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Barnes & Thornburg LLP (IN)
11 S. Meridian Street
Indianapolis, IN 46204

EXAMINER
BELYAVSKYI, MICHAIL A

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PHILIP S. LOW and MARY JO TURK[1]

Appeal 2016-004311
Application 13/463,447
Technology Center 1600

Before ERIC B. GRIMES, DEBORAH KATZ, and
JOHN E. SCHNEIDER, *Administrative Patent Judges*.

SCHNEIDER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for treating arthritis which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

STATEMENT OF THE CASE

> Rheumatoid arthritis (RA) is a systemic disease characterized by chronic inflammatory synovitis, usually involving peripheral joints. The synovial inflammation causes cartilage deterioration and bone erosion with consequent

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[1] Appellants identify the Real Party in Interest as Purdue Research Foundation. App. Br. 2.

> destruction of joint integrity. Rheumatoid factors, which are autoantibodies reactive with the Fc region of IgG, are found in more than two-thirds of patients with RA indicating that RA has an autoimmune component.
>
> RA is seen throughout the world in as much as 2% of the population, with 80% of RA patients developing the disease between the ages of 35 and 50. The clinical manifestations of RA include pain, swelling, and tenderness in the joints resulting in limitation of motion, weakness, fatigue, and weight loss. RA is a systemic disease and, consequently, has extra-articular manifestations, especially in patients with high titers of rheumatoid factors. These symptoms include rheumatoid nodules with an inner zone of necrotic material, a mid-zone of macrophages, and an outer zone of granulated tissue, muscle atrophy, osteoporosis, pulmonary fibrosis, and rheumatoid vasculitis which may result in cutaneous ulceration, digital gangrene, or neurovascular disease.

Spec. 1–2.

The Specification discloses a method for treating RA moderated by activated macrophages by killing the activated macrophages using ligands that bind to the activated macrophages. Spec. 2. The ligands are conjugated to a cytotoxin. *Id.*

Claims 20–37 are on appeal. Claim 20 is the sole independent claim and reads as follows:

> 20. A method of treating arthritis, said method comprising the step of administering to a patient suffering from arthritis an effective amount of a composition comprising a conjugate of the general formula
>
> A_b-X
>
> wherein the group A_b comprises folate, wherein folate binds to the folate receptor and is capable of binding to the activated macrophages, and wherein the group X comprises a cytotoxin that is an antifolate or a corticoid, wherein folate is conjugated

to the cytotoxin through a γ-carboxy moiety of a glutamic acid of folate.

The claims stand rejected under 35 U.S.C. § 103(a) as unpatentable over Nakashima[2] in view of Leamon[3], Kranz[4], Sudimack[5], Feldman[6],

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[2] Nakashima-Matsushita et al., *Selective Expression of Folate Receptor β and Its Possible Role in Methotrexate Transport in Synovial Macrophages from Patients with Rheumatoid Arthritis,* 42 Arthritis & Rheumatism 1609 (1999) ("Nakashima").
[3] Leamon and Low, *Selective Targeting of Malignant Cells with Cytotoxin-Folate Conjugates,* 2 J. Drug Targeting 101 (1994) ("Leamon").
[4] Kranz et al., US 5,547,668, issued Aug. 20, 1996 ("Kranz").
[5] Sudimack and Lee, *Targeted drug delivery via folate receptor,* 41 Adv. Drug Delivery Rev. 147 (2000) ("Sudimack").
[6] Feldman et al., US 6,270,766 B1, issued Aug. 7, 2001 ("Feldman").

Wedeking[7], as evidenced by Barrera[8], Weinberg[9], Nagayoshi[10], Guzaev[11], Mathias[12], Linder[13], and Ilgan.[14]

DISCUSSION

Issue

The issue with respect to this rejection is whether a preponderance of the evidence supports the Examiner's conclusion that claims 20–37 would have been obvious over Nakashima in combination with Leamon, Kranz, Sudimack, Feldman, Wedeking, as evidenced by Barrera, Weinberg, Nagayoshi, Guzaev, Mathias, Linder, and Ilgan.

