

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GREGORY A. KOPIA and ROBERT FALOTICO

Appeal 2008-0969
Application 10/292,299
Technology Center 3700

Decided: September 22, 2008

Before DONALD E. ADAMS, DEMETRA J. MILLS, and ERIC GRIMES,
Administrative Patent Judges.

ADAMS, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1-3, the only claims pending in this application. We have jurisdiction under 35 U.S.C. § 6(b).

INTRODUCTION

The claims are directed to a stent (claim 2), a method of treating restenosis using the stent (claim 3), and a combination of a stent and therapeutic (claim 1). Claims 2 and 3 are illustrative:

2. A stent comprising:

a plurality of struts, said struts expansible within the lumen of the body, and at least one of said struts containing a reservoir therein said reservoir filled with a therapeutic dosage amount of cladribine, said therapeutic dosage amount of cladribine placed on said stent in an effective amount to prevent restenosis in a body vessel.

3. A process for the treatment for restenosis via a stent having struts comprising the delivery of cladribine to a patient in therapeutic dosage amounts wherein said dosage amount is at least 40 nM contained on the struts of said stent.

The Examiner relies on the following prior art references to show unpatentability:

Müller et al.	US 5,744,460	Apr. 28, 1998
Brown et al.	US 6,071,305	Jun. 6, 2000
Chinery et al.	US 2001/0049349 A1	Dec. 6, 2001

Lechleitner et al., *The Immunosuppressive Substance 2-Chloro-2-Deoxyadenosine Modulates Lipoprotein Metabolism in a Murine Macrophage Cell-line (P388 Cells)*, 29(9) *Lipids* 627-633 (1994); DIALOG Abstract No. 03469296.

Cramer et al., *2-Chlorodeoxyadenosine in Combination With Cyclosporine Inhibits the Development of Transplant Arteriosclerosis in Rat Cardiac Allografts*, 29 *Transplantation Proceedings* 616 (1997).

The rejections as presented by the Examiner are as follows:

1. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Müller.

2. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Chinery.
3. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Cramer.
4. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Lechleitner.

We affirm the rejection of claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Müller. We also affirm the rejection of claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Chinery. We reverse both other grounds of rejection.

FINDINGS OF FACT (FF)

1. Brown teaches that “[r]estenosis refers to the re-narrowing of an artery after an initially successful angioplasty due to exaggerated healing which causes a proliferation of tissue in the angioplasty area” (Brown, col. 1, ll. 46-49).
2. Brown teaches that

[i]n order to prevent restenosis and vessel collapse, stents of various configurations have been used to hold the lumen of a blood vessel open following angioplasty. However, stents do not entirely reduce the occurrence of thrombotic abrupt closure due to clotting; stents with rough surfaces exposed to blood flow may actually increase thrombosis, and restenosis may still occur because tissue may grow through and around the lattice of the stent. To prevent restenosis and thrombosis in the area where angioplasty has been performed, antithrombic agents and other biologically active agents can be employed.

(Brown, col. 1, ll. 51-62.)

3. Brown teaches “a directional drug delivery stent which includes an elongated or tubular member having a cavity containing a biologically active agent. In one embodiment, the active agent is diffused from the reservoir directly to the walls of a body lumen” (Brown, Abstract). For clarity we reproduce Brown’s Figure 18 below:

