

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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

Appeal No. 2001-0766
Application No. 08/483,941

ON BRIEF

Before WINTERS, ADAMS, and GREEN, Administrative Patent Judges.

WINTERS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal was taken from the examiner's decision finally rejecting claims 1-6, 11, 16, 26 and 36, which are all of the claims remaining in the application.

Representative Claim

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

1. A selectable fusion gene comprising a dominant positive selectable gene fused to and in reading frame with a negative selectable gene, wherein the selectable fusion gene encodes a single bifunctional fusion protein which when expressed confers a dominant positive selectable phenotype and a negative selectable phenotype on a cellular host.

The References

In rejecting the appealed claims under 35 U.S.C. § 103, the examiner relies on the following prior art references:

McKnight, "The nucleotide sequence and transcript map of the herpes simplex virus thymidine kinase gene," Nucleic Acids Research, Vol. 8, No. 24, pp. 5949-5964 (1980)

Kaster et al.(Kaster), "Analysis of a bacterial hygromycin B resistance gene by transcriptional and translational fusions and by DNA sequencing," Nucleic Acids Research, Vol. 11, No. 19, pp. 6895-6911 (1983)

Sugden et al. (Sugden), "A Vector That Replicates as a Plasmid and Can Be Efficiently Selected in B-Lymphoblasts Transformed by Epstein-Barr Virus," Molecular and Cellular Biology, Vol. 5, No. 2, pp. 410-413 (1985)

Borrelli et al. (Borrelli), "Targeting of an inducible toxic phenotype in animal cells," Proceedings of the National Academy of Sciences, Vol. 85, pp. 7572-7576 (1988)

Germann et al. (Germann), "Expression of a Multidrug Resistance-Adenosine Deaminase Fusion Gene," Journal of Biological Chemistry, Vol. 264, No. 3, pp. 7418-7424 (1989)

Moolten et al. (Moolten), "Curability of Tumors Bearing Herpes Thymidine Kinase Genes Transferred by Retroviral Vectors," Journal of the National Cancer Institute, Vol. 82, No. 4, pp. 297-300 (1990)

Deliberations

Our deliberations in this matter have included evaluation and review of the following materials:

- (1) the instant specification, including claims 1-6, 11, 16, 26 and 36;
- (2) appellant's Brief on Appeal, received February 26, 1998 (certificate of mailing February 23, 1998), and appellant's Reply Brief, received July 27, 1998 (certificate of mailing July 23, 1998);

(3) the Examiner's Answer, mailed May 26, 1998;

(4) the Lupton declaration filed under the provisions of 37 CFR § 1.132, executed November 3, 1995; and

(5) the above-cited references relied on by the examiner.

The Rejections

The appealed claims stand rejected as follows:

(1) Claims 1, 2, 6, 11, 16, 26 and 36 under 35 U.S.C. § 103 as unpatentable over Germann in view of Borrelli or Moolten;

(2) Claim 3 under 35 U.S.C. § 103 as unpatentable over Germann in view of Borrelli or Moolten, as applied to claims 1, 2, 6, 11, 16, 26 and 36, further taken in view of Sugden; and

(3) Claims 4 and 5 under 35 U.S.C. § 103 as unpatentable over Germann, Borrelli or Moolten, and Sugden, as applied to claim 3, further taken in view of Kaster and McKnight.

The examiner's "base rejection" applies a combination of Germann and Borrelli, or Germann and Moolten, to claims 1, 2, 6, 11, 16, 26 and 36. Dependent claims 3, 4 and 5 stand rejected over the same combination of references, with Sugden, Kaster and McKnight also applied to reach additional limitations present in those claims. The examiner's rationale for the "base

rejection” of claims 1, 2, 6, 11, 16, 26 and 36 is set forth at pages 5-7 of the Examiner’s Answer as follows:

Germann et al. disclose the use of a[n] in-frame chimeric fusion gene between the genes encoding a dominant selectable marker and a protein of interest as a simple means of selecting for eukaryotic cells expressing the protein of interest and the use of retroviral vectors as the means of introduction of the chimeric genes into the cells. Germann et al. teach on page 7418, paragraph 1 the advantages of fusing the dominant selectable gene to the gene of interest in contrast to vectors in which the dominant selectable gene and unselectable gene of interest are under the control of different promoters i.e.[,] the use of a fusion gene encoding a chimeric protein ensures that the expression of both the selected and unselected constituents occurs in the selected cells.

Borrelli et al. and Moolten et al. each disclose that the expression of negative selectable markers, particularly the HSV1 thymidine kinase gene (HSV1-TK) within eukaryotic cells (which are naturally TK⁺), is useful for the selective elimination of particular cell types within a living organism. Moolten et al. further disclose the use of the neomycin phosphotransferase gene (NeoR) as a dominant selectable marker to select for cells expressing the HSV1-TK gene as well[] as vectors for the introduction of the HSV1-TK gene into cells which comprise both a dominant selectable marker (NeoR) and the negatively selectable gene (HSV1-TK) each under the control of a different promoter. Cells expressing the HSV1-TK gene are selected for by growing the transformed cells in the presence of neomycin.

