IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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| PFIZER INC., WYETH LLC, and WYETH PHARMACEUTICALS INC., Plaintiffs, | : | |
| v. | : | Civil Action No. 10-357-RGA |
| WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC.-FLORIDA, WATSON LABORATORIES, INC., RANBAXY LABORATORIES LIMITED, RANBAXY PHARMACEUTICALS, INC., and RANBAXY INC., Defendants. | : | |

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John C. Phillips, Jr., Esq., Wilmington, Delaware; John W. Bateman, Esq., Robert F. Vroom, Esq., Washington, D.C., Attorneys for Defendants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc.-Florida, Watson Laboratories, Inc., and Watson Pharma, Inc.

MEMORANDUM OPINION

January 30, 2013

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs, Pfizer Inc., Wyeth LLC, and Wyeth Pharmaceuticals Inc. (collectively, "Pfizer"), market an anti-transplant rejection medication based on rapamycin, also known as sirolimus, under the trade name Rapamune®. The Food and Drug Administration ("FDA") Orange Book lists U. S. Patent No. 5,100,899 (filed June 6, 1989) in connection with Pfizer's Rapamune® product.[1]

On or about December 16, 2009, Watson Laboratories, Inc.-Florida filed an Abbreviated New Drug Application ("ANDA") seeking approval to engage in the commercial manufacture, use and sale of a generic version of Rapamune®. Watson Laboratories, Inc.-Florida submitted a Paragraph IV Certification that the '899 patent is invalid and/or would not be infringed by Watson's generic. On or around March 16, 2010, Watson Laboratories, Inc.-Florida notified Pfizer that it had filed that ANDA. In April 2010, Pfizer initiated this litigation against Watson in connection with the Paragraph IV certifications contained in Watson's ANDA. In November 2010, Watson Laboratories, Inc.-Florida amended its ANDA; Pfizer filed a second amended complaint on January 3, 2011. (D.I. 53). The Ranbaxy defendants and Pfizer stipulated to dismissal of all claims between those parties. (D.I. 148).

The Court held a bench trial from April 30, 2012, through May 3, 2012, (D.I. 167, 168, 169), and post-trial briefing followed (D.I. 161, 166, 171, 174, 175). The Watson defendants concede infringement, (D.I. 134), but contend the asserted claims 1, 4, 5, and 7 of the '899 Patent are invalid as obvious under 35 U.S.C. § 103; invalid under 35 U.S.C. § 102(f) alone or in combination with § 103 because the asserted claims were derived from someone other than the

[1]The '899 Patent had its term extended such that it expires on July 7, 2013.

inventor; and invalid for failure to adequately describe the claimed subject matter under 35 U.S.C. § 112.[2]

## I. CLAIM CONSTRUCTION

The terms for which the parties requested claim construction in tandem with trial are construed as follows:

The term "inhibiting organ or tissue transplant rejection" is construed according to the '899 Patent's explicit definition: "[T]he term[] 'inhibiting organ or tissue transplant rejection' . . . refer[s] to increasing organ or tissue transplant acceptance (or decreasing the likelihood of organ or tissue transplant rejection) involving allografts, i.e., transplantation of organs or tissues from donor to recipient both of whom are in the same species (intraspecific), such as *Homo sapiens*." Col.2 ll.57-64; *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1380 (Fed. Cir. 2009) ("When a patentee explicitly defines a claim term in the patent specification, the patentee's definition controls.").

The term "inhibition of transplant rejection" is also construed according to the '899 Patent's explicit definition: "[T]he term[] 'inhibiting organ or tissue transplant rejection' . . . refer[s] to increasing organ or tissue transplant acceptance (or decreasing the likelihood of organ or tissue transplant rejection) involving allografts, i.e., transplantation of organs or tissues from donor to recipient both of whom are in the same species (intraspecific), such as *Homo sapiens*." Col.2 ll.57-64; *Martek*, 579 F.3d at 1380.

The term "a transplant rejection inhibiting amount" is also construed according to the

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[2] Watson asserted an "enablement" defense at trial but withdrew it in post-trial briefing. (D.I. 161, p.2, n.1).

'899 Patent's explicit definition: "As used herein, the term 'transplant rejection inhibiting amount' refers to the amount of rapamycin (or of rapamycin in combination with one or more other chemotherapeutic agents for inhibiting transplant rejection) which may be administered so as to inhibit transplant rejection in a mammal and to maintain transplant rejection inhibition, without causing severe toxic side-effects, e.g., nephrotoxicity, renal failure, etc." Col.3 ll.31-38; *Martek*, 579 F.3d at 1380.

