Trials@uspto.gov
571-272-7822

Paper No. 11
Entered: May 31, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN, INC., and GENENTECH, INC.,
Patent Owners.

Case IPR2018-00086
Patent 8,545,843 B2

Before ERICA A. FRANKLIN, SHERIDAN K. SNEDDEN, and JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

DECISION
Denying Institution of *Inter Partes* Review
35 U.S.C. § 314(a) and 37 C.F.R. § 42.108(c)

I. INTRODUCTION

Pfizer, Inc. ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–12 of U.S. Patent No. 8,545,843 B2 (Ex. 1001, "the '843 patent"). Paper 1 ("Pet."). Biogen, Inc., and Genentech, Inc. (collectively, "Patent Owners") filed a Preliminary Response. Paper 10 ("Prelim. Resp."). We have authority to determine whether to institute an *inter partes* review under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." *See also* 37 C.F.R. § 42.4(a). For the reasons set forth below, we deny the Petition.

A. *Related Matters*

Petitioner indicates that the '843 patent is at issue in *Genentech, Inc. v. Celltrion, Inc.*, Case No. 1:18-cv-00574 (D.N.J.), and *Celltrion, Inc. v. Genentech, Inc.*, Case No. 3:18-cv-00276 (N.D. Cal.). Paper 8. Patent Owners state that the '843 patent is at issue in *Genentech, Inc., Biogen Inc., and City of Hope v. Sandoz, Inc. and Sandoz International GMBH*, Case No. 2:17-cv-13507 (D.N.J.). Paper 7.

B. *The '843 Patent*

The '843 patent is titled "Treatment of Vasculitis." Ex. 1001, [54]. The '843 patent discloses therapeutic regimens for the "treatment of autoimmune diseases with antagonists which bind to B cell surface markers, such as CD19 or CD20." *Id.* at 1:14–16. Vasculitis is among the autoimmune disorders identified in the '843 patent specification. *Id.* at 3:47–4:6 ("Examples of autoimmune diseases or disorders include . . . vasculitis."). RITUXAN® (rituximab) is exemplified as an antibody that bides to the CD20 antigen. *Id.* at 8:40–43.

C. *Illustrative Claims*

Independent claims 1 and 2, reproduced below, are illustrative of the challenged claims of the '843 patent.

> 1. A method of treating vasculitis in a human who does not have rheumatoid arthritis or cancer comprising administering to the human a therapeutically effective amount of rituximab, wherein the administration of the rituximab consists of intravenous administration.

Ex. 1001, 29:39–43.

> 2. A method of treating vasculitis in a human who does not have rheumatoid arthritis or cancer comprising:
>
> a) administering to the human more than one intravenous dose of a therapeutically effective amount of rituximab; and
>
> (b) administering to the human glucocorticosteroid.

Id. at 29:44–30:4.

D. *Evidence Relied Upon*

Petitioner relies upon the following prior art references (Pet. 8–9, 29–36):

Belmont, H.M., et al., *Pathology and Pathogenesis of Vascular Injury in Systemic Lupus Erythematosus*, 39(1) ARTHRITIS & RHEUMATISM 9–22 (1996) (Ex. 1004).

Chan, O. and Shlomchik, Mark J., *A New Role for B Cells in Systemic Autoimmunity: B Cells Promote Spontaneous T Cell Activation in MRL*-lpr/lpr *Mice*, 160 J. IMMUNOLOGY 51–59 (1998) (Ex. 1003).

Danning, C.L., et al., *Vasculitis Associated with Primary Rheumatologic Diseases*, 10(1) CURRENT OPINION IN RHEUMATOLOGY, 58–65 (1998) (Ex. 1005).

George, J., et al., *Infections and Wegener's Granulomatosis—A Cause and Effect Relationship?* 90 QUARTERLY J. MED. 367–373 (1997) (Ex. 1007).

IDEC Pharmaceuticals Corporation and Genentech, Inc., Product label for Rituxan® (1997) (Ex. 1006) ("FDA label").

Maloney, D.G., et al., *"IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma*, 90(6) BLOOD 2188–2195 (1997) (Ex. 1011) ("Maloney I").

Mathieson, P.W., et al., *T and B Cell Responses to Neutrophil Cytoplasmic Antigens in Systemic Vasculitis*, 63(2) CLINICAL IMMUNOLOGY & IMMUNOPATHOLOGY 135–141 (1992) (Ex. 1008).

Physicians' Desk Reference, Rituxan™ (Rituximab), (53rd ed. 1999) (Ex. 1035) ("PDR label").

Rasmussen, N. and Petersen, J., *Cellular Immune Responses and Pathogenesis in c-ANCA Positive Vasculitides*, 6(2) J. AUTOIMMUNITY 227–236 (1993) (Ex. 1009)

Rituxan™ Full Prescribing Information, Genentech Wayback Machine Website ("Website label") (Ex. 1012).

Textbook of Rheumatology, (5th Ed., Kelley et al., eds.) (1997) ("Kelley") (Ex. 1010).

Petitioner also relies upon the Declaration of Elena M. Massarotti, M.D. (Ex. 1002) to support its contentions.

