

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte JONATHAN SCHNECK and SEAN O’HERRIN

Appeal 2007-1161¹
Application 09/954,166
Technology Center 1600

Decided: July 09, 2007

Before DONALD E. ADAMS, TONI R. SCHEINER, and
RICHARD M. LEOVITZ, *Administrative Patent Judges*.

LEOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 43-52 and 54-61. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF CASE

The claims are directed to a method of making a molecular complex comprising two first fusion proteins and two second fusion proteins. The first fusion protein comprises an immunoglobulin heavy chain comprising a

¹ Heard May 17, 2007.

variable region and an extracellular domain of a first transmembrane protein. The second fusion protein comprises a immunoglobulin light chain comprising a variable region and an extracellular domain of a second transmembrane protein. The method calls for expressing the fusion proteins in a host cell “whereby the two first and two second fusion proteins associate to form a first molecular complex comprising at least four fusion proteins.” The molecular complex has two (divalent) ligand binding sites, each site formed from a first and second transmembrane domain.

Claims 43-52 and 54-61, which are all the pending claims, are finally rejected over prior art (Br. 2). The Examiner relies on the following prior art as evidence of unpatentability:

Harris WO 941091 Apr. 28, 1994

Dal Porto, “A soluble divalent class I major histocompatibility complex molecule inhibits alloreactive T cells at nanomolar concentrations,” *Proc. Natl. Acad. Sci.*, Vol. 90, pp. 6671-6675, (1993).

Chang, “A general method for facilitating heterodimeric pairing between two proteins: Application to expression of α and β T-cell receptor extracellular segments,” *Proc. Natl. Acad. Sci.*, Vol. 91, pp. 11408-11412, (1994).

Matsui, “Kinetics of T-cell receptor binding to peptide/I-E^k complexes: Correlation of the dissociation rate with T-cell responsiveness,” *Proc. Natl. Acad. Sci.*, Vol. 91, pp. 12862-12866, (1994).

There is only one rejection at issue in this appeal. Claims 43-52 and 54-61 stand rejected under 35 U.S.C. § 103(a) as obvious over Matsui in view of Dal Porto, Chang, and Harris (Answer 3). The claims stand or fall together because separate reasons for patentability of any individual claim

were not provided. *See* 37 C.F.R. 41.37(c)(1)(vii). We select claim 43 as representative for the purpose of deciding all the issues in this appeal. Claim 43 reads as follows:

43. A method of making a first molecular complex comprising four fusion proteins, comprising the steps of:

expressing in a host cell a first fusion protein comprising (a) an immunoglobulin heavy chain comprising a variable region and (b) an extracellular domain of a first transmembrane polypeptide; and

expressing in a host cell a second fusion protein comprising (a) an immunoglobulin light chain comprising a variable region and (b) an extracellular domain of a second transmembrane polypeptide,

whereby two first and two second fusion proteins associate to form a first molecular complex comprising at least four fusion proteins, wherein the first molecular complex comprises two ligand binding sites, each ligand binding site formed by the extracellular domains of the first and second transmembrane polypeptides, wherein the first molecular complex has an affinity for a cognate ligand which is increased relative to a second molecular complex consisting of the extracellular domain of the first transmembrane polypeptide and the extracellular domain of the second transmembrane polypeptide.

FINDINGS OF FACT

1. T-cell antigen receptors (TCR) on the surface of T-cells react with antigen peptide/MHC complexes on the surface of antigen presenting cells (Specification 2-3).

2. T-cell receptors are normally comprised of two transmembrane proteins (e.g., α and β subunits) which form a heterodimer (Specification 4, 8, and Fig. 1A).

Matsui

3. Matsui describes soluble forms of MHC/protein complexes and T-cell receptor heterodimers (Matsui, p. 12862, col. 1; Answer 4) which lack the transmembrane domains responsible for anchoring them to the cell membrane.

4. The soluble TCR heterodimers bind to soluble peptide/MHC complexes in a cell free system (Matsui, p. 12862, col. 1).

5. The binding characteristics of soluble TCR heterodimers have been difficult to study because of their relatively low affinity for the peptide/MHC complex (Matsui, p. 12862, cols. 1-2; Answer 4).

