

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

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

Ex parte TODD K. ROSENGART and RONALD G. CRYSTAL

Appeal No. 2007-0531
Application No. 10/341,679

ON BRIEF

Before ADAMS, GREEN and LINCK, 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 1-4, 6, 7, 10 and 12-23, which are all the claims pending in the application.

Claim 1¹ is illustrative of the subject matter on appeal and is reproduced below:

1. A method of inducing collateral blood vessel formation in a heart, wherein the method comprises directly injecting to the heart, via multiple injections to different points on the internal surface of the heart, a dose of a pharmaceutical composition comprising (a) a pharmaceutically acceptable carrier and (b) an adenoviral vector comprising a DNA encoding an angiogenic peptide, such that collateral blood vessels are formed within the heart, wherein at least 2 of the multiple injections are administered within about 10 minutes.

¹ Claims 2-4, 6, 7, 10 and 12-23 depend directly or indirectly from claim 1.

The references relied upon by the examiner are:

Tischer et al. (Tischer)	5,219,739	Jun. 15, 1993
Hammond et al. (Hammond)	5,792,453	Aug. 11, 1998
Kovesdi et al. (Kovesdi)	5,851,806	Dec. 22, 1998
Ullrich et al. (Ullrich)	5,851,999	Dec. 22, 1998
Isner	6,121,246	Sep. 19, 2000
Wolff et al. (Wolff)	6,228,844	May 8, 2001

French et al. (French), "Direct in vivo gene transfer into porcine myocardium using replication-deficient adenoviral vectors," Circulation, Vol. 90, No. 5, pp. 2414-2424 (1994)

GROUND OF REJECTION

Claims 1-4, 6, 7, 10, 12 and 18 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Hammond and Tischer.

Claims 1, 3, 6, 10, 19 and 22 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Isner and Tischer.

Claims 1 and 12-18 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Isner, Tischer and Kovesdi.

Claims 1 and 19-21 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Isner, Tischer, Wolff and French.

Claims 1 and 22-23 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Isner, Tischer and Ullrich.

We reverse the rejection under 35 U.S.C. § 103 over the combination of Hammond and Tischer. We vacate all remaining rejections in favor of new grounds of rejection.

CLAIM CONSTRUCTION

Claim 1 is drawn to a method of inducing collateral blood vessel formation in a heart. The method comprises injecting a dose of a pharmaceutical composition directly into the internal surface of the heart. Claim 1 requires that the pharmaceutical composition comprise:

- (a) a pharmaceutically acceptable carrier and
- (b) an adenoviral vector comprising a DNA encoding an angiogenic peptide, such that collateral blood vessels are formed within the heart.

Claim 1 requires that the pharmaceutical composition is injected:

- (a) via multiple injections to different points on the internal surface of the heart and
- (b) that at least 2 of the multiple injections are administered within about 10 minutes.

In addition, as a result of a species election, the scope of the angiogenic peptide is restricted to VEGF₁₂₁. Final Rejection, page 2. Accordingly, we limit our consideration of the record to the elected angiogenic peptide species - VEGF₁₂₁. We take no position with respect to the patentability of the non-elected species. See Ex parte Ohsaka, 2 USPQ2d 1460, 1461 (Bd. Pat. App. & Int. 1987).

DISCUSSION

The combination of Hammond and Tischer:

Claims 1-4, 6, 7, 10, 12 and 18 stand rejected under 35 U.S.C. § 103 as being unpatentable over the combination of Hammond and Tischer.

The Examiner finds Hammond teaches²:

1. “a method for treating a heart disease . . . comprising delivering a transgene-inserted replication-deficient adenoviral vector to the myocardium of the patient by injection directly into one or both left and right coronary arteries^[3] . . . to transfect cardiac myocytes in the affected myocardium. . . .”⁴ Answer, page 4.
2. that the adenoviral vector comprises “a transgene coding for an angiogenic protein or peptide such as . . . VEGF” Id.

The Examiner finds that Hammond does not teach the use of VEGF₁₂₁.

Id. To make up for this deficiency, Examiner relies on Tischer. Examiner finds that Tischer teaches:

1. “expression vectors encoding human VEGF₁₂₁. . . .” Answer, page 5.
2. that VEGF₁₂₁ is “useful for a variety of wound healing applications in which angiogenesis . . . play[s] an important role” Id.
3. that VEGF₁₂₁ has a therapeutic advantage over longer forms of VEGF. Id.
4. that unlike longer forms of VEGF, VEGF₁₂₁ does not bind heparin, therefore during therapeutic applications more VEGF₁₂₁ protein is free to bind to the VEGF receptor, its half-life is increased as well as its distribution in the patients circulation. Id.