For the term "indefinite period of time" the Court adopts the construction "indefinite post-transplantation period, in some instances, for the lifetime of the subject." (D.I. 161, Ex. 1; D.I. 166 n.75).

## II. OBVIOUSNESS

### A. Standard of Review

A patent may not issue "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Generally, a party seeking to invalidate a patent as obvious must "demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *Procter & Gamble Co. v. Teva Pharms.*

*USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). The Supreme Court has warned, however, that, while an analysis of any teaching, suggestion, or motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007).

A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078-79 (Fed.Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966).

**B. Findings of Fact**

(1) The Scope and Content of the Prior Art

The '899 Patent was filed on June 6, 1989. '899 Patent at [22]. Pfizer does not assert any earlier invention date. (D.I. 166 at 24; D.I. 161 at 8).

Before the discovery of cyclosporin A ("CsA"), general antiproliferatives and anticancer drugs were used to combat transplant rejection. (Tr. 528-29, 401-03, 691; PTX 524 at 764). These general antiproliferatives were toxic. (Tr. 529, 401-03, 691; PTX 328 at 168). During the late 1970s and early 1980s, CsA was discovered and developed as an antirejection drug. (PTX

328 at 170). CsA's structure was in the prior art. (DTX 489 at 469). CsA was known to work specifically against T-cells via interleukin-2 ("IL-2"), rather than all dividing cells, making it a "selective anti-rejection agent" instead of a general antiproliferative. (Tr. 404-05; PTX 191 at 1573-74; PTX 142; DTX 509). Selective anti-rejection became a "gamechanger" and the "gold standard" of antirejection therapy. (Tr. 404-07, 534; PTX 55 at 810). CsA was less toxic than its predecessors, but was still nephrotoxic; that is, it damaged the kidneys of transplant patients. *E.g.*, (PTX 366; Tr. 533).

The prior art, namely work by Dr. Ochiai, showed another compound called FK-506 had the possibility of being developed as an immunosuppressant drug for organ transplantation. '899 Patent, col.1 ll.37-41; (DTX 494, DTX 495). While some, including the inventor on the '899 Patent, Sir Roy Calne[3], suspected FK-506 was nephrotoxic or generally toxic, this was not in the prior art. '899 Patent col.1, ll.40-45; (Tr. 457, 537-38, 817-19; PTX 82). Dr. Tanaka disclosed FK-506's structure, which has a unique structural component called a hemiketal moiety, which was assumed to have biological activity. (DTX 525, DTX 498, DTX 499, DTX 493). Whether the hemiketal moiety contributed to FK-506's immunosuppression was not in the prior art. (Tr. 739, 885, 897).

The prior art also showed rapamycin having a hemiketal moiety, while the remainder of the rapamycin and FK-506 molecules were substantially different.[4] (PTX 538, DTX 551, Tr. 92). As with FK-506, rapamacyin's hemiketal moiety was presumed to have biological activity, but

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[3] The Court presumes Plaintiffs were correct in addressing Sir Roy Calne as "Sir Roy" and adopts that style.

[4] CsA does not have a hemiketal moiety. (Tr. 82).

the nature of that activity was not known. (DTX 506). Rapamycin was first used as an anti-fungal agent, and then studied for its possible anti-cancer work. (Tr. 88-89, DTX 531, DTX 681, PTX 246).

Martel demonstrated rapamycin had immunosuppressive properties. (DTX 523; Tr. 90). Martel described rapamycin as an anti-fungal agent and disclosed that it appeared to have immunosuppressive qualities comparable to general antiproliferatives. '899 Patent, col.1 ll.58-62; (DTX 523; Tr. 418-19, 703-04). Martel disclosed this immunosuppression achieved by oral administration of 5-10 mg/kg/day of rapamycin, for 12, 14, and 17 days. (DTX 523 at 48-50).

Martel showed rapamycin has immunosuppressive activity in the cell-mediated arm of the immune system through experimental models mimicking autoimmune disease (the "EAE" and "AA" tests). (DTX 523). These tests show only that rapamycin was immunosuppressive in the cell-mediated arm of the immune system and had "potential usefulness in transplantation." (DTX 635 at 272). This arm is complex and controls multiple immune systems in the body, including infection, autoimmune disease, allergic and inflammatory reactions, transplant rejection, and resistance to cancer. (Tr. 683-84).