E. *Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability (Pet. 8–9):

Claims	Basis	Reference(s)
1–12	§ 103(a)	Chan, Belmont, Danning, and Rituxan Label[1]
3, 5, 7, 9, 12	§ 103(a)	Chan, Belmont, Danning, Rituxan Label, and Kelley
1–12	§ 103(a)	Chan, Belmont, Danning, Maloney I, and Kelley
1–12	§ 103(a)	George, Mathieson, Rasmussen, and Rituxan Label
3, 5, 7, 9, 12	§ 103(a)	George, Mathieson, Rasmussen, Rituxan Label, and Kelley
1–12	§ 103(a)	George, Mathieson, Rasmussen, Maloney I, and Kelley

[1] Petitioner states that "[a]s of May 1999, the Rituxan™ label was printed and disseminated in at least three different forms as evidenced by exhibits 1006, 1012, and 1035. In the grounds below, Petitioner cites each of three of these exhibits in parallel and refers to them collectively as the "Rituxan™ label." Pet. 30. Petitioner further states that "should the Board determine that one of the forms of the Rituxan™ label is not a prior-art printed publication, either one of the remaining forms can serve as suitable replacement because all three exhibits contain the identical teachings relied upon in this petition." *Id.* at 30–31.

II. ANALYSIS

A. *Level of Ordinary Skill in the Art*

The level of skill in the art is a factual determination that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

According to Petitioner, a person of ordinary skill in the art at the time of the invention "would include a practicing physician with at least an M.D. degree and three years of experience of treating patients with any form of primary or secondary vasculitis and/or researching treatments for primary or secondary vasculitis and/or researching treatments for primary or secondary vasculitis." Pet. 9 (citing Ex. 1002 ¶ 15). Petitioner further states that "[s]aid physician can either be a rheumatologist, hematologist, nephrologist, neurologist, or pulmonologist." *Id.* (citing Ex. 1002 ¶ 15). Patent Owners do not address Petitioner's position on this matter and do not propose their own description for a person of ordinary skill in the art at the time of the invention.

At this stage in the proceeding, we determine that Petitioner's description of the level of ordinary skill in the art is supported by the current record. Moreover, we have reviewed the credentials of Dr. Massarotti (Ex. 1002, Attachment A) and, at this stage in the proceeding, we consider her to be qualified to opine on the level of skill and the knowledge of a person of ordinary skill in the art at the time of the invention. We also note

that the applied prior art reflects the appropriate level of skill at the time of the claimed invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

B. *Claim Construction*

In an *inter partes* review, the Board currently 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). 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 the context of the entire disclosure. *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). Furthermore, "we need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

Petitioner contends that the term "vasculitis" should be interpreted to encompass "any form of vasculitis known to a POSA as of May 1999 . . . excepting from the claim scope vasculitis in patients with RA or cancer." Pet. 25. Patent Owners respond that "[b]ecause no issue raised in the Petition turns on Petitioner's proposed construction of 'vasculitis,' Patent

Owner[s] do[] not contest this interpretation for purposes of this proceeding, and the Board need not construe the term." Prelim. Resp. 12–13. In view of our analysis, we determine that construction of the claim term "vasculitis" is not necessary for purpose of this Decision. *See Nidec*, 868 F.3d at 1017.

C. *References Relied Upon*

1. Chan

Chan describes a study of MRL-*lpr/lpr* mice, a known murine model for systemic lupus erythematosus ("SLE"), in which the mice have further been engineered to lack B cells, in order to assess the role of B cells in SLE. Ex. 1003, 2. Chan does not discuss vasculitis secondary to SLE.

Comparing the extent of disease in MRL-*lpr/lpr* mice with and without B cells, Chan finds that "B cells have a major role in the spontaneous activation of T cells in MRL-*lpr/lpr* mice; in the absence of B cells, the numbers of both activated and memory phenotype T cells were markedly reduced." *Id.* at 6. Based on those findings, Chan concludes that "[t]he work provides in vivo evidence for the hypothesis that B cells are critical for systemic autoimmune disregulation via a direct effect on T cells." *Id.* Chan, therefore, posits that B cells play two major roles in SLE: the production of autoantibody that mediates tissue damage, as described in prior studies, and the activation of T cells. *Id.*at 2, 8.

Chan goes on to surmise that "[r]egardless of the mechanism(s) by which B cells promote the spontaneous activation and expansion of T cells in systemic autoimmunity, an implication of this phenomenon is that B cells would be an ideal target for lupus therapy." Ex. 1003, 7. In particular, Chan

hypothesizes that the "[e]limination of previously activated B cells would have the dual effect of ameliorating autoantibodies and of eliminating the reservoir of potent APC for autoreactive T cells. This, in turn, is predicted to delay the progression of disease. It may further be necessary to eliminate activated T cells as well." *Id.* Chan, thus, concludes that the role of the B cell as a "therapeutic target in the treatment of systemic autoimmune diseases" is ripe for "reevaluation," and indicates that "current studies" raise a number of questions, including "the effectiveness of targeting B cells in halting the progress of systemic autoimmune disease." *Id.* at 8.