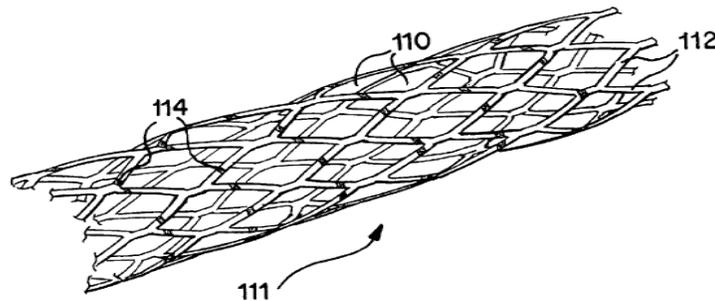
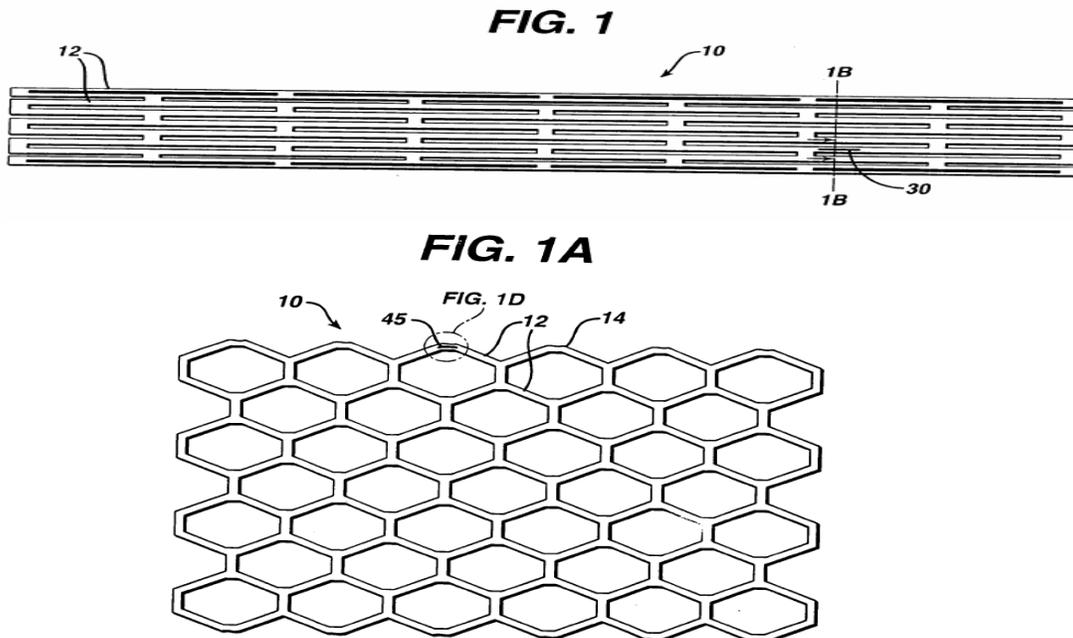


FIG. 18

- “FIG. 18 is a perspective view of an expanded stent according to an embodiment of [Brown’s] . . . invention” (Brown, col. 4, ll. 55-56). Brown teaches that “[a]t least some of the elongated members **112** contain groove portions **114** or cavities in which the active agent is located” (Brown, col. 13, ll. 28-30).
4. Brown also teaches that active agent can be coated on the stent by spraying, dipping, or by other conventional methods (Brown, col. 12, ll. 36-41).
 5. Brown teaches that “[t]he drugs which may be applied by the directional delivery stent include . . . restenosis preventing drugs . . . and tissue growth regulating drugs” (Brown, Abstract).
 6. Brown teaches that “[t]he stent **111** functions both to physically support the body lumen wall and also to prevent restenosis and thrombosis by

directionally delivering the active agent to a predetermined location, such as a body lumen wall” (Brown, col. 13, ll. 51-55).

7. Brown teaches that “by delivering the active agent . . . directly to the vessel walls, more efficient use of the active agent is possible and there is no exposure of thrombogenic polymers or agents to the blood vessel” (Brown, col. 13, ll. 60-63).
8. Brown teaches that active agents include, *inter alia*, restenosis preventing drugs which prevent smooth muscle cell growth on the inner surface wall of vessels, antiproliferatives, antioxidants, and antimetabolites (Brown, col. 5, ll. 13-19).
9. A stent within the scope of Appellants’ claimed invention is illustrated in Figures 1 and 1A of Appellants’ Specification, reproduced below:



“Figures 1 and 1A are top views and sectional views of a stent containing reservoirs as described in the present invention” (Spec. 9). According to Appellants, “any stent 10 having strut 12, can be modified to have a certain reservoir 30. Each of these reservoirs can be ‘open’ or

