UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.,
Petitioner,

v.

BIOGEN INC.,
Patent Owner.

Inter Partes Review No. IPR2018-00086
Patent No. 8,545,843 B2
Issued: October 1, 2013
Filed: September 20, 2010

Title: TREATMENT OF VASCULITIS

PETITION FOR *INTER PARTES* REVIEW

Mail Stop PATENT BOARD
Patent Trial and Appeal Board
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

OTHER AUTHORITIES

LIST OF EXHIBITS

Exhibit	Description
1001	John G. Curd and Antonio J. Grillo-Lopez, U.S. Patent No. 8,545,843 B2 "Treatment of Vasculitis," (issued Oct. 1, 2013) ("the '843 patent")
1002	Declaration of Elena M. Massarotti, M.D., in Support of Petition for *Inter Partes* Review
1003	Owen Chan and Mark J. Shlomchik, "A New Role for B Cells in Systemic Autoimmunity: B Cells Promote Spontaneous T Cell Activation in MRL-*lpr/lpr* Mice," J. Immunology, 160:51–59 (1998) ("Chan")
1004	Belmont et al., "Pathology and Pathogenesis of Vascular Injury in Systemic Lupus Erythematosus," Arthritis & Rheumatism 39(1):9–22 (1996) ("Belmont")
1005	Danning et al., "Vasculitis Associated with Primary Rheumatologic Diseases," Current Opinion in Rheumatology, 10(1):58–65 (1998) ("Danning")
1006	Rituxan™ (rituximab) labeling (Nov. 1997) ("FDA label")
1007	George et al., "Infections and Wegener's Granulomatosis—A Cause and Effect Relationship?" Quarterly J. Med., 90:367–373 (1997) ("George")
1008	Mathieson et al., "T and B Cell Responses to Neutrophil Cytoplasmic Antigens in Systemic Vasculitis," Clinical Immunology & Immunopathology, 63(2): 135–141 (1992) ("Mathieson")
1009	Niels Rasmussen and Jorgen Petersen, "Cellular Immune Responses and Pathogenesis in c-ANCA Positive Vasculitides," J. Autoimmunity, 6(2): 227–236 (1993) ("Rasmussen")
1010	Excerpts from Vols. 1 & 2 Textbook of Rheumatology 5th Ed. (Kelley et al., eds) (1997) ("Kelley Textbook")

1011	David G. Maloney et al., "IDEC-C2B8 (Rituximab) Anti-CD20 Monoclonal Antibody Therapy in Patients with Relapsed Low-grade Non-Hodgkin's Lymphoma," Blood, 90(6):2188–2195 (1997) ("Maloney I")
1012	Rituxan™ Full Prescribing Information, Genentech Wayback Machine Website ("Website label").
1013	Specks et al., "Response of Wegener's Granulomatosis to Anti-CD20 Chimeric Monoclonal Antibody Therapy," Arthritis & Rheumatism, 44(12): 2836–2840 (2001) ("Specks")
1014	Stone et al., "Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis," N.E. J. Med., 363(3):221–232 (2010) ("Stone")
1015	Press Release, National Institute of Allergy and Infectious Diseases (NIAID), "After 40 Years, NIH-Supported Researchers Identify Possible New Treatment for Severe Vasculitis,"(July 14, 2010) (copy filed with USPTO as disclosed by Applicants in the Sept. 9, 2010 Information Disclosure Statement) ("NIH Article")
1016	Drenkard et al., "Vasculitis in Systemic Lupus Erythematosus," Lupus, 6:235–242 (1997) ("Drenkard")
1017	Gary S. Hoffman and Ulrich Specks, "Antineutrophil Cytoplasmic Antibodies," Arthritis & Rheumatism, 41(9): 1521–1537 (1998) ("Hoffman")
1018	CGM Kallenberg and P Heeringa, "Pathogenesis of Vasculitis," Lupus, 7:280–284 (1998) ("Kallenberg")
1019	Roark et al., "Breakdown of B Cell Tolerance in a Mouse Model of Systemic Lupus Erythematosus," J. Experimental Medicine, 181:1157–1167 (1995) ("Roark")
1020	Takeuchi et al., "Upregulated Expression and Function of Integrin Adhesive Receptors in Systemic Lupus Erythematosus Patients with Vasculitis," J. Clinical Invest., 92:3008–3016 (1993) ("Takeuchi")
1021	Cupps et al., "Suppression of Human B Lymphocyte Function by Cyclophosphamide," J. Immunology, 128(6):2453–2457 (1982) ("Cupps")