The autoimmune disease models and results in Martel do not show that rapamycin would inhibit transplant rejection, or require that conclusion. (Tr. 229-31, 257-62, 423, 435, 685-87, 704-05). Dr. Keogh, who investigated rapamycin contemporaneously with Sir Roy, testified that Martel's tests were "dirty screens" that "are not mechanistically simple" and the AA test reflects inflammatory activity as well as immunosuppressive activity. (Tr. 229-31, 257-59). "They were not predictive screens for transplantation." (Tr. 259). Dr. Thomson admitted the tests are not organ transplantation rejection models. (Tr. 423, 435). Pfizer's expert, Dr. Hutchinson, did not

believe the AA model was a model for transplantation. (Tr. 705). At most, Martel showed one of ordinary skill that rapamycin had immunosuppressive activity and was worth evaluating further. (Tr. 258-29, 261-62). The prior art also showed rapamycin did not work by the IL-2 selective inhibition mechanism that CsA popularized and made the "gold standard." (PTX 142; DTX 509; Tr. 408, 732-33, 827).

Martel disclosed rapamycin not to be toxic, but rather, to be "well-tolerated" and that "[n]o drug-related adverse effects could be observed, other than a depression of the growth curve." (DTX 523 at 50; Tr. 366, 375, 784). Other prior art also indicated that rapamycin was not generally toxic. (DTX 630 at col.1 ll.14-17; DTX 681 at 539; PTX 246 at 803; DTX 633 at 17; Tr. 379-81). The prior art did not address whether rapamycin was nephrotoxic. (Tr. 454, 822-23).

A dissertation by Dr. Paiva, describing the process by which bacteria make rapamycin, showed rapamycin's structure and its similarities to FK-506's structure as disclosed by Tanaka. Dr. Paiva noted FK-506's use as an immunosuppressant agent with greater activity than CsA, and noted, "it would be interesting to compare directly rapamycin and FK-506 in their antifungal, antitumour, and immunosuppressant activity." (DTX 633). Dr. Paiva's subsequent witness statement went on to say, "it was totally obvious to me that if you were looking for alternative transplant agents, you should try rapamycin." This falls short of actually trying rapamycin in organ transplantation and showing it was an antirejection agent, and does not address toxicity.

The Patent Office was aware that FK506 had immunosuppressive activity and toxicity, through the Ochiai papers; that rapamycin had certain structural similarities to FK506, through the Tanaka paper; and Martel's disclosure and results. '899 Patent, col.1 ll. 37-41, 52-53, 58-62;

(DTX 38 at DTX0038_0038-0039).

(2) The Differences Between the Claims and the Prior Art

As construed, the claims at issue read as follows:

> Claim 1: "A method of [increasing organ or tissue transplant acceptance (or decreasing the likelihood of organ or tissue transplant rejection) involving allografts, i.e., transplantation of organs or tissues from donor to recipient both of whom are in the same species (intraspecific), such as *Homo sapiens*] in a mammal in need thereof, comprising administrating to said mammal a [amount of rapamycin (or of rapamycin in combination with one or more other chemotherapeutic agents for inhibiting transplant rejection) which may be administered so as to inhibit transplant rejection in a mammal and to maintain transplant rejection inhibition, without causing severe toxic side-effects, e.g., nephrotoxicity, renal failure, etc.]."
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> Claim 4: "The method according to claim 1, wherein said rapamycin is administered for a period of time comprising from about 1 to about 180 days."
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> Claim 5: "The method according to claim 1, wherein said rapamycin is administered orally."
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> Claim 7: "The method according to claim 1, wherein said rapamycin is administered for [an indefinite post-transplantation period, in some instances, for the lifetime of the subject] to maintain inhibition of transplant rejection."

The prior art taught that rapamycin had immunosuppressive qualities comparable to general antiproliferatives, which could be achieved via oral administration of 5-10 mg/kg/day for 12, 14, or 17 days, and that it was "well tolerated."

The prior art did not show any evaluation of rapamycin in animal transplantation models, much less increasing allograft acceptance in mammals, doing so without causing severe toxic side-effects, or maintaining inhibition of transplant rejection.

(3) The Level of Ordinary Skill in the Art

The parties agree that one of ordinary skill would often work in a team including a

medicinal chemist. (D.I. 161 at 25; D.I. 166 at 25). Dr. John Devlin, admitted as an expert in medicinal chemistry on Watson's behalf, testified that a person of ordinary skill in the art with respect to the '899 Patent would be a medicinal chemist and/or immunologist, with a clinician as a member of the drug discovery team. (Tr. at 111-12). Dr. Devlin testified the chemist would have had a Ph.D. in organic chemistry and experience in the development of immune regulatory drugs, while the immunologist would have a Ph.D. or M.D. in immunology or a related field, and experience in testing immunological drugs. *Id.* at 112-13. While Pfizer argues that a transplant surgeon, like the inventor on the '899 Patent, should be included in the definition of one of ordinary skill in the art, Pfizer introduced no expert testimony to that effect, and relies on the fact that the inventor of the '899 Patent was a transplant surgeon. (D.I. 166 at 24-25). Dr. Devlin's testimony proves the level of ordinary skill in the art.