- ‘closed’ as desired. These reservoirs can hold the drug to be delivered” (Spec. 10: 17-19).
10. Müller teaches “combinations of PKC-targeted . . . deoxyribo- and ribo-oligonucleotides and derivatives thereof with other chemotherapeutic compounds, as well as to pharmaceutical preparations and/or therapies” (Müller, Abstract).
 11. Müller teaches that the chemotherapeutic agent can be an antimetabolite such as cladribine (Müller, col. 22, ll. 22-62).
 12. Müller teaches the use of the therapeutic combination for the treatment of “smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following angioplasty” (Müller, col. 24, ll. 51-53).
 13. Chinery teaches “[a] method to enhance the cytotoxic activity of an antineoplastic drug comprising administering an effective amount of the antineoplastic drug to a host exhibiting abnormal cell proliferation in combination with an effective cytotoxicity-increasing amount of an antioxidant” (Chinery, Abstract).
 14. Chinery teaches that “[a]ntineoplastic agents (also known as cytotoxic agents) are often used in the treatment of hyperproliferative conditions” (Chinery, 1: ¶ 0004).
 15. Chinery teaches that the “[t]wo groups of drugs used in the treatment of hyperproliferative conditions are antimetabolites and alkylating agents” (*id.*).
 16. Chinery teaches that cladribine is an antineoplastic agent (Chinery, 12: ¶ 0152). According to Chinery, “[t]he term ‘antineoplastic agents,’ as used herein, refers to any substance that decreases abnormal cell proliferation” (Chinery, 11: ¶ 0143).

17. Chinery teaches that “[a]ntioxidants can also be used in combination with antineoplastic agents to treat cardiovascular proliferative disease such as post-angioplasty restenosis and atherosclerosis” (Chinery, 12 ¶ 0159).
18. Cramer teaches that cladribine (2-CdA) is an anticancer compound and also “inhibits the proliferative changes associated with the development of TA [(transplant arteriosclerosis¹)]” (Cramer, 616: col. 2, ll. 7-8 and 11-13).
19. Cramer teaches that “[t]he prevention of TA may depend on the development of more effective immunosuppression to prevent or treat chronic rejection without increasing the risk of adverse side effects” (Cramer, 616: col. 1, ll. 7-10).
20. Cramer teaches that “2-CdA has a prolonged, depletive effect on certain lymphocyte populations” (Cramer, 616: col. 2, ll. 2-3). According to Cramer, 2-CdA inhibits the proliferative changes associated with the development of TA and Cramer suggests that this effect is primarily due to the drug’s unique mechanism of immunosuppression (*id.* at 616: col. 2).
21. Lechleitner teaches that 2-CdA is an “immunosuppressive substance”, “was reported to **inhibit** monocyte functions at low concentration”, and that “[b]ecause macrophages play a key role in the formation of **atherosclerotic plaques**, it was of interest to study the effect of **2-CdA** on cellular lipid metabolism” (Lechleitner, Abstract). Using a macrophage cell line, Lechleitner reports that “[t]he addition of **2-CdA**, in concentrations ranging from 5-20 nM, induced a dose-dependent

¹ See, Cramer, 616: col. 1, l. 3.

decrease in cellular cholesterol content and in the amount of extracellular [C-14]oleic acid (OA) incorporated into the cholesteryl ester (CE) fraction” (*id.*).

DISCUSSION

1. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Müller.

Brown teaches that stents are used to prevent the re-narrowing of an artery due to the proliferation of the tissue in the area of the angioplasty (e.g., restenosis) and to prevent vessel collapse following angioplasty (FF 1 and 2). Appellants do not dispute and therefore concede that Brown’s stents have the structure recited in their claims² (*Cf.* FF 3 and 9).

Brown teaches, however, that despite the use of stents, restenosis may still occur because tissue may grow through and around the lattice of the stent (FF 2). To prevent restenosis in the area where angioplasty has been performed, Brown teaches the use of stents that contain or are coated with, *inter alia*, restenosis preventing drugs which prevent smooth muscle cell growth on the inner surface wall of vessels, antiproliferatives, antioxidants, or antimetabolites (FF 2-8; Ans. 5).

The Examiner recognizes, however, that Brown fails “to disclose cladribine as the drug which prevents restenosis” (Ans. 5). The Examiner relies on Müller to make up for this deficiency in Brown.

² Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii) (“Any arguments or authorities not included in the brief or a reply brief ... will be refused consideration by the Board, unless good cause is shown.”).

Müller teaches the use of a therapeutic combination of PKC-targeted deoxyribo- and ribo-oligonucleotides with the antimetabolite cladribine for the treatment of smooth muscle cell proliferation in blood vessels, such as occurs in restenosis following angioplasty (FF 10-12; Ans. 5).