6. To address this problem, Matsui uses an instrument for detecting protein-protein interactions in which specific binding between the soluble TCR heterodimer and peptide/MHC complex is detected by an optical phenomenon known as surface plasmon resonance (Matsui, p. 12862, col. 2).

Dal Porto

7. According to Dal Porto, “[s]oluble class I MHC-like molecules have been used to study T-cell responses” (Dal Porto, p. 6671, col. 2).

8. “Previously, soluble monovalent class I molecules have not effectively inhibited T-cell responses *in vitro* or *in vivo*” (Dal Porto, p. 6671, col. 2).

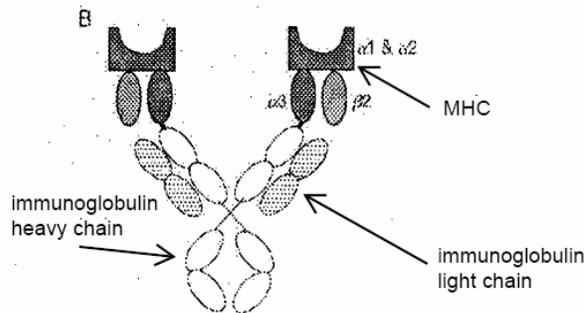
9. Dal Porto describes the production of a genetically engineered divalent class I MHC molecule which effectively inhibited lysis of target cells by T-

cells and had a high nanomolar affinity for T-cell clones which could be measured by a direct binding assay (Dal Porto, p. 6671, col. 1 (Abstract); p. 6672, col. 1; Answer 5).

10. Dal Porto's genetically engineered divalent class I MHC molecule comprises: 1) the extracellular MHC binding (H-2K^b) domain ($\alpha 1$, $\alpha 2$, and $\alpha 3$) joined to 2) the variable (V) region of IgG heavy chain, forming a chimeric protein (Dal Porto, p. 6672, cols. 1-2; Fig. 1B).

11. To make this molecule, the gene encoding the chimeric protein (H-2K^b/IgG) was expressed in a cell line (J558L) which also expresses an immunoglobulin light chain (Dal Porto, p. 6672, col. 1) and beta2-microglobulin.

12. The resulting molecule was purified from culture. Analysis showed that the molecule was divalent (containing two MHC binding sites), consisting "of dimers of a complex composed of chimeric heavy chain, immunoglobulin light chain, and β_2 -microglobulin (Fig. 1B)" (Dal Porto, p. 6673, col. 2). The structure of Dal Porto's molecule is reproduced in the figure below:



Dal Porto's figure shows a protein complex comprising chimeric heavy chain, immunoglobulin light chain, and β_2 -microglobulin.

13.

Dal Porto et al teach soluble divalent class I MHC/IgG molecules (H-2K^b/IgG) that demonstrate nanomolar affinities for T cell receptors and nanomolar concentrations of the soluble divalent H-2K^b/IgG molecule specifically inhibited lysis of target cells by . . . T cells, whereas soluble monovalent H-2K^b never inhibited the response of . . . T cells . . . and previous indirect measurements of the interaction between soluble monovalent MHC class I and T cells suggests affinities in the micromolar range.

(Answer 5). *See* Dal Porto, p. 6675 (Discussion).

Chang

14. “Generation of soluble T-cell receptor (TCR) molecules by a variety of genetic engineering methods have been hampered by inefficient pairing of α and β subunits in the absence of their respective transmembrane regions and associated CD3 components” (Chang, p. 11408 (Abstract); Answer 5).

15. To overcome this obstacle, Chang adds peptide segments to the carboxyl termini of the TCR α and β extracellular domains (Chang, p. 11408 (Abstract)).

16. These peptide segments “selectively associate to form a stable heterodimeric coiled coil termed a leucine zipper” (Chang, p. 11408 (Abstract)).

17. “This approach makes it possible to bring together at will two distinct subunit components” (Chang, p. 11412, col. 2). *See* Answer 5.

