UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/411,734	04/25/2006	Karl W. Mollison	089035.00226	4222

45159 7590 02/01/2013
SQUIRE SANDERS (US) LLP
275 BATTERY STREET, SUITE 2600
SAN FRANCISCO, CA 94111-3356

EXAMINER
BECKHARDT, LYNDSEY MARIE

ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
02/01/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SFRINIPDocket@squiresanders.com
Jessie.Kelly@squiresanders.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte KARL W. MOLLISON, ANGELA M. LeCAPTAIN,
SANDRA E. BURKE, KEITH R. CROMACK, PETER J. TARCHA,
YEN-CHIN CHEN, and JOHN L. TONER

Appeal 2011-011589
Application 11/411,734
Technology Center 1600

Before TONI R. SCHEINER, DEMETRA J. MILLS, and LORA M. GREEN, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

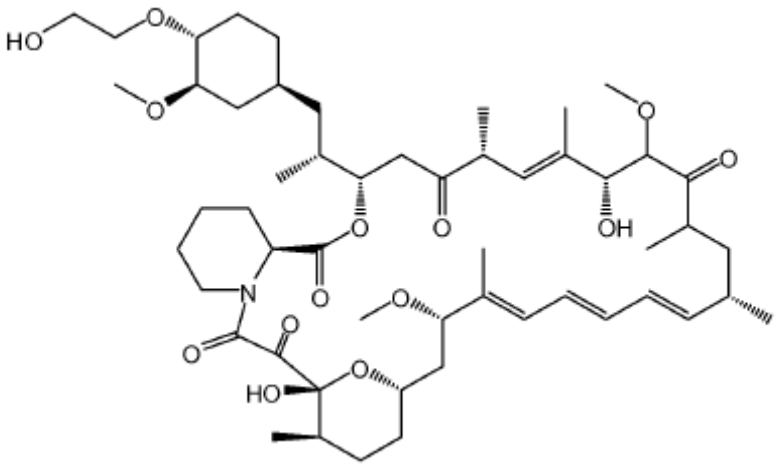
This is an appeal under 35 U.S.C. § 134 from the rejection of claims 1-5, directed to a medical device coated with 40-O-(2-hydroxyethyl)-rapamycin. The claims have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Claims 1-5 are pending and on appeal. Claim 1 is representative:

1. A medical device comprising a supporting structure having a coating on the surface thereof, said coating containing the therapeutic substance:



or a pharmaceutically acceptable salt or prodrug thereof in an amount from about 0.05 microgram to about 25 microgram per mm of the supporting structure, wherein local delivery of the therapeutic substance or a pharmaceutically acceptable salt or prodrug thereof via the medical device reduces the rate of restenosis to a level of about 0 % to about 35 %.

Claims 1-5 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Wright,[1] Zenke,[2] and Morris.[3]

FACT FINDINGS

1. Wright teaches that "[n]umerous agents are being actively studied as antiproliferative agents for use in restenosis" (Wright ¶ 27), and rapamycin is "[o]f particular interest" (*id.* at ¶ 28). According to Wright,

> Rapamycin is a macrolide antibiotic which blocks IL-2-mediated T-cell proliferation and possesses anti-inflammatory

---

[1] Wright et al., US 2001/0027340 A1, published October 4, 2001.
[2] Zenke et al, US 6,239,124 B1, issued May 29, 2001.
[3] Morris et al., US 5,516,781, issued May 14, 1996.

> activity. While the precise mechanism of rapamycin is still under active investigation, rapamycin has been shown to prevent the G_1 to S phase progression of T-cells through the cell cycle . . . The antiproliferative action of rapamycin is not limited to T-cells . . . [R]apamycin [also] prevents proliferation of both rat and human SMC [smooth muscle cells] in vitro . . . and human SMC migratin [sic, migration] can also be inhibited by rapamycin . . . Thus, rapamycin is capable of inhibiting both the inflammatory response known to occur after arterial injury and stent implantation, as well as the SMC hyperproliferative response. . . . These observations clearly support the potential use of rapamycin in the clinical setting of post-angioplasty restenosis.

(*Id.*).