1022	Andrassy et al., "Wegener's Granulomatosis with Renal Involvement: Patient Survival and Correlations Between Initial Renal Function, Renal Histology, Therapy and Renal Outcome," Clinical Nephrology, 35(4):139–147 (1991) ("Andrassy")
1023	Theoharides et al., "7 Control of Pain and Inflammation," in Essential of Pharmacology 2d ed. (Theoharis C. Theoharides, ed.) 217–258 (1996) ("Massarotti I")
1024	Tanya Doan and Elena Massarotti, "Rituximab," Drugs of Today, 41(12):785–797 (2005) ("Massarotti II")
1025	Declaration of Scott Bennett, Ph.D.
1026	U.S. Application No. 12/886,171, Amendment in Response to Non-Final Action (dated Apr. 11, 2011)
1027	U.S. Application No. 12/886,171 Non-Final Office Action (dated Mar. 20, 2012)
1028	U.S. Application No. 12/886,171, Amendment in Response to Final Office Action (dated Oct. 29, 2012)
1029	U.S. Application No. 12/886,171 Amendment to Accompany RCE (dated Nov. 20, 2012)
1030	U.S. Application No. 12/886,171, Notice of Allowability (dated May 24, 2013)
1031	E. William St. Clair "Chapter 10: Vasculitis," in Treatment of the Rheumatic Diseases: Companion to the Textbook of Rheumatology (Michael H. Weisman & Michael E. Weinblatt eds.) 137–157 (1995) ("St. Clair")
1032	Maloney et al., "IDEC-C2B8: Results of a Phase I Multiple-Dose Trial in Patients with Relapsed Non-Hodgkin's Lymphoma," J. Clinical Oncology, 15(10):3266–3274 (1997) ("Maloney II")
1033	Darrell R. Anderson, U.S. Patent NO. 5,736,137 "Therapeutic Application of Chimeric and Radiolabeled Antibodies to Human B Lymphocyte Restricted Differentiation Antigen for Treatment of B Cell Lymphoma," (issued April 7, 1998) ("the '137 patent")

1034	Fauci et al., "Effect of Cyclophosphamide upon the Immune Response in Wegener's Granulomatosis," N.E. J. Med., 285(27):1493–1496 (1971) ("Fauci")
1035	Physicians' Desk Reference® (53rd ed. 1999) (excerpted), "Rituxan™ (Rituximab)" ("PDR label")
1036	Maini et al., "Therapeutic Efficacy of Multiple Intravenous Infusions of Anti-Tumor Necrosis Factor α Monoclonal Antibody Combined with Low-Dose Weekly Methotrexate in Rheumatoid Arthritis," Arthritis & Rheumatism, 41(9):1552–1563 (1998) ("Maini")
1037	Remicade® (infliximab) labeling (August 1998) ("Remicade® label")
1038	Gail A. Leget and Myron S. Czuczman "Use of Rituximab, the New FDA-Approved Antibody," Current Opinion in Oncology, 10:548–551 (1998) ("Leget")
1039	Charles Marwick, "Monoclonal Antibody to Treat Lymphoma," J. Am. Med. Ass'n, 278(8):616, 618 (August 27, 1997) ("Marwick")
1040	Sean Henahan, "Anti-CD20 Antibodies Combining Well in Lymphoma Patients," Inpharma, 1136:9 (May 1998) ("Henahan")

I. INTRODUCTION

Petitioner Pfizer, Inc. requests *inter partes* review and cancellation of claims 1–12 of U.S. Patent No. 8,545,843 B2 ("the '843 patent"). These claims are generally directed to [1] methods of treating vasculitis (i.e., inflammation of blood vessels) in a patient without rheumatoid arthritis ("RA") or cancer; [2] using more than one intravenous administration of rituximab; and, for some claims, [3] in combination with glucocorticosteroids, e.g., prednisone, methylprednisolone, or dexamethasone. As shown below, the claimed invention would have been obvious to a person of ordinary skill in the art ("POSA") as of the earliest filing date of May 7, 1999, in light of 35 U.S.C. §102(b) prior art, including several prior art references that were not considered by the Examiner during prosecution of the '843 patent.