(4) Motivation to Combine

There was a motivation to combine Ochiai (FK-506's immunosuppressive activity), Tanaka (FK-506 having a hemiketal moiety, like rapamycin's, that was presumed to be biologically active), and Martel (rapamycin's immunosuppressive activity and tolerability) to further evaluate rapamycin for immunosuppressive activity, starting with the oral dosage disclosed in Martel. The field was searching for a nontoxic immunosuppressant.

While the hemiketal moiety's function in both FK-506 and rapamycin was unknown, the fact that rapamycin shared this distinctive structure with a known immunosuppressant would have encouraged further study of rapamycin, particularly in light of Martel's demonstration of suppression of cell-mediated immunity. While CsA's selective antirejection was the "gold standard," there is no evidence that potential general antiproliferatives, as rapamycin appeared to

be, would have been discarded or ignored. In other words, CsA's success does not completely squelch the motivation to further investigate a well-tolerated compound with immunosuppressive qualities comparable to general antiproliferatives.

The combination of Martel, Ochiai, and Tanaka does not show any activity by rapamycin in the transplant context, or evaluation of rapamycin in animal allograft models. There is no motivation to combine the references to perform the claimed method of increasing allograft acceptance in mammals, doing so without causing severe toxic side-effects, or maintaining inhibition of transplant rejection. Paraphrasing Watson, this combination of information about rapamycin provided motivation to "evaluate rapamycin as an anti-rejection agent" -- no more. (D.I. 161 at 84); *e.g.*, (Tr. 295; DTX 521 at PRP 00054008, PRP00054010). Watson has not shown clear and convincing evidence of any motivation to make the leap from the prior art to the claimed methods; rather, Watson has shown only a motivation to further investigate rapamycin's immunosuppression on a very general level. *See Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1304 (Fed. Cir. 2011).

Other researchers were inspired to investigate rapamycin based on its structure, similarity to FK-506, and immunosuppressive properties. Fisons found Martel in a literature search for structurally similar compounds, and in collaboration with Fujisawa, evaluated rapamycin based on the "structural and reported biological similarities" of rapamycin and FK-506. (DTX 667, ¶ 14; Tr. 223-24; DTX 530). Fisons and Fujisawa stopped short of the claimed methods. (PTX 799, ¶¶ 13, 19; PTX 805 at PRP00090738; PTX 815 at PRP00092249; Tr. 472-73; Tr. 753-55). These efforts are evidence of a motivation to combine the prior art to further investigate rapamycin's immunosuppressive qualities, not to perform the claimed methods.

Dr. Seghal at Wyeth-Ayerst also investigated rapamycin. The parties dispute whether this investigation was inspired by rapamycin's structural similarity to FK-506 and FK-506's immunosuppressive activity alone, or whether Dr. Seghal also knew of Sir Roy's investigation. In light of Martel's disclosure that rapamycin appeared to have immunosuppressive qualities, Sir Roy wrote to William Cressman at Wyeth in Radnor, Pennsylvania, to request a sample of rapamycin on October 14, 1987. After the request, Ayerst and Wyeth merged, and on February 8, 1988, Wyeth's Radnor office followed up on Sir Roy's request with a Statement of Investigator form, which Sir Roy returned on or around March 4, 1988. Wyeth-Ayerst's Princeton, NJ office sent Sir Roy a one gram sample of rapamycin, which he received by July 1, 1988. (D.I. 166 at 17).

At around the same time, Dr. Sehgal of Wyeth-Ayerst's Princeton, NJ office was considering rapamycin, as memorialized in an April 4, 1988 memo. (DTX 519). Dr. Sehgal did not note Sir Roy's request in his memo. At a May 20, 1988, meeting Dr. Sehgal recommended MLR and T-cell screening as well as preclinical animal studies of rapamycin based on FK-506's immunosuppressive activity, rapamycin's structural similarity to FK-506, and Martel "to determine if it had a role in organ transplant therapy." (DTX 521).

Sir Roy's request for rapamycin is mentioned in a "Post meeting note" of Dr. Sehgal's May 20 meeting. (DTX 521). A memo with the same date as the "Post meeting note" asked Radnor office staff that had reviewed Sir Roy's request to "please ensure that any external requests that you or your staff receive for samples of rapamycin are reviewed by Dr. S. Sehgal (Immunopharmacology Division). Dr. Sehgal has a great deal of experience with this compound." (DTX 194A). A June 1988 letter from a Wyeth-Ayerst Princeton researcher (Dr.

