

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 42

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte AXEL KAHN, GILDAS LE GAL LA SALLE,
JACQUES MALLET, MICHEL PERRICAUDET,
MARC PESCHANSKI, and JEAN-JACQUES ROBERT

Appeal No. 2001-0562¹
Application No. 08/460,478

ON BRIEF

Before WINTERS, ADAMS and GREEN, Administrative Patent Judges.

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 claims 81-102, 104-120, 122 and 123. Claims 124 and 125 are allowed. No other claims are pending in the application.

¹ This appeal is related to Appeal No. 2001-1167 (Application No. 08/460,814) and 2001-1961 (Application No. 08/459,994). Accordingly, these appeals were considered together.

Claims 81 and 122 are illustrative of the subject matter on appeal and are reproduced below:

81. A method for expressing a gene in mammalian central nervous system cells, which method comprises

modifying said cells to contain a replication-deficient recombinant adenovirus comprising said gene under the control of a promoter, wherein said gene encodes a polypeptide molecule functioning in said cells as a neurotransmitter-synthesizing enzyme, trophic factor, a growth factor, or a lysosomal enzyme, or wherein said gene is an antisense sequence, the transcription product of which blocks the expression in said cells of proteins responsible for neuropsychiatric disease, or of enzymes involved in the biosynthesis of said proteins or in the biosynthesis of glutamate; and

wherein the gene is expressed in said modified cells.

122. A method for treating Parkinson's Disease which method comprises stereotactically administering to the brain of a mammal suffering from Parkinson's Disease a pharmaceutical composition comprising a replication-defective adenovirus which infects central nervous system cells of said mammal and expressing a nucleotide sequence, contained in said adenovirus, which nucleotide sequence encodes a neurotransmitter-synthesizing enzyme whereby said subject is treated for Parkinson's disease.

The references relied upon by the examiner are:

Geller et al. ('979)	5,501,979	Mar. 26, 1996
Geller et al. ('945)	WO 92/07945	May 14, 1992

Braithwaite, "Semipermissive replication of adenovirus 5 in rat brain cells and evidence for an induction of cellular DNA replication in vivo," J. gen. Virol., Vol. 67, pp. 391-396 (1986)

Stratford-Perricaudet et al. (Stratford-Perricaudet), "Gene transfer into animals : the promise of adenovirus," Human Gene Transfer, Vol. 219, pp. 51-67 (1991)

Ikenaka et al. (Ikenaka), "Detection of brain-specific gene expression in brain cells in primary culture: A novel promoter assay based on the use of a retrovirus vector," The New Biologist, Vol. 4, No. 1, pp. 53-60 (1992)

Cohen-Haguenauer et al. (Cohen-Haguenauer), "Gene therapy: Realities and prospects, Pathologie Biologie, Vol. 40, No. 1, pp. 5-13 (1992)

Neve, "Adenovirus vectors enter the brain," Trends in Neuroscience, Vol. 16, No. 7, pp. 252-253 (1993)

Friedmann, "Gene therapy for neurological disorders," Trends in Genetics, Vol. 10, No. 6, pp. 210-214 (1994)

Orkin et al. (Orkin), "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy," pp. 1-41 (NIH, 1995)

GROUNDINGS OF REJECTION

Claims 122 and 123 stand rejected under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to support or enable how to make and/or use the claimed invention.

Claims 81, 82 and 85-102² stand rejected under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to support or enable the scope of the claimed invention.

Claims 81-100, 104-118, 122 and 123 stand rejected under 35 U.S.C. § 103 as being unpatentable over '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet.

Claims 81, 90, 91, 104, 108 and 109 stand rejected under 35 U.S.C. § 103 as being unpatentable over '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet and further in view of Ikenaka.

² We note the examiner's reference to claim 103 in his discussion of the rejections under 35 U.S.C. § 112, first paragraph. However, as the examiner recognizes, in the Communication from the Examiner (Paper No. 41, mailed July 29, 2000), claim 103 was cancelled. Accordingly, the statement of the claims under rejection herein is correct.

