IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BOSTON SCIENTIFIC SCIMED, INC. and BOSTON SCIENTIFIC CORPORATION, Plaintiffs, v. CORDIS CORPORATION and JOHNSON & JOHNSON, INC., Defendants.	)	Civ. No. 03-283-SLR
BOSTON SCIENTIFIC SCIMED, INC. and BOSTON SCIENTIFIC CORPORATION, Plaintiffs, v. CORDIS CORPORATION, GUIDANT CORPORATION, GUIDANT SALES CORPORATION, JOHNSON & JOHNSON, INC., and ADVANCED CARDIOVASCULAR SYSTEMS, INC., Defendants.	)	Civ. No. 03-1138-SLR

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MEMORANDUM OPINION

Dated: April 4, 2007
Wilmington, Delaware

ROBINSON, Chief Judge

I. INTRODUCTION

Plaintiffs Boston Scientific Scimed, Inc. and Boston Scientific Corporation (collectively "BSC") filed the above captioned related actions[1] against defendants Cordis Corporation, Johnson & Johnson, Incorporated, Guidant Corporation, Guidant Sales Corporation, and Advanced Cardiovascular Systems, Inc. (collectively "Cordis"), alleging that Cordis' Cypher stent infringes claims 33 and 40 of U.S. Patent No. 6,251,920 ("the '920 patent").[2]

Pending before the court are Cordis' renewed motion for summary judgment of non-infringement and invalidity (Civ. No. 03-283, D.I. 277; Civ. No. 03-1138, D.I. 289); BSC's motion to exclude Dr. Sabatini's testing evidence and related testimony (D.I. 480); and BSC's motion for summary judgment that claims 33 and 40 are not anticipated by Morris (D.I. 482). The court has jurisdiction over these matters pursuant to 28 U.S.C. § 1338.

II. BACKGROUND

The '920 patent generally relates to a method for treating or preventing cardiovascular pathologies by administration of a therapeutic agent. Claim 40[3] depends

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[1]Unless otherwise specifically noted, all references to docket items will be to those in Civ. No. 03-283.

[2]The '920 patent is found in D.I. 494, ex. 1; hereinafter, the court will not refer to the record in citing the '920 patent.

[3]Claim 40 reads: "The method of claim 33 wherein the administration is localized at a site of vascular trauma." ('920 patent, col. 62, ll. 13-14)

from claim 33[4] and discloses localized administration of the therapeutic agent at a site of vascular trauma. The accused stent, the Cypher stent, is a drug-eluting BX Velocity balloon expandable stent.

The pending motions comprise a second round of summary judgment proceedings based on testing by Cordis' expert, Dr. Sabatini. The extended proceedings were allowed by the court in an effort to illuminate, as fully as possible, the issues presented by this litigation. Of course, the parties disagree on the extent and scope of illumination provided by Dr. Sabatini's testing, confirming the fact once again for this judicial officer that mixing science, linguistics and litigation strategies rarely produces results that reverberate with scientific certainty.

III. STANDARD OF REVIEW

A court shall grant summary judgment only if "the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). The moving party bears the burden of proving that no genuine issue of material fact exists. See Matsushita

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[4]Claim 33 reads:

> A therapeutic method for preventing or treating a cardiovascular indication characterized by a decreased lumen diameter comprising administering to a mammal at risk of or afflicted with said cardiovascular indication, a cytostatic dose of a therapeutic agent, wherein the cytostatic dose is effective to increase the level of TGF-beta so as to inhibit smooth muscle cell proliferation, inhibit lipid accumulation, plaque stability, or any combination thereof.

('920 patent, col. 60, ll. 58-65)

Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 586 n.10 (1986). "Facts that could alter the outcome are 'material,' and disputes are 'genuine' if evidence exists from which a rational person could conclude that the position of the person with the burden of proof on the disputed issue is correct." Horowitz v. Fed. Kemper Life Assurance Co., 57 F.3d 300, 302 n.1 (3d Cir. 1995) (internal citations omitted). If the moving party has demonstrated an absence of material fact, the nonmoving party then "must come forward with 'specific facts showing that there is a genuine issue for trial.'" Matsushita, 475 U.S. at 587 (quoting Fed. R. Civ. P. 56(e)). The court will "view the underlying facts and all reasonable inferences therefrom in the light most favorable to the party opposing the motion." Pa. Coal Ass'n v. Babbitt, 63 F.3d 231, 236 (3d Cir. 1995). The mere existence of some evidence in support of the nonmoving party, however, will not be sufficient for denial of a motion for summary judgment; there must be enough evidence to enable a jury to reasonably find for the nonmoving party on that issue. See Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 249 (1986). If the nonmoving party fails to make a sufficient showing on an essential element of its case with respect to which it has the burden of proof, the moving party is entitled to judgment as a matter of law. See Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986).