Chang) to Sir Roy references "disrupted" communications between Wyeth and Ayerst's facilities, states that the Princeton office "fel[t] that rapamycin may be a potentially useful therapeutic agent in organ transplantation," notes that Sir Roy's request arrived "coincidentally" with the Princeton rapamycin work, and summarizes and encloses Martel. (DTX 526). Dr. Chang testified that the letter was "in response to Sir Roy's interest in rapamycin." (JTX0008 at 77:17-78:9).

Watson has attempted to connect the dots through the memo's "implication," the timing of the "Post meeting note" as compared to the meeting minutes themselves, the geography of Wyeth-Ayerst's office and Sir Roy's request, and "likely" conclusions from Dr. Chang's letter, to conclude Dr. Sehgal did not know about Sir Roy's request and so his investigation of rapamycin was based only on the prior art and was completely independent of Sir Roy's simultaneous work. This argument is less persuasive than the testimony by Dr. Chang, that Dr. Sehgal " knew about Sir Roy's sample request and interest in rapamycin all along," and by Dr. Lewis, a Wyeth-Ayerst researcher, that he learned of Sir Roy's request from Dr. Seghal prior to the May 1988 meeting. (JTX000 at 77-78; JTX0007 at 98:8-96:12). Dr. Seghal's pursuit of rapamycin is given little weight as evidence of a motivation to combine.

Dr. Sehgal asked Dr. Morris, also of Wyeth-Ayerst, to evaluate rapamycin in transplant rejection after Sir Roy's request. (DTX 431, PTX 387). Dr. Morris began his work in September, 1988, and published it after Sir Roy filed for his patent. In his papers, Dr. Morris noted that FK-506's properties, the structural similarities between FK-506 and rapamycin, and rapamycin's immunosuppressive properties made a "compelling case" for evaluating rapamycin as an antirejection agent. (DTX 539; *see also* DTX 639, PTX 387, PTX 387). Morris wrote to

Dr. Seghal that the use of rapamycin to inhibit allograft rejection was "obvious to anyone skilled in the field," but later explained that this statement was made out of anger over not receiving a patent and publication on the invention himself. (Tr. 460-65). Dr. Morris' work and opinions are not given great weight as evidence of motivation to combine or obviousness.

(5) Reasonable Expectation of Success

Watson has not shown a reasonable expectation of success; *i.e.*, a reasonable expectation that rapamycin would increase organ or tissue transplant acceptance, or that it could be administered to inhibit transplant rejection and maintain transplant rejection inhibition.

Rapamycin's structural resemblance to FK-506 did not create a reasonable expectation of success in increasing transplant acceptance. While rapamycin was known to share the hemiketal moiety with FK-506, that structure's function was unknown, and the rest of the molecules were known to be very different. Even presuming Watson's description of the person of ordinary skill's understanding of rudimentary molecule-target binding and activity is accurate (D.I. 161 at 22-24, 87-88), it does not compel the conclusion that because two molecules have one shared structural component, there is a reasonable expectation that the first and second molecules will have the same biological activity, particularly when - as here - the role of the shared structural component is unknown and the rest of each molecule is very different.

The evidence about rapamycin contradicts Watson's arguments regarding general theories of chemical binding. Rapamycin was known to operate via a different mechanism than FK-506. (PTX 142; DTX 509; Tr. 408-09). Other researchers, namely the Fisons and Fujisawa collaboration and Boehringer-Ingelheim, attempted to find immunosuppressive compounds based on the hemiketal moiety, and they failed. *See infra*, Section II(B)(6)(d) ("Failure of Others").

Adding Martel's disclosure of rapamycin's immunosuppressive activity to the analysis does not generate a reasonable expectation of success. Martel's demonstration of rapamycin's immunosuppressive qualities falls short of demonstrating antirejection in the transplant context. Watson argues one of ordinary skill would read Martel's EAE and AA tests to predict that rapamycin would inhibit transplant rejection, but Dr. Thomson's testimony on that point does not support that argument. *See* (D.I. 161 at 16-17, 86, citing Tr. 348-49, 353-54, 358-59). First, Dr. Thomson's testimony falls short of Watson's conclusion. (Tr. 348-49) (noting the EAE test "is a valuable tool to assess the ability of a drug to inhibit cell-mediated immunity under conditions that resemble human immunologic disease"). Dr. Thomson admitted the tests are not organ transplantation rejection models. (Tr. 423, 435).

