpreted in light of the Specification, is broadly drawn to encompass treatment with IL-1 antagonists. The Specification therefore must adequately describe that genus of compounds.

In this case, while the Specification does not specifically identify any IL-1 antagonists (FF 1), the prior art of Feldmann relied upon by the Examiner specifically discloses “[r]epresentative inflammatory mediators” that are IL-1 antagonists including anti-IL-1 antibodies and soluble IL-1 receptors (FF 2). Le and Marinova-Mutafchieva, relied upon by either Appellants or the Examiner, teach antibodies that inhibit IL-1 (FF 3–4).

The present case is therefore most closely analogous to *Capon*. In *Capon*, the prior art provided the underlying information regarding the members of the genus. *Capon* teaches that the “Board erred in holding that

the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.” *Capon v. Eshhar*, 418 F.3d 1349, 1358 (Fed. Cir. 2005).

In the instant case, the prior art teaches several species which fall within the claimed genus of compounds. Therefore, this situation is unlike that in *Ariad*, where the invention was drawn to an NF-κB inhibitor of which there was only, at best, a single example disclosed. *See Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1356 (Fed. Cir. 2010).

The Examiner finds that “[w]hilst human or murine IL-1 were known in the art, IL-1 from other mammalian species were not apparently known in the art. The identity of IL-1 from undescribed animal species is unpredictable” (Ans. 12).

We are not persuaded. In every situation where patent claims encompass generic administration, the argument could be raised that not every animal, or perhaps more narrowly mammalian, species has been specifically analyzed by the patentee. However, “[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention.” *Capon*, 418 F.3d at 1359.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that the disclosure of the Specification failed to demonstrate possession and descriptive support for Claim 1.

B. 35 U.S.C. § 103(a) over FDA and Feldmann

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that FDA and Feldmann render claim 1 obvious?

Findings of Fact

5. FDA teaches "Enbrel acts by binding tumour necrosis factor (TNF) . . . Enbrel competitively inhibits the binding of TNF molecules to the TNF receptor (TNFR) sites" (FDA 1).

6. FDA teaches that "Enbrel is an entirely new approach to management of moderate to severe RA. In clinical studies of patients with moderate to severe RA, Enbrel has been shown to reduce pain and duration of morning stiffness and improve the number of swollen and tender joints, enabling patients to better participate in daily activities" (FDA 1).

7. FDA teaches "Enbrel has been shown to provide dramatic symptomatic relief, even in patients who have not been successfully treated with current options" (FDA 1).

8. FDA teaches "Enbrel can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone" (FDA 1).

9. Feldmann teaches that in “one embodiment of the current invention, anti-CD4 antibody is used in conjunction with anti-TNF antibody” (Feldmann 8, ll. 3-4).

10. Feldmann teaches that “CD4+ T cell inhibiting agents include . . . antibodies to B cells including CD5+ B cells, such as CD19, 20” (Feldmann 6, ll. 7-17).

11. Feldmann teaches that “anti-B cell antibodies can be particularly useful in the current invention” (Feldmann 6, ll. 21-22).

12. Feldmann teaches a “method of treating autoimmune or inflammatory disease in a mammal comprising administering to said mammal a therapeutically effective amount of a combination of a CD4+ T cell inhibiting agent and a TNF antagonist” (Feldmann 37, ll. 3-7; claim 1).

13. Marina-Mutafchieva teaches that “we have shown that combined treatment with anti-CD4 and anti-TNF α results in synergistic reductions in inflammatory processes and Th1 activity, and this probably accounts for the profound therapeutic effect of this form of combination therapy in CIA [collagen induced arthritis]” (Marina-Mutafchieva 643, col. 2).

Principles of Law

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). “If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.” *Id.* at 417.

Analysis

We adopt the Examiner’s findings of fact and reasoning regarding the scope and content of the prior art (Ans. 5–6; FF 5–13) and agree that claim 1 is rendered obvious by FDA and Feldmann. We address Appellants’ arguments below.

Appellants contend “[s]ince Feldmann *et al.* proposes to add methotrexate therapy, this clearly teaches away from a claim directed to a method of treating patients that have failed methotrexate therapy” (App. Br. 5).