Based on this evidence, the Examiner finds that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Hammond by utilizing a recombinant adenoviral

² Hammond teaches that by transfecting cardiac myocytes in an affected myocardium with an adenoviral vector comprising VEGF and thereby expressing VEGF in the heart, angiogenesis in the affected region of the myocardium will be promoted. Hammond, column 4, lines 11-22.

³ The Examiner asserts that the “injection directly into one or both left and right coronary arteries” reads on “multiple injections to different points on the internal surface of the heart”. Answer, page 4. In addition, Examiner asserts that Hammond teaches the use of a multipurpose coronary catheter “that engages the coronary arteries, apparently at about the same time.” Id.

⁴ The Examiner asserts that the coronary arteries are parts of the heart. Answer, bridging sentence, pages 15-16.

vector expressing VEGF₁₂₁ as taught by Tischer. Answer, page 5. The Examiner asserts that the therapeutic advantages of VEGF₁₂₁ would serve to “enhance the desired therapeutic outcome” of Hammond’s method. Answer, bridging paragraph, pages 5-6.

Appellants assert that Hammond “does not disclose directly injecting a pharmaceutical composition to a heart” but instead “discloses intraarterial [(e.g. administration into the coronary arteries)] delivery of an expression vector.” Brief, page 3. Appellants explain that “the coronary arteries are not part of the heart, as evidenced by the schematics from the Texas Heart Institute^[5]. . . .” Brief, page 4. Appellants assert that Tischer discloses the direct injection of VEGF protein to the site of damaged cardiac muscle, but “does not disclose or suggest administering an adenoviral vector encoding VEGF via multiple injections directly to the heart, much less multiple injections that are administered within about 10 minutes.” Id.

We find that the weight of the evidence falls in favor of Appellants. While the coronary arteries may be attached to the heart, it is our opinion that the evidence of record establishes (see the two documents from the Texas Heart Institute) that a person of ordinary skill in the art would recognize that injection into the coronary arteries is not the same as injection on the internal surface of the heart as is required by Appellants’ claimed invention.

⁵ The Evidence Appendix of Appellants’ Brief, includes two documents from the Texas Heart Institute Heart Information Center (Texas Heart Institute): (1) “Anatomy of the Heart: The Coronary Arteries – Texas Heart Institute Heart Information Center,” (Dec. 28, 2005) <http://www.tmc.edu/thi/coroanat.html>; and (2) “Anatomy of the Heart – Texas Heart Institute Heart Information Center,” (Dec. 29, 2005) <http://www.tmc.edu/thi/anatomy2.html>. This evidence “was entered into the record by the Examiner as indicated in the ‘Advisory Action’ dated February 1, 2006.” Brief, Evidence Appendix.

Further, while Tischer teaches (column 13, lines 28-32) that a VEGF composition can be injected to the site of damaged cardiac muscle (e.g., into the heart), Tischer does not teach that at least 2 multiple injections are administered within about 10 minutes as is required by Appellants' claimed invention. At best, Tischer suggests the use of a micrometering pump over a period of time as an alternative to injection to the site of damaged cardiac muscle (id.), but even then fails to suggest multiple injections administered within about 10 minutes. We find the only suggestion of timing comes from the Examiner's assertion that Hammond uses a multipurpose coronary catheter "that engages the coronary arteries, apparently at about the same time." Answer, page 4, emphasis added. Therefore, even if a person would modify Hammond's method with the teachings of Tischer and inject an adenoviral construct into the heart, there is no evidence of record directing a person of ordinary skill in the art to administer at least 2 multiple injections within about 10 minutes.

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). In our opinion, Examiner failed to provide the evidence necessary to support a prima facie case of obviousness. If 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 rejection of claims 1-4, 6, 7, 10, 12 and 18 under 35 U.S.C. § 103 as being unpatentable over the combination of Hammond and Tischer.

