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Paper 13
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BOEHRINGER INGELHEIM INTERNATIONAL GMBH AND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,
Petitioner,

v.

GENENTECH, INC. AND BIOGEN IDEC, INC.,
Patent Owner.

Case IPR2015-00415
Patent 7,820,161 B1

Before FRANCISCO C. PRATS, ERICA A. FRANKLIN, and SHERIDAN K. SNEDDEN, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge.*

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Petitioner") filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 7,820,161 B1 (Ex. 1001, "the '161 patent"). Paper 3 ("Pet."). Genentech, Inc. and Biogen IDEC, Inc. (collectively, "Patent Owner") filed a Preliminary Response to the Petition. Paper 10 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted "unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). Upon considering the Petition and Preliminary Response, we determine that Petitioner has shown a reasonable likelihood that it would prevail in showing the unpatentability of claims 1, 2, 5, 6, 9, and 10. Accordingly, we institute an *inter partes* review of those claims.

A. Related Proceedings

Petitioner and Patent Owner identify no related proceedings, apart from two petitions filed by Petitioner, concurrently with the present petition, for *inter partes* review: Case IPR2015-00417 (U.S. Patent No. 7,976,838) and Case IPR2015-00418 (U.S. Patent No. 8,329,172). Pet. 4; Paper 4, 2. Patent Owner notes that although the three petitions involve the same counsel, the subject patents are "not formally related and do not have the same ownership." Paper 4, 2.

B. The '161 Patent (Ex. 1001)

The '161 patent relates to a method for treating rheumatoid arthritis ("RA") by administering more than one intravenous dose of a

therapeutically effective amount of rituximab and administering methotrexate. Ex. 1001, Abstract. Rituximab or "RITUXAN®," refers to the genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen. *Id*. at 2:29–31. Rituximab is also known as "C2B8." *Id*. at 2:31–32. Studies have shown that Rituximab binds human complement and lyses lymphoid B cell lines through complement-dependent cytotoxicity. *Id.* at 2:35–39. Methotrexate is an anti-metabolite, immunosuppressive, and chemotherapeutic agent. *Id*. at 10:7, 30–31; 27:48–49.

C. Illustrative Claim

Claim 1 of the '161 patent is illustrative and is reproduced below:

> 1. A method for treating rheumatoid arthritis in a human comprising: (a) administering to the human more than one intravenous dose of a therapeutically effective amount of rituximab; and (b) administering to the human methotrexate.

D. The Prior Art

Petitioner relies upon the following prior art references:

O'Dell	O'Dell, *Methotrexate Use In Rheumatoid Arthritis,* 23 RHEUMATIC DISEASE CLINICS OF NORTH AMERICA 779–796 (1997).	Ex. 1003
Rituxan® product label	IDEC Pharmaceuticals Corporation and Genentech, Inc., Product label for Rituxan® (1997).	Ex. 1006
Pincus	Pincus et al., *"No evidence of disease" in rheumatoid arthritis using methotrexate in combination with other drugs: A contemporary goal for rheumatology care?* 15 CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 591–596 (1997).	Ex. 1008

Tobinai	Tobinai et al., *Feasibility and pharmacokinetic study of a chimeric anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab) in relapsed B-cell lymphoma*, 9 Annals of Oncology 527–534 (1998).	Ex. 1013
Verhoeven	Verhoeven et al., *Combination Therapy in Rheumatoid Arthritis: Updated Systematic Review* 37 BRITISH J. RHEUMATOLOGY 612–619 (1998).	Ex. 1016
Kavanaugh	Kavanaugh et al., *Anti-TNF-α Monoclonal Antibody (mAh) Treatment of Rheumatoid Arthritis (RA) Patients with Active Disease on Methotrexate: Results of a Double-Blind, Placebo Controlled Multicenter Trial*, 39 ARTHRITIS RHEUMATOLOGY 575 (1996).	Ex. 1019
Kalden	Kalden et al., *Rescue of DMARD failures by means of monoclonal antibodies or biological agents*, 15 J. CLINICAL AND EXPERIMENTAL RHEUMATOLOGY S91–S98 (1997).	Ex. 1020
Boers	Boers et al., *Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis*, 350 LANCET 309–18 (1997).	Ex. 1022
Maloney	Maloney et al., *Phase I Clinical Trial Using Escalating Single-Dose Infusion of Chimeric Anti-CD20 Monoclonal Antibody (IDEC-C2B8) in Patients with Recurrent B-Cell Lymphoma*, 84 BLOOD 2457–2466 (1994).	Ex. 1023
Edwards	Edwards et al., *Rheumatoid Arthritis: The Predictable Effect of Small Immune Complexes in Which Antibody is Also*	Ex. 1025

	Antigen, 37 BRITISH J. RHEUMATOLOGY 126–130 (1998).	
Gryn letter	Letter from Jeffrey Gryn, MD to Ms. Beth Parker, dated May 6, 1998.	Ex. 1026

Petitioner also relies upon the Declaration of Joachim Kalden, M.D. (Ex. 1002).