The Examiner finds that Nakashima teaches that a folate antagonist ligand capable of binding to a folate receptor on an activated macrophage

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[7] Wedeking et al., US 6,093,382, issued July 25, 2000 ("Wedeking").
[8] Barrera et al., *Synovial Macrophage Depletion with Clodronate-Containing Liposomes in Rheumatoid Arthritis,* 43 Arthritis & Rheumatism 1951 (2000) ("Barrera").
[9] Weinberg et al., US 5,759,546, issued June 2, 1998 (Weinberg").
[10] Nagayoshi et al., *Effectiveness of Anti-folate Receptor β Antibody Conjugated with Truncated Pseudomonas Exotoxin in the Targeting of Rheumatoid Arthritis Synovial Macrophages,* 52 Arthritis & Rheumatism 2666 (2005) ("Nagayoshi").
[11] Guzaev et al., US 6,335,434 B1, issued Jan. 1, 2002 ("Guzaev").
[12] Mathias et al., *Synthesis of [^{99m}Tc]DTPA-Folate and Its Evaluation as a Folate-Receptor-Targeted Radiopharmaceutical,* 11 Bioconjugate Chem. 253 (2000) ("Mathias").
[13] Linder et al., *In Vitro Studies with α- and γ-Isomers of ^{99m}Tc-OXA-Folate Show Uptake of Both Isomers in Folate-Receptor (+) KB Cell Lines,* Proc. 47th Ann. Mtg Soc. Nucl. 119P (2000) ("Linder")
[14] Ilgan et al., *^{99m}TcEthylenedicysteine-Folate: A new Tumor Imaging Agent. Synthesis, Labeling and Evaluation in Animals,* 13 Cancer Biotherapy & Radiopharm. 427 (1998) ("Ilgan").

can be used to treat rheumatoid arthritis. Non-Final Act.[15] 3. The Examiner finds that Leamon discloses the use of folate-toxin conjugates as an effective therapeutic to kill cells that overexpress a folate receptor. *Id.* The Examiner finds that Feldman teaches treating arthritis using methotrexate. *Id.* The Examiner finds that Wedeking teaches the use of folate conjugates of either γ-isomers or α-isomers for therapeutic applications. *Id.* The Examiner concludes

> it would have been obvious to one of the ordinary skill in the art at the time the invention was made to use folate-cytotoxin conjugate to treat RA with a reasonable expectation of success because the prior art suggests that targeting and elimination of activated macrophages [that overexpress] folate receptor was an effective therapeutic for treatment of RA. Said targeting and elimination can be performed using conjugate, comprising a folate and cytotoxin successfully used in the in the prior art.

Non-Final Act. 4.

Appellants contend that Nakashima only suggests that folate receptor β (FR-β) is expressed on macrophages but does not actually show that FR-β is expressed. App. Br. 5–6. Appellants point to the Declaration of Dr. Low[16] to support this contention. App. Br. 7. Appellants also contend that Nakashima does not establish the FR-β number on synovial cells. *Id.* Appellants contend that Nakashima does not suggest any affinity for folate of the FR-β on synovial cells. App. Br. 8. Appellants contend that at the time the invention was made, the art taught that the affinity of FR-β for

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[15] Non-Final Action mailed Oct. 16, 2014.
[16] Declaration Under 37 C.F.R. § 1.132 of Dr. Phil S. Low, filed Feb. 17, 2015 ("Low Decl.").

folate was unpredictable. App. Br. 9. Appellants next argue that Nakashima only shows in vitro data and does not teach the effectiveness of the conjugate in vivo. *Id.* Appellants argue that Nakashima reaches away from the invention in that Nakashima is directed to decreasing levels of folate whereas the present invention would increase folate levels. App. Br. 10. Finally, Appellants argue that the additional references do not address the deficiencies of Nakashima. App. Br. 11–18.

Findings of Fact

We adopt the Examiner's findings as our own, including with regard to the scope and content of, and motivation to modify or combine, the prior art. The following findings are included for emphasis and reference purposes.

FF1. Nagayoshi teaches that

> Activated synovial macrophages are thought to play an important role in the pathogenesis of rheumatoid arthritis (RA). These macrophages release proinflammatory cytokines, proteinases, and other chemical mediators that lead to the development of synovitis and joint destruction. The removal of macrophages decreases the severity of joint disease in animal models of RA.

Nagayoshi 2666 (reference numbers omitted).

FF2. Barrera teaches

> Rheumatoid arthritis (RA) is a common autoimmune disorder that is characterized by chronic arthritis leading to irreversible joint destruction. The pathogenesis of RA is not fully understood, but current models are based on the recognition of peptides bound to HLA class II molecules on macrophages and other antigen-presenting cells by T cells.

Barrera 1951.

FF3. Barrera teaches that "the depletion of the lining macrophages does decrease cartilage destruction in chronic experimental arthritis." *Id.* 1957.

FF4. Nakashima teaches

> FR-β expression is selectively elevated in RA synovial macrophages and suggest that MTX is transported through FR-β in RA synovial macrophages. The findings suggest that folate antagonists with higher affinity for FR-β would be useful in the treatment of RA.

Nakashima 1609.

FF5. Nakashima states

> The observed significant inhibition supports the notion that a large part of MTX transport in RA SMC may be through FR, probably FR-β on RA synovial macrophages, and furthermore, that the target cells of MTX in RA SMC are synovial macrophages.

Nakashima 1615.

