

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 17

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte JEAN-YVES MARCEL PAUL BONNEFOY

Appeal No. 2000-1783
Application No. 08/817,719

ON BRIEF

Before SCHEINER, ADAMS and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 14-26, the only claims remaining in the application.

Claims 14, 15, 18, 19 and 21 are representative of the subject matter on appeal and read as follows:

14. A method of treating an autoimmune disorder comprising administering to a patient in need of such treatment an amount of an agent that binds CD23, and thereby blocks the interaction of CD23 with a ligand to which CD23 binds in vivo, sufficient to effect such treatment.

15. The method according to claim 14 wherein said agent is an antibody.

18. The method according to claim 14 wherein said ligand is CD21, CD11b or CD11c.

19. The method according to claim 14 wherein said autoimmune disorder is rheumatoid arthritis.

21. The method according to claim 14 wherein said autoimmune disorder is arthritis, lupus erythematosus, systemic lupus erythematosus, Mashimotos thyroiditis,

multiple sclerosis, diabetes, uveitis, dermatitis, psoriasis, urticaria, nephrotic syndrome, glomerulonephritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, Sjogren's syndrome, asthma, eczema, graft vs host disease or insulinitis.

The references relied on by the examiner are:

Bonnefoy et al. (Bonnefoy), "Inhibition of Human Interleukin 4-Induced IgE Synthesis by a Subset of Anti-CD23/Fc ϵ RII Monoclonal Antibodies," Eur. J. Immunol., Vol. 20, pp. 139-144 (1990)

Reiter et al. (Reiter), "Treatment of Rheumatoid Arthritis with Monoclonal CD4 Antibody M-T151," Arthritis and Rheumatism, Vol. 34, No. 5, pp. 525-536 (May 1991)

Hawkins et al. (Hawkins), "Adapting Antibodies for Clinical Use," BJM, Vol. 305, pp. 1348-132 (1992)

Burmester et al (Burmester), "Anti-CD4 Therapy in Rheumatoid Arthritis," Clinical and Experimental Rheumatology, Vol. 11 (Suppl. 8), pp. S139-s145 (1993)

Flores-Romo et al. (Flores-Romo), "Inhibition of an in Vivo Antigen-Specific IgE Response by Antibodies to CD23," Science, Vol. 261, pp. 1083-1041 (August 1993)

Bansal et al (Bansal), "Increased Levels of sCD23 in Rheumatoid Arthritis are Related to Disease Status," Clinical and Experimental Rheumatology, Vol. 12, pp. 281-285 (1994)

Armant et al. (Armant), "Regulation of Cytokine Production by Soluble CD23: Costimulation of Interferon γ Secretion and Triggering of Tumor Necrosis Factor α Release," J. Exp. Med., Vol. 180, pp. 1005-1011 (September 1994)

The claims stand rejected as follows:

- I. Claims 14-20 under the first paragraph of 35 U.S.C. § 112 (enablement).
- II. Claims 14, 15 and 18-21 under 35 U.S.C. § 103 as unpatentable over Bansal, Flores-Romo, Bonnefoy or Armant.
- III. Claims 14, 15 and 18-26 under 35 U.S.C. § 103 as unpatentable over Bansal, Flores-Romo, Bonnefoy or Armant in view of Reiter or Burmester.
- IV. Claims 14-21 under 35 U.S.C. § 103 as unpatentable over Bansal, Flores-Romo, Bonnefoy or Armant in view of Hawkins.

BACKGROUND

CD23, the low affinity receptor for IgE, "has pleiotropic activities including

mediation of cell adhesion, regulation of IgE and histamine release, rescue of B cells from apoptosis and regulation of myeloid cell growth.” Specification, page 1. “[Its] functional activities are mediated through the binding to specific ligands of cell-associated CD23, or sCD23 [(soluble CD23)], the latter acting in a cytokine-like manner.” Id. Ligands of CD23 include CD21 (CD23-CD21 interactions are believed to play a role in IgE production), and the β -integrins (cell adhesion molecules) CD11b and CD11c. Id., page 2. According to appellant, CD23 binding agents that block the interaction between CD23 and its ligands “work in vivo in treatment or prophylaxis of . . . autoimmune diseases.” Id., page 4.

DISCUSSION

Enablement

In its broadest aspect, the present invention is directed to treating autoimmune disorders by administering an agent that binds CD23 and blocks its interaction with a ligand it normally binds in vivo (e.g., claim 14).