E. The Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1–12 of the '161 patent on the following grounds (Pet. 42–43):[1]

Claims Challenged	Basis	References
1, 2, 5, 6, 9, 10	§ 103(a)	Edwards or Gryn letter in view of either O'Dell or Pincus or Kalden
1, 2, 5, 6, 9, 10	§ 103(a)	Edwards or Gryn letter in view of either O'Dell or Pincus or Kalden, and the Rituxan® Product Label or Maloney
3, 7, 11	§ 103(a)	Edwards or Gryn letter in view of either Verhoeven or Kavanaugh or Boers
4, 8, 12	§ 103(a)	Edwards or Gryn letter in view of the Rituxan® Product Label and either O'Dell or Pincus or Kalden
4, 8, 12	§ 103(a)	Edwards or Gryn letter in view of Tobinai and either O'Dell or Pincus or Kalden

[1] In the Petition, Petitioner discusses a number of references that are not included in any variable of the asserted grounds. Our analysis of the challenged claims is limited to the specific combinations of references that Petitioner identified in the grounds set forth in the Petition. Pet. 42–43.

II. ANALYSIS

A. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b) ; *In re Cuozzo Speed Techs., LLC*, No. 2014-1301___ F.3d ___, 2015 WL 2097949, at *5–8 (Fed. Cir. July 8, 2015). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Neither Petitioner nor Patent Owner proposes specific constructions for any claim term. Pet. 13–14; PO Resp. 7–8. In view of our analysis, we determine that construction of claim terms is not necessary for purpose of this Decision.

B. Obviousness over Combinations Including the Gryn Letter (Ex. 1026)

Petitioner asserts that claims 1–12 of the ’161 patent would have been obvious over combinations including the Gryn letter. Pet. 42–43.

The Gryn letter is signed by Dr. Jeffrey Gryn and addressed to Ms. Beth Parker, indicating, “Attn: Clinical Research.” Ex. 1026, 1. In the letter, Dr. Gryn introduces himself and then discusses his beliefs regarding the potential use of “Rituxin” [sic] to treat autoimmune diseases associated with, or caused by, antibodies. *Id*. Dr. Gryn explains in the letter that he is enclosing a copy of his curriculum vitae and concept sheet. *Id*. The letter

ends with a request: "Please let me know if IDEC is interested in sponsoring such a trial." *Id*. On the face of the letter appears a stamp indicating a "RECEIVED" date of May 14, 1998. *Id*.

Petitioner asserts that the Gryn letter is a "printed publication" because it was sent to a commercial entity, i.e., IDEC Pharmaceuticals, "without any confidentiality or other restrictions on use." Pet. 20 (citing *Garrett Corp. v. United States*, 422 F.2d 874, 878 (Ct. Cl. 1970) (discussing distribution to commercial companies as constituting publication)). Further, Petitioner asserts that the letter "became available as prior art at least by the day it was received," on May 14, 1998. *Id*. (citing MPEP § 2128.02) (discussing publication dissemination by mail).

Patent Owner asserts that the Gryn letter does not qualify as a "printed publication" because Petitioner has not established that the letter was publicly accessible before the priority date of the '161 patent. Prelim. Resp. 23. In particular, Patent Owner asserts that Petitioner has not provided any evidence to support its assertion that Dr. Gryn's letter was sent without any expectation of confidentiality or other restrictions on use. *Id*. Even absent such expectation or restrictions, Patent Owner asserts that Petitioner has failed to establish that providing the letter to one commercial entity amounts to a public accessibility. *Id*. at 24–25.

We agree with Patent Owner. Petitioner relies on one sentence from *Garrett Corp.*: "While distribution to government agencies and personnel alone may not constitute publication … distribution to commercial companies without restriction on use clearly does." Pet. 20 (quoting *Garrett Corp.*, 422 F.2d at 878). This reliance is misplaced as Petitioner does not assert that Dr. Gryn distributed his letter to commercial companies. Rather,

Petitioner asserts only that Dr. Gryn mailed his letter to a single commercial entity. Thus, even accepting this assertion as true, it does not represent the scenario addressed in *Garrett*, wherein distribution was directed to more than one company, as well as to other entities.

As recognized in *Garrett*, "[t]o be a 'publication' under the statute, a document must, among other things, be accessible to the public," wherein the public "constitutes that class of persons concerned with the art to which the document relates and thus most likely to avail themselves of its contents." *Id*. at 877–78. The factors bearing on whether a printed document was indeed published set forth in *Garrett*, include "the number of copies made, availability, accessibility, dissemination, and even intent." *Id*. at 878. Petitioner has not provided any specific assertions or evidence regarding these factors. Accordingly, we find that Petitioner has not established persuasively that the Gryn letter was publicly accessible so as to render it a printed publication under 35 U.S.C. § 102(b). We remain unpersuaded by Petitioner's reliance on MPEP § 2128.02, as this section is directed to establishing the date that a "journal article" or other "publication" becomes available as prior art. Petitioner has not established the Gryn letter is either of these.

Because Petitioner has not established that the Gryn letter is prior art, we determine that Petitioner has not set forth a reasonable likelihood that it would prevail in showing that claims 1–12 would have been obvious over combinations that rely, in part, on the teachings or suggestions of the Gryn letter.

C. Obviousness Over Edwards (Ex. 1025) in view of O'Dell (Ex. 1004) or Kalden (Ex. 1020)

Petitioner asserts that claims 1, 2, 5, 6, 9, and 10 would have been obvious over Edwards in view of O'Dell, Pincus, or Kalden. Pet. 42. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 26–41.

1. Edwards

Edwards is a journal article discussing a strategy to cure RA by destroying RF-producing B-cell clones (rheumatoid factor-producing B-cell clones) using "anti-CD20 antibodies and/or other agents." Ex. 1025, 129. The article presents this strategy in the form of a hypothesis that, in some respects, "refocuses attention on the possibility that permanent interruption of autoantibody production might effectively cure the disease." *Id*. at 126. According to Edwards, local and systemic events in the pathogenesis of RA suggest that "if B cells of pathogenic RF specificity are destroyed, the chance of them reappearing may be no greater than that of *de novo* appearance on the same genetic background." *Id*. at 128.