Second, Dr. Thomson's credibility was severely undermined by documents and testimony showing he substantively erred on deposition about these tests and that counsel for Watson, not Dr. Thomson, drafted Dr. Thomson's proposed corrections. (PTX 0986, Tr. 1175-92). In contrast, the testimony by Drs. Hutchinson and Keogh credibly convinces the Court that one of ordinary skill would not draw the conclusion that rapamycin would inhibit transplant rejection based solely on Martel's EAE and AA test results. (Tr. 229-31, 257-59, 705). As Dr. Devlin put it, Martel's result and rapamycin's structure indicated only that rapamycin was "a primary candidate to produce the same effect as FK-506." (Tr. 72). This falls short of a reasonable expectation of success that rapamycin would increase organ or tissue transplant acceptance or decrease the likelihood of organ or tissue transplant rejection.

Nor was there a reasonable expectation that rapamycin would increase organ or tissue transplant acceptance or decrease the likelihood of organ or tissue transplant rejection without

causing severe toxic side effects. It is true that Martel disclosed that rapamycin was "well tolerated," and some other prior art indicated rapamycin was not generally toxic. (DTX 523 at 50; Tr. 366, 375; DTX 630 at col.1 ll.14-17; DTX 681 at 539; PTX 246 at 803; DTX 633 at 17; Tr. 379-81). Even with knowledge of the Martel article, the Fisons/Fujisawa collaboration abandoned rapamycin thinking it was toxic, showing the prior art on toxicity did not provide a reasonable expectation of success without severe toxic side effects. (PTX 799, ¶¶ 13, 19; PTX 805 at PRP00090738; PTX 815 at PRP00092249; Tr. 472-73; Tr. 753-55).

(6) Objective Considerations of Nonobviousness

a. *Teaching Away*

The prior art taught away from narrowly using rapamycin as an antirejection agent according to the preferred "gold standard." Some prior art indicated rapamycin was a general antiproliferative (*e.g.*, Martel), while other prior art (*e.g.*, what the parties refer to as "the Merck abstracts") indicated rapamycin's mechanism was different from both CsA's "gold standard" and FK-506. (DTX 523, PTX 142, DTX 509). This prior art taught away from pursuing rapamycin as an antirejection agent as compared to CsA's "gold standard." As explained in the motivation to combine analysis, this teaching away does not mean rapamycin would have been wholly ignored, and in fact other researchers were investigating rapamycin. Yet the prior art did teach away from rapamycin meeting the standard set by CsA.

b. *Unexpected Results*

Plaintiffs' proffered unexpected results include: rapamycin's mechanism of action being different than FK-506's; lack of nephrotoxicity, whereas FK-506 is nephrotoxic; promotion of tolerance on dendritic cells, unlike FK-506; benefit to cancer patients, whereas FK-506 is cancer-

promoting; and benefit to coronary artery stenosis patients. As explained in finding there was not a reasonable expectation of success, rapamycin is structurally different from FK-506 and the activity of their shared hemiketal moiety is unknown. Rapamycin behaving differently from FK-506 is not unexpected. Plaintiffs have not proven that rapamycin's differences from FK-506 comprise unexpected results.

c. *Long-Felt Need*

It is undisputed that there was a long felt need for a new antirejection therapy as good or better than CsA, without toxic side effects. Rapamycin is prescribed far less frequently than many other antirejection therapies, including CsA and FK-506, but is efficacious and satisfies a need "for the patients who got it." (DTX 606; Tr. 1096:9-12, 1015:21-1017:7; PTX 214; PTX 306; PTX 274; PTX 268).

The parties dispute the legal scope of the long-felt need and whether rapamycin met that need. Both parties cite *Hoffman-La Roche Inc. v. Apotex Inc.*, 2012 WL 1637736 (D.N.J. May 7, 2012). In that case, the plaintiff failed to rebut the fact that the patented method was prescribed less frequently than other methods with an explanation of how that drug met a need that its predecessor had failed to resolve. *Id.* at *19 n.18. Here, Pfizer has shown that FK-506 and CsA are nephrotoxic while rapamycin is not, such that rapamycin meets a need that its predecessors have not. Rapamycin met a long felt need, even if on a small scale.

d. *Failure by Others*

Others tried, and failed, to create FK-506 derivatives with the hemiketal moiety and to evaulate and develop rapamycin as a potential immunosuppressant drug.