Claims 81, 101, 102, 104, 119 and 120 stand rejected under 35 U.S.C. § 103 as being unpatentable over '945 in view of Cohen-Haguenuer, Braithwaite and Stratford-Perricaudet and further in view of '979.

We reverse.

DISCUSSION

THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

The examiner relies (Answer, pages 10-13) on the teachings of Orkin, Neve and Friedmann to support the rejection of claims 81, 82, 85-102, 122, and 123. According to the examiner (Answer, pages 10-11) Orkin makes several conclusions that would lead one skilled in the art to conclude that the practice of the claimed invention would require undue experimentation. With reference to Neve, the examiner finds (Answer, page 11) the:

working examples disclosed in the specification show that for most sites of injection, the adenoviral infection was highly local, illustrating the need for one skilled in the art to know the precise location of the nervous system that the recombinant adenoviral vector needs to be injected for treating a given disease or studying a particular research problem.

With reliance on Friedmann, the examiner finds (Answer, page 11) there are "tremendous barriers to the practical application of gene therapy of the CNS, such as the high complexity of the CNS and the lack of knowledge of the genetic basis for the vast majority of neurological diseases and disorders."

The rejection of claims 81, 82 and 85-102:

While the examiner makes a number of comments with regard to claims 81, 82 and 85-102, the examiner concisely states his position at page 20 of the Answer:

the claims are not enabled for any and all means of delivering the adenovirus to CNS cells in vivo. The standing rejection of [these] claims ... could be overcome by limiting [these] claims ... such that when the adenovirus is administered to central nervous system cells in vivo, it is done so by stereotactical injection (as in claims 83 and 84).

To support this position, the examiner relies on Friedmann (Answer, page 13) arguing that Friedmann teach:

the CNS is not freely accessible through the general bloodstream (see Friedmann, page 210, col. 1, para. 2), so it is unclear how one can infect CNS cells by a systemic route, such as intravenous, oral, anal, respiratory delivery, since one skilled in the art would not expect the adenovirus to reach cells of the CNS, at least not in any effective quantity.

While we note that appellants argue (Reply Brief, page 2) that neither Friedman, nor the examiner define the phrase “freely accessible,” in our review of Friedmann, at page 210, column 1, paragraph 2, we are unable to find the phrase “freely accessible.” Instead, the first sentence of paragraph 2 on page 210, column 1, Friedman states “[i]t is now evident that assessments of the application of human gene therapy should be extended to neurological disorders.” In this same paragraph, Friedman states:

Disorders of the CNS ... were generally not prominent candidates for gene therapy in most early discussions ... the perceived physical inaccessibility of the CNS, and physiological barriers to the introduction of gene transfer vectors through the blood-brain barrier combined to make gene therapy seem less feasible in the CNS than in other organs.

In the third paragraph of page 210, column 1, Friedman states “[f]ortunately, these reservations regarding the feasibility of gene therapy for neurological disorders are now fading....” Therefore, we agree with appellants’ argument (Reply Brief, page 3) that “there is no basis in the record to support the

conclusion that ‘one of skill in the art would not expect the adenovirus to reach cells of the CNS” in an effective quantity.

Whether the disclosure is enabling, is a legal conclusion based on several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-37, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

We find no analysis of the Wands factors by the examiner. Instead, we find only the examiner’s unsupported conclusions as to why the specification does not enable the claimed invention. We remind the examiner that nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In the absence of a fact-based statement of a rejection based upon the relevant legal standards, the examiner has not sustained his initial burden of establishing a prima facie case of non-enablement. In our opinion, the examiner failed to provide the evidence necessary to support the rejection of claims 81, 82 and 85-102 under 35 U.S.C. §112, first paragraph. Accordingly, we reverse the rejection of claims 81, 82 and 85-102 under 35 U.S.C. §112, first paragraph.

