

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 54

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte PATRICK DENEFFLE, NICHOLAS DUVERGER,
MARINE LATTA-MAHIEU, and SANDRINE SEGURET

Appeal No. 2004-0456
Application No. 08/913,699

ON BRIEF

Before WILLIAM F. SMITH, ADAMS, and MILLS, Administrative Patent Judges.

MILLS, 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 38 and 43-46 and 48-56, which are all of the claims pending in this application.

Claim 38 is illustrative of the claims on appeal and reads as follows:

38. A method of stimulating cholesterol efflux in an individual comprising administering to the individual a replication defective recombinant virus comprising a nucleic acid sequence encoding human lecithin-cholesterol acyltransferase (LCAT) operably linked to at least one promoter sequence, wherein the nucleic acid encoding LCAT is expressed and the LCAT is secreted by way of an intracellular secretory pathway in an amount effective to stimulate cholesterol efflux in the individual by increasing high density lipoprotein-cholesterol serum concentration, and wherein said defective recombinant virus is delivered by way of the bloodstream of said individual.

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The prior art references relied upon by the examiner are:

Benoit et al. (Benoit)	WO 94/25073	Nov. 10, 1994
Baer et al. (Baer)	EP 0222591	May 20, 1987
Perricaudet et al. (Perricaudet)	WO 95/02697	Jan. 1995

McLean, et al. (McLean), "Human lecithin-cholesterol acetyltransferase gene: complete gene sequence and sites of expression," Nucleic Acids. Research, Vol. 14, No. 23, pp. 9397-9406 (1986)

Jolly, D., "Viral Vector Systems for Gene Therapy," Cancer Gene Therapy, Vol. 1, No. 1, pp. 51-64 (1991)

Grounds of Rejection

Claims 38, 43-45, 48-50, 55 and 56 stand rejected under 35 U.S.C. 103(a), as obvious over Benoit in view of Baer and McLean.

Claims 38, 43, 45, 46 and 51 stand rejected under 35 U.S.C. 103(a), as obvious over Benoit in view of Baer and McLean in further view of Perricaudet.

Claims 38 and 52-54 stand rejected under 35 U.S.C. 103(a), as obvious over Benoit in view of Baer and McLean in further view of Jolly.

We reverse these rejections.

DISCUSSION

35 U.S.C. § 103(a)

Claims 38, 43-45, 48-50, 55 and 56 stand rejected under 35 U.S.C. 103(a), as obvious over Benoit in view of Baer and McLean.

It is the examiner's position that (Answer, pages 3-4):

Benoit discloses replication defective adenoviruses, which are either Ad2 or Ad5 of human origin, and therefore animal origin, which comprises nucleotide sequences encoding one or more gene products involved in cholesterol and lipid metabolism, e.g. apoA-1 and lack sequences necessary for viral replication, such as all or part of E1A and E1B regions... The reference teaches that the gene can be present in the adenovirus as cDNA or genomic DNA (gDNA) ... and that the gene should comprise sequences necessary for its expression in infected cells and may also comprises sequences for secretion if the protein is normally secreted...Benoit et al. also discloses prophetic methods of administering such vectors to patients suffering from dyslipoproteinemias, and associated atherosclerosis by gene therapy with viral vectors such as retroviral vectors, adeno-associated viral vectors ... and that the replication defective adenovirus infects liver cells *in vivo*. ...The reference teaches pharmaceutical compositions comprising one or more of the replication defective recombinant adenoviruses at a concentration of between 10^4 to 10^{14} pfu/ml of virus... . The reference teaches that apoA-1 is the main protein of HDL and activates the lecithin:cholesterol acyltransferase (LCAT) responsible for efflux of cholesterol from cells.

The examiner admits that Benoit does not teach the replication defective recombinant viruses comprising a nucleic acid sequence encoding LCAT. Answer, page 4. In order to make up for this deficiency, the examiner relies on Baer and McLean. According to the examiner, (Id., at pages 4-5):

Baer et al. disclose the cDNA sequence encoding human LCAT, which includes the signal peptide for secretion of LCAT. The reference also discloses methods of treating dyslipoproteinemias resulting from LCAT deficiency using purified LCAT protein alone or together with apoA-1, and teaches that LCAT would reduce plasma cholesterol and cellular cholesterol by mobilizing cholesterol to HDL in serum and then out of the bloodstream, and would perhaps also aid in mobilizing cholesterol from atherosclerotic plaques...

McLean et al. teach the genomic DNA encoding human LCAT protein complete with its signal peptide for secretion...

