

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 39

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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

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Ex parte GREGORY F. HOLLIS, and GEORGE E. MARK

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Appeal No. 2003-0847  
Application No. 08/744,685

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HEARD: June 26, 2003

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Before SCHEINER, MILLS, and GREEN, Administrative Patent Judges.

GREEN, 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 6, 15-17, 19, 21-27 and 29-35. Claim 6 is representative of the subject matter on appeal, and reads as follows:

6. A homologous recombination insertional expression vector capable of expressing a recombinant gene in a NS/O cell, said vector comprising said recombinant gene and gamma 2A locus-specific DNA sequences capable of homologous recombination targeting into the NS/O gamma 2A locus, wherein said recombinant gene comprises a nucleic acid sequence encoding for a recombinant protein and a promoter transcriptionally coupled to said nucleic acid sequence, wherein said promoter is capable of providing for expression in said NS/O cell and said recombinant gene is capable of expression in said NS/O cell.

The examiner relies upon the following references:

Fell et al. (Fell A)	5,204,244	Apr. 20, 1993
Reff et al. (Reff)	5,998,144	Dec. 07, 1999

Fell et al. (Fell B) "Homologous Recombination in Hybridoma Cells: Heavy Chain Chimeric Antibody Produced by Gene Targeting," Proc. Natl. Acad. Sci. USA Vol. 86, pp. 8507-8511 (1989)

Delente, "Glycosylation Revisited," Trends in Biotechnology, Vol. 3, No. 9 (1985)

Yamawaki-Kataoka et al. (Yamawaki-Kataoka), "The Complete Nucleotide Sequence of Mouse Immunoglobulin  $\gamma$ 2a Gene and Evolution of Heavy Chain Genes: Further Evidence for Intervening Sequence-Mediated Domain Transfer," Nucleic Acids Research Vol. 9, pp. 1365-1381 (1981)

Morrison "Transfer and Expression of Immunoglobulin Genes," Ann. Rev. Immunol., Vol. 2 pp. 239-256, (1984)

Paul, "Regulation of Immunoglobulin Gene Expression," Fundamental Immunology, 3<sup>rd</sup> ed., Raven Press, Ltd, pp. 351-370 (1993)

Sambrook et al. (Sambrook), Molecular Cloning, A Laboratory Manual, 2nd Edition, pp. 16.8-16.15 Cold Spring Harbor Laboratory Press, (1989)

Claims 19, 23 and 27 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of filing, had possession of the claimed invention. Claims 6, 15-17, 19, 21-27 and 29-35 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure as filed fails to enable one skilled in the art to make and/or use the full scope of the claimed invention. Claims 6, 15-17, 19, 21-27 and 29-35 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that appellant regards as the invention. Finally, claims 6, 15-17, 19, 22, 23, 27 and 30 stand rejected under 35 U.S.C. § 103 as being rendered

obvious by the combination of Fell A or Fell B as combined with Yamawaki-Kataoka. After careful review of the record and consideration of the issues before us, we reverse all of the rejections of record. Note that in deciding this appeal, we have also considered the issues in related Appeal No. 2003-1594, Application No. 08/970,266.

### DISCUSSION

1. Rejection under 35 U.S.C. § 112, first paragraph (New Matter)

Claims 19, 23 and 27 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time of filing, had possession of the claimed invention.

As an initial matter, we note that the Examiner's Answer references two prior office actions in which the rejection is set forth, Paper Nos. 17 and 24. An Examiner's Answer should not, however, reference more than a single prior office action. See MPEP 1208 ("An examiner's answer should not refer, either directly or indirectly, to more than one prior Office action."). Moreover, where there is confusion of what constitutes the rejection, as there is in this case, the examiner's answer should set forth the rejection in its entirety in the answer rather than referencing the prior actions.