With regard to existing SLE treatments, Chan observes that preliminary results suggest that the combination of plasmapheresis and cyclophosphamide—a treatment approach that "target[s] autoantibodies and B cells (and probably T cells)"—is a "disease-modifying therapy" for SLE patients. Ex. 1003, 7.

2. Belmont

Belmont "reviews our understanding of the vascular injury characteristic of SLE." Ex. 1004, 10–11. Belmont identifies two types of vascular injury secondary to SLE: inflammatory and thrombotic. *Id.* at 1, 10. With regard to inflammatory vasculitis, Belmont discloses that such vasculitis "is most commonly due to the local deposition of immune complexes, particularly those containing antibodies to DNA, in blood vessel walls." Ex. 1004, 3. Concerning thrombotic vasculitis, Belmont teaches that "it appears to involve several different and complex mechanisms of interactions between the clotting system, antiphospholipid antibodies,

vascular endothelium, and antiendothelial cell antibodies (AECA)." Ex. 1004, 8.

Belmont reasons that information relating to the pathogenesis of the SLE-related vasculitis "should permit improved methods of identifying and evaluating novel forms of therapy for SLE, including the targeting of activated endothelium, based on our knowledge of the specific type of pathology and immunopathogenic mechanisms present." Ex. 1004, 11.

3. Danning

Danning is a review article that describes the clinical and pathogenetic features of vasculitis associated with SLE. Ex. 1005, 1. Danning discloses that "[v]asculitis is a rather infrequent complication of SLE" that may involve blood vessels of any size, but is most frequently diagnosed in "small arterioles and venules of the skin." *Id.*

Danning reiterates Belmont's teaching that "activation or injury of endothelial cells by autoantibodies" has been implicated in the "pathogenesis of lupus vasculitis." Ex. 1005, 2. Danning additionally discloses that "T-cell-mediated vascular injury may also play a role in some patients with vasculitis." *Id.*

4. George

George is a review article that analyzes the association between infections and the autoimmune disorder Wegener's granulomatosis ("WG"),

i.e., granulomatosis with polyangiitis ("GPA").[2] Ex. 1007, 1. Pertinent to the instant dispute, George observes that the "presence of autoantibodies to cells of the nonspecific immune system (i.e. anti-neutrophil cytoplasmic antibodies [("ANCA")]) may lend additional support for the hypothesis that infection may result in WG [i.e., GPA]." *Id.* at 2. George further explains that the "ANCA assay is of value in monitoring the activity of WG, since it correlates well with the disease activity, and intercurrent infections do not result in elevation of ANCA levels in WG. ANCA titres also increase prior to clinical relapses." *Id.* at 3 (internal citations omitted).

George posits that "[a]ctivation of the neutrophils by ANCA could thus be partly responsible for enhancement of the inflammatory processes observed in WG." *Id.* at 4. George acknowledges, however, that the "*in vivo* evidence implicating ANCA in the pathogenesis of WG is still scant and incomplete." *Id.* at 3. Notably, George does not suggest the possibility of treating GPA by reducing ANCA.

5. Mathieson

Mathieson describes a study of T-cell and B-cell responses to ANCA antigens. Ex. 1008, 1, 4. Mathieson reports that exposure of T-cells to ANCA antigen does not result in T-cell activation. *Id.* at 5. With regard to B-cells, Mathieson states that "circulating autoreactive B cells which

[2] The parties' note that GPA was previously known as "Wegener's granulomatosis," ("WG"), and is referred to as such in the asserted references. Pet. 2, n.1; Prelim. Resp. 8, n.1. Consistent with the nomenclature employed by the parties, we refer to the disease as "GPA."

produce ANCA" were observed *in vitro*, and remarks that the "B cell spot ELISA shows some promise in monitoring autoantibody production at the cellular level." *Id.* at 7.

Mathieson reasons that T-cells "may not be directly involved in the pathogenesis of SV [i.e., vasculitis]," and posits that the observed "lack of a proliferative T cell response may be because T cell involvement in SV is confined to the provision of B cell help." Ex. 1008 at 6. Mathieson notes, however, that the "role of ANCA in pathogenesis remains uncertain." *Id.* at 1.

6. Rasmussen

Rasmussen is a review article that describes the cellular immune response in classical ANCA ("c-ANCA") positive vasculitides. Ex. 1009, 1. Rasmussen discloses that "[i]mmunohistochemical examinations of nasal biopsies from untreated patients with active WG revealed the presence of substantial amounts of cells belonging to the immune system (CD3+, CD4+, CD8+, CD20+, CD38+, and CD68+)." *Id.* Rasmussen also teaches that nasal lesions having large amounts of CD20+ B lymphocytes and CD38+ plasma cells were found in 7 untreated GPA patients. *Id.* at 3. Rasmussen reasons that the "abundant" number of B lymphocytes and plasma cells present in the inflammatory lesions suggests that "c-ANCA was probably produced in the lesions." *Id.* at 7. Rasmussen additionally remarks that "[i]t is an intriguing consideration that the B lymphocytes in WG may have dual functions of being both antigen-presenting cells as well as giving rise to c-ANCA-producing plasma cells." *Id.* at 8.