The rejections based solely, or in-part, on the combination of Isner and Tischer:

In our opinion the combination of Isner and Tischer fails to teach injection of an adenoviral vector comprising VEGF₁₂₁ DNA directly to the internal surface of the heart. The Examiner relies on Wolff, Kovesdi, French and Ullrich to reach limitations of dependent claims. See Answer, pages 9-14. While the Examiner relies on French, the emphasis Examiner places on French is different than that set forth below. Accordingly, we vacate the pending rejections over the combination of Isner and Tischer (alone or in combination with Wolff, French, Kovesdi and Ullrich) in favor of the following new grounds of rejection.

Accordingly,

- the rejection of claims 1, 3, 6, 10, 19 and 22 under 35 U.S.C. § 103 as being unpatentable over the combination of Isner and Tischer is vacated;
- the rejection of claims 1 and 12-18 under 35 U.S.C. § 103 as being unpatentable over the combination of Isner, Tischer and Kovesdi is vacated;
- the rejection of claims 1 and 19-21 under 35 U.S.C. § 103 as being unpatentable over the combination of Isner, Tischer, Wolff and French is vacated; and
- the rejection of claims 1 and 22-23 under 35 U.S.C. § 103 as being unpatentable over the combination of Isner, Tischer and Ullrich is vacated.

NEW GROUNDS OF REJECTION

FACTS:

French teaches:

1. that in the field of cardiology, much interest has focused on developing techniques to introduce recombinant genes directly

into the vasculature and the heart. Page 2414, first column, main body, first paragraph.

2. “direct intramyocardial injection of replication-deficient adenovirus can program recombinant gene expression in the cardiomyocytes of a large animal species with relevance to human physiology.” Page 2414, second column, “Conclusions” section.
3. “[r]ecombinant vectors based on adenovirus serotype 5 (Ad5) represent an alternative means of introducing genes into the cardiovascular system.” Page 2414, second column, main body, first indented paragraph.
4. an experiment wherein ten injections of a replication-deficient adenovirus vector construct were made at 2.5-mm intervals in the anterolateral wall of the left ventricle, catheters were placed and the incision was closed. Page 2416, first column, first full paragraph.
5. “[r]eplication-deficient Ad5 vectors are capable of mediating recombinant gene expression after direct injection into adult porcine myocardium.” Pages 2420-2421, bridging paragraph.

French does not teach:

1. replication-deficient adenoviral constructs comprising VEGF₁₂₁.

Tischer teaches:

1. unlike longer forms of VEGF (e.g., VEGF₁₆₅), human VEGF₁₂₁ does not bind heparin. Column 2, lines 55-57.
2. “[t]he absence of heparin binding affinity [on VEGF121] leaves more of the protein free to bind to vascular endothelial cell growth factor receptor and increases the half-life and distribution of the protein in circulation.” Column 2, lines 57-61.
3. VEGF “can be applied to inner vascular surfaces by systemic or local intravenous application either as intravenous bolus injection or infusions. If desired, . . . [VEGF] can be administered over time using a micrometering pump.” Column 12, lines 53-57.

4. VEGF “can also be employed to repair vascular damage following myocardial infarction and to circumvent the need for coronary bypass surgery by stimulating the growth of a collateral circulation.” Column 13, lines 24-28.
5. VEGF can be directly injected “to the site of damaged cardiac muscle.” Column 13, lines 31-32.
6. that VEGF can be applied in conjunction with procedures that compress atherosclerotic plaques. Column 12, lines 48-52.

Tischer does not:

1. teach replication-deficient adenovirus constructs comprising VEGF₁₂₁.
2. teach injection of a replication defective recombinant adenoviral vector comprising VEGF₁₂₁ DNA directly to the internal surface of the heart. We do not interpret Tischer’s disclosure of injection to the site of damaged cardiac muscle to mean inject VEGF₁₂₁ on the inside surface of the heart.

Isner teaches:

1. “nucleic acid . . . capable of expressing an angiogenic protein (a protein capable of inducing angiogenesis . . .), when injected into ischemic tissue, induces angiogenesis. . . .” Column 2, lines 41-46.
2. “a method for treating ischemic tissue [(including ischemic cardiomyopathy and myocardial ischemia)] in a mammal which comprises injecting said tissue with an effective amount of a nucleic acid capable of expressing an angiogenic protein.” Column 2, lines 50-53.
3. “the term ‘angiogenic protein’ means any protein, polypeptide, murein or portion that is capable of, directly or indirectly, inducing the formation of new blood vessels. Such proteins include, for example . . . VEGF . . .” and more particularly, human VEGF₁₆₅. Column 3, lines 9-14 and 62-66.
4. “[t]he nucleic acid can be injected at multiple sites throughout the ischemic tissue.” Column 6, lines 27-28.