IV. ANALYSIS

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). A court should employ a two-step analysis in making an infringement determination. See Markman v. Westview Instruments, Inc., 52 F.3d 967, 976 (Fed. Cir. 1995). First, the court must construe the asserted claims to ascertain their meaning

and scope. Id. Construction of the claims is a question of law subject to de novo review. See Cybor Corp. v. FAS Techs., 138 F.3d 1448, 1454 (Fed. Cir. 1998). The trier of fact must then compare the properly construed claims with the accused infringing product. See Markman, 52 F.3d at 976. This second step is a question of fact. See Bai v. L & L Wings, Inc., 160 F.3d 1350, 1353 (Fed. Cir. 1998). Literal infringement occurs where each limitation of at least one claim of the patent is found exactly in the alleged infringer's product. See Panduit Corp. v. Dennison Mfg. Co., 836 F.2d 1329, 1330 n.1 (Fed. Cir. 1987). An accused product that does not literally infringe a claim may still infringe under the doctrine of equivalents if each limitation of the claim is met in the accused product either literally or equivalently. See Sextant Avionique, S.A. v. Analog Devices, Inc., 172 F.3d 817, 826 (Fed. Cir. 1999). The patent owner has the burden of proving infringement and must meet its burden by a preponderance of the evidence. See SmithKline Diagnostics, Inc. v. Helena Lab. Corp., 859 F.2d 878, 889 (Fed. Cir. 1988) (citations omitted).

As construed by the court, claims 33 and 40 of the '920 patent require that "the cytostatic dose of the therapeutic agent produces an increase in the amount of active TGF-beta, either by activating the latent form of TGF-beta or by stimulating the production of TGF-beta. **The increase in the amount of active TGF-beta** caused by the cytostatic dose **must inhibit** smooth muscle cell proliferation . . . ." (D.I. 459 at 3 (emphasis added)) In the court's October 14, 2005 memorandum opinion denying Cordis' motion for summary judgment of non-infringement, the court found there to be genuine issues of material fact in dispute, specifically:

> First, the parties acknowledge that rapamycin can be used as a cytostatic agent and that the Cypher stent may deliver a cytostatic dose of rapamycin which inhibits vascular smooth muscle cell proliferation.... Whether rapamycin causes an increase in the amount of active TGF-beta in effecting this result is a genuine issue in contention. Secondly, the evidence offered by Cordis that rapamycin does not increase TGF-beta levels in smooth muscle cells does not suggest whether rapamycin increases TGF-beta levels outside of vascular smooth muscle cells. If such an increase in TGF-beta levels occurs, evidence has been cited to suggest it may then inhibit vascular smooth muscle cell proliferation.... This is another issue, material to the court's infringement analysis, which remains in contention.

(D.I. 457 at 19)

As noted above, the record presently before the court includes testing conducted by Cordis' expert, Dr. Sabatini. It is informative to review in some detail the parties' competing evidence relating to infringement, before addressing the relevance of Dr. Sabatini's testing.

BSC offers in support of its infringement position the expert report of Dr. Leslie Z. Benet. Dr. Benet did not conduct any testing. He, instead, relies on various scientific papers to support his opinion that the Cypher stent infringes claims 33 and 40 of the '920 patent. More specifically, Dr. Benet reasons in his report (D.I. 404, ex. 3) as follows: TGF-beta is produced and secreted by most mammalian cells. (¶ 21) TGF-beta has been shown to inhibit the proliferation and migration of vascular smooth muscle cells ("VSMC"). (¶¶ 25-28) Rapamycin has been shown to stimulate the production of, or up-regulate, TGF-beta in a variety of cells. (¶ ¶ 22-24) Rapamycin also has been shown to inhibit VSMC proliferation; "[m]ore specifically, the rapamycin-FKBP12-mTOR complex interferes with the cell cycle by blocking proteins that activate the cell cycle and by stimulating (upregulating) cell cycle inhibitors such as cyclin-

dependent kinase inhibitor p27." (¶ 36) However, the "mTOR pathway of [rapamycin][5] action is only one possible explanation of how [rapamycin] works to inhibit VSMC proliferation. [Rapamycin], like almost all drugs, does not effect the human body in only one way.... Cordis has acknowledged [that] the mechanism of [rapamycin] action is not completely understood." (¶ 38) Indeed, "[o]ther investigators have postulated that the mechanism by which rapamycin inhibits growth overlaps with TGF-ß." (¶ 38) Dr. Benet concludes: "According to the evidence discussed above, it is clear that rapamycin inhibits VSMC proliferation by competing and/or overlapping mechanisms, and that **rapamycin's regulation of TGF-ß contributes** to the inhibition of VSMC proliferation." (¶ 39 (emphasis added))

