

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 29

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte ALBAN J. LINNENBACH,
HILARY KOPROWSKI, and
DORTHEE HERLYN

Appeal No. 2001-1258
Application No. 08/413,805

ON BRIEF

Before ADAMS, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, 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, 3, 4, 6, 7, 9, 10, 19-21, 24, 25, 30, and 31. Claims 26-29 are also pending but are not subject to any outstanding rejection. See the Examiner's Answer, page 2. Claims 1 and 4 are representative of the claims on appeal and read as follows:

1. A recombinantly-produced immunogenic polypeptide GA733-2E consisting of the amino acid sequence of SEQ ID NO: 2 substantially free from contamination with other proteinaceous materials.

4. A pharmaceutically acceptable composition which comprises as active ingredient, a pharmaceutically effective amount of immunogenic GA733-2E consisting of the amino acid sequence of SEQ ID NO: 2 in pharmaceutically acceptable carrier.

The examiner relies on the following references:

European Patent Application

Bumol

0 326 423

Aug. 2, 1989

Hussey et al. (Hussey), "A soluble CD4 protein selectively inhibits HIV replication and syncytium formation cells," Nature, Vol. 331, pp. 79-81 (1988)

Johnson et al. (Johnson), "Synthesis of soluble myelin-associated glycoprotein in insect and mammalian cells," Gene, Vol. 77, pp. 287-296 (1989)

Szala et al. (Szala), "Molecular cloning of cDNA for the carcinoma-associated antigen GA733-2," Proc. Natl. Acad. Sci., Vol. 87, pp.3542-3546 (1990)

Claims 1, 3, 4, 6, 7, 9, 10, 19-21, 24, 25, 30, and 31 stand rejected under 35 U.S.C. § 103 as obvious in view of the combined disclosures of Szala, Bumol, Hussey, and Johnson.

We affirm.

Background

"GA733-2 is a 40 kDa human cell surface glycoprotein antigen that is associated with carcinomas of various origins. Its biological function remains unknown. Hydrophobicity analysis of the protein sequence predicted by cDNA has suggested that the GA733-2 antigen is a type I membrane protein, i.e., it possesses signal peptide, extracellular domain, trans-membrane domain and intracellular anchor." Specification, page 2. The specification discloses a truncated variant of the GA733-2 antigen, designated GA733-2E, that consists of the signal peptide and extracellular domains of the full-length protein.

See page 9. The amino acid sequence of GA733-2E is shown in the specification's Figure 1 and in SEQ ID NO: 2.

The specification also states that

[t]he baculovirus-insect cell expression system has been well recognized for its ability to abundantly express recombinant proteins which most often resemble native protein with respect to function, immunoreactivity, and immunogenicity. Baculovirus has been exploited for production of a variety of enzymes, trans-membrane proteins, and secretory proteins such as tissue plasminogen activator, interleukin-2, and human beta interferon. A soluble variant of the cell surface protein CD4 has been generated by expressing a restriction enzyme cleaved portion of the CD4 cDNA [R.E. Hussey et al, Nature (Lond.), 331:78-81 (1988)].

Page 5 (bracketed material in original).

Discussion

Appellants state that “claims 4, 6, 7, 9, 10, 20, 21, 25-29, and 31[,] which are drawn to pharmaceutical compositions, should be considered independently of other claims (1, 3, 19, 24 and 30) in assessing patentability.” Appeal Brief, page 3. Appellants present separate arguments directed to the pharmaceutical compositions. Therefore, we will consider claims 1 and 4 as representative of the claims on appeal. Claims 3, 19, 24, and 30 will stand or fall with claim 1, and the remaining claims on appeal will stand or fall with claim 4. See 37 CFR § 1.192(c)(7)

Claim 1 is directed to a recombinantly produced, immunogenic polypeptide consisting of the amino acid sequence shown in SEQ ID NO: 2 “substantially free from contamination with other proteinaceous materials.” As discussed above, SEQ ID NO: 2 corresponds to the signal sequence and

extracellular domain of GA733-2. Claim 4 is directed to a composition comprising a pharmaceutically effective amount of the polypeptide of SEQ ID NO: 2 in a pharmaceutically acceptable carrier.

The examiner rejected the claims as obvious over the combined disclosures of Szala, Bumol, Hussey, and Johnson. The examiner accurately characterized Szala as teaching the cloning and expression of full-length GA733-2, as well as the predicted functional domains of the protein (signal sequence, extracellular domain, transmembrane domain, and cytoplasmic domain). Szala also teaches that the “cloning of cDNA for the tumor-associated GA733-2 antigen . . . will facilitate the production of antigen needed for immunization strategies.” Page 3542. In addition, Szala teaches that expression of the disclosed cDNA “will meet a critical need for tumor-associated antigen. For instance, it will now be possible to compare recombinant tumor-associated antigen with internal image anti-idiotypic antibodies as agents for the immunotherapy of carcinoma.” Page 3546. The examiner acknowledged that Szala does not disclose a truncated GA733-2 variant consisting only of the signal sequence and extracellular domain.

