

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opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.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. 19

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ALEJANDRO A. ARUFFO and NITIN DAMLE

Appeal No. 94-1696
Application 07/811,129¹

HEARD
November 15, 1996

Before WILLIAM F. SMITH, ELLIS and WALTZ, **Administrative Patent Judges**.

ELLIS, **Administrative Patent Judge**.

DECISION ON APPEAL

This is an appeal of the final rejection of claims 1 through 17, all the claims pending in the application.

Claims 1, 2 and 9 are illustrative of the subject matter on appeal and read as follows:

¹ Application for patent filed December 20, 1991.

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1. A soluble fusion molecule comprising a first region, having binding specificity for CD11a/CD18, operatively linked to a second region substantially corresponding to an immunoglobulin constant region.
2. The fusion molecule of claim 1, wherein the first region substantially corresponds to an extracellular portion of ICAM-2.
9. A method for activating T cells comprising contacting T cells with a ligand capable of binding to CD3 on said T cells and an effective costimulatory amount of a soluble fusion molecule to activate the T cells, said soluble fusion molecule comprising a first region, having binding specificity for CD11a/CD18, operatively linked to a second region substantially corresponding to an immunoglobulin constant region.

The references relied on by the examiner are:

Springer, T.A. "Adhesion Receptors of the Immune System," **Nature**, vol. 346, pp. 425-434 (1990).

Staunton et al., (Staunton), "Functional Cloning of ICAM-2, a Cell Adhesion Ligand for LFA-1 Homologous to ICAM-1," **Nature**, vol. 339, pp. 61-64 (1989).

Zettlmeissl, et al. (Zettlmeissl), "Expression and Characterization of Human CD4: Immunoglobulin Fusion Proteins," **DNA and Cell Biology**, vol. 9, pp. 347-353 (1990).

The references relied on by this merits panel are:

Altmann et al. (Altmann), "Cotransfection of ICAM-1 and HLA-DR Reconstitutes Human Antigen-Presenting Cell Function in Mouse L Cells," **Nature**, vol. 338, pp. 512-514 (1989).

Boyd et al. (Boyd), "Intercellular Adhesion 1 (ICAM-1) has a Central Role in Cell-Cell Contact-Mediated Immune Mechanisms," **Proc. Natl. Acad. Sci. USA**, vol. 85, pp. 3095-3099 (1988).

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de Fougerolles et al. (de Fougerolles), "Characterization of ICAM-2 and Evidence for a Third Counter-Receptor for LFA-1," **J. Exp. Med.**, vol. 174, pp. 253-267 (1991).

Dustin et al. (Dustin), "Induction by IL 1 and Interferon-(γ): Tissue Distribution, Biochemistry, and Function of a Natural Adherence Molecule (ICAM-1)," **The Journal of Immunology**, vol. 137, pp. 245-254 (1986).

Makgoba et al. (Makgoba), "ICAM-1 a Ligand for LFA-1-Dependent Adhesion of B, T and Myeloid Cells," **Nature**, vol. 331, pp. 86-88 (1988).

Nortamo et al. (Nortamo), "A Monoclonal Antibody to the Human Leukocyte Adhesion Molecule Intercellular Adhesion Molecule-2," **The Journal of Immunology**, vol. 146, pp. 2530-2535 (1991).

Claims 1 through 17 stand rejected under 35 U.S.C. § 103 as being unpatentable over Springer in view of Zettlmeissl.

Having carefully considered the entire record which includes, *inter alia*, the specification, the appellants' main Brief (Paper No. 12) and Reply Brief (Paper No. 15), the examiner's Answer (Paper No. 13) and Supplemental Answer (Paper No. 16), we find ourselves in substantial agreement with the appellants' position. Accordingly, we **reverse** the rejection. Our reasons follow.

Background

The appellants' invention is directed to soluble fusion proteins which comprise a first region capable of binding to the

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T cell receptor CD11a/CD18 (a.k.a. LFA-1) and a second region which "substantially corresponds" to an immunoglobulin constant region. LFA-1 (lymphocyte function-associated antigen 1) is a cell surface glycoprotein which promotes leukocyte adhesion in immunological and inflammatory reactions. In addition, the claimed invention is directed to methods for (i) activating T cells, (ii) increasing the proliferative response of CD4⁺ T cells, and (iii) inducing the production of IL-2 by T cells, by stimulating T cells with the referenced fusion proteins and a ligand which binds the T cell antigen receptor, CD3.