Vasculitis is a condition generally associated with at least 12 different diseases. EX1002 ¶76. Each disease has its own unique underlying immune response that causes vasculitis. The claims of the '843 patent cover the treatment of any form of vasculitis, with the exception of vasculitis in patients with RA or cancer that is expressly disclaimed. By May 1999, it would have been obvious to a POSA to treat at least two forms of vasculitis unassociated with rheumatoid arthritis or cancer—systemic lupus erythematosus ("SLE") and Granulomatosis with

Polyangiitis ("GPA")[1]—using more than one intravenous administration of rituximab in combination with a glucocorticosteroid (or "glucocorticoid") such as prednisone or methylprednisolone.

When rituximab was approved by the U.S. Food and Drug Administration ("FDA") in 1997, it was the only commercially available therapy that could safely and effectively deplete human B-cells (a type of immune cell) by specifically targeting, using more than one intravenous administration, the antigen CD20 (a protein on the surface of B-cells). EX1002 ¶67. Based on what was known in the art by no later than May 1999 about the body's immune system and the role that B-cells play in the pathogenesis of vasculitis, rituximab would have been a POSA's natural treatment option for vasculitis—particularly in SLE and GPA. As the Rituxan™ label further instructed, rituximab should be used with glucocorticosteroids (e.g., prednisone)—a class of drugs that were commonly part of treatment regimens for vasculitis—to mitigate hypersensitivity reactions associated with rituximab administrations. *Id*. ¶69.

[1] GPA was previously known as Wegener's granulomatosis. EX1002 ¶25 n.1. Although this disease could be referred to by either one of its names, this Petition will refer to it as GPA.

SLE. As its name implies, SLE (systemic *lupus* erythematosus) is the formal term for lupus. By May 1999, based on the results of an article by Chan, a POSA would have known that B-cells would be an "ideal target for lupus therapy." EX1003, 7. Independent of Chan's general teaching, a POSA would have also known from prior art publications by Belmont and Danning that vasculitis in SLE is triggered by two related mechanisms: (1) antibodies generated by B-cells, and (2) activated T-cells (another type of immune cell). EX1004, 6, 9; EX1005, 2. Specifically, Belmont in 1996 disclosed that the B-cell antibodies present in SLE patients target blood vessel walls, leading to vasculitis. EX1004, 6, 9. Similarly, Danning in 1998 disclosed that activated T-cells in SLE adhere to blood vessel walls, causing inflammation that leads to vasculitis. EX1005, 2. Chan taught that B-cells play a critical role in both of these mechanisms: B-cells both produce the antibodies associated with SLE and are involved in activating T-cells. EX1003, 5–6.

As explained by Petitioner's expert rheumatologist, Dr. Elena Massarotti, a POSA would have been motivated to administer rituximab to a SLE patient with vasculitis to deplete B-cells, thus targeting both of these known mechanisms that trigger vasculitis in SLE. EX1002 ¶101. Based on the prior art, including the Rituxan™ label—which taught that more than one intravenous administration of rituximab depleted human B-cells and encouraged taking rituximab with glucocorticosteroids—a POSA would have had a reasonable expectation of

successfully using this therapy to treat vasculitis associated with SLE in SLE patients. EX1002 ¶¶108–109.