Harris

18. “Harris et al teaches methods for producing bivalent (i.e., divalent) binding proteins comprising fusing binding domains via a linker to the N-

terminus of the variable regions of the heavy chain and the light chain”
(Answer 6).

19. “[T]he fusion proteins retain binding activity” (Answer 6). *See, e.g.,* Harris, p. 14.

20. “[T]he binding domains can include cell surface receptors (see [Harris] entire document, particularly pages 6-8, page 12, lines 15-19 and page 13, lines 7-16 and Figures 2, 6, 8 and 9)” (Answer 6).

Level of Skill

21. As summarized below, the evidence of record establishes that the technical skill of the ordinary skilled worker at the time the invention was made was high.

22. Each of Dal Porto, Chang, and Harris teach engineering of complexes of various types of fusion proteins.

23. Dal Porto describes heavy chain immunoglobulin grafted with MHC domains (Dal Porto, p. 6673. col. 2).

24. Chang discloses a dimeric fusion protein complex, where each fusion protein comprises an extracellular TCR domain fused to a coiled coil domain of leucine zippers (Chang, p. 11408).

25. Harris teaches various types of extracellular domains fused to light and heavy immunoglobulin chains (Harris, p. 6-7), similar in structure to Dal Porto’s molecule.

26. Thus, the skilled worker had the technical skill and knowledge to prepare fusion proteins, including the knowledge to select a receptor type (e.g., MHC or TCR) and a polypeptide to fuse it to (e.g., coiled coil, immunoglobulin light chain; immunoglobulin heavy chain),

27. In sum, the evidence establishes that a person of ordinary skill in the art was technically proficient in protein fusion technology and its use to improve the characteristics of many different types of binding fusion molecules, including heterodimeric TCRs (Chang) as claimed here.

DISCUSSION

The issue in this appeal is whether it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have replaced the soluble MHC chain in Dal Porto's divalent molecule (Dal Porto, Fig. 1B; Findings of Fact 10-12) with soluble T-cell heterodimer² in which the two TCR extracellular domains that comprise the heterodimer are fused to Dal Porto's immunoglobulin light chain and immunoglobulin heavy chain, respectively.

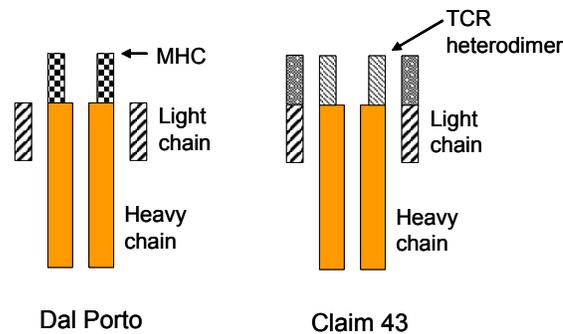
In making an obviousness determination, it is necessary to identify the differences between the claimed invention and the prior art, and then to determine whether these differences are obvious in view of the scope and content of the prior art and the level of skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 13-14, 148 USPQ 459, 465 (1966).

Appellants agree that there are two key differences between Dal Porto's engineered molecule and the molecular complex produced by the claimed method (Br. 13-14). First, the MHC extracellular domain fused to

² Claim 43 recites that the first fusion protein comprises a first extracellular and an immunoglobulin heavy chain, and that the second first fusion protein comprises a second extracellular domain and an immunoglobulin light chain. The Examiner's rejection focuses on the narrower embodiment in which the first and second extracellular domains are, respectively, the soluble extracellular domains of the first and second subunits of the T-cell receptor.

the immunoglobulin heavy chain in Dal Porto's molecule is replaced by the extracellular domain of a first transmembrane protein in the claimed complex. The first extracellular domain forms a ligand binding site with an extracellular domain of a second transmembrane protein. The rejection focuses on the narrower embodiment in which the extracellular domains are derived from TCR. Secondly, in the claimed molecular complex, the extracellular domain of the second transmembrane membrane protein is fused to the immunoglobulin light chain; in Dal Porto's molecule, the immunoglobulin light chain is not a fusion protein. (See Br. 13).