We find the teaching away argument unpersuasive. A teaching away requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Here, Feldmann never discourages treatment after methotrexate failure and Feldmann specifically teaches that in “one embodiment of the current invention, anti-CD4 antibody is used in conjunction with anti-TNF antibody” (FF 9). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. *In re Susi*, 440 F.2d 442, 446 n.3 (CCPA 1971).

Appellants contend that FDA

does state that Enbrel is indicated for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs), but suggests that it [“]be used in combination with methotrexate in those patients who do not respond adequately to methotrexate alone.” Accordingly, it does not teach use in patients who have failed methotrexate therapy as presently claimed.

(App. Br. 5).

We do not find this argument persuasive because FDA specifically teaches “Enbrel has been shown to provide dramatic symptomatic relief, even in patients who have not been successfully treated with current options” (FF 7) and that there are “patients who do not respond adequately to methotrexate alone” (FF 8). Thus, the ordinary artisan would have recognized that some patients have failed therapy with methotrexate alone and would therefore benefit from other therapies such as those taught by FDA and Feldmann (FF 6, 9–12).

Moreover, claim 1 is open, using the “comprising” transitional language, and therefore does not exclude further combination therapy with methotrexate, but rather limits the patient population to those for whom methotrexate alone is insufficient. This limited patient population is expressly identified in FDA as suitable for treatment with the anti-TNF α antagonist Enbrel (FF 7–8), reasonably rendering combination therapy in such patients obvious.

Appellants cite a variety of references contending that there are “reservations with the predictability of the mouse CIA model” including Williams,⁸ Londei,⁹ Feldmann 2010,¹⁰ van Holten,¹¹ Vierboom,¹² and Plater-

⁸ Williams et al., *Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis*, 89 Proc. Nat’l Acad. Sci. 9784–9788 (1992).

⁹ Londei et al., *Persistence of collagen type II-specific T-cell clones in the synovial membrane of a patient with rheumatoid arthritis*, 86 Proc. Nat’l Acad. Sci. 636–640 (1989).

Zyberk¹³. Appellants contend that

a skilled artisan would not extend results with an anti-CD4 antibody in the mouse CIA model to B-cell antibodies. The teaching in Marinova-Mutafchieva would not suggest that a combination of B-cell antibodies with anti-TNF α would achieve effects like those purportedly achieved by a combination of a “T-cell targeted therapy” with anti-TNF α .

(App. Br. 7).

We find the arguments regarding the cited art unpersuasive. Feldman 2010, van Holten, and Vierboom are post filing date art. However, references that are published “after the filing date of appellant’s application . . . are not, therefore, evidence of subject matter known to ‘any person skilled in the art’ as required by 35 U.S.C. § 112, paragraph 1.” *In re Gunn*, 537 F.2d 1123, 1128 (CCPA 1976). Moreover, none of these three references specifically addresses the prior art in this case.

Williams provides additional evidence that “anti-TNF- α/β treatment causes a significant reduction in the clinical and histopathological severity of

¹⁰ Feldmann et al., *Anti-TNF Therapy, from Rationale to Standard of Care: What Lessons Has It Taught Us?*, 185 *J. Immunology* 791–794 (2010) (“Feldmann 2010”).

¹¹ van Holten et al., *Treatment with recombinant interferon- β reduces inflammation and slows cartilage destruction in the collagen-induced arthritis model of rheumatoid arthritis*, 6 *Arthritis Research Today* R239–R249 (2004).

¹² Vierboom et al., *Preclinical models of arthritic disease in non-human primates*, 12 *Drug Discovery Today* 327–335 (2007).

¹³ Plater-Zyberk et al., *Anti-CD5 therapy decreases severity of established disease in collagen type II-induced arthritis in DBA/1 mice*, 98 *Clinical Experimental Immunology* 442–447 (1994).

collagen-induced arthritis” (Williams 9784, col. 2). With regard to Londei and Plater-Zyberk, neither of these references specifically addresses the use of anti-CD20 antibodies suggested by Feldmann (FF 10), nor do these references rebut the teaching of Marina-Mutafchieva that “we have shown that combined treatment with anti-CD4 and anti-TNF α results in synergistic reductions in inflammatory processes” (FF 13). We recognize that Marina-Mutafchieva, like Plater-Zyberk, is drawn to a mouse model, but as we balance all of the evidence with the specific teachings of FDA and Feldmann, we remain persuaded that the combination of anti-TNF α and anti-CD20 antibodies suggested by FDA and Feldmann for treatment of rheumatoid arthritis is obvious (FF 5–13).

