

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 20

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JAMES RASMUSSEN,
GARY BARSOMIAN and MICHEL BERGE

Appeal No. 1998-1719
Application No. 08/442,603

ON BRIEF

Before WINTERS, ADAMS and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge, issued a concurring opinion.

ADAMS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on the appeal under 35 U.S.C. § 134 from the examiner's final rejection of claim 14. Claim 14 is the only claim pending in this application, and is reproduced below:

14. A CHO cell comprising nucleic acid encoding enzymatically active human glucocerebrosidase, said cell being transformed with any plasmid selected from the group pGB20, pBG37¹ and pGB42.

¹ We note the following typographical error in appellants' Appendix, "pBG37" should read – pGB37 --. This typographical error is corrected herein.

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The references relied upon by the examiner are:

Clark et al. (Clark) 4,675,285 Jun. 23, 1987

Levinson et al. (Levinson) 4,713,339 Dec. 15, 1987

Martin et al. (Martin), "Glycosylation and Processing of High Levels of Active Human Glucocerebrosidase in Invertebrate Cells Using a Baculovirus Expression Vector," DNA, Vol. 7, No. 2, pp. 99-106 (1988)

GROUND OF REJECTION

Claim 14 is rejected under 35 U.S.C. § 103 as obvious over Martin in view of Levinson and Clark.

We reverse.

THE REJECTION UNDER 35 U.S.C. § 103:

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, and to the respective positions articulated by the appellants and the examiner. We make reference to the examiner's Answer² for the examiner's reasoning in support of the rejection. We further reference appellants' Brief³ for the appellants' arguments in favor of patentability.

The initial burden of presenting a prima facie case of obviousness rests on the examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

² Paper No. 18, mailed December 11, 1996.

³ Paper No. 16, received August 19, 1996.

In the Final Office Action⁴ (page 4), the examiner finds that the combination of Martin in view of Levinson and Clark teach the pGB20 plasmid. The examiner relies (Answer, pages 4-5) upon Martin to teach the glucocerebrosidase gene. The examiner states (Answer, bridging paragraph, pages 6-7) that:

Appellants argue that the glucocerebrosidase gene of Martin et al. is not the functional equivalent of applicant's gene segment. This is not persuasive because applicants have failed to show that the glucocerebrosidase gene of appellants is different in an unobvious manner from the gene of Martin et al. Appellants argue that their original gene segment was extensively modified but fail to show how the modified segment (included within the claimed plasmids) differs from the gene segment of Martin et al. ... Martin et al. state on page 100 that "the cDNA for human glucocerebrosidase was obtained from plasmid pUC19/GC ... This cDNA contained 5' and 3' untranslated sequences as well as the complete coding region for glucocerebrosidase." ... The nucleotide sequence of pUC19/GC is not given so it is not clear that the Eco RI – Xba I fragment of the cDNA insert of this plasmid contains the complete 5' and 3' non-coding regions of the human GCR gene but merely that at least some of these sequences are present.

Appellants' specification (page 18, lines 5-26) discloses:

To optimize expression of GCR in mammalian cells, we further modified the GCR.D21 ... the modifications were made using oligonucleotide directed mutagenesis ... to alter the nucleotide sequence near the GCR translation start to match the consensus sequence (CCACCATGG) for optimal translation in mammalian cells ... and to delete the excess sequence 3' of the gcr.D21C stop codon. ... A bicistronic gcr-dhfr expression vector for CHO cells was constructed as shown in Fig. 7 ... This vector, pGB20, contained gcr.D21C

Appellants' figure 6 illustrates the modifications made to obtain gcr.D21C, including the oligonucleotide directed mutagenesis of the GCR translation start to match the consensus sequence described on page 18 of the specification. Figure

⁴ Paper No. 13, mailed October 4, 1995.

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7 of the specification illustrates the ligation of gcr.D21C into the pGB14 plasmid to obtain pGB20.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). The examiner merely argues (Answer, page 8) that it would have been obvious to “trim the amount of untranslated sequences of a gene for optimization of the expression of the encoded protein....” The examiner fails to identify a teaching, and we find no such teaching of record, that would suggest to a person of ordinary skill in the art to modify the translation start site of the glucocerebrosidase gene as was done in appellants’ pGB20 construct. Levinson and Clark, relied upon by the examiner to teach other components of the plasmid, e.g., ampicillin resistance and a polyadenylation signal, fail to make up for the deficiencies found in Martin.

On these facts, we are constrained to reach the conclusion that the examiner failed to provide the evidence necessary to support a prima facie case of obviousness. Where the examiner fails to establish a prima facie case, the rejection is improper and will be overturned. In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Accordingly, we reverse the examiner’s rejection of claim 14 under 35 U.S.C. § 103 as obvious over Martin in view of Levinson and Clark.