The rejection of claims 122 and 123:

According to the examiner (Answer, page 6) the subject matter of claims 122 and 123 is “not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.” In response to appellants’ argument (Brief, pages 11-12), the examiner argues (Answer, pages 20-21):

Assay 9.2 (specification[,] page 20) is relevant to treatment of Parkinson’s Disease using an art accepted model for testing treatment of Parkinson’s Disease, ... [the examiner argues that] claims 122 and 123 are not commensurate in scope with the method employed in Assay 9.2, nor with the teachings in the specification, for example at page 9. The adenovirus in Assay 9.2 comprised nucleic acid encoding tyrosine hydroxylase and under transcription control of the RSV LTR promoter, not a generic neurotransmitter-synthesizing enzyme (as recited in claim 122) expressed under transcription control of any and all promoters. Claim 123 limits the neurotransmitter-synthesizing enzyme to tyrosine hydroxylase (not tyrosine kinase...). Also, the adenovirus was administered to the striatum of the brain (spec. page 20, line 10), not to the brain generally. As claimed, the invention embraces administering the adenovirus to any and all regions of the brain, not just to the striatum. The specification at pages 4-5 discloses a number of promoters, in general, that can be linked to the “gene”, in general, in the adenovirus. The only promoter explicitly taught for incorporation into an adenovirus for treatment of Parkinson’s Disease is the RSV LTR promoter. Furthermore, “ependymal, neural and glial promoters” are not specific promoters, but classes of promoters, and the specification does not disclose any specific promoters that fall into these classes of promoter. The specification must teach those of skill in the art how to make and how to use the invention as broadly claimed, not as narrowly disclosed.

Here the rejection under 35 U.S.C. §112, first paragraph, is more of a series of conclusions by the examiner than a fact-based, reasoned explanation as to why a person skilled in the art would not be able to make and use the claimed invention throughout its scope without undue experimentation. As set

forth in In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) 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. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.

On this record the examiner failed to analyze the claimed invention with reference to the factors set forth in Wands. In addition, the examiner failed to provide the evidence necessary to support a rejection under 35 U.S.C. § 112, first paragraph. We are unwilling to accept the examiner's conclusion (Answer, page 21) that "[t]he facts disclosed in Orkin et al., Neve, and Friedmann illustrate that gene therapy is a highly unpredictable art." Instead, we agree with appellants (Brief, page 14) that while "[t]he cited references ... offer sweeping generalizations – they do not address the invention recited in the claims on appeal ... [g]eneral conclusory statements regarding the state of the art are insufficient."

Accordingly, we reverse the rejection of claims 122 and 123 under 35 U.S.C. § 112, first paragraph, as being based on an insufficient disclosure to support or enable how to make and/or use the claimed invention.

THE REJECTIONS UNDER 35 U.S.C. § 103:

The rejection of claims 81-100, 104-118, 122 and 123:

According to the examiner (Answer, page 14) '945 "teaches various methods for gene transfer to neuronal and glial cells of the central nervous

system for potential therapeutic applications. The methods involve infecting ... a mammal with herpesvirus vectors....” The examiner recognizes (Answer, page 15) that ‘945 does not teach “replacing the herpesvirus vectors with adenoviral vectors.”

To make up for this deficiency, the examiner relies on Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet. According to the examiner (Answer, page 15) Cohen-Haguenauer teach “that either accessory cells or neurons can be infected with retroviral, herpesvirus or adenoviral vectors encoding products such as tyrosine hydroxylase.” The examiner finds (id.) that Cohen-Haguenauer teach “that post-mitotic neurons can be infected with herpesvirus or adenovirus vectors.” The examiner further finds (id.) that “Braithwaite discloses that adenovirus can also infect ependymal cells of the brain....” The examiner recognizes (Answer, page 16) that Stratford-Perricaudet discuss “the use of replication deficient adenoviral vectors for in vivo gene delivery [emphasis removed], such as in gene therapy.”

In view of these teachings, the examiner concludes (id.):

it would have been obvious to one of ordinary skill in the art at the time the invention was made to have exchanged the adenoviral vector backbone of Stratford-Perricaudet et al. for the herpes viral vector of Geller et al. in the method of Geller et al. for transfer of desired gene products to cells of the central nervous system with a reasonable expectation of success because Cohen-Haguenauer disclosed that adenoviral vectors could infect neurons in vivo while Braithwaite disclosed that adenovirus could infect glial cells in vivo.”