Cordis originally responded to Dr. Benet's opinion by citing to the singular lack of any testing to demonstrate that the rapamycin in the Cypher stent increases the levels of TGF-beta in vascular smooth muscle cells. Moreover, according to Cordis, the scientific papers upon which Dr. Benet relies for the proposition that the rapamycin in the Cypher stent serves to increase the levels of TGF-beta in vascular smooth muscle cells are inapposite, as they all employed systemic[6] administration of large doses of rapamycin[7] to test the effects of rapamycin on cells other than human vascular smooth muscle cells.[8] Finally, Cordis cited to scientific papers which contradict those relied on

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[5]"Rapamycin" is also known as "sirolimus."

[6]Versus local.

[7]Versus the dose emitted by the accused product, a drug-eluting stent.

[8]Six of the seven studies were done in animals.

by Dr. Benet, and which demonstrate that rapamycin does not increase TGF-beta levels in the kidneys or other cell types. (D.I. 423)

It was with this background that the court allowed Dr. Sabatini's test results to be made part of the record.[9] Dr. Sabatini conducted the following test described in the '920 patent:

> To determine whether an agent is a TGF-beta activator or TGF-beta production stimulator, an agent or mixture of agents is first tested on rat aortic vascular smooth muscle cells (rVSMCs) for their ability to stimulate the production of active TGF-beta in the culture medium as originally described for tamoxifen. See Grainger et al. (*Biochem. J.*, 294, 109 (1993)). The **key step** in demonstrating that cells have a reduced proliferation rate **as a result of TGF-beta** production and activation is that the effect can be fully reversed by neutralizing antibodies to TGF-ß. **Incomplete reversal of a decreased rate of proliferation is evidence for TGF-ß independent effect(s). . . .**

('920 patent, col. 25, ll. 47-58 (emphasis added)) Dr. Sabatini performed the test five times, twice in human cells and three times in rat cells. He first tested the cells with and without the presence of rapamycin. Without rapamycin, the cells proliferated; with rapamycin, they did not. He then performed the test with the addition of the TGF-beta antibody. He obtained lots of the same commercial TGF-beta antibody as identified in the '920 patent, which antibody was tested and certified by its manufacturer; Dr. Sabatini also obtained the human cells from the same company as had Dr. Grainger, the named inventor of the '920 patent. The test results were the same as with rapamycin alone - cell proliferation was inhibited; i.e., rapamycin's ability to inhibit VSMC proliferation was identical, whether TGF-beta was present or not. (D.I. 479, ex.

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[9]Dr. Sabatini's testing was conducted outside the scheduled expert discovery schedule, but before the case was to be tried.

36) Dr. Grainger testified that he had no concerns about the "implementation as opposed to the relevance of the experiment." (D.I. 478, ex. 22 at 523)[10] According to Cordis, then, the results of the '920 patent's neutralizing antibody screening test demonstrate that TGF-beta has no effect on rapamycin's ability to inhibit VSMC proliferation. Therefore, the limitation of claim 33 which requires the therapeutic agent "to increase the level of TGF-beta **so as to inhibit** smooth muscle cell proliferation" cannot be met.

BSC argues in response that Dr. Sabatini's testing "yielded an inconclusive and uninformative result." (D.I. 481 at 8) More specifically,

> BSC does not dispute that rapamycin can act through the mTOR pathway, but contends that rapamycin's effects are also exerted through the TGF-ß pathway implicated in claim 33. Thus, a fundamental factual question distinguishing the parties' infringement positions is whether or not rapamycin increases TGF-ß levels **so as to inhibit** vascular smooth muscle proliferation - that is, whether rapamycin's effects on vascular smooth muscle cell proliferation are **at least in part** due to increased TGF-ß and its signaling pathway. Dr. Sabatini's tests do not help answer this question, and thus cannot assist the trier of fact to determine whether [the Cypher stent] infringes the ['920 patent].

