

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 50

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte LOUIS N. CASTENET and PAMELA J. BJORKMAN

MAILED

SEP 23 1996

PAT & TM OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 95-2587
Application 08/004,492¹

HEARD: June 7, 1996

Before CAROFF, GRON and ELLIS, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal of the final rejection of claims 1, 2, 6, 8, 10, 11, and 30. Claims 12 through 29 are also pending, but were withdrawn from consideration by the examiner under 37 CFR § 1.142(b).

¹ Application for patent filed January 14, 1993. This application is a continuation of Application 07/819,413 filed January 10, 1992, now abandoned.

Appeal No. 95-2587
Application 08/004,492

Claim 1 is illustrative of the subject matter on appeal and reads as follows:

1. A soluble heterodimeric Fc receptor comprising a β_2 -microglobulin light chain, and a heavy chain derived from a mammalian, membrane-bound Fc receptor by truncating said membrane-bound Fc receptor heavy chain to include only extracellular domains, said soluble Fc receptor having pH-determinable binding capability for the Fc portion of at least one antibody or a complex of said antibody, wherein said soluble, mammal-derived Fc receptor is capable of binding to said antibody over a pH ranging from about 5.5 to about 6.5 and releasing said antibody over a pH ranging from about 7.5 to about 8.5.

The references relied on by the examiner are:

- Capon et al. (Capon) WO 89/02922 Apr. 6, 1989
- Yokoyama et al. (Yokoyama), "Secondary Structure of the Murine Histocompatibility Alloantigen H-2K^b. Relationship between Heavy Chain, β_2 -Microglobulin, and Antigenic Reactivity," Biochemistry, Vol. 24, pp. 3002-3006 (1985).
- Bjorkman et al. (Bjorkman), "Structure of the Human Class I Histocompatibility Antigen, HLA-A2," Nature, Vol. 329, pp. 506-512 (October 1987).
- Simister et al. (Simister I), "An Fc Receptor Structurally Related to MHC Class I Antigens," Nature, Vol. 337, pp. 184-187 (January 1989).
- Simister et al. (Simister II), "Cloning and Expression of the Neonatal Rat Intestinal Fc Receptor, a Major Histocompatibility Complex Class I Antigen Homolog," CSH Symposia on Quantitative Biology, Vol. LIV, pp. 571-580 (July 1989).
- Alexander et al. (Alexander), "The Transport of Class I Major Histocompatibility Complex Antigens is Determined by Sequences in the α_1 and α_2 Protein Domains," Immunogenetics, Vol. 31, pp. 169-178 (1990).

Appeal No. 95-2587
Application 08/004,492

The claims stand rejected as follows:²

I. Claims 1, 2, 6, 8, 10, 11 and 30 are rejected under 35 U.S.C. § 103 as being unpatentable over Simister I or Simister II in view of Bjorkman.

II. Claims 1, 2, 6, 8, 10, 11 and 30 are rejected under 35 U.S.C. § 103 as being unpatentable over Simister I or Simister II in view of Capon, Alexander, and Yokoyama.

We reverse.

Background

The present invention relates to an Fc receptor. The appellants disclose that the term "Fc receptor" refers to any one of several proteins which bind the Fc region of an immunoglobulin molecule.³ The Fc receptor molecule comprises a (i) hydrophobic,

² We note that in their Reply Brief the appellants point out that the examiner inadvertently omitted claim 10 from the rejections in the Examiner's Answer. The Reply Brief, p. 9. The appellants correctly presumed this to be an unintentional error and responded to the rejection as if the claim was included. The error was acknowledged by the examiner in the Supplemental Examiner's Answer and corrected. Accordingly, for purposes of this appeal, we include claim 10 in our consideration of the issues raised.

³ The specification, p. 3.

