

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 41

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ELIZABETH S. WARD

Appeal No. 1997-3322
Application 08/353,940

ON BRIEF

Before WILLIAM F. SMITH, Administrative Patent Judge, McKELVEY, Senior Administrative Patent Judge and MILLS, Administrative Patent Judge.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-4, 9-15 and 19-33, which are all of the claims pending in this application.

We reverse.

Claims 1 and 31 are illustrative of the claims on appeal and read as follow:

1. A cloning vector which expresses and secretes V_H or V_H T-cell receptor variable domain in a gram-negative cell, said secretion being into the bacterial periplasm or into a culture medium, said vector comprising the following elements in the 5' to 3' direction, said elements which are operatively linked:

- (a) an inducible promoter DNA sequence;
- (b) a leader sequence; and
- (c) a DNA sequence encoding a V_H or V_H T-cell receptor variable domain.

31. A method for expressing and secreting a T-cell receptor variable domain in a gram-negative bacterium, comprising the steps:

- a) culturing a gram-negative bacterium transformed with a vector, said vector comprising the following elements in the 5' to 3' direction, said elements which are operatively linked:
 - i) a lacZ inducible promoter DNA sequence;
 - ii) a leader sequence selected from the group consisting of pelB, ompA and phoA; and
 - iii) a DNA sequence encoding at least one of a V_H or V_H T-cell receptor variable domain; and
- b) adding about 0.1 to 1 mM of isopropylthiogalactopyranoside; to produce a T-cell receptor variable domain.

The prior art references of record relied upon by the examiner in rejecting the appealed claims are:

Novotny et al. (Novotny 1986), "Secondary, tertiary, and quaternary structure of T-cell-specific immunoglobulin-like polypeptide chains," Proc. Natl. Acad. Sci. USA, Vol. 83, pp. 742-46 (1986).

Skerra et al. (Skerra), "Assembly of a Functional Immunoglobulin F_v Fragment in Escherichia coli," Science, Vol. 245, pp. 1040-41 (1988).

Novotny et al. (Novotny 1991), "Assoluble, dingle-chain T-cell receptor fragment endowed with antigen-combining properties," Proc. Natl. Acad. Sci USA, Vol. 88, pp. 8646-650 (1991).

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Publications submitted by appellant include:

Soo Hoo et al. (Soo Hoo), "Characterization of a single-chain T-cell receptor expressed in Escherichia coli," Proc. Natl. Acad. Sci. USA, Vol 89, pp. 4759-763 (1992).

Kurucz et al. (Kurucz), "A bacterially expressed single-chain Fv construct from the 2B4 T-cell receptor," Proc. Natl. Acad. Sci. USA, Vol. 90, pp. 3830-834 (1993).

OPINION

In reaching our decision in this appeal, we have given careful consideration to the appellant's specification and claims, to the applied prior art references, and to the respective positions articulated by the appellant and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellant regarding the above-noted rejection, we make reference to the examiner's answer (Paper No. 40, mailed January 8, 1997) for the examiner's complete reasoning in support of the rejection, and to the appellant's brief (Paper No. 37, filed July 22, 1996) for the appellant's arguments thereagainst. As a consequence of our review, we make the determinations which follow.

TECHNICAL BACKGROUND

The two major classes of lymphocytes are B cells and T cells. The majority of T-cells recognize antigenic peptide bound to class I or II proteins of the major histocompatibility complex (MHC). The recognition of peptide MHC complexes is mediated by surface-bound T-cell receptors. These receptors are comprised of

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heterodimeric polypeptides, the majority of which are " and \$ polypeptides.

Specification, page 1.

The specification discloses two embodiments of the invention, the expression of single V" or V\$ T-cell receptor domains (specification, page 19, line 29 to page 20, line 30), and the co-expression of V" and V\$ T-cell receptor domains (specification, page 20, line 32, et seq.). The claimed invention relates to a cloning vector which expresses and secretes either V" or V\$ T-cell receptor variable domain in a gram-negative cell.

According to the invention the secretion must be into the bacterial periplasm or into a culture medium. The cloning vector comprises the following elements in the 5' to 3' direction, which are operatively linked: (a) an inducible promoter DNA sequence; (b) a leader sequence; and (c) a DNA sequence encoding a V" or V\$ T-cell receptor variable domain.

PROCEDURAL BACKGROUND

A Declaration under 37 CFR § 1.131 was submitted in the application on July 24, 1996. The Declaration was summarily dismissed by the examiner. We find the failure of the examiner to consider the Declaration under 37 CFR § 1.131 on the merits to be procedural error which would normally require remand of the application to the examiner for appropriate consideration. However, we have proceeded with consideration of the rejections of the claims under 35 U.S.C. §§ 102 and 103. Our reversal of the rejections

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under 35 U.S.C. §§ 102 and 103, notwithstanding consideration of the Declaration under 37 CFR § 1.131, renders moot the procedural error of the examiner.