Rasmussen observes, however, that "very little is known about the cellular immune response in c-ANCA positive vaculitides [sic]." Ex. 1009, 7. Rasmussen further cautions that "[w]ith the limited knowledge on the cellular immunological response in WG available today it is certainly appropriate to consider many more hypothetical mechanisms," and that "further investigations in WG are strongly warranted." *Id.* at 8.

7. Rituxan Label[3,4]

The Rituxan 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

[3] Consistent with Petitioner's assertion that the Rituxan Label existed in at least three different forms, i.e., Exhibits 1006, 1012, and 1035 by May 1999, and that "all three exhibits contain the identical teachings relied upon in this petition" (Pet. 30–31), our discussion of the Rituxan Label applies with equal force to each of Exhibits 1006, 1012, and 1035. For convenience, we provide citations to Exhibit 1006.

[4] Because we determine that Petitioner has not established a reasonable likelihood of prevailing on its assertion that an ordinarily skilled artisan would have had a reasonable expectation of success in combining the cited references to arrive at the claimed invention, we need not address whether Petitioner has sufficiently established that at least one of the Rituxan Label references (i.e., Ex. 1006, Ex. 1012, Ex. 1035) qualifies as a printed publication.

lymphoma ("NHL"). *Id.* The reference reports results from various clinical trials in which 375 mg/m^2 of Rituxan was administered intravenously weekly for four doses to patients having relapsed or refractory low-grade NHL ("LG-NHL"). *Id.* In particular, "[a]dministration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B-cells." *Id.* "B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by twelve months following completion of treatment." *Id.*

8. Maloney I

Maloney I describes a "phase II, multicenter study evaluating four weekly infusions of 375 mg/m^2 IDEC-C2B8 [("rituximab")] in patients with relapsed low-grade or follicular NHL." Ex. 1011, 1. In that study, 17 of the 37 patients enrolled exhibited clinical responses, i.e., partial or complete remission, to rituximab treatment. *Id.* at 5, Table 3. Maloney I further observes that "normal B cells were rapidly depleted from the peripheral blood of nearly all patients and remained depleted until nearly 6 months post treatment [sic], followed by a slow recovery." *Id.* at 6. Maloney I reports, however, that none of the patients with small lymphocytic lymphoma ("SLL"), another cancer implicating CD20 positive B cells, responded to rituximab treatment. *Id.* at 6; *see also id.* at 5. Maloney I reasons that the absence of response in SLL patients may result from the decreased expression of CD20 on the B-cells of SLL patients relative to the B-cells of LG-NHL patients. *Id.* at 6.

With regard to LG-NHL patients, Maloney I additionally observes that, "[d]espite this depletion of B cells, there was minimal change in the serum Ig levels and no increase in the frequency or severity of infectious complications." *Id.*

9. Kelley

Kelley discloses the use of combination therapy including "steroids plus cytotoxics," and more particularly, "glucocorticoid plus cyclophosphamide" to treat SLE. Ex. 1010, 51. Kelley specifically identifies methylprednisolone as a glucocorticoid appropriate for use in combination therapy with cyclophosphamide. *Id.*

Kelley additionally discloses the use of combination therapy including prednisone and cyclophosphamide to treat GPA. Ex. 1010, 83–84. Concerning the relationship between GPA and ANCA, Kelley notes that "c-ANCA, recognized as a sensitive and specific marker for Wegener's granulomatosis, is found in 90 percent of patients with classic Wegener's triad—upper airways involvement, respiratory involvement, and renal disease—although more localized, less classic forms of the disease have a lower rate of c-ANCA positivity." *Id.* at 82–83.

D. *Principles of Law*

"An obviousness determination requires finding both 'that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.'" *CRFD*

Research, Inc. v. Matal, 876 F.3d 1330, 1340 (Fed. Cir. 2017) (quoting *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–1368 (Fed. Cir. 2016)).

"In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). "Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998). An overly narrow "statement of the problem represents a form of prohibited reliance on hindsight," because "[o]ften the inventive contribution lies in defining the problem in a new revelatory way." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012).

"The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention." *Intelligent Bio-Sys., Inc.*, 821 F.3d at 1367. A reasonable expectation of success "does not require *certainty* of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

> However, to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Similarly, prior art fails to provide the requisite reasonable expectation of success where it teaches merely to pursue a general approach that seemed to be a promising field of

> experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id. (internal quotations omitted).

E. *The SLE Grounds*

Petitioner asserts three grounds of unpatentability based on Chan, Belmont, and Danning, in further combination with one or more of the Rituxan Label, Maloney I, and Kelley (collectively, "the SLE grounds"). Pet. 36–48, 55–56. Each of these three grounds of unpatentability relies on the same arguments concerning the rationale for, and reasonable expectation of success in, treating vasculitis in SLE with rituximab. *Id.* On the record before us, and for purposes of this decision, we agree with Patent Owners that Petitioner has not met its burden to establish a reasonable likelihood of success that it would prevail in showing that an ordinarily skilled artisan would have had reason for, or a reasonable expectation of success in using rituximab, in any dose, to treat vasculitis in SLE. Rather, as explained below, Petitioner's obviousness analysis, which frames the problem to be solved in terms of its solution, is tainted by hindsight. Furthermore, the cited combinations, at best, invite experimentation into the possibility of treating SLE vasculitis with rituximab, and are, therefore, inadequate to establish a reasonable expectation of success for purposes of this decision.