FF6. Nakashima also states "In conclusion, the present findings strongly suggest a role for FR-β in the transport of folic acid and folate derivatives in RA SMC and imply that folic acid antagonists with a high affinity for FR-β may be useful in the treatment of RA." *Id.*

FF7. Leamon discloses the use of cytotoxin-folate conjugates as tumor specific therapeutic agents. Leamon Abstract.

FF8. Wedeking discloses therapeutic agents comprising derivatives of folic acid coupled to a drug through the gamma carboxylate. Wedeking col. 8, ll. 61–64.

FF9. Methotrexate is a cytotoxin. Spec. 8.

Principles of Law

> [T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability. If that burden is met, the burden of coming forward with evidence or argument shifts to the applicant.
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

Analysis

Claim 20 is representative of the rejected claims and is reproduced above.

We agree with the Examiner that the subject matter of claim 20 would have been obvious to one of ordinary skill in the art at the time the invention was made. Nakashima teaches the use of folic acid antagonists to treat RA and that the target cells of methotrexate are synovial macrophages. FF4–6. Barrera teaches that the reduction of lining macrophages decreases cartilage damage in patients with RA. FF3. Leamon teaches the use of folate-cytotoxin conjugates to destroy cells. FF7. Wedeking teaches that the constructs can be formed by linking the active component through a γ-carboxy moiety of glutamic acid of a folate. FF8. One skilled in the art would have found it obvious to use the folate conjugates known in the art to treat RA as suggested by Nakashima. Further motivation would arise from

the teachings of Barrera that reduction of the macrophages would reduce joint damage. FF3.

Appellants contend that Nakashima does not actually show that FR-β is expressed on the macrophages, asserting that the data provided relies on populations of cells that are not exclusively macrophages. App. Br. 5–6. Appellants contend that one skilled in the art reading Nakashima, would not have a reasonable expectation of success in using conjugates that bind the FR-β to treat RA.

We have considered Appellants' arguments and find them unpersuasive. As shown above, Nakashima discusses the role of FR-β in the transport of methotexrate and that methotexrate targets synovial macrophages. FF4–6. Moreover, Nakashima specifically states that "folate antagonists with high affinity for FR-β would be useful in the treatment of RA." FF4. Based on the statements in Nakashima, one skilled in the art would have a reasonable expectation that administration of folate-conjugates would be effective in treating RA.

Appellants present the declaration of inventor Low in support of the attorney argument on pages 5 and 6 of the Appeal Brief regarding the data shown in Nakashima. *See* Low Decl. ¶ 2. Because we are not persuaded by the reasoning of Appellants' arguments in the brief regarding a reasonable expectation of success for the claimed methods, Dr. Low's mere agreement with these arguments is no more persuasive.

Appellants next argue that Nakashima does not teach the FR-β number on the synovial cells and that this would lead one skilled in the art to conclude that the conjugates are not effective. App. Br. 7–8. We find this

argument unpersuasive. The present claims only call for the folate to bind to a folate receptor and be capable of binding to macrophages. *See* claim 20 above. Nakashima teaches that folate receptors are present on the macrophages and that folates are capable of binding to them. FF4–6.

Appellants also contend that Nakashima teaches away from the present invention in that Nakashima is directed towards reducing folate levels whereas the present invention would increase folate levels. App. Br. 10. Again, we are unpersuaded.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). As the Examiner points out, Nakashima specifically teaches "that methotrexate is transported through FR in synovial macrophages from patients with rheumatoid arthritis." Ans. 5. The Examiner continues by noting that "Nakashima et al, further teach that folate antagonist with higher affinity to FR would be useful in the treatment of arthritis." Ans. 5. We agree with the Examiner that this does not constitute a teaching away from the invention because it does not discourage targeting the folate receptor. *Id.*

With respect to the secondary references, Appellants' argument that they do not cure the deficiencies of Nakashima are unpersuasive. As discussed above, the teachings of Nakashima are not deficient.

Finally, with respect to Wedeking, Appellants' argument that one skilled in the art would not have been motivated to use γ-isomers of folates

because of lower safety margins is unpersuasive. App. Br. 14–17. As the Examiner points out, Wedeking teaches the use of both α and γ-isomers. Ans. 6. That Wedeking teaches that the α-isomer may be preferred does not negate from Wedeking's teaching regarding the γ-isomer. "The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . . alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed." *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Conclusion

We conclude that a preponderance of the evidence supports the Examiner's conclusion that claim 20 would have been obvious over Nakashima in combination with Leamon, Kranz, Sudimack, Feldman, Wedeking, as evidenced by Barrera, Weinberg, Nagayoshi, Guzaev, Mathias, Linder, and Ilgan.

Claims 21–37 have not been argued separately and therefore fall with claim 20. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection under 35 U.S.C. § 103(a).

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