First, Fujisawa and Fisons collaborated in pursuing rapamycin and stopped short of the

claimed invention. Fujisawa discovered FK-506 and its immunosuppressive qualities, and collaborated with Fisons on exploring rapamycin as a potential immunosuppressive based on its structural resemblance to FK-506. Each company tested rapamycin in an MLR screen, which evaluates a compound's potential anti-rejection qualities, and found it to have immunosuppressive qualities. (Tr. 235-36; PTX 799, ¶¶ 11-13). At least one of the companies concluded rapamycin was toxic, and at least one of the companies concluded rapamycin's mechanism was "cytotoxicity," meaning rapamycin worked as a general anti-proliferative. (PTX 799, ¶¶ 13, 19; PTX 805 at PRP00090738; PTX 815 at PRP00092249; Tr. 472-73; Tr. 753-55). Fisons was aware of the Martel article. (DTX 667, ¶ 14; DTX 244; Tr. 235). Fisons and Fujisawa met in April, 1988, and shared their conclusions. (PTX 805, 808). Neither company pursued rapamycin further.

Defendants' expert Dr. Devlin worked at Boehringer-Ingelheim ("BI") in 1987. At that time, Dr. Devlin knew the structure and immunosuppressive qualities of FK-506 and its relation to rapamycin, and was aware of the Martel and Tanaka articles. (Tr. 119-20). Armed with this information, Dr. Devlin recommended BI make smaller molecules with hemiketal moieties - not that BI investigate rapamycin itself. (Tr. 121). Neither Dr. Devlin nor BI investigated rapamycin's potential antirejection properties. (Tr. 123). Dr. Devlin testified that BI's work was "a failure." (Tr. 124).

Dr. Devlin also wrote a review article regarding the design and synthesis of immunoregulatory compounds, received for publication in May, 1988, that described FK-506's "cyclosporin-like profile" and hemiketal moiety, and rapamycin's results in Martel and hemiketal moiety and "conformational distinction from FK-506," and encouraged "a detailed comparison of

these macrolides." (DTX 503). The plain text of the article does not go so far as to suggest evaluating rapamycin for anti-transplant rejection, and Dr. Devlin's testimony that it does is not credible, particularly in light of his and BI's decision not to pursue rapamycin. *See* (Tr. 133). Nor did a later 1992 article state that Dr. Devlin's 1988 article suggested such evaluation; it simply repeated Dr. Devlin's encouragement of "a detailed comparison of these macrolides." (PTX 387). It is undisputed that Dr. Devlin's articles are not prior art.

These attempts constitute failure by others. None of these attempts to develop an immunosuppressant based on rapamycin's structure and Martel independently conceived and reduced to practice using rapamycin in a method of increasing transplant acceptance and maintaining that inhibition without causing severe side effects.

**C. Conclusions of Law**

"[A]lthough the standard of proof does not depart from that of clear and convincing evidence, a party challenging validity shoulders an enhanced burden if the invalidity argument relies on the same prior art considered during examination by the [PTO]." *See Creative Compounds, LLC v. Starmark Labs.*, 651 F.3d 1303, 1313 (Fed. Cir. 2011). Watson has failed to meet this burden. At most, Watson has shown a motivation to combine the prior art to continue investigating rapamycin's immunosuppressive properties, and a reasonable expectation that such properties would continue to be developed at an incremental pace. This fails to show that the claimed subject matter as a whole - a method for inhibiting transplant rejection in mammals without causing severe side effects - would have been obvious. "Patents are not barred just because it was obvious to explore a new technology or general approach that seemed to be a promising field of experimentation." *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566

F.3d 989, 997 (Fed. Cir. 2009).

Watson has failed to prove by clear and convincing evidence that the '899 Patent is invalid, particularly in light of the secondary considerations of nonobviousness proven by Pfizer: teaching away, long felt need, and failure by others. The presumption that the '899 Patent is valid remains undisturbed.

## III. WRITTEN DESCRIPTION

The written description "must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed.Cir. 2010) (en banc). The test is whether the disclosure "conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* This requires an "objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Id.*

Watson contends that the asserted claims of the '899 Patent are invalid under 35 U.S.C. § 112, ¶ 1 for lack of written description. The patent discloses effective rapamycin administration in dogs, rats, and pigs, with adverse events in dogs and pigs. The dogs suffered a "species-specific reaction" of vasculitis. '899 Patent, col.6 ll.11-24. The patent also discloses that 5 of the 10 pigs contracted interstitial pneumonitis "probably due to over-immunosuppression." *Id.* tbl.2; col.6 ll.67-68.

The parties agree that generally, "pharmaceutical patents are not required to have examples from many different animal models to satisfy the written description requirement." (D.I. 171 at 31). Watson's narrow argument hinges on its assertion that the '899 Patent is "unusual" because it claims avoiding severe toxic side effects, and that because side effects vary

between species, more is required to satisfy the written description requirement than with the typical pharmaceutical patent. (D.I. 171 at 32, 51). In other words, Watson argues that interspecies toxicity variation makes the written description requirement more stringent for pharmaceutical patents that claim an absence of side effects, than for those that do not, and that the '899 Patent in particular does not meet this heightened requirement.