Based on these facts, the Examiner concludes that “[i]t would have been obvious to use the drug combination of Muller [sic] et al. (which includes cladribine) as the drug which prevents restenosis in the Brown et al stent” (Ans. 5).

Appellants disagree. Appellants provide separate arguments for claim 3. Therefore, we limit our discussion to representative claims 2 and 3. Claim 1 will stand or fall with claim 2. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 2:

Claim 2 is drawn to a stent comprising a plurality of struts. Claim 2 requires that the struts are expansible within the lumen of the body, and that at least one of the struts contains a reservoir filled with a therapeutic dosage amount of cladribine. According to claim 2, the therapeutic dosage amount of cladribine placed on the stent is an amount that is effective to prevent restenosis in a body vessel.

According to Appellants, Müller “simply identifies a ‘laundry list’ of molecules possible as chemotherapies. While cladribine can certainly be grouped as an ‘antimetabolite,’ its function *vis-à-vis* restenosis in a body vessel is certainly not suggested” (App. Br. 4). We disagree.

Brown teaches the use of a stent containing or coated with an antimetabolite for the treatment of restenosis. Müller teaches the use of a therapeutic combination of PKC-targeted deoxyribo- and ribo-

oligonucleotides with the antimetabolite cladribine for the treatment of smooth muscle cell proliferation in blood vessels, such as restenosis following angioplasty (FF 10-12). Accordingly, we find no error in the Examiner's conclusion 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 use Müller's cladribine composition as the antimetabolite in Brown's stent. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007). Further, while Müller's cladribine composition includes another ingredient, PKC-targeted deoxyribo- and ribo-oligonucleotides, Appellants' claim 2 does not exclude the presence of other ingredients.

For the foregoing reasons, we affirm the rejection of claim 2 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Müller. Claim 1 falls with claim 2.

Claim 3:

Claim 3 is drawn to a process for the treatment for restenosis via a stent having struts comprising the delivery of cladribine to a patient in therapeutic dosage amounts. Claim 3 requires that the dosage amount is at least 40 nM contained on the struts of said stent.

The Examiner relies on the combination of Brown and Müller as discussed above. The Examiner recognizes, however, that Müller "fail[s] to disclose the claimed dosage amount of cladribine" (Ans. 6). Nevertheless, the Examiner finds that "it is old and well known in the art to vary the dosage of a drug, depending on the specific needs of the patient" (*id.*).

Stated differently, where, as here, the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Therefore, the Examiner concludes that “[i]t would have been obvious to provide the claimed dosage amount since an amount effective to prevent restenosis would fall within the claimed range” (Ans. 6).

In response, Appellants assert that “since none of the references describe the treatment of restenosis, it is not surprising that none of the references would further describe the adequate way to deal with restenosis, and the therapeutic dosage amount for doing so” (App. Br. 5). For the reasons and facts set forth above, we disagree.

Accordingly, we affirm the rejection of claim 3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Müller.

2. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Chinery.

Brown is discussed above. The Examiner finds that Brown “fail[s] to disclose cladribine as the drug which prevents restenosis” (Ans. 3-4). The Examiner relies on Chinery to make up for this deficiency in Brown. Chinery teaches the use of the antineoplastic drug cladribine in combination with an antioxidant to treat post-angioplasty restenosis (FF 13-17; Ans. 4).

Based on these facts, the Examiner concludes that “[i]t would have been obvious to use the drug combination of Chinery et al. (which includes cladribine) as the drug which prevents restenosis in the Brown et al. stent” (Ans. 4).

Appellants disagree. Appellants provide separate arguments for claim 3. Therefore, we limit our discussion to representative claims 2 and 3. Claim 1 will stand or fall with claim 2. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 2:

Claim 2 is discussed above.

According to Appellants, “Chinery, at best, teaches that the combination of . . . antioxidants with other drugs may be useful in preventing restenosis. Chinery does not teach that cladribine alone will prevent restenosis” (App. Br. 3). There is, however, no requirement in claim 2 that cladribine be used alone. Further, Chinery expressly discloses the use of a combination of antioxidant with an antineoplastic agent, such as cladribine, to treat post-angioplasty restenosis (FF 16-17). Accordingly, we are not persuaded by Appellants’ arguments (App. Br. 3; Reply Br. 2).

For the foregoing reasons, we affirm the rejection of claim 2 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Chinery. Claim 1 falls together with claim 2.