GPA. GPA is primarily and strongly associated with anti-neutrophil cytoplasmic antibodies ("ANCA"), which are protein chains that attack the blood vessel walls and lead to vasculitis. As taught by a 1997 publication by George, ANCA are largely responsible for exacerbating the damage to blood vessel walls. EX1007, 4. As explained by Dr. Massarotti, George would have motivated a POSA looking to treat GPA patients to use therapies that reduce or eliminate ANCA and that target the source of this pathogenic marker. EX1002 ¶¶130–131.

The prior art Mathieson and Rasmussen publications taught that ANCA can be reduced or eliminated by depleting human B-cells, which have a principal role in the production of ANCA. *Id.* ¶¶134–135. In 1992, Mathieson reported that B-cells "activate" T-cells, which in turn trigger B-cells to produce ANCA. EX1008, 5; EX1002 ¶52. Likewise, in 1993, Rasmussen taught that B-cells specifically expressing the CD20 antigen were responsible for the production of ANCA. EX1009, 7.

Again, the prior art 1997 Rituxan™ label taught that multiple intravenous doses of rituximab deplete human B-cells by targeting the CD20 antigen and encouraged using rituximab with glucocorticosteroids. EX1006, 1; EX1012, 1; EX1035, 6. Thus, a POSA would have been motivated to treat vasculitis in patients

with GPA by using more than one intravenous administration of rituximab with glucocorticosteroids—with a reasonable expectation of success. EX1002 ¶139.

In short, whether treating SLE or GPA, a POSA would have arrived at the obvious method of using rituximab to treat vasculitis covered by claim 1 of the '843 patent, which claims 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." *Id*. ¶4. The other eleven claims of the '843 patent merely recite the additional non-inventive limitations requiring that, consistent with the prior art Ritxuan™ label and Maloney I, rituximab be administered in more than one intravenous dose and that glucocorticosteroids (e.g., prednisone) be included in the treatment regimen.

During prosecution, the Examiner also initially found obvious (based on different references) the originally-filed claims covering a method treating vasculitis that included patients with RA, because when "RA vasculitis patients were treated for RA as per Edwards et al., the RA vasculitis would also be treated … because they were receiving antiCD20 antibody." EX1027, 17. Patent Owner overcame the obviousness rejections in "light of [the Examiner's] amended claims and applicant[']s arguments regarding unexpected results." EX1030, 6, 7–9. As discussed in more depth below, however, Patent Owner never actually showed that

the results of rituximab and glucocorticosteroid therapy were unexpected—much less different "in kind" from what was reasonably expected in view of the prior art. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013).

Petitioner thus respectfully requests that the Board institute *inter partes* review and cancel claims 1–12 of the '843 patent as unpatentable under 35 U.S.C. §103(a).

II. MANDATORY NOTICES

Pursuant to 37 C.F.R. §42.8(b), Petitioner states as follows:

1. ***Real Parties-in-interest.*** Petitioner Pfizer, Inc. is the real party-in-interest for this Petition. No other parties exercised or could have exercised control over this petition; no other parties funded or directed this Petition. *See Office Patent Trial Practice Guide*, 77 Fed. Reg. 48756, 48759–60 (Aug. 14, 2012).

2. ***Related matters*****.** The '843 patent is not currently subject to any litigation to the best of Petitioner's knowledge. Petitioner here has also filed a petition for *inter partes* review of U.S. Patent No. 7,820,161 (IPR2017-01115). Case IPR2017-01115 has subsequently been joined with Case IPR2016-01614, which has been instituted for trial. *See Pfizer, Inc. v. Biogen, Inc. and Genentech, Inc.*, Case IPR2017-01115, Paper 13 at 6–7 (PTAB July 18, 2017). The '161 patent is directed to a method of treating RA using rituximab in combination with methotrexate, and the '843 patent claims priority to the same provisional application as the '161 patent.

3. ***Lead and back-up counsel*****.** Petitioner identifies the following:

- *Lead counsel*: Jovial Wong (Reg. No. 60,115)
- *Back-up counsel*: Charles B. Klein*
- *Back-up counsel*: Eimeric Reig-Plessis*

* Back-up counsel to seek *pro hac vice* admission.