To the best of our understanding, the examiner is objecting to the reference to the selectable markers xanthene-guanine phosphoribosyltransferase (gpt) and dihydrofolate reductase (dhfr). The

examiner acknowledges that “the specification does describe expression vectors in general and selectable markers in a vector,” but asserts that it “does not indicate that it was intended (1) that these vectors encode gpt or dhfr or even if these vectors do, that (2) the coding regions for these genes would be removed and shuttled to other vectors. The specification only contemplated using expression vectors listed in the specification and cloning the DNA encoding the desired protein into the expression vector (see page 7, lines 6-7).” Examiner’s Answer, page 4.

Appellants, pointing to the specification at page 6, lines 20-25, and page 7, lines 1-5, contend that the disclosure as filed “provides written description support for the use of the selectable markers gpt and dhfr in different vectors by general descriptions of selectable markers and examples of vectors containing gpt and dhfr.” Appeal Brief, page 7.

Page 6 of the specification states that (emphasis added):

Specifically designed vectors allow the shuttling of DNA between hosts such as bacteria-yeast or bacteria-animal cells. An appropriately constructed expression vector should contain: an origin of replication for autonomous replication in host cells, selectable markers, a limited number of useful restriction enzyme sites, a potential for high copy number, and active promoters.

The paragraph bridging pages 6 and 7 provides examples of commercially available mammalian expression vectors, wherein gpt and dhfr are among the selectable markers used in those expression vectors.

To satisfy the written description requirement, the disclosure as originally filed must convey with reasonable clarity to those skilled in the art that the

inventor was in possession of the invention. See Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000).

We find that the disclosure as filed conveys to the skilled artisan that appellants were in possession of the claimed invention, i.e., the use of the gpt and dhfr as selectable markers in vectors other than those specifically listed in the specification. The disclosure as filed teaches the general use of selectable markers, and also discloses the use of the gpt and dhfr markers, albeit in specifically exemplified vectors.

2. 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 6, 15-17, 19, 21-27 and 29-35 stand rejected under 35 U.S.C. § 112, first paragraph, as the disclosure fails to enable one skilled in the art to make and/or use the full scope of the claimed invention.

According to the rejection as it is set forth in Paper No. 17,

the specification, while being enabling for a homologous recombination insertional expression vector for the expression of a murine immunoglobulin gamma 2A polynucleotide in NS/O cells wherein said vector comprises said polynucleotide in said cell and murine immunoglobulin gamma 2A locus specific DNA sequences for targeting, a transcription unit encoding a selectable marker, an origin of replication, and a CMV-IEp promoter, does not reasonably provide enablement for a homologous recombination insertional expression vector for the expression of any recombinant gene in any mammalian cells wherein said vector comprises said gene in said cell and any immunoglobulin gamma 2A locus-specific DNA sequences for targeting and a transcription unit encoding any selectable marker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Paper No. 17, page 8.

According to the examiner, the specification fails to enable the full scope of the claims because “[i]t remains unclear which regions of the gamma 2A locus are to be used in the vector to target any ‘recombinant gene’ to the gamma 2A locus,” and “how any ‘recombinant gene’ will be expressed at such a locus.” Id. at 9. The rejection asserts that the specification only describes the use of the germline gamma 2A gene for homologous recombination into the gamma 2A locus.

The rejection also contends that the specification does not address how any “recombinant gene” will be expressed in the gamma 2A locus through the claimed vector, such as, by providing the promoter and enhancer regions that will be used to drive expression. According to the rejection,

it is unclear if any “recombinant gene” will actually be expressed. Expression of any “recombinant gene” can be inhibited from expression due to anti-sense – tertiary structure formation from a constitutively expressed complementary gene pre-existing in the cell. The specification does not provide an enabling description which addressed this issue.

Id. at 10.

The rejection asserts further that “immunoglobulin gene expression is quite unique,” and cites Paul and Morrison as evidence of the difficulties that may be associated with immunoglobulin gene expression. See id. at 10-12. The examiner then restates the conclusion that “[t]he specification fails to enable a vector comprising any recombinant gene, including a human immunoglobulin gene which targets any immunoglobulin gamma 2A locus in any mammalian cell.” Id. at 12.