It is beyond dispute that SLE vasculitis, i.e., non-neoplastic blood vessel inflammation secondary to the autoimmune disorder lupus (Ex. 1002 ¶¶ 24–25, 27, 29, 31), and LG-NHL, a group of blood cancers, are markedly

different diseases. Indeed, each of the challenged claims is expressly limited to a method of treating vasculitis in a human who does not have cancer. Ex. 1001, 29:39–30:43. Nevertheless, Petitioner contends that an ordinarily skilled artisan would have had reason to, and a reasonable expectation of success in, administering rituximab, a known LG-NHL therapy, to treat SLE vasculitis, because both diseases implicate B-cells, and because rituximab was the only available therapy for safely depleting CD20+ B-cells at the time of invention of the '843 patent. Pet. 36–37, 40–42.

In particular, Petitioner contends that an ordinarily skilled artisan would have sought to combine the cited references in order to arrive at the claimed treatment for vasculitis because:

> (1) B-cells are responsible for the production of antibodies and the activation of T-cells (Belmont and Danning); (2) B-cell depletion would be expected to be effective to inhibit these two sources of vasculitis in SLE (Chan); (3) multiple intravenous doses of rituximab safely and effectively deplete B-cells (Rituxan™ label);[5] and (4) none of the references relies on studies of patients with RA or cancer.

Pet. 40 (citing Ex. 1002 ¶ 107).

Petitioner additionally asserts that an ordinarily skilled artisan "would have reasonably expected rituximab to be an effective treatment for vasculitis in SLE patients because rituximab B-cell depletion therapy would

---

[5] Petitioner contends that "Maloney I provided the same disclosures as the Rituxan™ label," and, thus, asserts that "[f]or the same reasons discussed in parts IX.A–B and IX.C–D, claims 1–12 of the '843 patent would have been obvious over the same combinations of references using Maloney I instead of the Rituxan™ label (EX1006 or EX1012 or EX1035)." Pet. 55.

eliminate or reduce the two primary sources of the immune response causing vasculitis in SLE." *Id.* at 40–41 (citing Ex. 1002 ¶ 107). Specifically, Petitioner contends that an ordinarily skilled artisan "would have reasonably expected that the effectiveness of rituximab in depleting B-cells described by the [Rituxan] label for NHL would carry over to patients with SLE" because "rituximab targets both healthy and malignant cells." *Id.* at 41 (citing Ex. 1002 ¶ 108). Petitioner further argues that the reduction in SLE disease activity observed in B-cell deficient mice as compared to controls would have caused an ordinarily skilled artisan to expect "B-cell depletion resulting from rituximab to provide a therapeutic benefit in a human patient with manifestations of vasculitis in SLE." *Id.* at 42 (citing Ex. 1002 ¶ 109).

We do not find Petitioner's arguments persuasive. As an initial matter, contrary to Petitioner's implication (Pet. 40), the only cited references that disclose the use of rituximab in disease treatment, the Rituxan Label and Maloney I, describe the use of rituximab to treat LG-NHL patients by depleting CD20+ malignant B-cells. *See*, *e.g.*, Ex. 1006, 1; Ex. 1011, 1. Thus, to the extent those references disclose the depletion of CD20+ normal B-cells, it is in the context of treating a neoplastic disorder characterized by malignant B-cells. *See*, *e.g.*, Ex. 1006, 1; Ex. 1011, 2. The references do not suggest, and Petitioner does not sufficiently explain why an ordinarily skilled artisan would expect that the ancillary depletion of non-malignant CD20+ B-cells seen in LG-NHL patients would "carry over" to, and provide treatment for, SLE vasculitis patients (Pet. 41).

None of the references on which Petitioner relies describes any study of, or treatment parameters for, the use of rituximab to treat SLE or SLE vasculitis. Nor do those references address the characteristics of SLE B-cells as compared to LG-NHL B-cells that an ordinarily skilled artisan would have considered in evaluating the potential for using rituximab to treat SLE vasculitis. For example, even though the prior art suggests that the efficacy of rituximab treatment varies depending on the number of B-cells present, as well as the extent of CD20 expression on those cells (Maloney I, 6), none of the cited references addresses the number of B-cells observed in SLE or SLE vasculitis versus LG-NHL patients, or the relative prevalence of CD20 expression on the B-cells found in these distinct patient populations.

Neither does Petitioner identify any disclosure to suggest that rituximab would target the previously activated B-cells associated with SLE (*see* Ex. 1003, 7), or decrease the presence of the antibodies or activated T-cells that Petitioner identifies as the triggers for SLE vasculitis (Pet. 38–39). To the contrary, Maloney I reports that "minimal change in the serum Ig levels" was observed with rituximab treatment (Ex. 1011, 6), suggesting that rituximab was not known to decrease antibodies. *See also* Ex. 1006, 1 ("only 14% of patients had reductions in IgG and/or IgM serum levels, resulting in values below the normal range.").