2. Wright mentions rapamycin analogs in the context of experiments involving drug eluting stents ("Agents: Rapamycin (Sirolimus) Structural Analogs (Macrocyclic Lactones) and Inhibitors of Cell-cycle Progression") (Wright ¶ 31), but no particular analogs are disclosed, and rapamycin is used in all of the working examples (*id.* at ¶¶ 32-56).

3. According to Wright, rapamycin coated stents are useful "for inhibition of cell proliferation to prevent neointimal proliferation and restenosis" (Wright ¶ 41).

4. Morris teaches that restenosis and intimal thickening following vascular injury, i.e., following angioplasty, are "produced by a rapid and selective proliferation of vascular smooth muscle cells with increased new basal lamina" (Morris, col. 1, l. 45 - col. 2, l. 9). Specifically, Morris teaches that intimal thickening can be divided into three sequential steps: "1) initiation of smooth muscle cell proliferation following vascular injury, 2) smooth muscle cell migration to the intima, and 3) further proliferation of

smooth muscle cells in the intima with deposition of matrix" (*id.* at col. 1, ll. 24-29, 41-43).

5. Morris teaches that "intimal smooth muscle cell proliferation [does] not involve the immune system, but is growth factor mediated" (*id.* at col. 3, ll. 28-30), as shown by conflicting, mostly negative results, obtained using the immunosuppressive agent, cyclosporin A, in an attempt to prevent restenosis and reduce intimal smooth muscle cell proliferation following angioplasty (*id.* at col. 2, ll. 21-60).

6. Morris discloses that rapamycin, on the other hand, inhibits intimal smooth muscle cell proliferation following transplantation, and also following injury to native blood vessels (Morris, col. 3, ll. 16-31), and discloses "a method of preventing or treating hyperproliferative vascular disease . . . by administering an antiproliferative effective amount of rapamycin . . . via a vascular stent impregnated with rapamycin" (*id.* at col. 3, ll. 45-50).

7. The compound depicted in Appellants' claim 1 is 40-O-(2-hydroxyethyl)-rapamycin, a hydroxyl ethyl ether of rapamycin. It differs from rapamycin in having a $-CH_2-CH_2-OH$ group at the 40-O-position, instead of hydrogen.

8. Zenke discloses co-administration of the IL-2 transcription inhibitor, cyclosporin A, and 40-O-(2-hydroxyethyl)-rapamycin, a "derivative of rapamycin [with] improved formulation and pharmacokinetic properties" (Zenke, col. 1, l. 51-53; col. 2, ll. 34-36) for treatment and prevention of transplant rejection and a number of autoimmune and inflammatory diseases (*id.* at col. 3, l. 28- col. 4, l. 19).

9. Zenke teaches "although cyclosporin A is highly effective in preventing and treating acute rejection episodes in transplant patients and hence contributes to long-term graft survival, chronic rejection, manifest as arteriostenosis due to vascular smooth muscle proliferation in the graft (graft-vessel disease), remains a serious problem for some patients after transplantation" (*id.* at col. 2, ll. 6-12). However, co-administration of 40-O-(2-hydroxyethyl)-rapamycin with cyclosporin "is useful to treat, e.g. ameliorate, or prevent not only acute rejection, but also chronic rejection" (*id.* at col. 2, ll. 40-42).

10. Further according to Zenke, "the indications for which this combination is of interest include . . . autoimmune and inflammatory conditions and conditions associated with or causal to transplant rejection" (Zenke, col. 3, ll. 28-31), e.g. "[c]hronic rejection of a transplanted organ, in particular, prevention of graft vessel disease, e.g., characterized by stenosis of the arteries of the graft as a result of intima thickening due to smooth muscle proliferation and associated effects" (*id.* at col. 3, ll. 42-46).

DISCUSSION

The Examiner finds that Wright discloses a stent having a coating "containing rapamycin or its structural analogs" (Ans. 4), but "does not specifically recite the hydroxyethyl rapamycin analog as claimed" (*id.*). However, the Examiner cites Zenke as evidence that "the analog [40-O-(2-hydroxyethyl)-rapamycin] is well known" (*id.*). The Examiner concludes that it would have been obvious to "to use the ZENKE exemplified rapamycin analog in the WRIGHT device since WRIGHT explicitly states that other analogs would be useful" (*id.*), and because "rapamycin and hydroxyethyl

rapamycin differ in a single functional group, a -CH_2-CH_2-OH at the 40-O-position, versus an OH group" (*id.* at 6), and "the preponderance of evidence points to the hydroxyethyl rapamycin analog and rapamycin having similar properties" (*id.*).