The rejection also argues that the claims encompass expression in any mammalian cell, and are not limited to NS/O cells. Moreover, citing Reff and Delente, the rejection asserts that aberrant glycosylation of recombinant proteins may be a problem in NS/O cells, and such glycosylation may affect the structure, stability and solubility of any expressed protein. The rejection concludes:

In view of the insufficient guidance, inadequate examples, and the lack of predictability of the art as evidenced by Reff [ ], Paul, Morrison [ ] and Delente [ ] with regard to expressing any gene coding for a functional protein in any mammalian cell with the homologous recombination insertional expression vector encompassed by the scope of the broadly written claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Id. at 13.

Appellants argue that the Patent Office bears the initial burden of presenting a prima facie case of unpatentability, and that the examiner has not met that burden. We agree.

“[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original). “[It] is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any

statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.” Id. at 224, 169 USPQ at 370. Here, the examiner has not provided “acceptable evidence or reasoning which is inconsistent” with the specification, and therefore has not met the initial burden of showing nonenablement.

First, although the examiner recognized the applicability of the Forman or Wands factors, see Paper No. 17, page 8, the rejection did not set forth a systematic analysis of those factors. We recommend that in order to make a clear record that is susceptible to meaningful review, that a systematic analysis of the relevant factors be set forth in the rejection.

Second, although the rejection is concerned that the claims read on the expression of any recombinant gene, the examiner has not provided sufficient evidence demonstrating why it would require an undue amount of experimentation by one skilled in the art to express genes other than those exemplified by the specification using the claimed homologous recombination insertional vector. The rejection makes reference to the lack of guidance as to promoters and enhancers, but presents no evidence that it would require an undue amount of experimentation by one skilled in the art to determine the appropriate enhancers and promoters. Moreover, although the rejection asserts that expression of a recombinant gene may be inhibited by expression of anti-sense—tertiary structure formation from a constitutively expressed complementary gene pre-existing in the cell, the examiner has not presented any evidence that such tertiary structure formation is an issue to the expression of

recombinant proteins in general, nor that its is an issue with respect to the claimed homologous recombination insertional expression vector.

Third, the rejection is concerned with the difficulties that may be associated with immunoglobulin gene expression. The rejection, does not however, address why it would require an undue amount of experimentation to express immunoglobulin genes in the claimed homologous recombination insertional vectors, especially as the specification exemplifies the expression of a recombinant antibody. Moreover, a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph. See Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 218 (CCPA 1976), In re Cook, 439 F.2d 730, 732, 169 USPQ 298, 300 (CCPA 1971).

Finally, the rejection is concerned with the breadth of the claims and that the claims encompass expression in any mammalian cell, and are not limited to NS/O cells. That concern is not understood, however, as the claim requires that the recombinant gene be capable of being expressed in NS/O cells. That the recombinant gene may or may not be capable of being expressed in other cell types by the claimed homologous recombination insertional vector is irrelevant. Moreover, the fact that aberrant glycosylation of recombinant proteins may be a problem in NS/O cells, and such glycosylation may affect the structure, stability and solubility of any expressed protein, also does not render the claims non-

enabled, because, again, a claim may encompass inoperative embodiments and still meet the enablement requirement of 35 U.S.C. § 112, first paragraph.

Because the rejection fails to set forth a prima facie case that the specification fails to enable one skilled in the art to make and/or use the full scope of the claimed invention, it is reversed.

3. 35 U.S.C. § 112, Second Paragraph

Claims 6, 15-17, 19, 21-27 and 29-35 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that appellant regards as the invention.