The following figure illustrates these differences:



The figure depicts the structure of Dal Porto's molecule contrasted with an embodiment of claim 43.

Obviousness requires a teaching that all elements of the claimed invention are found in the prior art and "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

Dal Porto teaches that the binding affinity and efficacy of soluble MHC was improved by grafting the MHC to immunoglobulin heavy chain, and producing a soluble divalent molecule comprising the chimeric heavy

chain/MHC complexed with immunoglobulin light chain (Dal Porto, p. 6675 (Discussion); Findings of Fact 8-13). The Examiner contends that Dal Porto's success with soluble MHC would have prompted the skilled worker to apply its system to soluble TCR heterodimers in order to increase their binding affinity (Answer 7-8), which were known to have been difficult to study because of their relatively low binding affinity (Matsui, p. 12862, cols. 1-2; Findings of Fact 3-6; Answer 6-7).

Chang is relied upon by the Examiner for teaching that assembly of the TCR subunits into a heterodimer is facilitated by attaching each subunit to peptide segments which "selectively associate" to form stable dimers (Chang, p. 11408; Findings of Fact 14-17; Answer 5). Thus, the Examiner contends that that Chang provides "a strong suggestion . . . to modify Dal Porto . . . by fusing both TCR α and β extracellular segments . . . to the N-terminus of the antibody heavy and light chains . . . to facilitate heterodimer formation" (Answer 11).

Harris is cited for teaching methods of producing complexes of two fusion proteins which having binding activity (Findings of Fact 18-20; Answer 6) and that "binding domains can be fused via a linker to the N-terminus of the variable regions of immunoglobulin . . . chains without altering the binding function of the fusion proteins" (Answer 7).

Appellants contend that a person of ordinary skill in the art would not have been motivated to have combined the references as asserted by the Examiner. They argue that Masui teaches a method to directly measure the interaction between the soluble forms of TCR and MHC; thus, Matsui solved the problem (Br. 14). They also assert that Chang "teaches no other method of associating proteins other than by using leucine zipper

components” which have a “very different secondary structure” from immunoglobulin chains, and therefore the skilled worker would not have been motivated to replace its leucine zipper with immunoglobulin chains to enhance T-cell heterodimer interactions (Br. 14).

In regard to Harris, Appellants state:

Harris explicitly teaches one of ordinary skill *not* to include a complete immunoglobulin molecule in its binding proteins. In fact, use of a complete immunoglobulin molecule would render the Harris binding proteins unsatisfactory for one of their intended purposes (to avoid undesirable effector functions). There is, therefore, no suggestion in Harris to include both heavy and light immunoglobulin chains, which are present in molecular complexes of the invention.

(Br. 15).

Finally, Appellants contend that it was well known that TCRs associate to form functional binding sites in the absence of their transmembrane domain, so no additional manipulations would have been necessary as suggested by the Examiner (Br. 15). Accordingly, they conclude that even if there were reason to modify Dal Porto, “the modification would have been to substitute one of the TCR or class II MHC extracellular domains for the MHC class I α chain in the fusion protein, to express the other extracellular domain by itself, and to permit the two extracellular domains to associate as the prior art taught they would” (Br. 15).

In our opinion, the Examiner has the better arguments. Matsui’s teaching of the low-affinity of soluble heterodimeric TCR (Matsui, p. 12862 (Abstract); Findings of Fact 5) coupled with Dal Porto’s teaching that both the affinity and effectiveness of soluble MHC can be improved by grafting

the soluble MHC to a immunoglobulin scaffold would have prompted one of ordinary skill in the art to have applied the same approach to TCR in order to improve its binding affinity.³

Appellants dismiss this rationale, arguing that that Matsui “solves the problem” (Br. 14). However, as they acknowledge (Br. 14), Matsui did not remedy the low affinity of heterodimeric TCRs; they worked around it by utilizing a technique that facilitated the measurement of low-affinity TCR binding (Matsui, p. 12862, col. 2; Findings of Fact 6). Precise teachings directed to the specific subject matter of a claim are not required to reach a conclusion of obviousness. *KSR*, 127 S. Ct. at 1741, 82 USPQ2d at 1396. “[T]he teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.” *In re Kahn*, 441 F.3d 977, 987-988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). In this case, the TCR binding problem identified in Matsui, and acknowledged in the Specification, would have led one of ordinary skill in the art to have applied Dal Porto’s teachings to solve it.