In the case before us, the examiner has predicated his conclusion of obviousness on the teachings of Springer and Zettlmeissl.² Springer is a review article which describes the phenomenon of cellular adhesion with respect to T cell receptors

² We note in passing that the examiner refers to the Staunton publication, a reference which was not included in the statement of the rejection. Purportedly, Staunton teaches the cloning of the ICAM-2 molecule and, thus, demonstrates that the nucleotide and amino acid sequences of said molecule were known in the art. Answer, p. 2. However, we point out that it is well established that "[w]here a reference is relied on to support a rejection, whether or not in a 'minor capacity,' there would appear to be no excuse for not positively including the reference in the statement of the rejection." *In re Hoch*, 428 F.2d 1341, 1342, n. 3, 166 USPQ 406, 407, n. 3 (CCPA 1970). Accordingly, since the examiner did not include Staunton in the statement of the rejection, we have not considered any statements or arguments made by the examiner concerning this reference.

and its critical role in an immune response. Springer discloses, *inter alia*, that three T cell receptor molecules, LFA-1 (CD11a/CD18), LFA-2 (CD2) and LFA-3, "account for the antigen-independent adhesion that is induced by the prolonged antigenic stimulation of T cells *in vitro* and presumably help localize activated T cells to sites of antigen accumulation in the lymph nodes *in vivo*." [Footnotes omitted.] Springer, p. 426, col. 1, lines 7-11. Springer further discloses that the counter receptor on the target cell for LFA-1 is ICAM-1 or ICAM-2 (intercellular cell molecule). *Id.*, sentence bridging cols. 1 and 2. Springer still further discloses that ICAM-1 and ICAM-2 are members of an immunoglobulin superfamily; structurally, ICAM-2 has two immunoglobulin-like domains and ICAM-1 has five.

Zettlmeissl discloses the construction of a soluble fusion protein which comprises a first region encoding the T cell receptor CD4 and a second region derived from different parts of human IgG₁ or IgM heavy-chain constant regions. According to Zettlmeissl, such fusion proteins are promising therapeutic agents for HIV (human immunodeficiency virus) infections.

Discussion

The examiner argues (Answer, p. 3) that

it would have been ***prima facie*** obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Springer to those of Zettlmeissl, et. [sic] al., to obtain a soluble ICAM-2/IgG fusion protein, wherein the ICAM-2 molecule is operatively linked to the IgG molecule. This fusion protein could be used in combination with an anti-CD3 antibody to co-stimulate T-cell activation and thus achieve T-cell proliferation and IL-2 production.

From a fair reading of the applied prior art, it is difficult for us to discern on what basis this conclusion was reached. As we understand it, the examiner's overall position is that because it was technologically feasible for those of ordinary skill in the art to make a fusion protein comprising one type of T cell receptor molecule and an immunoglobulin heavy chain constant region, it would have been obvious to such persons to make fusion proteins comprising any molecule involved in the phenomenon of antigen recognition, regardless of its role (T cell receptor ***versus*** ligand; MHC receptor ***versus*** ligand for lymphocyte function-related antigens, etc.) or its cellular association (T cell ***versus*** endothelial, epithelial, fibroblast, etc.). In our opinion, the examiner has confused the level of skill in the art with the teachings of the prior art. ***In re Kratz***, 592 F.2d 1169, 1175, 201 USPQ 71, 76 (CCPA 1979) (The court "rejected the

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argument that undirected skill in the art of one in the pertinent art is an adequate substitute for statutory skill in the art").

It is well established that the examiner has the initial burden of establishing that the teachings of the applied prior art would have suggested the claimed invention to one of ordinary skill in the art and that such person would have had a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). However, this suggestion must be in the prior art and not in the appellants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). In the case before us, we do not find any teaching or suggestion in the applied prior art as to why one of ordinary skill would have combined Springer and Zettlmeissl to arrive at the invention described in claim 1. Nor do we find that any such teachings have been pointed out by the examiner. Rather, the only source we find for the examiner's reasoning is the appellants' own disclosure. See, for example, p. 4 of the specification which states that "[t]he fusion molecules of the present invention can be utilized as costimulatory agents for the activation of T cells and in methods for increasing ... the induction of IL-2 by T cells." Thus, since, on this record, the only reason given for combining the prior art of record comes

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from the specification, we concur with the appellants that the examiner has engaged in impermissible hindsight to arrive at the conclusion that the invention of claim 1 is obvious over Springer and Zettlemeissl. *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); *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-313 (Fed. Cir. 1983) *cert. denied* 469 U.S. 851 (1984) ("To imbue one of 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").