4. ***Service information*****.** Petitioner identifies the following:

- *Email address*: rituximabIPR@winston.com
- *Mailing address*: WINSTON & STRAWN LLP
  1700 K Street, NW
  Washington, DC 20006
- *Telephone number*: (202) 282-5000
- *Fax number*: (202) 282-5100

Please address all correspondence to lead counsel at the address shown above. Petitioner consents to electronic service at the above listed email address.

III. REQUIREMENTS FOR REVIEW

a. ***Grounds for standing*****.** Petitioner certifies that (1) the ’843 patent is available for *inter partes* review; and (2) Petitioner is not barred or estopped from requesting review of the ’843 patent on the grounds identified in this Petition. The required fee is paid through the Patent Review Processing System. The Office is

authorized to charge fee deficiencies and credit overpayments to Deposit Acct. No. 50-1814.

b. ***Identification of challenge.*** Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1–12 of the '843 patent pursuant to the following statement of the precise relief requested:

Ground	Claims	Basis	References
I.A	1–12	§103(a)	Chan (EX1003); Belmont (EX1004); Danning (EX1005); Rituxan™ label (EX1006 or EX1012 or EX1035)
I.B	3, 5, 7, 9, 12	§103(a)	Chan (EX1003); Belmont (EX1004); Danning (EX1005); Rituxan™ label (EX1006 or EX1012 or EX1035); Kelley Textbook (EX1010)
II.A	1–12	§103(a)	George (EX1007); Mathieson (EX1008); Rasmussen (EX1009); Rituxan™ label (EX1006 or EX1012 or EX1035);
II.B	3, 5, 7, 9, 12	§103(a)	George (EX1007); Mathieson (EX1008); Rasmussen (EX1009); Rituxan™ label (EX1006 or EX1012 or EX1035); Kelley Textbook (EX1010)

III	1–12	§103(a)	Chan (EX1003); Belmont (EX1004); Danning (EX1005); Maloney I (EX1011); Kelley Textbook (EX1010)
IV	1–12	§103(a)	George (EX1007); Mathieson (EX1008); Rasmussen (EX1009); Maloney I (EX1011); Kelley Textbook (EX1010)

IV. LEVEL OF ORDINARY SKILL IN THE ART

In light of the specification, the prosecution history, and the state of the art as of May 7, 1999, a POSA for purposes of the ’843 patent 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. Said physician can either be a rheumatologist, hematologist, nephrologist, neurologist, or pulmonologist. EX1002 ¶15.

V. THE PRIOR ART AND THE ’843 PATENT

A. Vasculitis is a disorder, disease, or immune response that directly or indirectly causes the inflammation of blood vessel walls.

Vasculitis comprises a “diverse group of disorders characterized by inflammation of the blood vessel wall.” EX1018, 1; EX1010, 60. Vasculitis “may involve arteries of any size; therefore, different vasculitic syndromes may have a

spectrum of clinical and pathologic features." EX1010, 60. When treating vasculitis, "[c]linicians must rely on their clinical suspicion of vasculitis supported by appropriate laboratory and pathologic data to diagnose specific vasculitic syndromes." *Id.* To aid in this effort, vasculitis disorders were broadly classified as one of two types: primary vasculitis or secondary vasculitis. EX1018, 1.

1. The prior art taught that targeting B-cells could treat vasculitis in SLE because it targets the key component of the immune response that triggers vasculitis in SLE patients.

As a disease where manifestations of vasculitis "may be associated with or complicated by an underlying malignancy or connective tissue disease," manifestations of vasculitis in SLE are considered a secondary vasculitis. EX1010, 66. As a general matter, secondary vasculitis is caused when the underlying disease generates an immune response that targets the blood vessel wall. EX1005, 1; EX1002 ¶25. That immune response is specific to the underlying disease and depends upon the particular pathogenic mechanisms of that disease. EX1005, 1; EX1002 ¶24. As discussed below, the prior art taught that targeting B-cells could treat manifestations of vasculitis in SLE.

a. As of May 1999, patients suffering from a severe manifestation of SLE needed a new, safe, and therapeutically effective treatment.