In response, appellants argue (Brief, page 16) that the examiner “has not provided a clear and convincing showing of how the references would have

motivated one of ordinary skill in the art to combine their teachings to arrive at the claimed invention.” According to appellants (Reply Brief, page 5) “there is no suggestion in Cohen-Hageunauer or the other secondary references that it would have been desirable to substitute Geller’s herpesvirus vectors for an adenovirus vector.” We agree.

As set forth in In re Dow Chemical Co., 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988), “[t]he consistent criterion for determination of obviousness is whether the prior art would have [1] suggested to one of ordinary skill in the art that this process should be carried out and [2] would have a reasonable likelihood of success, viewed in the light of the prior art.” With regard to the first criterion, we remind the examiner that a prima facie obviousness based on a combination of references requires that the prior art provide “a reason, suggestion, or motivation to lead an inventor to combine those references.” Pro-Mold and Tool Co. v. Great Lakes Plastics Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

[E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . . The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular.

In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (citations omitted). The suggestion to combine prior art references must come from the cited references, not from the application’s disclosure. See Dow. Stated differently, while the examiner recognizes (Answer, pages 15-16) that adenoviral vectors can infect cells of the central nervous system, where in the

prior art applied is there a suggestion that would motivate one of ordinary skill in the art to substitute adenoviral vectors for the herpes virus taught by Geller.

While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocol taught by the prior art, the modification is not obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 211 USPQ 1125, 1127 (Fed. Cir. 1984). On this record, we see no such reason to modify the references as applied.

With regard to the second criterion set forth in Dow, we are not persuaded by the examiner's reliance on Stratford-Perricaudet and Cohen-Haguenauer for the teachings that adenovirus might be useful for gene therapy, thereby providing the "motivation" to support the combination relied on by the examiner. Instead, we agree with appellants (Brief, page 21) that "[w]hen viewed as a whole, Stratford-Perricaudet, at best, provides a general teaching that further experimentation might at some point establish that adenovirus vectors are useful in gene therapy applications for treating neurological diseases." In this regard, we remind the examiner that "[a] general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." In re Deuel, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). While a "general incentive" may make an approach "obvious to try" it does not make the invention obvious. "Obvious to try" is not the standard of obviousness under 35 U.S.C. § 103. In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988).

Accordingly, we reverse the rejection of claims 81-100, 104-118, 122 and 123 under 35 U.S.C. § 103 as being unpatentable over '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet.

The rejection of claims 81, 90, 91, 104, 108 and 109:

The examiner relies (Answer, page 18) on the teachings of '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet as described above. However, the examiner notes (id.) that no glial cell specific promoters were taught in this combination of references. However, to make up for this deficiency the examiner relies (id.) on Ikenaka to teach "a glial cell specific promoter of the GFAP gene."

In response appellants argue (Brief, page 22), Ikenaka does not cure the deficiency in the combination of '979, '945, Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet. We agree.

Accordingly, we reverse the rejection of claims 81, 90, 91, 104, 108 and 109 under 35 U.S.C. § 103 as being unpatentable over '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet and further in view of Ikenaka.

The rejection of claims 81, 101, 102, 104, 119 and 120:

The examiner relies (Answer, page 18) on the teachings of '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet as described above. However, the examiner notes (id.) that "[n]one of the references taught heterologous genes known to encode lysosomal enzymes known to be deficient or defective in neurological disorders." To make up for this deficiency the

examiner relies (Answer, page 19) on '979 to teach "using a herpes viral vector to deliver genes encoding lysosomal enzymes, such as an hexosaminidase, glucocerebrosidase, hypoxanthine and phosphoribosyl transferase (HGPRT) known to be involved in human diseases, to cells of the nervous system both for basic and clinical research (gene therapy) involving diseases affecting the nervous system...."

In response appellants argue (Brief, page 23), '979 does not cure the lack of evidence of a teaching, suggestion, or motivation to combine these references." For the reasons set forth, supra, we agree.

Accordingly, we reverse the rejection of claims 81, 101, 102, 104, 119 and 120 under 35 U.S.C. § 103 as being unpatentable over '945 in view of Cohen-Haguenauer, Braithwaite and Stratford-Perricaudet and further in view of '979.

REVERSED

Sherman D. Winters)	
Administrative Patent Judge)	
)	
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