Issues

1. Claims 31 and 32 stand rejected under 35 U.S.C. § 102 as anticipated by Novotny 1991.
2. Claims 1-4, 9-15, 19-30 and 33 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Novotny 1991.
3. Claims 1-4, 9-15, 19-33 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Novotny 1986 in view of Skerra.

DECISION ON APPEAL

Rejection under 35 U.S.C. § 102

Claims 31 and 32 stand rejected under 35 U.S.C. § 102 as anticipated by Novotny 1991.

To support a rejection of a claim under 35 U.S.C. § 102(b), it must be shown that each element of the claim is found, either expressly described or under principles of inherency, in a single prior art reference. See Kalman v. Kimberly-Clark Corp., 713 F.2d 760, 772, 218 USPQ 781, 789 (Fed. Cir. 1983), cert. denied, 465 U.S. 1026 (1984).

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Claim 31 specifically requires a step of “adding about 0.1 to 1mM isopropylthio-galactopyranoside (IPTG) to produce a T-cell receptor variable domain.” Novotny 1991 describes 5mM IPTG is required to induce expression of the single chain T-cell receptor. Novotny, page 8647.

The appellant argues that Novotny 1991 cannot serve as an anticipating reference because it does not disclose a step of adding about 0.1 to 1mM isopropylthio-galactopyranoside (IPTG) to produce a T-cell receptor variable domain or a method of expressing and secreting a T-cell receptor domain in a gram-negative cell. The examiner does not address or rebut these arguments in the Examiner’s Answer. We do not find these elements of claim 31 described in Novotny 1991, and therefore reverse the rejection under 35 U.S.C. § 102(b) of the examiner as to claims 31 and 32. Rejection under 35 U.S.C. § 103

Claims 1-4, 9-15, 19-30 and 33 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Novotny 1991.

The examiner’s states that Novotny 1991 discloses the production of small, soluble, single chain T-cell receptor (TCR) fragments that carry an intact TCR antigen combining site (V" , V\$) in E. coli. The examiner finds that the disclosure of Novotny differs from the claimed invention in the disclosure of an additional genetic sequence and a linker. “That is, Novotny teaches expression of a heterodimer comprising a linker, rather than monomer

units minus the linker.” Examiner’s Answer, page 5. It is the examiner’s position that it would have been obvious to one of ordinary skill in the art to have separately cloned the single chain TCR V α and V β genes according to the methods of Novotny 1991 for purposes of co-expression of respective genes since it would be expected that the three-dimensional dimer structure would more closely resemble a native conformation. Examiner’s Answer, pages 5-6.

The appellant presents several arguments which remain unrebutted by the examiner. First, the appellant argues that its vector claims require secretion of a single T-cell receptor domain in a bacterial periplasm or a culture medium. Appellant submits that Novotny 1991 tried and failed to produce secreted T-cell domains. Brief, page 11. Novotny 1991 specifically states that “cell fractionation experiments failed to detect scTCR in the periplasm.” Novotny page 8649, column 2.

Secondly, Novotny 1991 describes a gene encoding the “TCR protein, specific for the hapten fluorescein in the context of major histocompatibility complex class II and composed of one V α and V β domain joined by a flexible [oligonucleotide] linker, assembled in an Escherichia coli plasmid.” [Emphasis added.] Novotny 1991, Abstract.

In contrast, appellant’s claim a vector including, “(c) a DNA sequence encoding a V α or V β T-cell receptor variable domain”, i.e., the DNA sequence encodes either V α or V β T-cell receptor variable domain and not both as in Novotny 1991. The specification

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indicates that V" domain secretion levels were lower when co-expressed with the V\$ polypeptide, than when expressed as a single domain. This was speculated to be attributed to limitations on the amount of protein which can be secreted into the E. coli periplasm, i.e., V\$ secretion may compete with V" secretion. Specification, page 21. Thus, there appears to be an advantage associated with expression and secretion of single T-cell receptor domains, as claimed. A vector which encodes a single V" or V\$ T-cell receptor variable domain, and its advantages do not appear to be suggested by a vector encoding both V" and V\$ T-cell receptor variable domains linked together, as taught by Novotny 1991.