The examiner cites Bumol as disclosing vectors for producing the GA733-2 antigen in prokaryotic and eukaryotic host cells.¹ The examiner points in particular to the “prokaryotic expression vector pLKSA that contains the [GA733-2] coding sequence from which the DNA coding for the 49 C-terminal

¹ Bumol refers to the protein as the “KSA” antigen, but the examiner asserts, and Appellants do not dispute, that KSA and GA733-2 are alternative names for the same protein.

amino acids (the transmembrane and cytoplasmic domains, the signal peptide and the propeptide have been deleted.” Examiner’s Answer, page 5. The examiner acknowledges that Bumol’s truncated variant is missing the first 81 amino acids of SEQ ID NO: 2, but asserts that

Bumol et al. makes [sic] clear that the signal peptide and propeptide (amino acids 1-81) were deleted in the exemplified embodiment to facilitate production in prokaryotes because prokaryotes do not efficiently process eukaryotic signal peptides and the propeptide portion was deleted because it is not found on the cell surface (extracellularly).

Id.

The examiner cited Johnson and Hussey as showing that those of skill in the art would have been motivated to express a truncated GA733-2 variant consisting of the signal peptide and extracellular domain in eukaryotic cells, specifically insect cells using a baculovirus expression vector. Both Johnson and Hussey disclose production of soluble variants of cell-membrane proteins using a baculovirus/insect cell expression system. Johnson discloses production of soluble myelin-associated glycoprotein (sMAG). The sMAG construct expressed by Johnson encoded the signal sequence and extracellular domain of MAG but was deleted for the transmembrane domain and intracellular domain. See Figure 1. Johnson reported that insect cells transformed with the recombinant construct expressed “high levels of sMAG” and that the recombinant proteins were bound by anti-MAG antibodies. See page 292. Hussey discloses production of soluble CD4. The baculovirus expression vector used by Hussey was disclosed to “terminate[] just before the transmembrane region.” Figure 1

legend. Hussey reported that expression in insect cells allowed purification of milligram quantities (i.e., large amounts) of soluble CD4. See page 78 (abstract), see also the legend to Figure 2 (“Yields were routinely 1-2 mg secreted T4_{ex1} or T4_{ex2} proteins per litre SF9 cells.”).

The examiner concluded that it would have been obvious, in view of the combined teachings of Szala, Bumol, Johnson, and Hussey, to recombinantly produce a soluble variant of GA733-2 consisting of the first 265 amino acids (SEQ ID NO: 2), i.e., a soluble variant consisting of the signal sequence and the extracellular domain but deleted for the transmembrane domain and cytoplasmic domain. The examiner pointed to Szala’s disclosure of the need for large quantities of the GA733-2 antigen as motivation to produce the soluble GA733-2 variant in a baculovirus/insect cell expression system, which is shown by Johnson and Hussey to efficiently produce recombinant proteins. The examiner acknowledged that the soluble GA733-2 variant disclosed by Bumol was also deleted for the signal sequence and propeptide, but pointed to Johnson and Hussey as evidence that such deletions would have been recognized as unnecessary for expressing a soluble GA733-2 variant in eukaryotic cells such as insect cells. Thus, the examiner concluded that the polypeptide of claim 1 would have been prima facie obvious.

With respect to claim 4, the examiner concluded that it would have been obvious “to produce pharmaceutically acceptable compositions with adjuvants or pharmaceutically acceptable carriers in order to immunize animals or raise antibodies or produce antisera as suggested by both Szala et al. and

Bumol et al.” Examiner’s Answer, page 7. Therefore, the examiner concluded that claim 4 would also have been prima facie obvious.

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness.” In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). “[A] proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have had a reasonable expectation of success.” In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991) (citation omitted).

In this case, we agree that the cited references support a prima facie case of obviousness. Szala teaches the complete DNA sequence of the GA733-2 gene and the complete amino acid sequence of the encoded polypeptide, and specifies the sequences making up the various domains of the polypeptide. See the paragraph bridging pages 3544 and 3545. Bumol discloses a soluble GA733-2 variant, albeit for expression in prokaryotic cells and lacking the signal sequence and so-called propeptide. See page 13, lines 31-59. These teachings by themselves may not have rendered the instantly claimed GA733-2 variant obvious, in that they do not seem to suggest a variant that lacks the transmembrane and cytoplasmic domains while retaining the signal sequence and entire extracellular domain.

However, the examiner also relies on Johnson and Hussey. These references disclose production of soluble variants of other membrane proteins in insect cells, using baculovirus vectors. Johnson and Hussey show, as the examiner correctly points out, that soluble variants of membrane proteins need only be deleted for the transmembrane and cytoplasmic domains in order to be expressed efficiently by insect cells. We also note, although the examiner did not rely on it, that the instant specification admits that “[t]he baculovirus-insect cell expression system has been well recognized for its ability to abundantly express recombinant proteins which most often resemble native protein with respect to function, immunoreactivity, and immunogenicity.” Page 5.

