

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.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. 46

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte **INDER M. VERMA, and
DANIEL C. ST. LOUIS**

Appeal No. 2000-1930
Application No. 08/232,452

ON BRIEF

Before ADAMS, GRIMES, 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 21-36. Claims 21, 29 and 30 are representative of the subject matter on appeal, and read as follows:

21. A gene therapy method comprising:

implanting in the loose connective tissue of the dermis of a subject, a collagen matrix containing transduced subject-derived primary fibroblasts, wherein said transduced fibroblasts are infected with a recombinant retroviral vector that comprises exogenous genetic material encoding a gene product, and wherein said transduced fibroblasts express said gene product.

29. Transduced primary fibroblasts contained in a collagen matrix suitable for implantation into the loose connective tissue of the dermis of a subject, wherein said transduced fibroblasts are infected with a recombinant retroviral vector that contains exogenous genetic material encoding a gene product, wherein said transduced fibroblasts express said gene product, and wherein expression of said gene product is under the control of a constitutive promoter.

30. A method for immunizing a subject against immunogenic, exogenous material, said method comprising:
 - implanting in the loose connective tissue of the dermis of a subject, an extracellular collagen matrix containing transduced subject-derived primary fibroblasts, wherein said transduced fibroblasts are infected with a recombinant retroviral vector containing exogenous genetic material encoding an immunogenic gene product, and wherein said transduced fibroblasts express said gene product.

The examiner relies upon the following references:

Bell et al. (Bell), "The reconstitution of living skin," The Journal of Investigative Dermatology, Vol. 81, No. 1, pp. 2s-10s (1983)

Miller et al. (Miller), "Transfer of genes into human somatic cells using retrovirus vectors," Cold Spring Harbor Symposia on Quantitative Biology, Vol. LI, pp.1013-1019 (1986)

Garver Jr., et al. (Garver I), "Production of glycosylated physiologically 'normal' human α_1 -antitrypsin by mouse fibroblasts modified by insertion of a human α_1 -antitrypsin cDNA using a retroviral vector," Proc. Natl. Acad. Sci. USA, Vol. 84, pp.1050-1054 (1987)

Palmer et al. (Palmer), "Efficient retrovirus-mediated transfer and expression of a human adenosine deaminase gene in diploid skin fibroblasts from an adenosine deaminase-deficient human," Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 1055-1059 (1987)

Selden et al. (Selden), "Implantation of genetically engineered fibroblasts into mice: Implications for gene therapy," Science, Vol. 236, pp. 714-718 (1987)

Garver Jr., et al. (Garver II), "Clonal gene therapy: Transplanted mouse fibroblast clones express human α 1-antitrypsin gene in vivo," Science, Vol. 237, pp. 762-764 (1987).

Gospodarowicz, "[9] isolation and characterization of acidic and basic fibroblast growth factor," Methods in Enzymology, Vol. 147, pp. 106-119 (1987)

Anson et al. (Anson), "Towards gene therapy for hemophilia B," Mol. Biol. Med., Vol. 4, pp. 11-20 (1987)

Claims 21, 24-28, 30 and 33-36 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Miller, Anson or Palmer as combined with Bell. Claims 22, 23, 31 and 32 stand rejected under 35 U.S.C. § 103(a) as being obvious over the above combination as further combined with Gospodarowicz. Claims 21, 24-30 and 33-36 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Garver I, Garver II or Selden as combined with Bell. Finally, claims 22, 23, 31 and 32 stand rejected under 35 U.S.C. § 103(a) as being rendered obvious over the preceding combination as further combined with Gospodarowicz. After careful review of the record and consideration of the issues before us, we reverse.

DISCUSSION

Claims 21, 24-28, 30 and 33-36 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Miller, Anson or Palmer as combined with Bell. In addition, claims 21, 24-30 and 33-36 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Garver I, Garver II or Selden, as also combined with Bell. As the issues on appeal with respect to the above combinations are substantially identical, the rejections will be addressed together.