Appeal No. 95-2587
Application 08/004,492

transmembrane domain (those amino acids responsible for the attachment of the Fc receptor to the membrane) of the molecule, (ii) heavy chain, and (iii) β_2 -microglobulin light chain. According to the specification, Fc receptors can be either soluble or bound to the membrane of numerous cell types. See the specification, p. 5. However, prior to the appellants' invention, Fc receptors required the presence of surfactants in order to be solubilized in an aqueous solution.

As stated in claim 1 above, the present invention is directed to a soluble, heterodimeric Fc receptor comprising a β_2 -microglobulin light chain and a mammalian heavy chain which is derived from a membrane-bound Fc receptor. Using recombinant DNA technology, the transmembrane domain of the molecule was removed resulting in the production of a soluble, yet still functional, molecule. The appellants report that the present invention is useful for purifying antibodies from solutions containing a mixture of proteins. The Brief, p. 3, lines 1-3.

Discussion

I.

Simister I and Simister II each disclose the isolation of an Fc receptor (FcRn) present on intestinal epithelial cells of the neonatal rat.⁴ The Fc receptor protein was analyzed by SDS-polyacrylamide electrophoresis and found to consist of two components, a large subunit, p51, having a molecular weight of approximately 45,000-53,000 Daltons and a smaller subunit, p14, having a molecular weight of approximately 14,000 Daltons. The smaller subunit was identified as β -2 microglobulin (β 2m). The complete amino acid sequence of p51 were determined using standard, recombinant DNA techniques. Simister suggests that the primary structure of the p51 subunit "has three extracellular domains and a transmembrane region which are all homologous to the corresponding domains of class I major histocompatibility complex (MHC) antigens." Simister I, the abstract; Simister II, p. 571, col. 2, para. 1.

Bjorkman discloses that human leukocyte antigen (HLA) molecules (also known as class I histocompatibility antigens) are

⁴ The Simister I and II disclosures are substantially identical. Accordingly, we will address the teachings jointly.

Appeal No. 95-2587
Application 08/004,492

membrane glycoproteins found on the surface of almost all cells. Bjorkman describes the crystallographic structure of HLA-A2. The preparation of crystallized HLA-A2 particles involves, *inter alia*, digesting the plasma membrane of a human lymphoblastoid cell line with papain to remove the transmembrane anchor and crystallizing the resultant, soluble fragment.⁵

The examiner argues that in view of the teachings of the Simister references as to the similarity between FcRn and other MHC class I molecules, it would have been obvious to one of ordinary skill in the art to generate a soluble FcRn molecule by digesting with papain. The Examiner's Answer, p. 2. The examiner urges that:

[o]ne would have been so motivated to do so a) in order to perform crystallographic studies on FcRn which has similar characteristics as the papain-cleaved protein disclosed by Bjorkman et al., or b) because of the art-recognized utility of soluble Fc receptors for use in purification and assay protocols (as established in several of the references cited by applicants).

Id.

We find this position untenable.

⁵ Bjorkman reports that "[p]apain cleaves the HLA heavy chain at residue 271, thirteen residues from the transmembrane region, yielding a molecule composed of α_1 , α_2 , α_3 , β_2m ." See p. 507, col. 2, para. 2.

Appeal No. 95-2587
Application 08/004,492

It cannot be gainsaid that the examiner has the initial burden under 35 U.S.C. § 103 of presenting a *prima facie* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-1472, 223 USPQ 785, 787-788 (Fed. Cir. 1985). In citing prior art under such a rejection, the examiner must demonstrate that the combined teachings therein would have suggested to those of ordinary skill in the art that they should make the claimed invention, and that such persons would have had a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). The suggestion must be in the prior art and not in the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988) (Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984).")