Edwards explains that, although attempting to selectively destroy B-cell clones exhibiting RF specificity may be ineffective, a better strategy may be to kill all mature B cells. *Id*. According to Edwards, doing so should allow only anti-non-self-B-cell clones to re-emerge because these clones, and not pathogenic IgG RF-producing clones, develop from clones with germline sequences by sequential affinity-based selection under control of corresponding T-cell responses. *Id*. at 129. Mature B cells can be destroyed using an anti-B-cell antibody, i.e., anti-CD20 antibody. *Id*.

Edwards describes several detailed aspects of the hypothesis that need to be tested, and explains that means for such testing are available. *Id*.

Edwards characterizes "[t]he ultimate test of the hypothesis [as] the efficacy of destruction of RF-producing B-cell clones by anti-CD20 antibodies and/or other agents." *Id*. According to Edwards, "[t]he chance that RF B-cell clones can be abrogated permanently is uncertain," but because it may lead to curing RA, "it is worth trying." *Id*.

2. O'Dell

O'Dell is a journal article discussing the importance of methotrexate in managing RA and its use in combination therapy. Ex. 1003, 779. At the time O'Dell was written, methotrexate was considered "the disease-modifying antirheumatic drug (DMARD) most commonly used to treat RA," due to its efficacy and tolerability. *Id*. However, methotrexate rarely induces remission, which is the therapeutic goal for all patients with RA. *Id*. O'Dell explains that combination therapies most commonly used in clinical practice included methotrexate, and suggests that methotrexate used in combination therapy represents a treatment approach that is "a step closer to the goal of remission." *Id*. at 790, 792. O'Dell states that the most common combinations are methotrexate-hydroxychloroquine and methotrexate-sulfasalazine. *Id*. at 790. According to O'Dell, continued research on combination therapies that include biologic agents and methotrexate is necessary. *Id*. at 792.

3. Kalden

Kalden is a journal article discussing the development of different monoclonal antibodies and other biological agents to treat RA. Ex. 1020 Abstract. Kalden explains that clinical rheumatologists "have long recognized that the treatment repertoire available for patients with rheumatoid arthritis (RA) is by no means satisfactory." *Id*. at S-91.

According to Kalden, as the knowledge in the art increases due to recent develops in the fields of clinical immunology and molecular biology, "novel avenues for treatment of this disease entity have been explored and developed." *Id*. For example, Kalden refers to a study combining methotrexate and the repeated administration of anti-TNF-α MAb cA2 as demonstrating that "combination therapy might be an important therapeutic approach for RA patients whose disease is not completely controlled by [methotrexate] alone." *Id*. at S-96. The article concludes that "biological agents such as anti-CD4 monoclonals or other anti-inflammatories might be of special value in combination with drugs such as [methotrexate] and other immunosuppressive compounds." *Id*.

4. Analysis

Independent claims 1, 5, and 9, each requires treating RA in a human comprising administering more than one intravenous dose of a therapeutically effective amount of rituximab, and methotrexate.

At the outset, we note that Petitioner does not assert that either Edwards, O'Dell or Kalden teaches or suggests administering "more than one intravenous dose of a therapeutically effective amount of rituximab," as required by the challenged claims. Nor does Petitioner assert, with respect to the grounds limited to these references, that doing so would have been known in the art. For at least these reasons, Petitioner has not shown sufficiently a reasonable likelihood of prevailing in showing that claims 1, 2, 5, 6, 9, and 10 would have been obvious over Edwards in view of O'Dell or Kalden.

D. Obviousness Over Edwards (Ex. 1025) in view of O'Dell (Ex. 1004), or Kalden (Ex. 1020), and the Rituxan® Product Label (Ex. 1006) or Maloney (Ex. 1023)

Petitioner asserts that claims 1, 2, 5, 6, 9, and 10 would have been obvious over Edwards in view of O'Dell or Kalden, and in further view of the Rituxan® Product Label or Maloney. Pet. 42. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 26–44.

1. Rituxan® Product Label

The Rituxan® Product Label describes Rituxan® (rituximab) as a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Ex. 1006, 1. The product is formulated for intravenous administration and is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma. *Id*. The recommended dosage of Rituxan® is 375 mg/m^2 given as an IV infusion once weekly for four doses. *Id*. at 2. Infusion rates for first and subsequent infusions are described. *Id*.

2. Maloney

Maloney is a journal article discussing a Phase I clinical trial using single-dose (ranging from 10 to 500 mg/m^2) infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. Ex. 1023, 2457.

3. Analysis

Petitioner asserts that a person of ordinary skill in the art would have been motivated with a reasonable expectation of successfully treating RA by administering a combination of methotrexate and rituximab based on the teachings of Edwards in view of either O'Dell or Kalden. Pet. 36, 43.

Specifically, Petitioner asserts that Edwards suggested treating RA "by depleting B-cells with anti-B-cell (CD20) antibodies and specifically rituximab (a/k/a IDEC-C2B8)." Pet. 31. Additionally, Petitioner asserts that a person of ordinary skill in the art would have understood from O'Dell or Kalden that combination therapies including methotrexate were gaining recognition as an important approach for treating RA. *Id*. at 34–35, 44, 46–47. In particular, with respect to biologic agents, Petitioner asserts that O'Dell concludes that continued research on combinations including biologic agents and methotrexate is necessary, *id*. at 25, and that Kalden concludes that biological agents might be of "special value" in combinations with methotrexate, *id*. at 29. According to Petitioner, these prior art teachings would have suggested to a person of ordinary skill in the art to treat RA by administering to a patient a combination of methotrexate and a biologic agent, such as rituximab, to improve previously unsatisfactory treatment outcomes. *Id*. at 36, 43.