Moreover, Petitioner's contention that "rituximab reasonably would have been expected to be effective to treat vasculitis in patients with SLE as well as NHL because over 90 percent of the human's B-cells express the target antigen of rituximab" (Pet. 41) misstates the cited evidence. Each of

the exhibits Petitioner identifies as supporting that assertion discloses that the rituximab antigen is "expressed on *>90% of B-cell non-Hodgkin's lymphomas (NHL)* but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues." Ex. 1006, 1; Ex. 1012, 1; Ex. 1035, 7 (emphasis added; internal citations omitted).[6] Indeed, Petitioner does not identify any evidence of record to confirm that the rituximab antigen is expressed on B-cells implicated in SLE vasculitis. *Compare* Pet. 36 (stating, without citation, that Chan discloses that CD20 B-cells are the key agents in the immune response that trigger vasculitis in SLE) *with* Ex. 1003 (lacking discussion of CD20+ expression on B-cells implicated in SLE vasculitis).

Chan's experiments in MRL-*lpr/lpr* mice generated without B cells do little to bridge the gaps in Petitioner's obviousness analysis. The reduction in SLE disease activity observed in mice that never had B-cells in the first place (Ex. 1003, 2), and thus, by Petitioner's reasoning, would not be expected to exhibit SLE disease activity (Pet. 36–37), fails to inform the essential inquiry—namely, whether B-cell depletion alleviates existing SLE vasculitis. The fact that mice born without B-cells exhibit less SLE activity than those with B-cells invites further investigation of the role of B-cells in

[6] Petitioner does not cite to Dr. Massarotti's testimony that "over 90% of the human's B-cells express the target antigen of rituximab" (Ex. 1002 ¶ 108) to support this proposition. Nevertheless, for completeness, we note that Dr. Massarotti does not identify any support for that testimony, and we, therefore, give it little weight. 37 C.F.R. § 42.65(a).

that disease. Petitioner has not established persuasively that such speculative results would have motivated an ordinarily skilled artisan to reach for rituximab and reasonably expect that rituximab would treat SLE vasculitis.

Indeed, Chan and Belmont make plain that, at the time of invention of the '843 patent, B-cell depletion was, at most, a "promising field of experimentation" in the study of SLE vasculitis. *Medichem*, 437 F.3d at 1165. Chan explains that the role of the B cell as a "therapeutic target in the treatment of systemic autoimmune diseases" is ripe for "reevaluation," and indicates that "the effectiveness of targeting B cells in halting the progress of systemic autoimmune disease" remains an open question. Ex. 1003, 8. Belmont discloses that a more complete understanding of the disease pathogenesis in SLE vasculitis "should permit improved methods of identifying and evaluating novel forms of therapy for SLE," and emphasizes "the targeting of activated endothelium" as a prospective avenue for exploration. Ex. 1004, 11. Similarly, the suggestion by Maloney II[7] that the "possible treatment of patients with autoimmune diseases caused by autoreactive antibodies" is one "potential application[]" for rituximab (Ex. 1032, 11) underscores that, at the time of invention of the '843 patent, B-cell depletion was, at most, a "promising field of experimentation" in the study of SLE vasculitis. *Medichem*, 437 F.3d at 1165.

---

[7] Maloney et al., *IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin's Lymphoma*, 15(10) J. Clinical Oncology 3266–3274 (1997) ("Maloney II") (Ex. 1032).

Petitioner's contention that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, treating SLE vasculitis patients with rituximab dosing regimen identified on the Rituxan Label (and taught by Maloney I) (Pet. 43) fails for the same reasons set forth above. In view of the known differences between SLE vasculitis and LG-NHL, including the fact that LG-NHL is a neoplastic disease, and the absence of information concerning the characteristics of the SLE B-cells and LG-NHL B-cells, Petitioner's assertion that an ordinarily skilled artisan would have sought to treat SLE vasculitis patients with the same dosage regimen recommended for LG-NHL patients simply because rituximab depleted B-cells in LG-NHL patients—and expected that treatment to be successful—is inadequately supported. Indeed, Petitioner's hedge that an ordinarily skilled artisan "would have been motivated to follow (or at least start with) the treatment regimen of the Rituxan™ label" (Pet. 44), without further discussion of how proper dosing might be determined, seems to recognize that, to the extent an ordinarily skilled artisan would have sought to use rituximab as an SLE vasculitis treatment at all, the teachings of the cited combination amount, at most, to an invitation to experiment in order to arrive at an appropriate treatment schedule.