In the case before us, we find no suggestion in the prior art that the teachings of the Simister and Bjorkman publications should be combined. As discussed above, the Simister references

Appeal No. 95-2587
Application 08/004,492

teach the characterization of the two components comprising the intact FcRn, and they disclose the amino acid sequence of the larger p51 subunit. The publications do not suggest making a soluble Fc receptor or the removal of the transmembrane domain for any purpose. As we previously noted, Bjorkman discloses the digestion of plasma membranes with papain to extract human class I histocompatibility antigen, HLA-A2, for X-ray crystallographic studies. However, we find no suggestion in the reference as to the digestion of a membrane-bound Fc receptor using papain, or other available means. On this record, we only find these suggestions in the appellants' disclosure. Accordingly, we agree with the appellants, that the examiner has relied on impermissible hindsight in making her determination of obviousness. *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.") *W.L. Gore*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) ("To imbue one of

Appeal No. 95-2587
Application 08/004,492

ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.")

Even if we assume, *arguendo*, that the proposal by Simister that the p51 subunit resembles an MHC class I heavy chain, in combination with Bjorkman's teaching to remove of the transmembrane portion of class I MHC molecules, would have suggested the claimed invention to one of ordinary skill in this art, the prior art must also establish that such person would have had a reasonable expectation of successfully producing a soluble, heterodimeric Fc receptor having the claimed antibody-binding characteristics. *In re O'Farrell, supra*. To that end, we note the appellants' arguments that the present invention was not obvious over the teachings of the cited prior art because it was not known what would be the effect of papain on a membrane-bound rat Fc receptor. The Brief, p. 15, line 25- p. 16, line 1; the Reply Brief, p. 4. The appellants have submitted two declarations by Dr. Raghavan which demonstrate that when soluble Fc receptor is digested with papain under the conditions

Appeal No. 95-2587
Application 08/004,492

disclosed in the Bjorkman reference, the molecule is rapidly degraded.

We acknowledge that the declarations of Dr. Raghavan do not address the issue of the effects of papain on membrane-bound FcRn; however, the results do not discredit the appellants' position that one of ordinary skill in the art would not have expected to produce a functional, soluble Fc receptor using the techniques disclosed by Bjorkman. Conspicuous in its absence from this record, is any factual evidence from the examiner to support her arguments on p. 4 of the Answer that there would have been a reasonable expectation of success in making the claimed invention using the techniques described by Bjorkman.

Accordingly, Rejection I is reversed.

II.

Capon discloses that "adhesions are cell surface glycoproteins having an extracellular domain which is homologous to a member of the immunoglobulin gene superfamily, excluding, however, highly polymorphic members of this superfamily selected from the group of class I and class II major histocompatibility antigens, immunoglobulins and T-cell receptor α , β , γ , and δ

Appeal No. 95-2587
Application 08/004,492

chains." See Capon, p. 6, lines 18-23. Capon describes the construction of several CD4 adhesion variants, the most preferred are those in which the transmembrane and cytoplasmic domains are removed. Capon, p. 18, lines 6-12. The transmembrane-deleted adhesion variants are water soluble, having little or no affinity for cell membrane lipids, and thus, their recovery from cell culture is greatly facilitated. See Capon, p. 18, lines 14-26. Purportedly, the CD4 adhesion variants are useful in the treatment of human immunodeficiency virus (HIV) infections.

Alexander discloses that the external domains, α_1 , and α_2 , of class I histocompatibility complex antigens are responsible for the transport of the protein to the cell surface.

Yokoyama discloses that digestion of the murine histocompatibility antigen H-2Kb with papain generates a heavy chain fragment consisting mostly of the extracellular portion of the molecule. See Yokoyama, Fig. 3. Yokoyama also discloses that it was necessary to associate β_2m with the heavy chain fragment in order to maintain the biological activity (alloantigenic reactivity) of the protein. See Yokoyama, p. 3004, col. 2, para. 2.

The examiner argues that it would have been obvious to one of ordinary skill in the art to modify the p51 heavy chain taught

Appeal No. 95-2587
Application 08/004,492

by the Simister references by deleting the transmembrane and intracellular regions as taught by Capon, in order to make soluble FcRn for the same reasons, listed above, as in the previous rejection. She urges that Alexander demonstrates that "the transmembrane and intracellular domains would not have been necessary for proper transport of the truncated protein so produced." See the Examiner's Answer, p. 3. In addition, she urges that Yokoyama establishes that the truncated protein would properly associate with the β 2m light chain.