Petitioner further relies on the Declaration of Dr. Joachim Kalden (Ex. 1002) as providing evidence that a person of ordinary skill in the art "would have been aware, at minimum, of a synergistic therapeutic result from combining an antibody like rituximab with methotrexate to treat RA." Pet. 36–37 (citing Ex. 1002, ¶¶ 67, 82–83). Dr. Kalden explains that when foreign antibodies like rituximab are administered to humans, e.g., to treat RA, the immune system "produces antibodies to fight the therapeutic antibodies," potentially reducing the effectiveness of the therapeutic antibody. Ex. 1002, ¶ 83. According to Dr. Kalden, because methotrexate was known to have immunosuppressive properties, a person of skill in the art would have expected that in combination therapies, the methotrexate

would suppress the immune response against the biologic, and thus improve the ability of the biologic to treat RA. *Id*.

To address the administration and dosage regimen recited in the claims, Petitioner relies on the teachings of either the Rituxan® Product Label or Maloney. Pet. 22. Petitioner asserts that the logical starting point for using rituximab to treat RA would have been the dosing regimen described in the Rituxan® Product Label, i.e., 375 mg/m^2 given as an IV infusion once weekly for four doses, which Petitioner asserts falls within the therapeutically effective amount recited in dependent claims 2, 6, and 10. Pet. 39 (citing Ex. 1002, ¶¶ 39, 73, 86). Petitioner asserts also that in Maloney's study, rituximab was administered in amounts falling within the range recited by those dependent claims. *Id*. Further, according to Petitioner, it would have obvious to a person of ordinary skill in the art at the time of the invention to have tried to optimize the dose of rituximab for treating RA patients through routine experimentation. *Id*. (citing Ex. 1002, ¶ 87).

Patent Owner asserts that a person of ordinary skill in the art would not have accepted Edwards' suggestion to treat RA with rituximab because each underlying premise of Edwards' hypothesis was inconsistent with scientific literature at the time of the invention. PO Resp. 28. Specifically, Patent Owner asserts that the first premise of Edwards' hypothesis is that RA is mediated by autoantibodies, i.e., rheumatoid factors ("RFs"), which bind to immunoglobulin G ("IgG") antibodies. *Id*. at 26. According to Patent Owner, the theory that rheumatoid factor ("RF") plays a central role in mediating RA was "inconsistent" with knowledge in the art that "some patients with RA do not exhibit RFs, while on the other hand, RFs are found

in many people who do not have RA." *Id*. at 29 (citing Ex. 1014, Declaration of Dr. Ronald F. van Vollenhoven,[2] ¶ 21). Further, Patent Owner asserts that a leading textbook at the time explained that "although elevated levels of RF may be found in RA patients, 'its absence in patients with seronegative rheumatoid arthritis argues against it being a causative factor in joint disease.'" *Id*. (citing Ex. 2005,[3] 243). Additionally, Patent Owner asserts that it was known that removing RFs from the blood of chronic RA patients did not provide a clinical benefit. *Id*. (citing Ex. 2010,[4] Abstract). Further, Patent Owner relies on a study, Ex. 2011,[5] that Patent Owner describes as being "of dubious ethical status," and that Dr. van Vollenhoven characterized as "a rather dubious experiment," which concluded that injecting RFs into healthy patients did not cause them to develop RA. Pet. 29; Ex. 1014, ¶ 21.

Based on the record before us, we are not persuaded that a person of ordinary skill would have rejected Edwards' suggestion to treat rheumatoid arthritis based on knowledge in the art that Patent Owner alleges to be inconsistent with Edwards' hypothesis. To begin, although Dr. van Vollenhoven stated that "some patients with RA do not exhibit RFs, while on the other hand, RFs are found in many people who do not have RA," he

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[2] The declaration of Dr. Vollenhoven was submitted during the prosecution of US Application No. 09/564,288 that eventually issued as the '161 patent. (Ex. 1014).
[3] Tighe and Carson, *Rheumatoid Factors*, TEXTBOOK OF RHEUMATOLOGY, 5th ed. 241–249 (1997) ("Tighe").
[4] Dwosh et al., *Plasmapheresis Therapy in Rheumatoid Arthritis*, NEJM 1124–1129 (1983) ("Dwosh").
[5] Harris and Vaughan, *Transfusion Studies in Rheumatoid Arthritis*, ARTHRITIS AND RHEUMATISM, 47–55 (1961)("Harris").

also acknowledged that, in the art, "RF had long been known to have an association with RA," but that is was not a "one-to-one association." Ex. 1014, ¶ 21. Additionally, although Tighe notes an argument against considering RF as a causative factor in joint disease, i.e., the absence of RF in patients with seronegative RA, Tighe affirmatively states that analysis of seronegative RA patients "indicates a contributory role for rheumatoid factor in disease, since these patients generally display milder synovitis than the seropositive patients and seldom develop extra-articular rheumatoid disease." Ex. 2005, 243. Further, although Dwosh observed that removing RFs from the blood of chronic RA patients did not provide a clinical benefit, the article acknowledges that "[a]lternative explanations for the results observed are possible," including that the disposable plastic ware used may have absorbed low-molecular-weight inflammatory mediators during both cycles of plasmapheresis therapy. Ex. 2010, 1128. Similarly, in Harris, the ethically "dubious experiment" relied upon by Patent Owner, the authors explain that the failure to produce disease in patients subjected to the administration of RF factor "does not, however, necessarily preclude the possibility that the rheumatoid factor is an antibody." Ex. 2011, 52. More specifically, Harris explains that its study faced "quantitative and qualitative limitations," namely that there was "no good evidence … to indicate how many cells would be required for transferring rheumatoid factor production." *Id*.