Accordingly, the rejection is reversed.

New Ground of Rejection under 37 CFR § 1.196(b)

Under the provisions of 37 CFR § 1.196(b) we make the following new grounds of rejection.

Claims 1, 3, 4, 6, 9, 11, 12, 14, 15 and 17 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, and concise exact terms as to enable one skilled in the art to make

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and use the full scope of said invention, and for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

It is well established that any analysis of the claims under the first paragraph of § 112 must first "begin with the determination of whether the claims satisfy the requirements of the second paragraph." *In re Moore*, 439 F.2d 1232, 1235, 169 USPQ 236, 238 (CCPA 1971). That is, in order to appreciate what, in fact, is the invention before us, the claims must "set out and circumscribe a particular area with a reasonable degree of precision and particularity." *Id.* Here, we find that the claims are indefinite in the recitation of a first region "having binding specificity for CD11a/CD18." It is not clear which proteins or polypeptides the appellants intend. For example, the specification teaches the construction of fusion proteins comprising either ICAM-1 or ICAM-2 (Example 6); however, Makgoba (Exhibit 10)³ discloses that several other molecules function as ligands for LFA-1. Makgoba, p. 86, sentence bridging cols. 1-2.

³ Exhibits 1, 4, 6, 7, 10 and 14 were attached to Paper No. 5.

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According to Makgoba,

[t]hese include: (1) LB-2, a B-cell activation marker which inhibits both B- and myeloid homotypic-cell adhesion; and (2) 84H10, which was identified by screening for preferential binding to myeloid leukaemic cells and subsequently shown to inhibit the adhesion of such cells to bone-marrow stromal cells (footnotes omitted).

In addition, antibodies specific to LFA-1 (CD11a/CD18) would have "binding specificity for CD11a/CD18."⁴

We acknowledge that the claims should be read in light of the prior art and the specification as they would be interpreted by one skilled in the art. *In re Sneed*, 710 F.2d 1544, 1548, 218 USPQ 385, 388 (Fed. Cir. 1983); *In re Moore, supra*. Yet, at the same time, since during the prosecution of a patent application, the claims "must be interpreted as broadly as their terms reasonably allow," our reviewing court instructs us not to read limitations appearing in the specification into the claims. *In re Zletz*, 893, F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989); *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 866-867, 228 USPQ 90, 93 (Fed. Cir. 1985); *In re Prater*, 415 F.2d 1393, 1404-1405, 162 USPQ 541, 550-551 (CCPA 1969) (before an

⁴ See the rejection under 35 U.S.C. § 102(b), on pp. 13-14, *infra*.

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application is granted there is no reason to read into the claims limitations from the specification). Thus, in view of the prior art of record, we do not find that those skilled in the art would have interpreted the appellants' claims as being limited to ICAM-2 fusion proteins as stated by the examiner, or even to ICAM-1 fusion proteins but, rather, such persons would find the scope of the claims to be indeterminable, since they read on a fusion protein comprising any molecule capable of binding to the LFA-1 receptor.

With that in mind, we point out that 35 U.S.C. § 112, first paragraph requires that the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright* 999 F.2d 1557, 1561, 27 USPQ 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 495-96, 20 USPQ2d 1438, 1444-45 (Fed. Cir. 1991). The factors to be considered in assessing undue experimentation were set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These 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.

In the case before us, the specification provides only two working examples of fusion proteins which are capable of binding to CD11a/CD18; i.e., fusion proteins comprising ICAM-1 or ICAM-2. The specification fails to provide any guidance as to (i) the construction of fusion proteins comprising other, structurally different, polypeptides, such as those indicated by Makgoba, *supra*, which have the claimed binding specificity, or (ii) how to identify and isolate other such polypeptides. Moreover, the structural features of molecules having the claimed binding characteristics are unpredictable. That is, it is not possible to predict the structure of an LFA-1 ligand from the disclosed ICAM-1 and ICAM-2 sequences.⁵ Accordingly, in view of the breadth of the claim language, the limited number of working examples, the unpredictable nature as to the types of ligands capable of binding to the LFA-1 receptor, we hold that one skilled in the

⁵ We note that the specification discloses that "the two most N-terminal domains of ICAM-1 and ICAM-2 which contribute to their interactions with LFA-1" only have 34 % identity on the amino acid level. Specification, p. 12, lines 26-27. Moreover, ICAM-1 has three additional "immunoglobulin-like" domains which appear to play a role in the avidity for LFA-1. Specification, sentence bridging pp. 12-13.