Watson does not prove by clear and convincing evidence that interspecies toxicity varies so much more than interspecies efficacy that more written description is necessary for the '899 Patent because its claims address side effects. Watson asserts that a person skilled in the art at the time the '899 Patent was filed "generally believed that the efficacy of a drug . . . could be extrapolated from one species to the next," but cites only an article from 3 years after the patent was filed. (D.I. 161 at 69, citing PTX 387). Dr. Hardy's testimony that Watson cites addresses interspecies variation for both efficacy and side effects, without differentiating between the two. *Id.* (citing Tr. 1123-24). Sir Roy's testimony that Watson cites addresses interspecies variation for side effects, but does not prove that it is more onerous than interspecies variation for efficacy. *Id.* (citing Tr. 631-32).

Watson has failed to establish, by clear and convincing evidence, that Sir Roy was not in possession of the claimed invention.

**IV. DERIVATION**

Section 102(f) prohibits the issuance of a patent to a person or persons who derive the conception of an invention from any other source or person. *See Price v. Symsek*, 988 F.2d 1187, 1190 (Fed.Cir. 1993). To prove derivation under § 102(f), the patent challenger must establish prior conception of the invention by another and communication of that conception to the

patentee. *Id.*

Watson asserts that Dr. Raymond Keogh, of Fisons, "conceived of using rapamycin as an anti-rejection agent" and communicated to Sir Roy all the elements of claim 1 except for "the element of a 'transplant rejection inhibiting amount of rapamycin' (*i.e.*, an amount of rapamycin that would inhibit transplant rejection and not cause severe toxic side effects)." (D.I. 161 at 105, 106). Watson points to Dr. Keogh's testimony that he told Sir Roy about the existence of rapamycin, its structural similarity to FK-506, the Martel article, and Fison's request for a rapamycin sample. (Tr. 241-42, 244). Watson asserts that the remaining element of claim 1, and claims 4, 5, and 7, would be obvious from Dr. Keogh's disclosure of the Martel article to Sir Roy. (D.I. 161 at 106, 106 n.29).

Pfizer responds that even if Dr. Keogh told Sir Roy all of this (while challenging Dr. Keogh's testimony as uncorroborated), the content Dr. Keogh shared was in the prior art except for the sample request. As set forth *supra*, Watson has failed to show by clear and convincing evidence that the prior art (specifically, rapamycin's structural resemblance to FK-506, FK-506's immunosuppressive activity, and Martel) renders the claims at issue obvious. The argument falls even further short of showing derivation because Dr. Keogh himself did not believe the prior art rendered the claims obvious; he did not believe Martel predicted rapamycin's usefulness in transplantation, and he believed FK-506 was toxic. (Tr. 230-31, 258-59; DTX 249). Dr. Keogh does not believe he invented what is claimed in the '899 Patent. (Tr. 246-47).

Watson's addition of Dr. Keogh's sample request to its obviousness / derivation analysis does not meet Watson's burden. Requesting a sample is not an element of the claims, nor is it necessary or sufficient to enable one skilled in the art to practice the claims. Watson responds

that the sample request somehow "connected together the other pieces of information . . . into the obvious idea of using rapamycin to inhibit transplant rejection," which in turn would have made it obvious for Sir Roy to evaluate rapamycin in animal testing. (D.I. 171 at 52-53). This unsupported and logically flawed argument fails to provide clear and convincing evidence that Dr. Keogh conceived of the claimed invention in its entirety and communicated it to Sir Roy.

**V. Conclusion**

For the reasons stated above, the Court concludes that the asserted claims of the '899 Patent are not invalid due to obviousness, written description, or derivation. The parties will be directed to submit a proposed order by which the Court may enter final judgment consistent with this Opinion.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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|---|---|---|
| PFIZER INC., WYETH LLC, and WYETH PHARMACEUTICALS INC., Plaintiffs, | : | |
| v. | : | Civil Action No. 10-357-RGA |
| WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC.-FLORIDA, WATSON LABORATORIES, INC., RANBAXY LABORATORIES LIMITED, RANBAXY PHARMACEUTICALS, INC., and RANBAXY INC., Defendants. | : | |

ORDER

For the reasons set forth in the Opinion issued this date, **IT IS HEREBY ORDERED** that within seven days of the date of this Order, the parties shall jointly submit a proposed form of judgment consistent with the Opinion issued this date.

Entered this 30th day of January, 2013.

United States District Judge