Patent Owner asserts that the second premise of Edwards' hypothesis is that B cells that generate IgG RF and corresponding daughter plasma cells develop by chance mutations. PO Resp. 27. According to Patent Owner, by April 1999, scientific literature had refuted this theory because, for example,

one study showed that genes encoding RFs are present in the germ line of most people. *Id*. at 30 (citing Ex. 2012,[6] 5). Further, Patent Owner asserts that data existed suggesting that an exogenous stimulus. *Id*. (citing Ex. 1014, ¶ 23). For example, Patent Owner refers to a study "associating RA in certain people with exposure to cats and the microbes they harbor." *Id*. (citing Ex. 2013,[7] 734).

Based on the record before us, we remain unpersuaded that a person of ordinary skill would have rejected Edwards' suggestion to treat rheumatoid arthritis based on the studies Patent Owner alleges to be inconsistent with Edwards' second hypothesis. The studies, Exhibits 2012 and 2013, referred to by the Patent Owner are abstracts only, and do not describe the study parameters or potential limitations of the study. Moreover, these abstracts do not discuss the potential role of chance mutations in the generation of IgG RF. Further, the portion of Dr. van Vollenhoven's declaration relied upon by Patent Owner does not refer specifically to any study and concludes only that "no evidence that RF in patients with RA was uniquely the result of a chance somatic mutation." Ex. 1014, ¶ 23.

Patent Owner asserts that the third premise of Edwards' hypothesis is that killing all B cells of pathogenic RF specificity could cure RA because the chance of such cells re-emerging after destruction would be low. PO

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[6] Carson, *Role of Rheumatoid Factor B Cells in Normal and Pathologic Antigen Presentation*, Abstract, 1 ARTHRITIS RESEARCH Supp. 1, 5 (1999).
[7] PS Penglis et al., HLA DR4; A Link Between Rheumatoid Arthritis and Cat Exposure, Abstracts presented at the Annual Scientific Meeting of the Australian Rheumatology Association, 734 (1998).

Resp. 27. According to Patent Owner, this theory is based upon an erroneous assumption that plasma cells are short-lived and dissipate rapidly, as Patent Owner asserts that Edwards later acknowledged. *Id*. at 30 (citing Ex. 2014,[8] 825). Patent Owner asserts that an article published in March 1998, Ex. 2015,[9] also discusses the longevity of the plasma cells, describing the half-life extending for multiple years. *Id*. at 31.

Although the authors of Edwards later acknowledged that plasma cells are short-lived and dissipate rapidly, they also observed that previously held "unclear thinking may have been felicitous, and that at least some autoantibodies do disappear relatively rapidly after B-lymphocyte depletion, which perhaps reflects an origin from a sub-population of short-living plasma cells." Ex. 2014, 825. Further, the authors note that the assumptions regarding the longevity of plasma cells were held by "[m]any investigators." *Id*. In other words, at the time of the invention, even in view of Slifka, skilled artisans had different understandings regarding the longevity of plasma cells. Thus, based on the information presented at this stage of the proceeding, we are not persuaded by Patent Owner's assertion that skilled artisans would not have considered treating RA using rituximab based upon the express suggestion in Edwards to do so.

Next, Patent Owner asserts even if a skilled artisan would have accepted Edwards' hypothesis, Petitioner has not articulated any reason why

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[8] Edwards et al., *B-lymphocyte Depletion Therapy in Rheumatoid Arthritis and Other Autoimmune Disorders*, 30 BIOCHEMICAL SOCIETY TRANSACTIONS 824–828 (2002)(Edwards 1999).
[9] Slifka et al., *Humoral Immunity Due to Long-Lived Plasma Cells*, 8 IMMUNITY 363–372 (1998)("Slifka").

the skilled artisan would have combined Edwards' teaching with any reference in a manner that arrived at the claimed inventions, requiring administration of rituximab and methotrexate. PO Resp. 33, 36–38, 40–41. We disagree. As discussed previously, Petitioner has explained that a person of ordinary skill in the art at the time the invention would have understood from each of O'Dell and Kalden, that combination therapies including methotrexate were gaining recognition as an important approach to treating RA. Pet. 34–35, 44, 46–47. Petitioner explained that O'Dell and Kalden encouraged the development of combination therapy including a combination of methotrexate and a biologic agent. *Id*. at 25, 29. Further, Petitioner asserts that a skilled artisan would have been motivated by these teachings to treat rheumatoid arthritis using a combination including methotrexate, and would have had a reason to select rituximab as the biologic agent, based upon Edwards' teaching. *Id*. at 36, 43. Although O'Dell and Kalden do not discuss rituximab as an exemplary biologic agent, each reference specifically addresses monoclonal antibodies. Ex. 1003, 792; Ex. 1020, S-96. O'Dell and Kalden are not cited as anticipatory references. The suggestion to select rituximab as the biologic agent to treat RA is provided by Edwards.