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art would not have been able to make and use the claimed invention, absent undue experimentation. *In re Wands, supra.*

Claims 2, 5, 7, 10, 13 and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of a region "substantially corresponding to an extracellular portion of ICAM-2." It is not clear which proteins or polypeptides the appellants intend.

Claims 1, 3, 4 and 6 are rejected under 35 U.S.C. § 102(b) as being unpatentable over Altmann (Exhibit 1), Boyd (Exhibit 4) and Dustin (Exhibit 7).

As a preliminary matter we point out that the examiner's statement that "the claims are directed to a soluble ICAM-2/IgG fusion protein," is incorrect. Answer, p. 2. Only claim 8 is so limited. As we discussed above, the specification discloses the construction of fusion proteins comprising ICAM-1 and ICAM-2 fusion proteins. See Example 6. Moreover, we also point out that claims 1, 3, 4 and 6 are directed to any molecule having a first region which is capable of binding to LFA-1. This would include, *inter alia*, ligands such as ICAM-1, ICAM-2, ICAM-3, etc., and biologically-active portions thereof. In addition, we

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interpret the referenced claims to include polyclonal and monoclonal antibodies which have "binding specificity for CD11a/CD18 [LFA-1]." Accordingly, we find that the teachings of Altmann, Boyd and Dustin as to anti-LFA-1 antibodies anticipate the claimed invention.

We acknowledge that claims 1 and 6 are directed to a "soluble fusion molecule," and a "recombinant fusion molecule," respectively; however, we find no difference between the product made by the appellants' process of fusing the two claimed regions and the anti-LFA-1 antibodies described by the prior art. *In re Thorpe*, 777 F.2d 695, 697, 227 USPQ 964, 966 (Fed. Cir. 1985) ("The patentability of a product does not depend on its method of production"). Thus, in our opinion, the anti-LFA-1 antibodies taught by the prior art are identical to the claimed product(s).

Other Issues

Upon return of this application to the corps, the examiner should consider whether the 35 U.S.C. § 112, second paragraph, rejection as to the indefiniteness of the phrase "substantially

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corresponding to" should be revisited.⁶ The specification definition⁷ notwithstanding, it does not appear that this phrase clearly sets forth the metes and bounds of the claimed invention. ***In re Moore, supra; but cf. In re Mattison***, 509 F.2d 563, 564, 184 USPQ 484, 486 (CCPA 1975). In view of all possible substitutions described in the specification, it is not clear whether a "region substantially corresponding to an immunoglobulin constant region" encompasses the "immunoglobulin-like" domains of ICAM-1 and ICAM-2. If so, references such as Makgoba (Exhibit 10) and Nortamo (Exhibit 14) which teach purified ICAM-1, and references, such as de Fougerolles (Exhibit

⁶ In the first office action, mailed March 2, 1992 (Paper No. 2), the examiner rejected claims 1 through 17 under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of a region which "substantially corresponds to" an immunoglobulin constant region. Paper No. 2, p. 3. However, the examiner withdrew the rejection "in response to the Applicants' amendments." Paper No. 6, mailed September 30, 1992, p. 4. To that end we find that the appellants filed an amendment in Paper No. 4, submitted July 6, 1992, which added the phrase "ligand capable of binding to CD3 on said T cells, and a costimulatory," to claims 12 and 15. However, we do not find that these amendments affect the rejected phrase. Rather, we find that the appellants rely on the specification definitions at pp. 8-10. Paper No. 4, p. 4.

⁷ We recognize that the appellants have provided definitions of "correspond" and "substantially" on pp. 8 through 10 of the specification.

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6), etc., which teach the cloning and expression of ICAM-1 or ICAM-2 would "read on" the products described in claims 1 through 8. That is, it is not clear whether references which teach purified ICAM-1 or ICAM-2 "read on" soluble molecules having (i) a first region which is capable of binding LFA-1 or "substantially corresponding to an extracellular portion of ICAM-2," and (ii) a second region "substantially corresponding to an immunoglobulin constant region.

Any request for reconsideration or modification of this decision by the Board of Patent Appeals and Interferences based upon the same record must be filed within one month from the date of the decision (37 CFR § 1.197). Should appellant[s] elect to have further prosecution before the examiner in response to the new rejection under 37 CFR § 1.196(b) by way of amendment or showing of facts, or both, not previously of record, a shortened statutory period for making such response is hereby set to expire two months from the date of this decision.

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

REVERSED; 37 CFR § 1.196(b)

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Administrative Patent Judge)	
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