SLE is a systemic autoimmune disease that targets many organs in the body and is associated with antibody production. EX1010, 31. One of the pathogenic

hallmarks of SLE "is the recurrence of widespread and diverse vascular lesions." EX1004, 1. Vasculitis in SLE "may affect a variety of organs, including the skin, peripheral and central nervous systems, gastrointestinal tract, lung, heart, and genitourinary system." EX1005, 1. When vasculitis is present, it could have been considered "serious and life threatening." EX1010, 47.

Thus, physicians initiated "aggressive therapy" that included high-dose glucocorticosteroids (typically prednisone or methylprednisolone) and, in certain circumstances, cyclophosphamide, a cytotoxic chemotherapy agent. *Id.* Although the combination of cyclophosphamide and glucocorticosteroids could successfully treat vasculitis in SLE, it was "accompanied by a high incidence of adverse side effects," including life-threatening infections. *Id.* at 52–53.

As a general immunosuppressant therapy, cyclophosphamide could slow down the immune response and taper the production of antibodies. EX1002 ¶29. However, repeated administrations of cyclophosphamide over an extended period of time was toxic for the patient. EX1010, 49–50. Likewise, glucocorticosteroids were potent generalized immunosuppressants—which, while effective, were also toxic if patients received them on over an extended period of time. EX1002 ¶30.

Thus, as of May 1999, physicians were looking for a less toxic treatment regimen that was therapeutically effective to treat vasculitis in SLE. *Id.* ¶31.

b. Vasculitis in SLE is triggered by two separate mechanisms in the underlying immune response: antibodies and activated T-cells.

The prior art in 1996 taught that when a patient's SLE manifested vasculitis, its principal triggers were either antibodies or activated T-cells. Belmont disclosed that one of vasculitis' triggers in SLE was antibodies—inflammatory vasculitis (one type of vasculitis in SLE patients) was driven by the "local deposition of immune complexes, particularly those containing antibodies to DNA, in blood vessel walls." EX1004, 3. And thrombotic vasculitis (another type of vasculitis in SLE patients) was strongly linked with the "presence of antibodies to negatively charged phospholipids," also known as antiphospholipid antibodies. *Id.* at 10.

While antibodies were one pathogenic source of vasculitis in SLE, the prior art taught in 1998 that activated T-cells were another. EX1005, 2. Patients with vasculitis in SLE had T-cells that "showed a significant increase in adhesion to cytokine-activated endothelial cells." EX1020, 4. That is, the increased adhesion molecules meant that T-cells can cause injury to the blood vessel wall, causing inflammation associated with vasculitis. EX1002 ¶49. Thus, the activated T-cell can activate other immune cells to damage the blood vessel walls and cause vasculitis. EX1005, 2; EX1002 ¶49.

In short, as of May 1999, physicians understood that vasculitis was driven by two components in the immune system: antibodies and activated T-cells. EX1005, 2; EX1004, 16.

c. Chan taught that targeting B-cells in SLE decreases antibodies and the amount of activated T-cells.

In 1998, Chan taught that B-cells would be an "ideal target for lupus therapy." EX1003, 7. In a study assessing the comparison of SLE in mice with or without B-cells, Chan disclosed that B-cells have a role in SLE in addition to producing tissue-damaging antibodies. *Id.* at 1. Indeed, Chan demonstrated that there is "a second major role for B cells in SLE" in that they can activate T-cells. *Id.*

Chan taught that these results "provide[] in vivo evidence for the hypothesis that B cells are critical for systemic autoimmune disregulation via a direct effect on T cells." *Id.* at 6. Moreover, Chan noted that this study indicates that "B cell deficiency completely blocks autoimmune pathology, including the infiltration of T cells." *Id.* Indeed, more than 75% of T-cells in the B-cell deficient mice were dependent on the presence of B-cells. *Id.* Because of this observation, Chan encouraged the use of therapies that target the B-cells in patients with SLE. *Id.* at 7.