The concurrence believes that the examiner has met her burden because “[a]ppellants have admitted that the modification they made to the pGB20 translation start site was known in the art to optimize expression in mammalian cells.” The concurring opinion refers to a passage of appellants’ specification (page 18) finding that “[t]his passage is an admission that a consensus translation start site had been disclosed in the prior art and that such a translation start site was known to provide optimal translation in mammalian cells.” In support of this opinion, the concurrence relies upon In re Nomiya, 509 F.2d 566, 570-71, 184 USPQ 607, 611 (CCPA 1975) for the proposition that “[i]nformation that an applicant admits is in the prior art ‘may be considered ‘prior art’ for any purpose, including use as evidence of obviousness.’” The concurrence also relies on, In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 687 (Fed. Cir. 1986) for the proposition that “the prior art as a whole must be considered [and] ... the teachings are to be viewed as they would have been viewed by one of ordinary skill.” We disagree with this line of reasoning.

We first note that our concurring colleague’s reasoning bears little relationship to the reasoning presented to us on the record by the examiner. Nevertheless, assuming arguendo that appellants’ statements at page 18 of the specification constitute admitted prior art⁵, we find no reason, suggestion or motivation stemming from the prior art to modify Martin, in the manner proposed by the examiner. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). In our judgment, the only reason or

⁵ We do not find it necessary to determine if, or to what extent, the statements at page 18 of the specification constitute admitted prior art.

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suggestion to modify the references, as suggested by the concurrence, to arrive at the present invention comes from appellants' specification. As our appellate reviewing court noted in In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966) "[i]t is impermissible to first ascertain factually what appellants did and then view the prior art in such a manner as to select from the random facts of that art only those which may be modified and then utilized to reconstruct appellants' invention from such prior art."

On this record, the examiner acknowledges (Answer, page 7) that "the disclosure of Martin et al. is unclear." Then, after recognizing that the teachings in the Martin reference were less than clear, the examiner states (Answer, page 8):

Even if the gene fragments of Martin et al. differ from appellants gene fragment as stated in the appeal brief, this is not an unobvious difference. The disclosure of a gene clearly suggests to the ordinary skilled artisan additional fragments of nucleic acid which encode the same nucleotide sequence with less non-coding sequence as, absent evidence to the contrary, the skilled artisan would clearly consider all gene fragments which include the entire coding sequence to be functionally equivalent for the expression of the encoded protein. Furthermore, it was well known in the art to trim the amount of untranslated sequences of a gene for optimization of the expression of the encoded protein as such untranslated sequences can include sequences which produce plasmid or message instability or introduce elements such as upstream ATG codons which decrease the amount of protein produced but are not necessary for expression of the desired protein.

Initially, we believe that it is improper to base a rejection on a reference that is less than clear. As stated in In re Warner, 379 F.2d 1011, 1017, 154 USPQ 173, 178 (CCPA 1967), cert. denied, 389 U.S. 1057 (1968) "[t]he Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may

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doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis.”

In addition, where we need specificity in the examiner’s analysis, to lead us to the modifications made in pGB20, we are only met with vagueness and generalities. We find no appreciation in the examiner’s statement that Martin could or should be modified in the manner suggested in the concurring opinion. It does not appear to us that the examiner fully appreciated the degree of specificity required to get from the gene taught by Martin, to the claimed pGB20 construct claimed.

Furthermore, to the extent that the concurrence relies on Nomiya, we note that figures 1 and 2 at issue in Nomiya were labeled “prior art”. In Nomiya, the examiner’s first rejection of the appealed claims identified and specifically recognized that figures 1 and 2 illustrated the prior art. Nomiya 509 F.2d at 570, 184 USPQ at 611. Thus, from the very first rejection, Nomiya had notice of the “prior art” relied upon and an opportunity to address this “prior art.” That is not the case here.

The Nomiya court also recognized, in reversing the examiner’s rejection under 35 U.S.C. § 103, that “[t]he court must be ever alert not to read obviousness into an invention on the basis of the applicant’s own statements; that is, we must view the prior art without reading into that art appellant’s teachings.” Nomiya 509 F.2d at 571, 184 USPQ at 612.

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On the record presented, the examiner failed to meet her burden of establishing a prima facie case of obviousness within the meaning of 35 U.S.C. § 103.

Having determined that the examiner has not established a prima facie case of obviousness, we find it unnecessary to discuss the Barsomian Declaration executed June 10, 1992, relied on by appellants to rebut any such prima facie case.

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Other Issues:

We encourage the examiner to consider whether a deposit of the biological materials is necessary, in this application, in order to comply with the requirements of 35 U.S.C. § 112, first paragraph.