5. replication defective recombinant adenoviral vectors may be used as delivery vehicles for the DNA encoding the angiogenic protein. Column 5, lines 51-64.
6. gene transfer on acute hindlimb ischemia, which comprises the injection DNA encoding angiogenic protein into five different sites in three major thigh muscles of a rabbit. The rate of each injection was approximately 5 seconds, after completing 5 injections the skin was closed. Column 7, lines 45-65.
7. “that it may be desirable to use nucleic acids encoding two or more different proteins in order to optimize the therapeutic outcome. For example, DNA encoding two angiogenic proteins, e.g., VEGF and bFGF can be used” Column 6, lines 4-8.

Isner does not teach:

1. VEGF₁₂₁.
2. injection of an replication defective recombinant adenoviral vector comprising VEGF₁₂₁ DNA directly to the internal surface of the heart.

Kovesdi teaches:

1. multiply replication deficient adenoviral vectors for use in gene therapy. Column 5, lines 55-59 and column 7, lines 27-29.
2. “multiply replication deficient adenoviral vectors [that] can accommodate the insertion and expression of larger fragments of foreign DNA than is possible with singly replication deficient adenoviral vectors. . . .” Column 5, lines 50-53.
3. that a preferred embodiment of the present inventive adenoviral vector include[s, inter alia,] . . . E1⁻ E4⁻ . . . adenoviral vectors, which can also be E3⁻.” Column 8, lines 35-38.
4. a multiply replication deficient adenoviral vector that “is deficient in the E1, E3, and E4 regions.” Example 2, column 16, lines 31 -column 18, line 26.
5. the multiply replication deficient adenoviral vector “Ad_{GV}CFTR.10” that “is deficient in the E1 and E3 regions.” Example 1, column 15, line 45 – column 16, line 29.

6. two generations of the Ad_{GV}CFTR.10 “designated Ad_{GV}CFTR.10L and Ad_{GV}CFTR.10R, dependent on the direction in which the CFTR expression cassette is placed in the E1 region in relation to the vector genome as shown in FIG. 1. . . .” Column 15, lines 51-57.

Kovesdi does not teach:

1. a replication-deficient adenoviral vector comprising VEGF.
2. the injection of a replication defective recombinant adenoviral vector comprising VEGF₁₂₁ DNA directly to the internal surface of the heart.

Principles of Law:

“The test for obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them.” In re Rosselet, 347 F.2d 847, 851, 146 USPQ 183, 186 (CCPA 1965).

Obviousness does not require absolute predictability of success. For obviousness under § 103, all that is required is a reasonable expectation of success. In re O’Farrell, 853 F.2d 894, 904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

Analysis:

Claims 1-4, 6, 10, 19, 20 and 22

French teaches that those of ordinary skill in the art, in the field of cardiology, are interested in introducing recombinant genes directly into the heart for the treatment of disease. French demonstrates that multiple injections of a

replication-deficient adenoviral vector comprising a reporter gene into different points on the internal surface of the heart can program recombinant gene expression in cardiomyocytes. While French acknowledges that more work may be necessary before adenoviral vectors can be used for phenotypic modulation⁶, French opens the door for a person of ordinary skill in the art interested in treating heart damage with therapeutic adenoviral constructs.

Isner was interested in treating heart disease including ischemic cardiomyopathy and myocardial ischemia in a mammal. Isner developed a method whereby ischemic cardiomyopathy and myocardial ischemia can be treated with the use of a replication-deficient adenoviral vector comprising a nucleic acid capable of expressing an angiogenic protein, such as VEGF₁₆₅, with or without another gene expressing a different angiogenic protein. While Isner does not teach the direct injection of this adenoviral construct to the inside surface of the heart, Isner teaches that an adenoviral construct comprising angiogenic proteins can be used to treat heart related injuries. Therefore, a person of ordinary skill in the art would recognize that Isner took the teachings of French one step further to demonstrate that a therapeutic adenoviral construct can be utilized to treat heart related injuries. Isner, therefore, alleviates French's concerns that more work is needed.