Chan concluded: "Regardless of the mechanism(s) by which B cells promote the spontaneous activation expansion of T cells in system autoimmunity, *an implication of this phenomenon is that B cells would be an ideal target for lupus therapy*." *Id.* (emphasis added). Moreover, "[i]t would not be sufficient to target

antibodies alone; in fact, this strategy as executed by plasmapheresis[2] does not work. Elimination of previously activated B cells would have the dual effect of ameliorating autoantibodies and of eliminating the reservoir of potent [antigen presenting cells] for autoreactive T cells." *Id.* Thus, the idea of targeting B-cells in SLE looked quite promising: Chan expressly predicted that depleting B-cells would successfully target both the antibody and T-cell mechanisms underlying SLE. EX1002 ¶42.

2. The prior art taught that targeting B-cells would be an effective treatment for the blood vessel inflammation that occurs in GPA because B-cells directly and indirectly produce ANCA.

Primary vasculitis diseases, such as GPA, are caused by an immune response that directly results in inflammation of the blood vessel walls. EX1018, 2; EX1002 ¶25. This immune response "occur[s] separate[ly] from any known underlying disease." EX1010, 60. That is, unlike SLE where the underlying immune response might cause vasculitis, the immune response in primary vasculitis diseases principally cause vasculitis. EX1002 ¶25. The different primary vasculitis diseases are further classified based on the "size of involved blood vessels, characteristic histopathology, and pattern of clinical involvement." EX1010, 60.

[2] Plasmapheresis is the process by which circulating antibodies are removed from the bloodstream. EX1003, 7.

As of May 1999, it was known that one of the mechanisms primarily contributing to blood vessel wall damage in primary vasculitis such as GPA was ANCA-mediated cell damage. *Id.* at 61. In particular, GPA was known to be "[s]trongly associate[d] with anti-neutrophil cytoplasmic antibodies"—i.e., ANCA. EX1018, 2, Table 1. And as shown below, it was also know that targeting B-cells could reduce or eliminate ANCA.

a. Patients diagnosed with GPA had poor prognoses with conventional therapies and needed improved therapies.

GPA is an autoimmune disease characterized by granulomatous lesions and vasculitis. EX1010, 80; EX1002 ¶32. "Generally, the disease is considered to be a continuum, beginning with limited organ involvement and progressing with variable speed to a more generalized form with nose, lung, and kidney involvement." EX1010, 80.

The earliest signs and symptoms of GPA start in the upper respiratory tract. *Id.* at 81. Left untreated, the disease ultimately spreads to the kidneys and is fatal. *Id.* at 83. Before the 1960s, a diagnosis of GPA "was almost uniformly fatal and renal failure was the main cause of death." *Id.* Glucocorticosteroid therapy was usually initiated first, "but overall mortality was not altered appreciably." *Id.* When cyclophosphamide was introduced into the field around 1970, "the course of [the] disease [was] altered favorably." *Id.*

Although glucocorticosteroid therapy and cyclophosphamide were capable of inducing the disease into remission, many patients with GPA continued to relapse. *Id.* This treatment also caused "substantial side effects." *Id.* For example, "aggressive treatment with corticosteroids and cytotoxic agents [e.g., cyclophosphamide] carries a substantial risk of producing severe infections, lymphomas, and, in the case of cyclophosphamide, cystitis, bladder cancer, and rarely, fatal lung fibrosis." EX1017, 11. As of May 1999, it was known that the resulting toxicity from sustained use of a glucocorticosteroid and cyclophosphamide therapy "prompted a search for alternative regimens of treatment." EX1010, 83.

b. The discovery that ANCA is strongly associated with GPA and produced by B-cells provided new opportunities to improve therapies to treat GPA.

New opportunities to treat GPA began to present themselves when ANCA was discovered in 1982. EX1017, 1. ANCA antibodies are responsible for targeting the blood vessel cell walls, which leads to tissue damage. *Id.* at 6. Shortly thereafter, researchers found that the presence of ANCA strongly correlates with the development of vasculitis. *Id.* By May 1999, it was well established that patients with GPA would be ANCA-positive—indeed, GPA had "[t]he most clear-cut association" with ANCA, and a GPA diagnosis was confirmed if the patient was ANCA-positive. *Id.* at 1, 4. It was known that ANCA is present in about "90 percent

of patients with classic Wegener's [i.e., GPA]." EX1010, 82. This discovery opened new pathways to treat GPA.