According to Patent Owner, a person of ordinary skill in the art would not have combined rituximab with any other drug based on the Edwards' suggestion that it may cure RA. PO Resp. 33. Alternatively, Patent Owner asserts that if a skilled artisan did not believe that rituximab would kill all mature B cells, then the goal would have been to combine it with agents that also target and kill B cells like rituximab. *Id*. at 33–35. Further, Patent Owner relies on a 2004 internet article addressing a Phase 2 trial involving

the administration of rituximab with methotrexate to rheumatoid arthritis patients. Ex. 2001.[10] In the article, the author characterizes Dr. Edwards as being concerned that the results of the trial may suggest that rituximab should be used with methotrexate. *Id*. Although Dr. Edwards initiated the trial, he is quoted as saying, "To me, it's completely illogical, because the 2 treatments are unrelated, they're not doing the same thing." *Id*.

Based on the information presented at this stage of the proceeding, we are not persuaded by Patent Owner's assertions that a person of skill in the art at the time of the invention would not have treated RA by administering two medications having different mechanisms of action. Indeed, the artisan would have understood from at least Kalden that a combined treatment of methotrexate with monoclonal antibodies, TNF-α and anti-CD4, "successfully abolished the development of inflammatory joint disease in a synergetic manner." Ex. 1020, S-96. Moreover, we note that despite the apparent comments of Dr. Edwards relating to his Phase 2 Trial, relied upon by Patent Owner, the trial included administering a combination of methotrexate and rituximab, with effective results. Ex. 2001, 2. As suggested by each of O'Dell and Kalden, the state of the art at the time of the invention was to develop and provide methotrexate in combination with other DMARDS or biologic agents to better achieve the goal of remission in RA therapy. Ex. 1003, 790–92; Ex. 1020, S-96.

Patent Owner asserts that Petitioner fails to address or establish that skilled artisans would have had a reasonable expectation of success in

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[10] Chustecka, *Rituximab in RA: "we should aim for permanent remission,"* Medscape Medical News, http://www.medscape.com/viewarticle/537826.

combining Edwards with any other references and arriving at a method of treating RA. PO Resp. 35. According to Patent Owner, Edwards "would have failed to inspire a reasonable expectation of success because it concedes that the prospect of successfully eliminating RF-producing B cells to cure RA is 'uncertain.'" *Id*. at 34–35 (citing Ex. 1025, 129).

Based on the information presented at this stage of the proceeding, we are not persuaded by Patent Owner's assertions. Petitioner explained that a person of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in treating RA by administering a combination of methotrexate and rituximab because (a) methotrexate was established already as a standard treatment for RA, as discussed in O'Dell and Kalden, (b) the prior art encouraged its use in combination therapy, including a biologic, and (c) Edwards suggested treating RA by administering rituximab, a biologic drug known to be safely administered. Pet. 42–44. The reasonable expectation of successfully treating RA using a combination of methotrexate and rituximab provided by these this knowledge in the art is not rendered unreasonable by Edwards' acknowledgement that "[t]he chance that RF B-cell clones can be abrogated permanently is uncertain." Ex. 1025, 129. *See In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988) ("The reasonable expectation of success requirement for obviousness does not necessitate an *absolute certainty* for success.") (emphasis added). Indeed, despite this uncertainty, Edwards emphasized that "perhaps for the first time there is a strategy that would logically lead to disease cure. We propose that it is worth trying." *Id*.

Regarding the Rituxan® Label and Maloney, Patent Owner asserts that neither of these references cures the alleged deficiencies asserted

regarding the combination of Edwards and O'Dell or Kalden. PO Resp. 41–42. As previously discussed, at this stage in the proceeding, Patent Owner has not established that a deficiency exists regarding a reason to combine Edwards and either O'Dell or Kalden with a reasonable expectation of success. The Rituxan® Label is included in the combination because it provides administration and dosing instructions for rituximab. Pet. 32, 39. The Rituxan® Label describes a recommended dosage of 375 mg/m^2, given as an IV infusion once weekly for four doses. Ex. 1006, 2.

Patent Owner asserts that the dosing schedule disclosed by the Rituxan® Label is to treat non-Hodgkin's lymphoma, and Petitioner has not articulated a reason why skilled artisans would have applied that dosing to treat RA. PO Resp. 44. We disagree. Relying on the declaration of Dr. Kalden, Petitioner asserts that, to a person of ordinary skill in the art, the logical starting point for using rituximab to treat RA would have been the dosing regimen described in the Rituxan® Product Label. Pet. 32, 39 (citing Ex. 1002, ¶¶ 39, 73, 86). Referring to the dosage disclosed in the Rituxan® Product Label, Dr. Kalden states, "this FDA-endorsed dosing regimen was a natural starting point for doctors who wanted to use rituximab to treat other disorders." Ex. 1002, ¶ 39. Moreover, although Edwards suggests using rituximab for such an "off label" use, doing so was based upon the same mechanism of action described by the Rituxan® Label, i.e., to kill B cells. Ex. 1025, 129. The Rituxan® Label explains that administering the recommended dosage "resulted in a rapid and sustained depletion of circulating and tissue-based B cells." Ex. 1006, 1.

Thus, based on the information presented at this stage of the proceeding, Petitioner has shown sufficiently that there is a reasonable

likelihood that Petitioner would prevail in showing that claims 1, 2, 5, 6, 9, and 10 would have been obvious over Edwards in view of O'Dell or Kalden, and in further view of the Rituxan® Product Label.