Tischer teaches that VEGF can be employed to treat a damaged heart resulting from vascular damage following myocardial infarction, or in conjunction with procedures that compress atherosclerotic plaques, by stimulating the growth of collateral circulation. According to Tischer VEGF can be directly injected to

⁶ French, page 2414, second column 2, last sentence under "Conclusions".

the site of damaged cardiac muscle. In addition, Tischer teaches that VEGF₁₂₁ has advantages over VEGF₁₆₅, which include an increased half-life. Therefore, Tischer adds to the teachings of Isner by teaching that VEGF, or more preferably the therapeutically advantageous VEGF₁₂₁, can be introduced directly to the site of the damaged cardiac muscle.

Taken together French, Isner and Tischer teach the use of an adenoviral vector comprising a nucleic acid capable of expressing VEGF₁₂₁, with or without another gene expressing a different angiogenic protein, to treat a damaged heart by administering multiple injections into different points on the internal surface of the heart to program recombinant gene expression in cardiomyocytes and thereby treat a damaged heart by inducing collateral blood vessel formation in the heart. Following the teachings of the combined references, each injection would take approximately 5 seconds, resulting in 10 different injections in less than one minute.

Therefore, we conclude that a person of ordinary skill in the art at the time the invention was made who was seeking to treat a damaged heart would have found it prima facie obvious to induce collateral blood vessel formation in a heart by administering a dose of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a replication-deficient adenoviral vector comprising a DNA encoding VEGF₁₂₁ at multiple injections to different points on the internal surface of the heart. In addition, a person of ordinary skill in the art would have found it prima facie obvious to administer at least 2 of the multiple injections within about 10 minutes. Based on the combined teachings of French,

Isner and Tischer a person of ordinary skill in the art would have had a reasonable expectation of successfully inducing collateral blood vessel formation in the heart with this method of treatment.

Accordingly, we conclude that claims 1-4, 6, 10, 12, 19, 20 and 22 are prima facie obvious under 35 U.S.C. § 103 over the combination of French, Isner and Tischer.

Claims 13-18

The combination of French, Isner and Tischer is discussed above. While this combination of references teaches replication-deficient adenoviral vectors, they do not specifically describe the replication-deficient adenoviral vectors set forth in Appellants' claims 13-18. Kovesdi, however, teaches multiply replication deficient adenoviral vectors as set forth in Appellants' claims 13-18. According to Kovesdi, these multiply replication deficient adenoviral vectors are useful in gene therapy applications, and allow for the insertion and expression of larger fragments of foreign DNA than singly replication deficient adenoviral vectors.

Therefore, we conclude that a person of ordinary skill in the art at the time the invention was made would have found it prima facie obvious to substitute the multiply replication defective adenovirus vectors taught by Kovesdi for the replication defective adenovirus vector used in the method taught by the combination of French, Tischer, and Isner. Accordingly, we find claims 13-18 prima facie obvious under 35 U.S.C. § 103 over the combination of French, Isner and Tischer, as applied to claims 1-4, 6, 10, 12, 19, 20 and 22, and further in view of Kovesdi.

Claims 7, 21 and 23

Claims 7, 21 and 23 are now free from rejection.

Claim 7 is depends from and further limits the method of claim 1 to require that the multiple injections are administered simultaneously. The combination of references set forth above does not teach simultaneous injections.

Claim 21 ultimately depends from and further limits the number of multiple injections in the method of claim 1 to comprise at least 15 injections. In our opinion, while the combination of references relied upon above teach injections for an extended period, they do not place a numeric value on the number of injections that would be included in this period of administration.

Claim 23 ultimately depends from and further limits the DNA of claim 1 to encode an angiogenic peptide and an angiogenic peptide receptor. We recognize Examiner's reliance on Ullrich to teach the angiogenic peptide receptor Flk-1. Answer, page 13. We find, however, that Ullrich does not teach the use of Flk-1 nucleic acid to induce angiogenesis in vivo. To the contrary, Ullrich teaches the use of nucleic acids of Flk-1 to inhibit the translation of the receptor. See e.g., Ullrich, column 18, lines 37-45. Accordingly, we find no suggestion to combine Ullrich with the combination of references set forth above.

Therefore, in the event of further examination before the examiner, we encourage the examiner to take a step back and consider whether any available prior art could be applied against these claims either alone or in combination.

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 CFR § 41.50(b) (July 2006). 37 CFR § 41.50(b) provides “[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review.”

37 CFR § 41.50(b) also provides that the appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .

(2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED; 41.50(b)

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Donald E. Adams)	
Administrative Patent Judge)	
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Lora M. Green)	APPEALS AND
Administrative Patent Judge)	
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