The examiner notes two principal concerns in concluding that “[t]he specification does not enable any person skilled in the art . . . to make and use the invention commensurate in scope with [the] claims.” Answer, page 4. First, the examiner argues that “[t]he specification discloses the treatment of rheumatoid arthritis in mice but does not disclose the treatment of any other autoimmune disease” (Id.), thus “[a]ppellant has not established in vivo therapeutic efficacy . . . [for] the numerous autoimmune diseases encompassed by the claims” (Id., page 5), even though “[t]he therapy of autoimmune diseases . . . is highly experimental and unpredictable” (Id., page 4). Second, the examiner argues that “the claims encompass an enormous number of potential CD23 binding agents,” but “[t]he specification does not disclose the administration of a binding

agent to CD23 other than anti-CD23 antibodies to treat autoimmune diseases.” Id.

“The first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without ‘undue experimentation.’ In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is ‘undue.’” In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original).¹ Nevertheless, “[w]hen rejecting a claim under the enablement requirement of section 112,” it is well settled that “the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.” In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

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Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatApplnt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Thus, the dispositive issue here is not whether appellant has established that the disclosure is broadly enabling for the scope of the claims, rather, the issue is whether the PTO has met its “initial burden of setting forth a reasonable explanation as to why” it is not. Keeping this in mind, we consider the specific reasons provided by the examiner in support of her position.

With respect to the unpredictability associated with treatment of autoimmune diseases, the examiner argues that “[n]umerous and variable parameters contribute in determining the extent to which CD23 binding agents such as anti-CD23 antibody [] will function in vivo, including cross-reactivity with related antigens, affinity constant, isotype, rate of clearance from the blood, bioavailability, localization, and distribution of antibody within the body.” Answer, pages 4-5. This argument is not persuasive. Even assuming that all of these parameters contribute to therapeutic efficacy, the examiner has not begun to establish (as by an analysis in keeping with that set forth in Wands) that their optimization would have required undue experimentation.

With respect to CD23 binding agents, the examiner argues that “there is no evidence in the specification . . . that the enormous number of functionally defined CD23 binding agents can be readily obtained without undue experimentation because the specification does not provide guidance as to critical structural characteristics of CD23 binding agents.” Answer, page 4. However, the specification does provide guidance: on page 12, the specification teaches that determining whether an agent may be useful in the treatment of autoimmune diseases “comprises whether or not the agent is capable of blocking the interaction between CD23 and CD11b, or the interaction between CD23 and CD11c, or the interaction between CD23 and CD21, or the interaction between CD23 and a 70 to 85 KDa . . . or a 115 KDa protein expressed on

endothelial cells.” Moreover, on page 9, the specification indicates that “CD23 binds to SCRs [(short consensus repeats)] 5-8 and 1-2 on CD21” and “[t]he binding of CD23 to SCRs 5-8 is a lectin-like interaction,” while “CD23 binding to SCRs1-2 is a protein-protein interaction.”

We accept, for the sake of argument, that it would be time consuming to determine whether an agent that binds CD23 also blocks interaction between CD23 and one of its ligands. Nevertheless, the examiner does not question the ability of one skilled in the art to follow the disclosed processes. As explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

Finally, the examiner relies on Bonnefoy to establish “that some but not all anti-CD23 antibodies inhibit IgE production,” thus, “the ability of a particular anti-CD23 agent to inhibit CD23 mediated function” is unpredictable. Answer, page 5.

Nevertheless, as appellant points out, “[i]f the antibody did not block the CD23 ligand interaction, as required by the present claims, then failure to inhibit the CD23 response

was surely unsurprising.” Brief, page 6.

In our view, the reasons cited in support of the examiner’s rejection do not provide a reasonable basis to question the adequacy of the disclosure provided for the claimed invention, and the evidence of record is insufficient to support the examiner’s conclusion that “it would take undue trials and errors to practice the claimed invention.” Answer, page 5. Accordingly, the rejection of the claims under the first paragraph of 35 U.S.C. § 112 is reversed.

Obviousness

There are three separate rejections of the claims; each relies, at least in part, on the same four references (Flores-Romo, Bonnefoy, Bansal and Armant) in the alternative, so we will discuss the rejections together.

Flores-Romo teaches that CD23 is a low-affinity IgE receptor and that it interacts specifically with CD21, thereby modulating IgE production. In an in vivo model of an allergen-specific IgE response, administration of CD23-specific antibody resulted in up to 90 percent inhibition of antigen-specific IgE synthesis. Because IgE mediates many allergic responses, Flores-Romo suggests that CD23 “could be important in allergic disease.” Abstract.