Claim 3:

Claim 3 is discussed above.

The Examiner relies on the combination of Brown and Chinery as discussed above. The Examiner recognizes, however, that Chinery “fail[s] to disclose the claimed dosage amount of cladribine” (Ans. 4).

Nevertheless, the Examiner finds that “it is old and well known in the art to vary the dosage of a drug, depending on the specific needs of the patient” (*id.*). Stated differently, where, as here, the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the

optimum or workable ranges by routine experimentation. *Aller*, 220 F.2d at 456 (CCPA 1955). Therefore, the Examiner finds that “[i]t would have been obvious to provide the claimed dosage amount since an amount effective to prevent restenosis would fall within the claimed range” (Ans. 4-5). We find no error in the Examiner’s prima facie case of obviousness.

For the foregoing reasons, we are not persuaded by Appellants’ assertion that “since none of the references describe the treatment of restenosis, it is not surprising that none of the references would further describe the adequate way to deal with restenosis, and the therapeutic dosage amount for dosing so” (App. Br. 5).

Accordingly, we affirm the rejection of claim 3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Chinery.

3. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Cramer.

Brown is discussed above. The Examiner finds that Brown “fail[s] to disclose cladribine as the drug which prevents restenosis” (Ans. 6). The Examiner relies on Cramer to make up for this deficiency in Brown.

While Cramer teaches that cladribine is an anticancer compound, Cramer teaches that cladribine’s effect on the development of transplant arteriosclerosis is “primarily due to the drug’s unique mechanism of immunosuppression” (FF 18). An immunosuppressive drug is not one of the categories of drugs that Brown teaches is effective in preventing restenosis (*see* FF 8). Therefore, it is unclear on this record why Cramer’s teaching that cladribine is effective against transplant arteriosclerosis due to its immunosuppressive properties would lead a person of ordinary skill in this

art at the time the invention was made to combine cladribine with Brown's directional drug delivery stent (which is effective in treating, *inter alia*, restenosis due to the drug component's ability to function as an antiproliferative, antioxidant, or antimetabolite). Further, while Cramer teaches that cladribine is an anticancer compound (FF 18), Cramer is completely silent with respect to whether cladribine's anticancer effect is related to any mechanism (e.g., antiproliferative, antioxidant, or antimetabolite) taught by Brown to be effective in preventing restenosis.

Simply stated, we do not find, and the Examiner has failed to identify, any nexus between the teachings of Cramer and those of Brown. At best, we have the Examiner's conjecture that "[i]t would have been obvious to use the drug combination of Cramer et al. (which includes cladribine) as the drug which prevents restenosis in the Brown et al. stent" (Ans. 7). The evidence does not, however, support this conclusion.

Accordingly, we reverse the rejection of claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Cramer.

4. Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Lechleitner.

Brown is discussed above. The Examiner finds that Brown "fail[s] to disclose cladribine as the drug which prevents restenosis" (Ans. 8). The Examiner relies on Lechleitner to make up for this deficiency in Brown.

Lechleitner teaches that cladribine is an immunosuppressive substance and induces a dose-dependent decrease in cellular cholesterol content in a macrophage cell line (FF 21).

An immunosuppressive drug is not one of the types of drugs Brown teaches as effective in preventing restenosis (*see* FF 8). Therefore, it is unclear on this record why Lechleitner would lead a person of ordinary skill in this art at the time the invention was made to combine the immunosuppressive cladribine with Brown's teaching of a stent comprising an antiproliferative, antioxidant, or antimetabolite to treat restenosis.

Simply stated, we do not find, and the Examiner has failed to identify, any nexus between the teachings of Lechleitner and those of Brown. At best, we have the Examiner's conjecture that "[i]t would have been obvious to use the drug of Lechleitner et al. (cladribine) as the drug which prevents restenosis in the Brown et al. stent" (Ans. 8). There is, however, an insufficient evidentiary basis on this record to draw this conclusion.

Accordingly, we reverse the rejection of claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Lechleitner.

CONCLUSION

In summary, we affirm the rejection of claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Müller. We also affirm the rejection of claims 1-3 under 35 U.S.C. § 103(a) as unpatentable over the combination of Brown and Chinery. We reverse both other grounds of rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Appeal 2008-0969
Application 10/292,299

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