Moreover, contrary to Petitioner's implication (Pet. 43), effective SLE therapies were available at the time of invention of the '843 patent. For example, Chan discloses that the combination of plasmapheresis and cyclophosphamide is a "disease-modifying therapy" for SLE patients. Ex. 1003, 7. Kelley similarly teaches that the use of combination therapy

including "steroids plus cytotoxics," and more particularly, "glucocorticoid plus cyclophosphamide" is effective to treat SLE. Ex. 1010, 51. Indeed, the fact that Petitioner attempts to define the problem to be solved as excluding these known, efficacious therapies, in favor of searching for "new therapies . . . that could match or improve the effectiveness of existing treatments for SLE . . . without increasing toxicity" (Pet. 36) highlights the hindsight bias that runs throughout Petitioner's obviousness arguments. *See Monarch Knitting*, 139 F.3d at 881.

For the foregoing reasons, therefore, we determine that the information presented in the Petition fails to establish a reasonable likelihood that Petitioner would prevail in challenging: claims 1–12 as obvious under § 103(a) in view of Chan, Belmont, Danning, and the Rituxan Label; claims 3, 5, 7, 9, and 12 as obvious under § 103(a) in view of Chan, Belmont, Danning, the Rituxan Label, and Kelley; and claims 1–12 as obvious under § 103(a) in view of Chan, Belmont, Danning, Maloney I, and Kelley.

F. *The GPA Grounds*

Petitioner asserts three grounds of unpatentability based on George, Mathieson, and Rasmussen, in further combination with one or more of the Rituxan Label, Maloney I, and Kelley (collectively, "the GPA grounds"). Pet. 47–56. Each of these three grounds of unpatentability rely on the same arguments concerning the rationale for, and reasonable expectation of success in, treating GPA with rituximab. *Id.* On the record before us, and

for purposes of this decision, we agree with Patent Owners that Petitioner has not met its burden to establish a reasonable likelihood of success that it would prevail in showing that an ordinarily skilled artisan would have had either a rationale for making the proposed combinations, or a reasonable expectation of success in using rituximab, in any dose, to treat GPA. Rather, as with the SLE grounds, Petitioner's obviousness analysis is impermissibly based on hindsight, and the cited combinations provide, at most, an invitation for further experimentation, not the required reasonable expectation of success.

GPA, a primary vasculitis (Ex. 1002 ¶ 25), is a distinct disease from LG-NHL, and the treatment of LG-NHL patients is explicitly excluded from the scope of the challenged claims (Ex. 1001, 29:39–30:43). Nevertheless, akin to the arguments presented in the SLE grounds, Petitioner asserts that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, administering rituximab to treat GPA because both LG-NHL and GPA implicate B-cells, and because rituximab was the only therapy available for sale designed to safely deplete CD20+ B-cells at the time of invention of the '843 patent. Pet. 36–37, 50–52.

Specifically, Petitioner contends that an ordinarily skilled artisan would have sought to combine the cited references in order to arrive at the claimed treatment for vasculitis because:

> (1) ANCA is associated with GPA and ANCA levels correlate with disease activity (George); (2) B-cells are responsible for the direct and indirect production of ANCA (Mathieson and Rasmussen); (3) multiple intravenous doses of rituximab safely

> and effectively deplete B-cells (Rituxan™ label); and (4) none of the references relies on studies of patients with RA or cancer.

Pet. 51 (citing Ex. 1002 ¶ 139).

Petitioner acknowledges that the asserted references do not disclose the use of rituximab to treat GPA, but nevertheless asserts that an ordinarily skilled artisan "would have reasonably expected rituximab to work in treating vasculitis manifested by GPA in view of FDA's conclusion that rituximab effectively depleted B-cells to treat another disease associated with B-cells, non-Hodgkin's lymphoma." Pet. 51 (citing Ex. 1002 ¶ 140). Petitioner further argues that an ordinarily skilled artisan would have had a reasonable expectation of success in making the claimed combination because of the "known relationship between ANCA levels and disease activity." *Id.* at 52 (citing Ex. 1007, 3). In particular, Petitioner contends that "A POSA would have reasonably expected that when ANCA levels fall following B-cell depletion, GPA disease activity would also decrease. . . . Accordingly, a POSA would have reasonably expected B-cell depletion resulting from rituximab to provide a therapeutic benefit in a patient with GPA." *Id.* (citing Ex. 1007, 3; 1002 ¶ 141).

Petitioner's obviousness analysis hinges on the assertion that an ordinarily skilled artisan would reasonably have expected that reducing ANCA levels through B-cell depletion would treat GPA. Pet. 52. But Petitioner does not identify evidence of record sufficient to establish a reasonable likelihood of success that it would prevail in showing that an ordinarily skilled artisan would have understood that ANCA causes GPA, or that a reduction in ANCA levels would treat GPA. To the contrary, George,

the reference on which Petitioner relies for the proposition that reducing ANCA levels would treat GPA (Pet. 48–49, 52), discloses only that ANCA levels "correlate[] well" with GPA disease activity, and increase prior to clinical relapse (Ex. 1007, 3). Indeed, George cautions against making the leap from correlation to causation proposed by Petitioner, expressly recognizing that "[t]he *in vivo* evidence implicating ANCA in the pathogenesis of WG [i.e., GPA] is still scant and incomplete" (Ex. 1007, 3). George additionally explains that, although "[a]ctivation of the neutrophils by ANCA could thus be partly responsible for enhancement of the inflammatory processes observed in WG," it remains uncertain "how infections eventually lead to the *local* damage observed within the vessel walls and renal system." *Id.* at 4.