Miller is cited by the rejection for teaching retrovirus-mediated gene transfer and expression in diploid human fibroblasts, where upon re-implantation, a protein product is provided to the patient. Anson is cited for its demonstration of the secretion of factor IX from human fibroblasts after retrovirus-mediated gene transfer, and for its teaching that the fibroblasts may be reintroduced to the patient by subcutaneous injection or as part of a full thickness skin equivalent structure. Finally, Palmer is cited for disclosing the use of retrovirus-mediated gene transfer of the adenosine deaminase gene in human diploid fibroblasts, and also for teaching that the fibroblasts may be reintroduced to the patient by subcutaneous injection or as part of a full thickness skin equivalent structure. The rejection concedes that “[n]one of the above three references teaches the reintroduction of genetically modified fibroblasts by implantation of a collagen matrix containing said cells into the loose connective tissue of the dermis.” Examiner’s Answer, page 4.

Garver I and II are cited by the examiner for teaching mouse fibroblasts that have been genetically modified to express human α 1-antitrypsin, and their implantation into mice. Garver II is also cited for its teaching that as the α 1-antitrypsin was secreted into the bloodstream, “gene therapy need not target the cell type that normally produces the protein of interest.” Id. at 6. Selden is cited for its disclosure of genetically modified fibroblasts that secrete human growth hormone, and their implantation into mice. Again, the examiner admits that “[n]one of the above three references teaches the reintroduction of

genetically modified fibroblasts by implantation of a collagen matrix containing said cells into the loose connective tissue of the dermis.” Id. at 7.

Bell is relied upon for its teaching of a method of producing a full-thickness skin equivalent. As part of that process, Bell teaches a method of producing a dermal equivalent lattice wherein fibroblasts are mixed with collagen, serum and medium, resulting in a gel-like structure containing the fibroblasts. According to the rejection, the dermal equivalent lattice “is tissue-like” in consistency, and the cells contained within it have the properties of the cells of intact skin.

The rejection over the combination with Miller, Anson and Palmer concludes:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to embed the genetically modified fibroblasts of [Miller], [Anson] or [Palmer] in a collagen-containing dermal equivalent as taught by [Bell], and then to implant the dermal equivalent into the dermis of the subject to be treated. The skilled artisan would have been motivated to use the technology of [Bell], given the explicit reference to Bell’s earlier publication by both [Anson] and [Palmer]. There would have been a reasonable expectation of success, given the knowledge that the dermal equivalent lattice of [Bell] is tissue-like in consistency and the fibroblasts within have the characteristics of normal dermal fibroblasts, as taught by [Bell]. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Id. at 5.

The obviousness statement with respect to the combination over Garver I Garver II or Selden is identical, except for the motivational statement. The examiner asserts that “[t]he skilled artisan would have been motivated to use the

technology of [Bell], given the knowledge that cells implanted in a collagen matrix remain viable for up to 2 years.” Id. at 7.

Appellants argue that nothing in Miller, Anson, Palmer, Garver I, Garver II or Selden teaches or suggests the placement of a collagen matrix containing transduced fibroblasts into the loose connective tissue of a subject. Bell, appellants assert, does not cure the deficiencies of the above references as it is drawn to the production of a full-thickness skin equivalent. According to appellants, there is no teaching in Bell of any utility for the collagen matrix alone, and Bell does not teach or suggest that the collagen matrix may be implanted in the loose connective tissue of the dermis. Appellants maintain that, at most, all the combination suggests is transplantation of a full-thickness skin equivalent graft. We agree.

We also note that review was hampered by the lack of claim-by-claim analysis. For example, claim 29 is drawn to a product—the transduced primary fibroblasts contained in a collagen matrix. The rejection, however, only addresses the method, wherein the step of implanting the collagen matrix into the loose connective tissue of the dermis is required. In addition, the rejection does not address other limitations in the claims, such as the use of the method to immunize a subject against an immunogen, as required by claim 30.