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have inserted cDNA of Baer et al. or the genomic DNA of McLean et al. encoding the human LCAT into the replication defective adenovirus of Benoit et al., either in place of, or in addition to the nucleic acid sequence encoding apoA-1 and administered it to an individual with the effect of stimulating cholesterol efflux. One [would] have had a reasonable expectation of success in making the virus since all components required were known and Benoit et al. taught how to make them, and success in administering the virus to patients and expressing the LCAT and apoA-1, if present, in liver cells, since Benoit et al. taught that the virus could be administered *in vivo* and the transgene expressed in liver cells. One would also [have] had a reasonable expectation of success that at least some cholesterol efflux would occur since Benoit et al. taught that expression of human apoA-1 would also have that effect. One would have done so because Benoit et al. taught that gene therapy held much promise for treating dyslipoproteinemias by supplying the gene encoding a protein that was deficient, e.g. apoA-1, and Baer et al. taught that LCAT protein, alone or with apoA-1 protein could be administered to treat dyslipoproteinemias due to LCAT deficiency, with the result of mobilizing cellular and atherosclerotic plaque cholesterol to HDL and hence out of the cells and bloodstream. These teachings would clearly motivate one of ordinary skill in the art to make the recited viral vector comprising the gene encoding human LCAT and administer it to individuals for delivery and expression of the transgene(s) *in vivo* for clinical research.

Appellants respond, arguing the examiner has failed to set forth a prima facie case of obviousness (Brief, page 6) as there is no clear and particular evidence of record to support the Office's conclusion that one of ordinary skill in the art would have been motivated to combine the teachings of Benoit, Baer, and McLean to arrive at the claimed invention.

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Appellants argue that (Brief, page 7-8):

The Office's rationale for combining Benoit, Baer, and McLean is based upon impermissible selective "picking and choosing" of specific components from the cited references. ...[T]he office is employing an impermissible "obvious to try" standard in concluding it would have been obvious to combine Baer's or McLean's nucleic acid encoding an LCAT with Benoit's recombinant viral vector, or to use it to stimulate cholesterol efflux in an individual.

Appellants also submit that, "if the prior art of record provides only a speculative basis for investigating the effect of administering LCAT 'to determine if such such [sic] treatments might be useful...!', then it does not provide a reasonable expectation of successfully practicing the claimed invention." Brief, pages 9-10.

We agree with appellants that the examiner has failed to establish a prima facie case of obviousness with the cited evidence before us. Prima facie obviousness under 35 U.S.C. § 103 requires that the prior art would have led a person of ordinary skill in the art to make the claimed invention, with a reasonable expectation of success. See, e.g., In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1443 (Fed. Cir. 1991) "[O]bvious to try" is not the standard under § 103." In re O'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1680 (Fed. Cir. 1988). "An 'obvious-to-try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." In re Eli Lilly & Co., 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

In this case, we agree with appellant that the cited references may have made it “obvious to try” to stimulate cholesterol efflux in an individual by administering a replication defective virus comprising a nucleic acid sequence encoding LCAT, but they do not support a prima facie case under § 103.

We do not agree with the examiner that the prior art establishes a reasonable expectation of success of obtaining stimulation of cholesterol efflux in an individual. In particular, Baer, page 8, lines 35-41, states that LCAT “should be administered under the guidance of a physician, and pharmaceutical compositions will contain an effective amount of the enzyme in conjunction with a conventional pharmaceutical carrier. The dosage will vary depending upon the specific purpose for which the lecithin:cholesterol acyltransferase is administered, usually at dosage levels sufficient to bring the patient's plasma Lecithin:cholesterol acyltransferase to at least about 25% of the lecithin:cholesterol acyltransferase activity in normal pooled plasma.” Thus, Baer would reasonably appear to suggest that LCAT must be expressed at sufficiently high levels to achieve stimulation of cholesterol efflux.

The examiner argues that “the rejection provides evidence and reasoning that it would have been obvious to practice the claimed method **to evaluate the 'promise' or feasibility of using gene therapy to deliver LCAT** or to deliver LCAT and apoA-1 for the treatment of dyslipoproteinemia.” [Emphasis added.] Answer, page 9. However, we do not find that the combination of references before us provides a reasonable expectation of success that if the LCAT of Baer or McLean is expressed in an

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adenoviral vector system and administered in the bloodstream of an individual that it would be expected to be expressed in an effective amount or at a level which would be sufficient to stimulate cholesterol efflux. While we might agree with the examiner that it would have been obvious to try to express or “evaluate the promise of” LCAT in the adenoviral vector system of Benoit to achieve such an effect, we do not find the cited references support a reasonable expectation of success at achieving the result of cholesterol efflux stimulation.

Nor do we find that Perricaudet or Jolly overcome the deficiencies of the primary combination of Benoit, Baer and McLean. The rejection of claims 38 and 43-46 and 48-56 for obviousness is reversed.

CONCLUSION

The rejection of claims 38, 43-45, 48-50, 55 and 56 under 35 U.S.C. 103(a), as obvious over Benoit in view of Baer and McLean; claims 38, 43, 45, 46 and 51 under 35 U.S.C. 103(a) as obvious over Benoit in view of Baer and McLean in further view of Perricaudet; and claims 38 and 52-54 under 35 U.S.C. 103(a), as obvious over Benoit in view of Baer and McLean in further view of Jolly are reversed.

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