Again, we point out that the burden is on the examiner to demonstrate that the teachings of the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention, and that such persons would have had a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). As discussed above, we find no teaching or suggestion in the Simister publications to produce a soluble derivative of membrane-bound FcRn. Moreover, the examiner acknowledges on p. 3 of the Answer that Capon specifically excludes class I MHC antigens from his disclosed invention, thus, we are unable to discern on what basis she concludes that the recombinant DNA techniques employed by

Appeal No. 95-2587
Application 08/004,492

Capon to remove the transmembrane portion of adhesions suggest a similar deletion in the p51 chain of FcRn. Here, we concur with the appellants' arguments on pp. 20-21 of the Brief that Capon clearly "teaches away" from the claimed invention. That is, we do not find that the teachings of Capon provide even the slightest suggestion that the transmembrane region of the FcRn be removed in order to make a soluble protein.

Having concluded that the examiner has not, in the first instance, established a *prima facie* case of obviousness based on the teachings of the Simister and Capon references, we do not find the Alexander and Yokoyama publications to be of any particular relevance, since they were employed for their cumulative effect on the teachings of Capon. We agree with the appellants' statement on p. 23 of the Brief that Yokoyama is the most germane art of record. However, we also find no suggestion, except from the appellants' specification, to combine these teachings with the FcRn receptor taught by Simister.

As previously noted, the burden is on the examiner to provide reasons, based on the prior art, for making the claimed soluble, heterodimeric Fc receptors. *In re Dow Chemical, supra.* In the present case the examiner has not met that burden; rather

Appeal No. 95-2587
Application 08/004,492

she has confused the level of skill in the art with the actual teachings of the prior art. See *In re Kratz*, 592 F.2d 1169, 1175, 201 USPQ 71, 76 (CCPA 1979) (The court "rejected the argument that undirected skill of one in the pertinent art is an adequate substitute for statutory prior art.")

In our opinion, the combined teachings of the references would, at best, suggest that it would have been "obvious to try" to make soluble FcRn by removing the transmembrane regions of the molecule. *In re Geiger*, 815 F.2d 868, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987); *In re Goodwin*, 576 F.2d 375, 377, 198 USPQ 1, 3 (CCPA 1978). "An 'obvious-to-try' situations exists when a general disclosure may pique the scientist's curiosity such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

Again, even if we assume, arguendo, that the teachings of the Simister references combined with the removal of the transmembrane portion of class I MHC molecules as taught by Capon

Appeal No. 95-2587
Application 08/004,492

and Yokoyama would have suggested the claimed invention to one of ordinary skill in this art, the prior art must also establish that one would have had a reasonable expectation of successfully producing a soluble, heterodimeric Fc receptor having the claimed antibody-binding characteristics. *In re O'Farrell, supra*. The appellants have argued on pp. 24-25 of the Brief and pp. 6-8 of the Reply Brief, that due to the unpredictable nature of protein folding, it was not certain that a functional, truncated Fc receptor would be produced using recombinant DNA techniques. Conspicuous in its absence from this record is any rebuttal of this argument by the examiner. Accordingly, since the evidence of nonobviousness unquestionably outweighs the evidence of obviousness, we reverse this rejection.

Rejection II is reversed.

Appeal No. 95-2587
Application 08/004,492

The decision of the examiner is reversed.

REVERSED

Marc L. Caroff

MARC L. CAROFF)
Administrative Patent Judge)

Teddy S. Gron

TEDDY S. GRON)
Administrative Patent Judge)

Joan Ellis

JOAN ELLIS)
Administrative Patent Judge)

BOARD OF PATENT
APPEALS AND
INTERFERENCES

Appeal No. 95-2587
Application 08/004,492

Shirley L. Church
1063 Morse Avenue
11-306
Sunnyvale, CA 94089