The burden is on the examiner to make a prima facie case of obviousness, and the examiner may meet this burden by demonstrating that the prior art would lead the ordinary artisan to combine the relevant teachings of the references to arrive at the claimed invention. See In re Fine, 837 F.2d 1071,

1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). In other words, there must be some teachings, suggestions or motivations in the art to make the combination. Furthermore, it is the prior art, and not appellants' invention, that must establish the obviousness of the claimed invention. See In re Dance, 160 F.3d 1339, 1343, 48 SPQ2d 1635, 1637 (Fed. Cir. 1998). Finally, in order for meaningful appellate review to occur, the examiner must present a full and reasoned explanation of the rejection. See, e.g., In re Lee, 277 F.3d 1338, 1342, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002).

In this case, the rejection has not set forth a prima facie case of obviousness because the examiner has not set forth any teaching, suggestion or motivation supplied by the prior art that would suggest the combinations of record. The rejection acknowledges that Bell "does not suggest implanting the dermal equivalent lattice alone," but the examiner asserts that is because retrovirally modified fibroblasts had not been available at the time Bell had been published, and that two of the references, Anson and Palmer, specifically cite Bell. Examiner's Answer, page 9. The examiner asserts that the level of skill in the art is high, i.e., possessing a Ph.D. or a M.D, and thus "one of ordinary skill in the gene therapy art would have had the intellectual capacity to modify the prior art and would not have slavishly followed the teachings of [Bell] without modification." Id. at 10. In addition, the examiner contends that the dermal equivalent lattice was well characterized by Bell, and the use of the lattice would moot the need for a full thickness skin graft, and the problems associated

therewith, such as increased risk of infection and permanent disfigurement. See id.

Both Anson and Palmer cite Bell, but in the context of a full-thickness skin equivalent transplant. Thus, Anson cites Bell in teaching that “[g]enetically modified fibroblasts could be reintroduced into patients . . . as part of a full-thickness skin equivalent structure, an artificial skin of cultured fibroblasts and keratinocytes that is quickly vascularized following engraftment.” Anson, page 18. Similarly, in citing Bell, Palmer teaches that “genetically modified fibroblasts could be reintroduced into patients as part of a full-thickness skin-equivalent structure, an artificial skin of cultured fibroblast and epidermal cells that is quickly vascularized when transplanted onto freshly prepared graft beds.” Palmer, page 1059. If, as the examiner suggests, the level of skill in the art is so high, and the risks associated with full-thickness skin grafts so well known, then why didn’t one of the references cited in the rejection suggest the use of the collagen-matrix taught by Bell? While a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the protocol taught in 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, 221 USPQ 1125, 1127 (Fed. Cir. 1984). As acknowledged by the examiner, Bell does not teach or suggest uses for the collagen lattice alone, thus, on this record, we see no reason to modify the references as applied.

OTHER ISSUES

As noted above, the examiner never separately addressed the patentability of the product of claim 29. Upon return of the application, the examiner may wish to consider the patentability of the product separately from the method of use. The combination of Palmer or Anson with Bell suggests the use of a full-thickness skin equivalent to introduce genetically modified fibroblasts, and one of the intermediates would possibly be the collagen matrix of Bell combined with the genetically modified fibroblasts of Palmer or Anson or one of the other references cited by the examiner. But as this is not the rejection of record, and as appellants have not had the opportunity to address the issue of a possible intermediate with respect to the product claim, we are raising the issue here, and not affirming the rejection over the combination as to the product of claim 29.

CONCLUSION

Because the rejections of record have failed to set forth a prima facie case of obviousness, they are reversed. In addition, the examiner may wish to address the patentability of the product of claim 29 separately from the method claims that were the sole focus of the rejections of record.

REVERSED

DONALD E. ADAMS)	
Administrative Patent Judge)	
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)	
)	BOARD OF PATENT
ERIC GRIMES)	
Administrative Patent Judge)	APPEALS AND
)	
)	INTERFERENCES
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