Appellants argue that Harris teaches away from complete antibodies because “the effector functions intrinsic to the complete antibodies . . . have led to undesirable interactions” (Harris, p. 1-2; Br. 11-12). We do not find

³ Consistent with the Examiner’s reasoning that there was motivation to improve the affinity of soluble TCR for peptide/MHC complexes, Appellants state in the Specification that “to specifically regulate immune responses, soluble molecules with high affinities/avidities for . . . peptide/MHC complexes are needed” (Specification 7-8).

this argument persuasive because the claims at issue are not limited to how the claimed complex is utilized. Harris's statement, at most, appears to apply only when antibodies are used in a milieu where certain properties, such as "complement binding," would be unwanted (Harris, p. 2, ll. 5-8).

Appellants also contend that even if there were reason to modify Dal Porto, "the modification would have been to substitute one of the TCR or class II MHC extracellular domains for the MHC class I α chain in the fusion protein, to express the other extracellular domain by itself, and to permit the two extracellular domains to associate as the prior art taught they would" (Br. 15). We do not agree.

In its normal configuration, each of the two TCR extracellular domains of the T-cell receptor is linked to a unique transmembrane segment which together form a heterodimer (Specification 4, 8, and Fig. 1A; Findings of Fact 2). Chang's soluble synthetic TCR heterodimer – where the TCR extracellular domains are appended to peptides which themselves dimerize together – mimics this normal T-cell receptor configuration. Thus, the most logical and normal structure of a soluble synthetic TCR is one in which each extracellular domain is fused to a separate peptide segment. The skilled worker, in adopting Dal Porto's strategy to enhance the binding affinity of soluble TCR, would have been motivated to graft one extracellular domain to the immunoglobulin heavy chain and the other to the light chain in order to mimic the native TCR configuration.

Moreover, as argued by the Examiner, Chang's disclosure that dimerization between soluble TCR subunits can be improved by grafting each subunit to proteins which themselves associate together would have led the skilled worker to fuse the second T cell receptor subunit to the

immunoglobulin light chain of Dal Porto's divalent molecule to achieve the same result taught by Chang.

Obviousness is determined with respect to the level of skill of the person of ordinary skill in the art. The evidence of record provided by the Examiner establishes that the technical skill of the ordinary skilled worker at the time the invention was made was high (Findings of Fact 21). Each of Dal Porto, Chang, and Harris teach engineering of complexes of various types of fusion proteins (Findings of Fact 22). Dal Porto describes heavy chain immunoglobulin grafted with MHC domains (Dal Porto, p. 6673, col. 2; Findings of Fact 23). Chang discloses a dimeric fusion protein complex, where each fusion protein comprises an extracellular TCR domain fused to a coiled coil domain of leucine zippers (Chang, p. 11408; Findings of Fact 24). Harris teaches various types of extracellular domains fused to light and heavy immunoglobulins (Harris, p. 6-7; Findings of Fact 25), similar in structure to Dal Porto's molecule. Thus, the skilled worker was technically proficient in protein fusion technology and its use to improve the characteristics of many different types of binding molecules, including heterodimeric TCRs (Chang) as claimed here (Findings of Fact 26, 27). Fusion of one TCR subunit to a light chain and the other TCR subunit to the heavy chain is the same class of technical manipulation performed in Dal Porto, Chang, and Harris and, as concluded above, well within the level of ordinary skill in the art.

For the foregoing reasons, we find that the Examiner has presented adequate evidence to establish prima facie obviousness of the claimed method. We affirm the rejection of claim 43. Claims 44-52 and 54-61 fall

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with claim 43 because separate arguments for their patentability were not presented.

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

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