REVERSED

Sherman D. Winters)	
Administrative Patent Judge)	BOARD OF PATENT
)	
)	APPEALS AND
)	
Donald E. Adams)	INTERFERENCES
Administrative Patent Judge)	

GRIMES, Administrative Patent Judge, concurring.

Although I agree that the obviousness rejection should be reversed, I respectfully disagree with the majority's analysis of the prima facie case. The majority concludes that the prima facie case fails because the examiner "fails to identify a teaching, and we find no such teaching of record, that would suggest to a person of ordinary skill in the art to modify the translation start site of the glucocerebrosidase gene as was done in appellants' pGB20 construct." However, Appellants have admitted that the modification they made to the pGB20 translation start site was known in the art to optimize expression in mammalian cells.

The modification of the glucocerebrosidase translation start site in pGB20 is explained in Appellants' specification as follows:

To optimize expression of GCR in mammalian cells, we further modified the GCR.D21 BglIII cassette containing the gcr gene. In general, with reference to Fig. 6, the modifications were made using oligonucleotide directed mutagenesis . . . to alter the nucleotide sequence near the GCR translation start to match the consensus sequence (CCACCATGG) for optimal translation in mammalian cells (as described by Kozak, 1986, 44 Cell 283-292).

Page 18. This passage is an admission that a consensus translation start site had been disclosed in the prior art and that such a translation start site was known to provide optimal translation in mammalian cells.

Information that an applicant admits is in the prior art "may be considered 'prior art' for any purpose, including use as evidence of obviousness under 35 U.S.C. § 103." In re Nomiya, 509 F.2d 566, 570-71, 184 USPQ 607, 611 (CCPA 1975). In addition, when considering obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been

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viewed by one of ordinary skill.” In re Hedges, 783 F.2d 1038, 1039, 228 USPQ 685, 687 (Fed. Cir. 1986).

Here, even though the references relied on by the examiner do not teach Appellants’ modification to the translation start site in the pGB20 plasmid, Appellants have admitted that this modification was known in the art to provide optimal translation in mammalian cells. Since the prior art as a whole must be considered in determining the obviousness of a claimed invention, I conclude that the references relied on by the examiner, viewed as they would have been viewed by one of ordinary skill, support a prima facie case of obviousness.

“When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over.” In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976). “If a prima facie case is made in the first instance, and if the applicant comes forward with reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed.” In re Hedges, 783 F.2d at 1039, 228 USPQ at 686.

Here, Appellants have provided evidence that the claimed host cells unexpectedly secrete the recombinant glucocerebrosidase enzyme. In a declaration under 37 CFR § 1.132, applicant Gary Barsomian states that

[g]lucocerebrosidase is known to be a lysosomal enzyme which, like other lysosomal enzymes, is targeted to lysosomes within mammalian cells. This means that one skilled in the art would normally expect such an enzyme to be retained within the cell once expressed, and not secreted into the medium in any significant amounts. Accordingly, it was unexpected to discover that

glucocerebrosidase could be secreted into a culture medium in significant amounts by mammalian cells.

Barsomian declaration, ¶ 5.

Declaratory evidence as to issues of fact is entitled to substantial weight. In re Alton, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996). The examiner has not disputed Dr. Barsomian's statements that a person of ordinary skill in the art would expect a lysosomal enzyme such as glucocerebrosidase to be targeted to lysosomes in mammalian cells, and that its secretion from the claimed cells was unexpected. Rather, she argues that secretion of glucocerebrosidase from the claimed cells does not overcome the prima facie case because "the skilled artisan would have expected the claimed CHO cells to be useful regardless of the ability of the cells to secrete the glucocerebrosidase."

In order to outweigh a prima facie case of obviousness, evidence of unobviousness must show unexpected property of a significant aspect of the invention. See In re Eli Lilly & Co., 902 F.2d 943, 947, 14 USPQ2d 1741, 1745-46 (Fed. Cir. 1990). However, "when an applicant demonstrates substantially improved results . . . and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary." In re Soni, 54 F.3d 746, 751, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (emphases in original).

Here, Appellants have presented un rebutted evidence that the claimed cells display not merely an improvement in a known property, but a property that was unknown and unexpected based on the prior art. Since the disclosed utility of the

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claimed cells lies their ability to produce recombinant glucocerebrosidase, and since the improved property relates to production of recombinant glucocerebrosidase, the unexpected property relates to a significant aspect of the claimed invention. Therefore, I find it sufficient to overcome the prima facie obviousness suggested by the prior art.

In sum, I find no defect in the examiner's prima facie case. I would, however, reverse on the basis of Appellants' evidence of unexpected results.

Eric Grimes
Administrative Patent Judge

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