Similarly, Bonnefoy teaches that anti-CD23 antibodies inhibit antigen-specific IgE response in atopic patients (i.e., patients with IgE-associated type 1 allergies).

“Since [Bonnefoy] and [Flores-Romo] teach that anti-CD23 inhibits the production of anti-IgE responses,” the examiner concludes that “one with skill in the art . . . would be motivated to administer anti-CD23 antibody to autoimmune diseases mediated by IgE such as asthma as is claimed in claims 14 and 21.” Answer, page 6.

However, appellant points out that “allergic asthma is an IgE-related disease,” but “[i]ntrinsic non-atopic asthma,” the form of asthma encompassed by the claims, “is

a non-IgE related disorder.” Brief, page 7. Further, appellant argues that “[t]here is no evidence in the literature to suggest that antigen-specific IgE plays any role in either triggering or perpetuating autoimmunity.” Id., page 8. On this record, we agree with appellant that “[t]he use of antibodies to block [antigen]-induced IgE production, therefore, has no relevance whatsoever to the claimed method.” Id.

Bansal describes elevated levels of sCD23 in patients with rheumatoid arthritis (RA) and suggests that “[i]t is possible that features of autoantibody production, B cell hyperactivity and hypergammaglobulinaemia (increased levels of circulating γ -globulins) observed in RA are mediated by high levels of sCD23.” Page 282.

Armant teaches that sCD23 has multiple IgE-independent biological activities including costimulation of IL-2 or IL-12-induced IFN- γ production and direct triggering of TNF- α , IL-1 α , IL-1 β , and IL-6 release by peripheral blood mononuclear cells. Page 1005. Armant suggests that “sCD23 is a proinflammatory cytokine that, in addition, may play an important role in the control of the immune response via the enhancement of IFN- γ production.” Abstract.

The examiner concludes that “[o]ne with ordinary skill in the art would have been motivated to treat arthritis by administering anti-CD23 antibodies because [Bansal teaches] that soluble CD23 levels are elevated in rheumatoid arthritis and that hypergammaglobulinaemia . . . may be mediated by high levels of soluble CD23 with the expectation that the administration of anti-CD23 would downregulate the hypergammaglobulinaemia . . . in rheumatoid arthritis patients and downregulate the inflammatory process in autoimmune diseases by inhibiting the sCD23 induced release of mediators of the inflammatory process as taught by Armant.” Answer, page 7.

However, appellant cites Bansal as evidence that the nature of the relationship

between sCD23 and IFN- γ production and hypergammaglobulinaemia was not well understood at the time of the invention, and that Bansal actually suggests “that raised levels of sCD23 are the result of increased levels of IgG, not the cause.” On page 284, Bansal reports that the “significantly higher levels of sCD23 [found] in normal males relative to normal females . . . is also evident in patients with RA.” “As CD23 expression and its solubilization to sCD23 is regulated principally by IL-4 mediated stimulation and [IFN- γ] mediated inhibition,” Bansal suggests that this sex difference might be explained by “increased levels of IFN- γ binding IgG in normals [sic] males compared to normal females[, which] would in turn decrease the levels of immunologically active free IFN- γ in males, leading to increased levels of sCD23.” Bansal, page 284.

On balance, we agree with appellant that “the [e]xaminer has not made a case for why a skilled person would have been motivated [by the teachings of Flores-Romo, Bonnefoy, Bansal or Armant] to treat someone with an autoimmune condition such as rheumatoid arthritis with an anti-CD23 agent.” Brief, page 11.

Finally, Reiter, Burmester and Hawkins were cited with respect to additional limitations of some of the dependent claims on appeal, but do nothing to remedy the underlying deficiency in the examiner's conclusion of obviousness.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Each of the three rejections of the claims under 35 U.S.C. § 103 is reversed because the examiner has not established that treatment of autoimmune diseases by administering CD23 binding agents would have been suggested by the prior art.

CONCLUSION

On consideration of the record, the rejections of the claims under the first

paragraph of 35 U.S.C. § 112, and under 35 U.S.C. § 103 are reversed.

REVERSED

Toni R. Scheiner)
Administrative Patent Judge)
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) BOARD OF PATENT
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Donald E. Adams) APPEALS AND
Administrative Patent Judge)
) INTERFERENCES
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Eric Grimes)
Administrative Patent Judge)