Mathieson and Rasmussen likewise highlight that the roles of ANCA and B-cells in GPA require further study. Ex. 1008, 1 ("The role of ANCA in pathogenesis remains uncertain."); Ex. 1009, 8 ("It is an intriguing consideration that the B lymphocytes in WG may have dual functions of being both antigen-presenting cells as well as giving rise to c-ANCA-producing plasma cells."). In addition, Kelley observes that the c-ANCA marker is not present in all GPA patients. Ex. 1010, 52–83 ("c-ANCA, recognized as a sensitive and specific marker for Wegener's granulomatosis, is found in 90 percent of patients with classic Wegener's triad—upper airways involvement, respiratory involvement, and renal disease—although more localized, less classic forms of the disease have a lower rate of c-ANCA positivity.").

Moreover, for the reasons previously set forth with regard to the SLE grounds, we determine that Petitioner has not demonstrated a reasonable likelihood of success that it would prevail in establishing that an ordinarily skilled artisan would have had reason for, or a reasonable expectation of success in, treating GPA with rituximab. As explained above concerning the SLE grounds, the only cited references that disclose the use of rituximab in disease treatment, the Rituxan Label and Maloney I, describe the use of rituximab to treat LG-NHL patients by depleting CD20+ malignant B-cells. *See, e.g.*, Ex. 1006, 1; Ex. 1011, 1. The references do not suggest, and Petitioner does not sufficiently explain why an ordinarily skilled artisan would expect, that the ancillary depletion of non-malignant CD20+ B-cells seen in LG-NHL patients (Ex. 1006, 1; Ex. 1011, 2) would treat GPA patients.

None of the references on which Petitioner relies describes any study of, or treatment parameters for, the use of rituximab to treat GPA. Nor do those references address the characteristics of GPA B-cells as compared to LG-NHL B-cells that an ordinarily skilled artisan would have considered in evaluating the potential for using rituximab to treat GPA, such as the relative number of B-cells observed in these distinct patient populations, the prevalence of expression of CD20 on the relevant B-cells, or the ability of rituximab to reduce ANCA levels or decrease the number of activated T-cells. In fact, to the extent the evidence of record suggests anything at all about rituximab and GPA, the teaching by Maloney I that "minimal change in the serum Ig levels" was observed with rituximab treatment (Ex. 1011, 6)

may suggest that rituximab would not have been expected to decrease ANCA levels, since ANCA is an antibody. *See also* Ex. 1006, 1 ("only 14% of patients had reductions in IgG and/or IgM serum levels, resulting in values below the normal range.").

Petitioner's assertion that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, treating GPA patients with rituximab dosing regimen identified on the Rituxan Label (and taught by Maloney I) (Pet. 50–51, 52–53) fails for the same reasons. In view of the known differences between GPA and LG-NHL, including the fact that LG-NHL is a neoplastic disease, Petitioner's contention that an ordinarily skilled artisan would have had reason for, and a reasonable expectation of success in, treating GPA patients with the same protocol used for LG-NHL patients simply because rituximab depleted B-cells in LG-NHL patients is unpersuasive.

Lastly, as addressed above with regard to SLE vasculitis, Petitioner's attempt to define the problem to be solved as excluding known, efficacious GPA therapies, such as the prednisone and cyclophosphamide combination therapy taught by Kelley (Ex. 1010, 83–84), in favor of searching for "new therapies . . . that could match or improve the effectiveness of existing treatments for . . . GPA without increasing toxicity" (Pet. 36) highlights the hindsight bias that runs throughout Petitioner's obviousness arguments. *See Monarch Knitting*, 139 F.3d at 881.

For the foregoing reasons, therefore, we determine that the information presented in the Petition fails to establish a reasonable

likelihood that Petitioner would prevail in challenging: claims 1–12 as obvious under § 103(a) in view of George, Mathieson, Rasmussen, and the Rituxan Label; claims 3, 5, 7, 9, and 12 as obvious under § 103(a) in view of George, Mathieson, Rasmussen, the Rituxan Label, and Kelley; and claims 1–12 as obvious under § 103(a) in view of George, Mathieson, Rasmussen, Maloney I, and Kelley.

III. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition does not establish a reasonable likelihood that Petitioner would prevail in showing that claims 1–12 of the '843 patent are unpatentable.

IV. ORDER

In consideration of the foregoing, it is

ORDERED that the Petition is DENIED and no trial is instituted.

PETITIONER:

Jovial Wong
Charles B. Klein
Eimeric Reig-Plessis
WINSTON & STRAWN LLP
jwong@winston.com
cklein@winston.com
ereigplessis@winston.com

PATENT OWNERS:

Michael R. Fleming
Gary N. Frischling
Keith A. Orso
Yite John Lu
Andrew E. Krause
David Gindler
IRELL & MANELLA LLP
mfleming@irell.com
gfrischling@irell.com
korso@irell.com
yjlu@irell.com
akrause@irell.com
dgindler@irell.com