We also agree with the Examiner that the “reference to antiCD4 antibody and the mouse model of Feldmann et al. is irrelevant, because the claims are not drawn to use of antiCD4 antibody. Appellants’ comments regarding antiCD5 antibody are also equally irrelevant because the claims are not drawn to the use of antiCD5 antibody” (Ans. 16).

Conclusion of Law

The evidence of record supports the Examiner’s conclusion that FDA and Feldmann render claim 1 obvious.

C. 35 U.S.C. § 103(a) over FDA and Curd

The issue with respect to this rejection is: Does the evidence of record support the Examiner’s conclusion that FDA and Curd render claim 1 obvious?

Findings of Fact

14. Curd teaches a “method of treating an autoimmune disease in a mammal comprising administering to the mammal a therapeutically effective amount of an antagonist which binds to a B cell surface marker” (Curd, col. 2, ll. 60–64).

15. Curd teaches that “[e]xamples of autoimmune diseases or disorders include, but are not limited to . . . rheumatoid arthritis” (Curd, col. 3, ll. 50–62).

16. Curd teaches that “[e]xemplary B cell surface markers include the . . . CD20 . . . leukocyte surface markers” (Curd, col. 3, ll. 13–17).

17. Curd teaches that the “preferred antagonist comprises an antibody” (Curd, col. 4, ll. 31–32).

18. Curd teaches that “the patient is optionally further treated with any one or more agents employed for treating RA such as . . . methotrexate” (Curd, col. 27, ll. 39–49).

Analysis

We adopt the Examiner’s findings of fact and reasoning regarding the scope and content of the prior art (Ans. 6–7; FF 5–8, 14–18) and agree that claim 1 is rendered obvious by FDA and Curd. We address Appellants’ arguments below.

Appellants contend that “[s]ince Curd *et al.* proposes to add methotrexate therapy, this clearly teaches away from a claim directed to a method of treating patients that have failed methotrexate therapy” (App. Br. 9).

We do not find this argument persuasive because FDA specifically teaches “Enbrel has been shown to provide dramatic symptomatic relief, even in patients who have not been successfully treated with current options” (FF 7) and that there are “patients who do not respond adequately to methotrexate alone” (FF 8). Thus, the ordinary artisan would have recognized that some patients have failed therapy with methotrexate alone and would therefore benefit from other therapies such as those taught by FDA and Curd (FF 6, 14–17).

Moreover, claim 1 is open, using the “comprising” transitional language, and therefore does not exclude further combination therapy with methotrexate as optionally suggested by Curd (FF 18), but rather limits the patient population to those for whom methotrexate alone is insufficient. This limited patient population is expressly identified in FDA as suitable for treatment with the anti-TNF α antagonist Enbrel (FF 7–8), reasonably rendering combination therapy in such patients obvious.

Conclusions of Law

The evidence of record supports the Examiner’s conclusion that FDA and Curd render claim 1 obvious.

D–F. 35 U.S.C. § 103(a)

Appellants reiterate the same arguments regarding treating patients that have failed methotrexate therapy that we found unpersuasive already over FDA and Feldmann or FDA and Curd. We remain unpersuaded for the reasons given above.

SUMMARY

In summary, we reverse the rejection of 1, 2, 5, 6, 11–13, 16–20, 22, and 25 under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

We affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over FDA and Feldmann. Claims 2–6, 11–22, and 25 fall with claim 1.

We affirm the rejection of claim 1 under 35 U.S.C. § 103(a) as obvious over FDA and Curd. Claims 2–6, 11–15, 20–22, and 25 fall with claim 1.

We affirm the rejection of claims 16–19 under 35 U.S.C. § 103(a) as obvious over FDA, Curd, and Feldmann.

We affirm the rejection of claims 1–6, 11–23, and 25 under 35 U.S.C. § 103(a) as obvious over Le, Feldmann, and FDA.

We affirm the rejection of claims 1–6, 11–15, 20–23, and 25 under 35 U.S.C. § 103(a) as obvious over Le, Curd, and FDA.

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

AFFIRMED