The examiner contends that the exact meaning for the phrase “immunoglobulin gamma 2A locus” is unknown. The rejection is concerned that the immunoglobulin 2A locus is not present in humans, and that it is not clear that the locus is present in species other than mice. The rejection concludes that “it is impossible for one skilled in the art to determine the metes and bounds of the claims.” Paper No. 17, page 7.

The rejection appears to be concerned with the breadth of the claims, i.e., that the claims read on an immunoglobulin gamma 2A locus that is not derived from murine cells. However, “breadth is not to be equated with indefiniteness,” and the rejection is reversed. In re Miller, 441 F.2d 689, 693, 169 USPQ 597, 600 (CCPA 1971); see also In re Hyatt, 708 F.2d 712, 714-15, 218 USPQ 195, 197 (Fed. Cir. 1983).

4. 35 U.S.C. § 103(a)

Claims 6, 15-17, 19, 22, 23, 27 and 30 stand rejected under 35 U.S.C.

§ 103 as being rendered obvious by the combination of Fell A or Fell B as combined with Yamawaki-Kataoka.

Fell A is relied upon for teaching homologous recombination in hybridoma cells. Fell B is relied upon for teaching a process for producing chimeric antibodies using novel recombinant vectors. According to the rejection, “[t]he recombinant DNA constructs of the invention can be used to transfect antibody producing cells so that targeted homologous recombination occurs in the transfected cells leading to gene modification and the production of chimeric antibody molecules by the transfected cells.” Paper No. 17, page 16. The rejection acknowledges that both references fail to teach the use of a murine gamma 2A sequence.

Yamawaki-Kataoka is cited for teaching the complete nucleotide sequence of mouse immunoglobulin gamma 2A gene. The rejection concludes:

From the knowledge of the murine immunoglobulin [gamma 2A] gene sequence and the teachings of [Fell A or Fell B] it would have been obvious to one skilled in the art at the time the invention was made to modify the vectors of [Fell A or Fell B] to include to include the IgG2A sequence [to] [sic] permit locus-specific homologous recombination into the immunoglobulin [gamma 2A] gene locus. Therefore 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 [Fell A or B] to that of Yamawaki-Kataoka [ ] to obtain an expression vector for the expression of recombinant immunoglobulin genes in mouse cells. A person of ordinary skill in the art would have been motivated to produce the claimed method to express immunoglobulin genes of interest.

Id. at 16-17.

The burden is on the examiner to set forth a prima facie case of obviousness. See In re Alton, 76 F.3d 1168, 1175, 37 USPQ2d 1578, 1581

(Fed. Cir. 1996). With respect to an obviousness rejection based on a combination of references, as the court has stated, “virtually all [inventions] are combinations of old elements.” Environmental Designs, Ltd. V. Union Oil Co., 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S.P.Q. (BNA) 8, 12 (Fed. Cir. 1983) (“Most, if not all, inventions are combinations and mostly of old elements.”). Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. The United States Court of Appeals for the Federal Circuit, our reviewing court, however, has stated that “the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references.” Ecolchem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1371, 56 USPQ2d 1065, 1073 (Fed. Cir. 2000).

The rejection fails to show that one of ordinary skill in the art would have been motivated to target the gamma 2A locus as a site for homologous recombination. Fell A and B teach the expression of recombinant genes by homologous recombination. Yamawaki-Kataoka discloses the complete nucleotide sequence of the murine gamma 2A locus. We can find no teaching or suggestion in those references, nor does the examiner point to one, that would lead one of ordinary skill to target the gamma 2A locus as the site for the

homologous recombination. Thus, the rejection fails to provide motivation to combine Yamawaki-Kataoka with either Fell A or B, and the rejection is reversed.

CONCLUSION

Because the examiner has failed to set forth a prima facie case of unpatentability in the rejections of record, those rejections are reversed.

REVERSED

Toni R. Scheiner	)	
Administrative Patent Judge	)	
	)	
	)	BOARD OF PATENT
Demetra J. Mills	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
Lora M Green	)	
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