Thus, we agree with the examiner that it would have been obvious to a person of ordinary skill in the art, in view of the cited references, to express a soluble variant of GA733-2 in an insect cell/baculovirus expression system, because that system was well-known to efficiently produce recombinant proteins. We also agree that it would have been obvious to express the GA733-2 soluble derivative consisting of SEQ ID NO: 2, because that amino acid sequence corresponds to exactly the amino acids disclosed by Szala to make up the signal sequence and entire extracellular domain of GA733-2. While Bumol’s soluble GA733-2 derivative was also deleted for the signal sequence and propeptide, Bumol expressly states that those regions were deleted in order to express the polypeptide in prokaryotic cells, whereas Johnson and Hussey show that those regions need not be deleted in order to produce the polypeptide in insect cells.

With regard to the pharmaceutically acceptable composition of claim 4, we agree with the examiner that such a composition would have been obvious as well. For example, Bumol teaches that recombinant GA733-2 could be used to create novel antibodies (page 16, lines 57-62) or “for development of potential anti-adenocarcinoma vaccines” (page 17, lines 14-15). These teachings would have suggested combining the recombinant, soluble GA733-2 variant with a pharmaceutically acceptable carrier such as water or physiological saline. Thus, the pharmaceutically acceptable composition of claim 4 would have been prima facie obvious in view of the cited references.

Appellants argue that the cited references do not suggest the claimed polypeptide. Appellants argue that Szala and Bumol do not teach a GA733-2 variant truncated only at the C-terminus (Appeal Brief, page 6) and that “Johnson and Hussey fail to teach or suggest GA733, much less any modifications thereof” (Appeal Brief, page 8).

This argument is not persuasive. “Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references.” In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). The test of obviousness is “whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention.” In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). For the reasons discussed in detail above, we conclude that the combined teachings of the cited references would have

suggested both the GA733-2 variant of claim 1 and the pharmaceutically acceptable composition of claim 4.

Appellants also argue that Hussey teaches away from the claimed invention. Appellants argue that Hussey “teaches that it is not predictable that a soluble protein will have the biological activity of the full-length protein.” (Appeal Brief, page 10). Therefore, Appellants argue, “the examiner has failed to establish that there is a reasonable expectation that the secreted protein would be immunogenic and that it would be useful as in a pharmaceutical composition.” (Appeal Brief, page 11).

This argument is not persuasive. Appellants have pointed to no specific passage in Hussey to support their position that the truncated CD4 variants had biological activities that differed from that of the full-length protein. Our review of the reference has turned up no such passage. In fact, as relevant to immunogenicity, Hussey discloses that “each of three anti-CD4 monoclonal antibodies (19Thy5D7, 18T3A9, and OKT4A) . . . reacts with T4_{ex1} and T4_{ex2} protein.” Page 81, right-hand column. T4_{ex1} and T4_{ex2} are two truncated CD4 variants. See page 78, right-hand column. In addition, Johnson discloses that a soluble MAG variant produced in insect cells reacted with anti-MAG antibodies. See page 292. Finally, Appellants’ specification admits that “[t]he baculovirus-insect cell expression system has been well recognized for its ability to abundantly express recombinant proteins which most often resemble native protein with respect to function, immunoreactivity, and immunogenicity.” Page 5.

“Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success.” In re O’Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988). In this case, we find that the references would have provided the required reasonable expectation of success.

Finally, Appellants argue that the references do not suggest the composition of claim 4. (See the Appeal Brief, pages 7-8). Appellants argue that “Szala and Bumol teach the use of antibodies for the treatment of carcinomas. These teachings are not applicable to the present invention, which recite[s] pharmaceutical compositions containing the immunogenic polypeptide GA733-2E.” Page 7. Appellants argue that “faced with the teaching of administration of antibodies (i.e., passive immunotherapy), one of skill in the art would not have been motivated to prepare a pharmaceutical composition containing an immunogenic polypeptide (i.e., active immunotherapy).” Page 8.

This argument is also not persuasive. Claim 4 is directed to a “pharmaceutically acceptable composition” that comprises a “pharmaceutically effective amount” of truncated GA733-2 and a “pharmaceutically acceptable carrier.” We agree with the examiner that this claim language reads on a composition containing the GA733-2 variant suggested by the cited references, and a carrier such as water, to be administered to an animal in order to raise antibodies against GA733-2.

Appellants seem to interpret the claim language to require a composition that is administered to a patient for treatment (e.g., of cancer), but nothing in the

claim language supports such a limited construction. For example, claim 4 does not require that the claimed composition contain an amount of truncated GA733-2 that is therapeutically effective for the treatment of any specific disease. Nor does the specification provide a definition of “pharmaceutically effective amount” that would distinguish the claimed composition from the one made obvious by the prior art. It is well-established that “in proceedings before the PTO, claims in an application are to be given their broadest reasonable interpretation consistent with the specification.” In re Sneed, 710 F.2d 1544,1548, 218 USPQ 385, 388 (Fed. Cir. 1983). So interpreted, claim 4 reads on the composition suggested by the examiner’s references.

Summary

The references cited by the examiner support a prima facie case of obviousness, which has not been effectively rebutted. We therefore affirm the rejection under 35 U.S.C. § 103.

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

AFFIRMED

Donald E. Adams)	
Administrative Patent Judge)	
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Demetra J. Mills)	
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
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