Thirdly, the appellant argues that Novotny 1991 is not prior art to the present application in view of a Declaration submitted under 37 CFR § 1.131. The examiner failed to consider the Declaration under 37 CFR § 1.131 on the merits relying on In re Schlittler and Uffer, 234 F.2d 882, 883, 110 USPQ 304, 305 (CCPA 1956), for the proposition that a printed publication does not constitute a reduction to practice¹, but is evidence of conception only.

We find the examiner's failure to consider the Declaration under 37 CFR § 1.131 on the merits to be error. The facts presented in Schlittler suggest that, in the context of establishing whether a printed publication can be cited as a prior art reference

¹ 37 CFR § 1.131 requires that a declaration must include facts showing completion of the invention in this country.

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under 35 U.S.C. § 102(a), such a publication must provide knowledge that the invention has been completed by a reduction to practice. This is not the context in which the printed publication of Ward accompanying the Declaration under 37 CFR § 1.131 presents itself. In fact, it is well settled that in consideration of Affidavits under 37 CFR § 1.131, “office practice does not always insist upon the first records which were made and that consideration of other records made prior to the date involved is not prohibited by the rule.” Ex parte Harrington, Jr., 1967 Dec. Comm’r Pats. 4 (Bd. App. 1966).

We do not now comment on the sufficiency of the Declaration submitted under 37 CFR § 1.131, but only state that its failure to be considered by the examiner is error. We cannot sustain the rejection of the claims under 35 U.S.C. § 103 in view of Novotny 1991, for the reasons discussed herein.

35 U.S.C. § 103

Claims 1-4, 9-15, 19-33 stand rejected under 35 U.S.C. § 103 as unpatentable for obviousness over Novotny 1986 in view of Skerra.

Rejection of claimed subject matter as obvious under 35 U.S.C. § 103 in view of a combination of prior art references requires consideration of whether prior art would have suggested to those of ordinary skill in art that they should make claimed composition or device, or carry out claimed process, and whether prior art would also have revealed that

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such person would have a reasonable expectation of success; both the suggestion and reasonable expectation of success must be founded in prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991).

Novotny 1986 explores the possibility that the difference in antigen recognition between B and T cells derives from a structural difference in their respective antigen specific receptors. Novotny 1986 compared the extracellular segments of the T-cell receptor " , \$ and (polypeptide chains and the terminal segment of the T-cell T8 antigen chain with the corresponding immunoglobulins whose three-dimensional structure are known. It was concluded that the binding sites of the antigen-specific T-cell " , \$-chain receptors and of the antibodies are very similar in their overall geometry. Novotny 1986, abstract. Novotny 1986 does not disclose a vector which expresses and secretes T-cell " or \$-chain receptors in gram negative bacteria, as claimed.

Skerra is relied on by the examiner for the disclosure of an expression system which allows for the production of a completely functional variable fragment of an antibody in E. coli. Skerra suggests that the variable domains of the phosphorylcholine-binding antibody were secreted together into the periplasmic space. It is argued by the examiner that "it would have been prima facie obvious for one of ordinary skill in the art have substituted one of the genes encoding the T-cell receptor variable domain (" or \$) of

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Novotny 1986 for the DNA expressing the functional antigen-binding fragment of Skerra, in the expression system of Skerra for the production and secretion of T-cell receptor variable domain, since Novotny 1986 provides ample motivation for the interchange describing the structural relatedness of the respective molecules.” Examiner’s Answer, page 6. The examiner also argues that appellant has not put forth any reason why one of ordinary skill in the art would not expect transcription and translation based on the combined teachings set forth above. Examiner’s Answer, page 9.

However, we find ample appellant argument and reasons of record why one of ordinary skill in the art would not have been provided with a reasonable expectation of success of the ability to secrete T-cell receptor domains, particularly domains linked together. Brief, page 12. Novotny 1991 clearly states that they were unable to express T-cell receptor domains in the periplasm of E. coli. Appellant also makes of record Kurucz and Soo Hoo, evidencing the inability to secrete soluble T-cell receptor domains in E. coli even after the filing date of the present application. We perceive Novotny 1991 to be closer prior art than the combination of Novotny 1986 and Skerra. Novotny 1991 casts doubt on the expectation of success suggested by the examiner to be found in the combination of Novotny 1986 and Skerra, as Novotny 1991 discloses an inability to express V" or V\$ T-cell receptor domains in the periplasm of E. coli. In view of the above,

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the rejection of the claims under 35 U.S.C. § 103 over Novotny 1986 and Skerra is reversed.

CONCLUSION

The rejections of the claims under 35 U.S.C. § 102 and 103 are reversed.

REVERSED

WILLIAM F. SMITH
Administrative Patent Judge

FRED E. McKELVEY
Senior Administrative Patent Judge

DEMETRA J. MILLS
Administrative Patent Judge

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