Appellants contend that "[t]he ether bond between rapamycin and the 2-hydroxyethyl is a much less labile bond" and "the functional group 2-hydroxyethyl can impart significantly different properties, [thus] one skilled in the art would not expect that 40-O-(2-hydroxyethyl)-rapamycin and rapamycin have similar properties" (App. Br. 5).

Appellants further contend that "Wright teaches delivery of rapamycin . . . to inhibit ***neointimal tissue proliferation*** and thereby prevent restenosis" (*id.*), which is consistent with Morris' teachings that "restenosis is caused by smooth muscle proliferation and migration" (*id.*), and that cyclosporin A, an immunosuppressant, "does not necessarily inhibit intimal proliferation" of smooth muscle cells (*id.* at 6). Thus, Appellants contend, "the treatment of hyperproliferative vascular disease uses rapamycin's ***anti-proliferative activity*** rather than its ***immunosuppressive activity***" (*id.*).

Appellants contend that "Zenke discloses that 40-O-(2-hydroxyethyl)-rapamycin and IL-2 transcription inhibitors, in particular cyclosporin[] A, act synergistically in immunosuppression" and the combination "is useful in the treatment of ***transplant rejection, certain autoimmune and inflammatory diseases***" (*id.* at 6-7).

Appellants contend that Morris "teaches that immune response and intimal smooth muscle cell proliferation are two distinct pathways" (*id.* at 6), thus, "Wright, Morris, and Zenke show that 40-O-(2-hydroxyethyl)-rapamycin and rapamycin have different utilities" (*id.* at 7), and "it is not

predictable whether an immunosuppressant such as 40-O-(2-hydroxyethyl)-rapamycin as taught in Zenke can inhibit intimal smooth muscle cell proliferation [and] thereby inhibit restenosis" (*id.*).

Finally, Appellants contend that "so little was know[n] about rapamycin itself . . . , not to mention 40-O-(2-hydroxyethyl)-rapamycin" (Reply Br. 3), that "knowledge of the existence of 40-O-(2-hydroxyethyl)-rapamycin, which Zenke . . . [discloses] for a use worlds apart from that contemplated by Wright not to mention only in combination with cyclosporin, might foster an invitation to experiment but certainly without any expectation of success given what was known at the time about the compounds " (*id.*).

Appellants' arguments are not persuasive, even if we accept, for the sake of argument, that one skilled in the art would not have expected rapamycin and 40-O-(2-hydroxyethyl)-rapamycin to have similar properties based on their similarity of structure alone. That is, we agree with the Examiner that one skilled in the art would have had reason to expect rapamycin and 40-O-(2-hydroxyethyl)-rapamycin to have similar antiproliferative properties given the teachings of the prior art.

As Appellants point out, Morris teaches that the immunosuppressant, cyclosporin A, is largely ineffective in preventing or inhibiting intimal proliferation of smooth muscle cells (App. Br. 6; FF5). This is consistent with Zenke's teaching that "cyclosporin A is highly effective in preventing and treating acute rejection episodes in transplant patients . . . [but] chronic rejection, manifest as arteriostenosis due to *vascular smooth muscle proliferation* . . . remains a serious problem for some patients after transplantation" (FF 9 (emphasis added)). Zenke teaches that this particular

problem can solved by administering 40-O-(2-hydroxyethyl)-rapamycin along with cyclosporin A, i.e., the combination "is useful to treat, e.g. ameliorate, or prevent not only acute rejection, but also chronic rejection" (*id.*). The logical inference is that 40-O-(2-hydroxyethyl)-rapamycin, like rapamycin itself, also inhibits vascular smooth muscle proliferation.

That being the case, we agree with the Examiner that one of ordinary skill in the art would reasonably have expected rapamycin and 40-O-(2-hydroxyethyl)-rapamycin to have similar properties with respect to inhibiting smooth muscle cell proliferation, and that it would have been obvious to substitute one for the other on Wright's stent.

SUMMARY

The rejection of claims 1-5 under 35 U.S.C. § 103(a) as unpatentable over Wright, Zenke, and Morris is affirmed.

TIME PERIOD FOR RESPONSE

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

AFFIRMED

lp