Therefore, as positive selection for cells which express the HSV1-TK gene is possible only in mutant TK⁻ cells (whereas both Borrelli et al. and Moolten et al. teach that one would desire to produce cells which are naturally TK⁺ expressing this gene), it would have been obvious to one of ordinary skill in the art to construct a vector comprising a chimeric gene fusion between the HSV1-TK gene and a dominant selectable marker (such as NeoR) in order to be able to select for cells expressing this useful gene within any cell type. One of ordinary skill in the art would have been motivated to fuse the HSV1-TK gene to the dominant selectable marker instead of using a vector similar to that of Moolten et al. by the advantages of such a strategy taught by Germann et al. It would have been further obvious to transduce this vector into eukaryotic cells and to grow these cells under the selection pressure of the dominant selectable

gene in order to select those cells expressing the HSV1-TK gene (i.e., the negatively selectable gene).

We disagree with that line of reasoning and, accordingly, reverse all of the appealed § 103 rejections.

In proceedings before the PTO, the examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. The examiner can satisfy this burden “only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.”

In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir.

1992)(footnote omitted). As set forth in In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000):

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.... Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher....

Most if not all inventions arise from a combination of old elements.... Thus, every element of a claimed invention may often be found in the prior art.... However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention.... Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. (Citations omitted.)

Here, the motivation asserted by the examiner for combining references is Germann's disclosure that fusing a positive selectable gene to an unselectable gene ensures expression of the unselectable gene. Extrapolating from that disclosure, the examiner argues that Germann would provide incentive for fusing a positive selectable gene to a negative selectable gene, such as disclosed in the remaining references, to ensure expression of the negative selectable gene. However, Moolten is the only reference relied on disclosing a vector with both a dominant positive selectable gene and a negative selectable gene; and Moolten does not disclose any problem expressing these genes, even though each is under the control of a different promoter. Moolten is not faced with the problem addressed by Germann, and Moolten's non-fusion vector does not suffer from the disadvantages discussed by Germann with respect to gene expression.

Germann discloses preparing fusion proteins to ensure expression of genes which "have no selectable phenotype associated with their expression" or genes which encode "an unselected protein" (page 7418, column 1, first full paragraph of text). As stated by Germann, "[t]aken together the results indicate that the human MDR1 gene may be used as a dominant selectable marker to introduce nonselectable genes in the form of gene fusions into human cells" (page 7424, column 1, first full paragraph, emphasis added). In contrast, all of the claims on appeal require a negative selectable gene. Because Germann discloses the advantages of fusion constructs only with respect to nonselectable genes, the artisan of ordinary skill would not have been led by Germann to prepare a fusion protein containing a negative selectable marker of the type disclosed in the other references. We find nothing in Germann leading the artisan of ordinary skill to apply Germann's fusion construct technique to negative

selectable genes, disclosed in the secondary references and recited in the appealed claims.

The examiner argues (Examiner's Answer, page 11) that the claim term "negative selectable gene" encompasses any gene which is not positively selectable, and therefore encompasses the nonselectable genes disclosed by Germann as suitable for inclusion within a fusion construct. However, that argument is not supported by the specification's definition of the term "negative selectable gene," or by Germann. As discussed above, Germann discloses that fusion constructs are advantageous because they ensure expression of genes which "have no selectable phenotype associated with their expression" or genes which encode "an unselected protein" (page 7418, column 1, first full paragraph of text). In contrast, on page 18, lines 13-16, appellant's specification defines "negative selectable gene" as "any gene which, upon being transduced into a host cell, expresses a phenotype permitting negative selection (i.e.,] elimination) of stable transductants." Thus, in contrast to the genes disclosed in Germann, the claimed genes, and those disclosed in the references applied in combination with Germann, all have a selectable phenotype associated with their expression. The examiner's position to the contrary, notwithstanding, Germann's disclosure of "nonselectable genes" does not encompass the negative selectable genes recited in the claims, or disclosed by the references applied in combination with Germann.

On this record, the examiner has not established adequate reason, suggestion or motivation stemming from the prior art which would have led a person having ordinary skill to combine Germann and Borrelli, or Germann and Moolten, in the manner proposed. Nor do the remaining references relied on by the examiner cure the deficiencies of the proposed combination of Germann and

Borrelli, or Germann and Moolten. The examiner has not established that the cited prior art would have led a person having ordinary skill to apply the fusion techniques described by Germann to the negative selectable genes disclosed in the remaining references. A review of appellant's specification and claims makes it clear that the prior art could be modified in the manner proposed by the examiner. However, "[t]he mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Mills, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

For these reasons, we conclude that the examiner has not established a prima facie case of obviousness of claims 1-6, 11, 16, 26 and 36, within the meaning of 35 U.S.C. § 103. We find it unnecessary to discuss the Lupton declaration, filed under the provisions of 37 CFR § 1.132, relied on by appellant as rebutting any such prima facie case.

The examiner's decision rejecting claims 1-6, 11, 16, 26 and 36 under 35
U.S.C. § 103 is reversed.

REVERSED

SHERMAN D. WINTERS)	
Administrative Patent Judge)	
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DONALD E. ADAMS)	BOARD OF PATENT
Administrative Patent Judge)	APPEALS AND
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)	INTERFERENCES
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LORA M. GREEN)	
Administrative Patent Judge)	

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Morrison & Foerster
755 Page Mill Road
Palo Alto, CA 94304-1018

SDW/jlb