Patent Owner challenges Petitioner's reliance on Maloney, asserting that the reference teaches administering only *single* doses of rituximab to treat non-Hodgkin's lymphomas. PO Resp. 44. We agree with Patent Owner that Maloney does not teach or suggest administering "more than one dose" of rituximab as required by the claims.

Thus, based on the information presented at this stage of the proceeding, Petitioner has not shown sufficiently that there is a reasonable likelihood that Petitioner would prevail in showing that claims 1, 2, 5, 6, 9, and 10 would have been obvious over Edwards in view of O'Dell or Kalden, and in further view of Maloney.

E. Obviousness Over Edwards (Ex. 1025) and either Verhoeven (Ex. 1016), Kavanaugh (Ex. 1019), or Boers (Ex. 1022)

Petitioner asserts that dependent claims 3, 7, and 11 would have been obvious over Edwards in view of either Verhoeven, Kavanaugh, or Boers. Pet. 43. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 44–52.

1. Verhoeven

Verhoeven is a journal article reviewing combination therapy in rheumatoid arthritis. Ex. 1016, 612. In particular, Verhoeven explains that "[i]n early RA patients, step-down bridge therapy that includes corticosteroids leads to much enhanced efficacy at acceptable or low toxicity." *Id*.

2. Kavanaugh

Kavanaugh is a journal article discussing a study involving

administering chimeric α-TNF monoclonal antibody (ca2) in RA patients with active disease after receiving three months of therapy with methotrexate. Ex. 1019, A575. Patients continued treatment with methotrexate and were allowed doses of non-steroidal anti-inflammatory drugs and prednisone. *Id*. Treatment in all groups was generally well-tolerated, and the authors concluded that adjunctive therapy with an anti-TNF-α monoclonal antibody may be an important therapeutic approach for RA patients with disease incompletely controlled by methotrexate. *Id*.

3. Boers

Boers is a journal article discussing the effectiveness of a combined RA therapy including combined step-down prednisolone, methotrexate, and sulphasalazine. Ex. 1022, 1.

4. Analysis

Claim 3 depends from independent claim 1, claim 7 depends from independent claim 5, and claim 11 depends from independent claim 9. Thus, the methods of claims 3, 7, and 11 require treating RA comprising administering more than one intravenous dose of a therapeutically effective amount of rituximab, and administering methotrexate.

Patent Owner asserts that Petitioner combines Edwards with Verhoeven, Kavanaugh, or Boers without setting forth how any of the combined references renders obvious the independent claims. PO Resp. 44. We agree with Patent Owner. A petition for *inter partes* review "must specify where each element of the claim is found in the prior art patents or printed publications relied upon." 37 C.F.R. § 42.104(b)(4). Petitioner has not explained with adequate specificity how the combination of Edwards and Verhoeven, Kavanaugh, or Boers renders obvious the inventions of

dependent claims 3, 7, or 11. Rather, with respect to these claims, Petitioner's discussion is limited to how each of Verhoeven, Kavanaugh and Boers suggest combining a glucocorticosteroid with methotrexate. Pet. 40–41, 48–49. In particular, each of these combinations lacks a teaching or suggestion to administer more than one intravenous dose of a therapeutically effective amount of rituximab in combination with the corticosteroid-methotrexate combination. *See id*.

Accordingly, based on the information presented at this stage of the proceeding, Petitioner has not shown sufficiently that there is a reasonable likelihood that Petitioner would prevail in showing that claims 3, 7, and 11 are unpatentable over Edwards and either Verhoeven, Kavanaugh, or Boers.

F. Obviousness Over Edwards in view of the Rituxan® Product Label or Tobinai, and either O'Dell or Kalden

Petitioner asserts that claims 4, 8, and 12 would have been obvious over Edwards in view of the Rituxan® Product Label or Tobinai, and either O'Dell or Kalden. Pet. 43. Patent Owner opposes Petitioner's assertion. Prelim. Resp. 52–54.

1. Tobinai

Tobinai is a journal article discussing a clinical trial of rituximab for treatment of patients with relapsed B-cell lymphoma. Ex. 1013, 527. The study design involved a dose-escalation in two steps. *Id*. at 528. A starting dosage of 250 mg/m^2/infusion was administered to six initial patients. *Id*. Then, if an acceptable number of initial patients avoided developing critical toxicities, an escalated dose of 375 mg/m^2/infusion was administered to a different set of patients. *Id*. The article states, "No intrapatient dose escalation was allowed." *Id*.

2. Analysis

Based on the information presented at this stage of the proceeding, Petitioner has not shown sufficiently that there is a reasonable likelihood of prevailing in showing that claims 4, 8, and 12 are unpatentable over Edwards in view of the Rituxan® Product Label or Tobinai, and either O'Dell or Kalden. In particular, Petitioner has not shown sufficiently that either the Rituxan® Product Label or Tobinai teaches or suggests "administering an initial dose of the rituximab followed by a subsequent dose, where the mg/m^2 dose of the rituximab in the subsequent dose exceeds the mg/m^2 dose of the rituximab in the initial dose," as required by claims 4, 8, and 12.

According to Petitioner, the Rituxan® Product Label teaches this limitation by describing a "first infusion" of 50 mg/hr. and a "subsequent infusion" that is 100 mg/hr. Pet. 41. However, this disclosure relates to infusion rates and not dosage amounts. Ex. 1006, 2. The Rituxan® Product Label provides only one dosage amount for such infusions, i.e., 375 mg/m^2. *Id*.