(Id. at 10) BSC contends that "[i]t is impossible to determine if one pathway is masking another or compensating for another"; therefore, it is "not possible to draw any reliable conclusion from [Dr. Sabatini's] negative data about the effect that rapamycin has on TGF-ß or the TGF-ß signaling pathway." (Id. at 12) To put the point another way, according to BSC, "although a neutralizing antibody experiment may demonstrate that

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[10]The court finds that Dr. Sabatini followed standard testing protocol, as called for in the '920 patent. To the extent that BSC's motion to exclude Dr. Sabatini's testing is based on the premise that such testing was flawed in its implementation, it is denied.

rapamycin can act through a pathway other than TGF-ß, these data do not exclude TGF-ß from having a **viable** role." (Id. at 13 (emphasis added))

Of course, claim 33 of the '920 patent does not require that TGF-beta merely "contribute" to or play a "viable role" in the inhibition of VSMC proliferation. Rather, the cytostatic dose of the therapuetic agent must effectively increase the level of TGF-beta, and the increase in the amount of active TGF-beta **"must inhibit** smooth muscle cell proliferation"; i.e., the level of TGF-beta must be a causative, "but for" factor in the inhibition of VSMC proliferation. The neutralizing antibody screening test described in the '920 patent and conducted by Dr. Sabatini is the only test identified of record to determine whether there is a causal connection between the level of TGF-beta and VSMC proliferation in the presence of a therapeutic agent; the '920 patent directs that "incompete reversal of a decreased rate of proliferation is evidence for TGF-ß independent effect(s)." ('920 patent, col. 25, ll. 53-58)[11]

The question before the court is whether BSC has identified sufficient evidence to raise a genuine issue of material fact so as to overcome summary judgment. The court concludes that BSC has not done so. Dr. Sabatini's testing demonstrates that the presence or absence of TGF-beta has no effect on rapamycin's ability to inhibit VSMC proliferation. As a matter of law, if TGF-beta has **no** effect, then it certainly cannot be a

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[11]The court notes that BSC and Dr. Benet relied on the disclosure of the neutralizing screening test in support of enablement (D.I. 403 at 13; D.I. 494, ex. 3, ¶ 49); Dr. Grainger relied on the negative results from the neutralizing antibody screening test to reject agents as ones that did not work through TGF-beta (D.I. 491, ex. 19 at DJG 006069); and Dr. Benet explained that, in order to test whether rapamycin inhibited VSMC proliferation as a result of TGF-beta, he would have to perform the neutralizing antibody screening test described in the '920 patent (D.I. 491, ex. 2 at 187-188; D.I. 405, ex.52 at 75-76).

causative factor in rapamycin's ability to inhibit VSMC proliferation. BSC has countered the testing results with no more than an hypothesis[12] that TGF-beta "contributes" to or plays a "viable role" in the mechanism through which rapamycin inhibits VSMC proliferation. There is nothing in the record, however, that explains what such descriptors mean or how they can be measured; in other words, BSC's hypothesis relegates TGF-beta to playing some undefined role in rapamycin's ability to inhibit VSMC proliferation. Truth be told, the court is not confident at this juncture that BSC's hypothesis passes muster under Daubert, as BSC apparently contends that it is not possible to determine with reasonable certainty how the rapamycin in the Cypher stent works to inhibit VSMC proliferation. At best, BSC's hypothesis is not inconsistent with Dr. Sabatini's experimental results; that is, even if TGF-beta levels were increased in the presence of rapamycin, TGF-beta plays no significant, causative role in rapamycin's ability to inhibit VSMC proliferation. Therefore, the Cypher stent cannot infringe claims 33 and 40 as construed by the court.

IV. CONCLUSION

Based on the evidence of record, no reasonable juror could find for BSC on the issue of infringement. Consequently, Cordis' renewed motion for summary judgment of non-infringement (Civ. No. 03-283, D.I. 477; Civ. No. 03-1138, D.I. 289) is granted. BSC's motion to exclude Dr. Sabatini's testing (D.I. 480) is denied. BSC's motion for summary judgment that claims 33 and 40 are not anticipated by Morris (D.I. 482) is granted, as Cordis only posed its anticipation defense in the event claims 33 and 40

[12]Admittedly consistent with the scientific papers identified by Dr. Benet.

were found to be broad enough to include within their scope the Cypher stent. (D.I. 492 at 4) An order shall issue.

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ORDER

At Wilmington this 4th day of April, 2007, consistent with the memorandum opinion issued this same date;

IT IS ORDERED that:

1. Defendants' renewed motion for summary judgment (Civ. No. 03-283, D.I.

477; Civ. No. 03-1138, D.I. 289) is granted.

2. Plaintiffs' motion to exclude Dr. Sabatini's testing evidence and related testimony (D.I. 480) is denied.

3. Plaintiffs' motion for summary judgment on anticipation (D.I. 482) is denied.

United States District Judge