Petitioner asserts also that Tobinai teaches the dose-escalation required by claims 4, 8, and 12. Pet. 41. However, the dose-escalation described by Tobinai involves administering an initial dose to a first set of patients and administering an escalated dose in a second set of patients. Ex. 1013, 528. Indeed, Tobinai teaches away from the dose-escalation required by the claims by stating that "[n]o intrapatient dose escalation was allowed." *Id*.

G. Secondary Considerations of Nonobviousness

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17 (1966). Notwithstanding what the teachings of the prior art would have suggested to one with ordinary skill in the art at the time of the invention, the totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the claimed invention would not have been obvious to one with ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984).

Such a conclusion, however, requires the finding of a nexus to establish that the evidence relied upon traces its basis to a novel element in the claim and not to something in the prior art. *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). All types of objective evidence of nonobviousness must be shown to have nexus. *In re GPAC Inc*., 57 F.3d 1573, 1580 (Fed. Cir. 1995) (nexus generally); *Rambus Inc. v. Rea*, 731 F.3d 1248, 1256 (Fed. Cir. 2013) (long-felt need); *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996) (commercial success); *In re Kao*, 639 F.3d at 1069 (unexpected results). Regarding claims 1, 2, 5, 6, 9, and 10, we have considered Patent Owner's asserted evidence of secondary considerations.

1. Long-Felt Need

Patent Owner asserts that the claimed methods address a long-felt need for a new way to treat RA. PO Resp. 55. In support of this assertion, Patent Owner refers only to statements made by the inventors of the '161 patent, Ex. 1032, 27, and to a statement by Dr. van Vollenhoven, Ex. 1015, ¶

5. *Id*. Dr. van Vollenhoven's statement, however, indicates only that the claimed treatment method represents an "important advance for the treatment of patients suffering from … rheumatoid arthritis," without characterizing the advance as addressing a long-felt need. Ex. 1015, ¶ 5. Based on the information presented at this stage of the proceeding, we are not persuaded that Patent Owner has shown sufficiently that the claimed combination therapy for RA satisfied a long-felt need.

2. Commercial Success

Additionally, Patent Owner asserts that the claimed methods have led to significant commercial success, based on worldwide sales of rituximab. PO Resp. 35 (citing, e.g., Ex. 2023,[11] 47). However, the overall sales are described as being attributable to the use of rituximab in oncology, e.g., to treat non-Hodgkin's lymphoma, as well as to its use in immunology. *See, e.g.*, Ex. 2023, 47 ("[I]t remains difficult to precisely determine the sales split between Rituxan use in oncology and immunology settings."). Based on the information presented at this stage of the proceeding, we are not persuaded that Patent Owner has shown sufficiently the commercial success of the claimed methods.

3. Unexpected Results

Patent Owner also asserts that the claimed treatment methods produce unexpected results. PO Resp. 56. In support of this assertion, Patent Owner refers to the Edwards 2004 study demonstrating that "the claimed combination of rituximab with methotrexate provided greater therapeutic effects than rituximab alone in patients who 'had active rheumatoid arthritis

[11] US Securities and Exchange Commission Form 10-K (2008).

despite [prior] treatment with methotrexate." *Id*. (citing Ex. 1033,[12] Abstract, Fig. 2; Ex. 1014, ¶¶ 28–31). The conclusions of the study, however, were that significant improvement in disease symptoms were observed in patients administered rituximab "alone or in combination with either cyclophosphamide or continued methotrexate." Ex. 1033, Abstract. In other words, in all groups treated with rituximab, alone or in combination, significant improvement in disease symptoms occurred. Patent Owner has not explained sufficiently how these results establish that the results of the claimed method were unexpected compared with the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."); *see also In re Geisler*, 116 F.3d 1465, 1469-70 (Fed. Cir. 1997) (existence of unexpected results is a question of fact and the party asserting such existence has the burden of proving the results are, in fact, unexpected); *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (a showing of unexpected results must be commensurate in scope with the breadth of the claims). Based on the information presented at this stage of the proceeding, we are not persuaded that Patent Owner has shown sufficiently the asserted results of the claimed methods of treating RA would have been unexpected.

Thus, based on the information presented at this stage of the proceeding, we are not persuaded that Patent Owner has shown sufficiently the existence of secondary considerations.

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[12] Edwards et al., *Efficacy of B-Cell-Targeted Therapy with Rituximab in Patients with Rheumatoid Arthritis*, NEJM 2582–2581 (2004).

H. Remaining Grounds

The remaining grounds including Pincus challenge the same claims in the same manner as those previously discussed. Accordingly, we exercise our discretion by declining to proceed on the remaining obviousness grounds of unpatentability. *See* 37 C.F.R. § 42.108(a).

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that Petitioner would prevail in showing that claims 1, 2, 5, 6, 9, and 10 of the '161 patent are unpatentable.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim.

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that pursuant to 35 U.S.C. §314 (a), an *inter partes* review is instituted as to claims 1, 2, 5, 6, 9, and 10 of the '161 patent on the following grounds of unpatentability:

A. Claims 1, 2, 5, 6, 9, and 10 under 35 U.S.C. § 103(a) as unpatentable over Edwards, the Rituxan® Product Label, and O'Dell; and

B. Claims 1, 2, 5, 6, 9, and 10 under 35 U.S.C. § 103(a) as unpatentable over Edwards, the Rituxan® Product Label, and Kalden;

FURTHER ORDERED that no other proposed grounds of unpatentability are authorized.

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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