In 1992, Mathieson explored the relationship between ANCA and the body's immune cells. EX1008, 1. Mathieson demonstrated that T-cells were not activated in the absence of B-cells. Therefore, in the absence of B-cells, the immunological response that causes the inflammation characterizing vasculitis in GPA disappears, or at the very least is subdued. EX1002 ¶53.

Mathieson collected peripheral blood lymphocytes (i.e., B-cells and T-cells) from 36 patients with primary vasculitis and studied both types of cells in separate cell lines. EX1008, 1. Mathieson exposed the collected cells to the antigen that was thought to cause the immune response underlying GPA. *Id.* Reporting on the *in vitro* analysis of the B-cells following exposure to the antigen, Mathieson observed that B-cells produce ANCA and activate T-cells. *Id.* With respect to the T-cells, however, Mathieson observed that "no [T-cell activation] could be demonstrated" when the T-cells were exposed to the antigen. *Id.* at 5. Mathieson's analysis confirmed this observation: "T cell involvement in [vasculitis] is confined to the provision of B cell help." *Id.* at 6. Mathieson thus concluded that T cells "may not be directly involved in the pathogenesis of [vasculitis]." *Id.* Instead, B-cells had a principal role in the pathogenesis of GPA. *Id.*; EX1002 ¶¶51–53.

In short, Mathieson disclosed that B-cells have a role beyond ANCA production. They are one of the principal actors in the immune response that lead to the activation of T-cells, which then exacerbates the immune response causing the GPA patient's vasculitis. *See id.*; EX1002 ¶54.

Not only did the prior art teach that B-cells activate T-cells in the immune response that causes GPA, additional prior art confirmed that B-cells are responsible for ANCA production—including B-cells expressing the CD20 antigen. Rasmussen EX1009, 3. Because of their interest in ANCA, Rasmussen reported on the results of observing patients with active GPA. *Id.* at 1. Rasmussen noted that samples of the studied nasal biopsies "revealed the presence of substantial amounts of cells belonging to the immune system (CD3+, CD4+, CD8+, CD20+, CD38+ and CD68+)." *Id.*

Rasmussen discovered that the nasal lesions contained "large amounts of CD20+ B lymphocytes and CD38+ plasma cells in clusters in 7 untreated [GPA] patients." *Id.* at 3. Given the "abundant" amount of CD20 B-cells present in the nasal passages, Rasmussen confirmed "that c-ANCA was probably produced in the lesions." *Id.* at 7. Because the "immune response leading to production of c-ANCA [involves] the full spectrum of immunocompetent cells normally engaged in the production of IgG in response to a foreign antigen, i.e. a microbial antigen," Rasmussen disclosed that CD20 B cells generate ANCA-producing plasma cells. *Id.*

Rasmussen also predicted that "the B lymphocytes in [GPA] may have dual functions of being both antigen-presenting cells as well as giving rise to c-ANCA-producing plasma cells." *Id.* at 8. Thus, Rasmussen disclosed, like Mathieson, that B-cells have a role in activating the T-cells in the immune response that causes vasculitis. *Id.*; EX1002 ¶¶55–59.

c. By May 1999, ANCA-targeted therapy offered a new opportunity for physicians to treat GPA.

Armed with the new knowledge about the different roles of the immune cells in GPA and the sources of ANCA, "therapy tailored to even imperfect correlations between disease activity and ANCA" was a promising idea in May 1999—particularly if such a therapy avoided serious side effects of long-term cyclophosphamide-glucocorticosteroid combination therapy EX1017, 11. For example, George taught that a patient's ANCA levels "correlate[] well with the disease activity" in GPA. EX1007, 3. As levels of ANCA rise in the bloodstream, so does the disease activity. *See id.* And a rise in ANCA is usually a precursor to the patient's relapse of the disease. *Id.*; EX1017, 11. Indeed, "[p]ersistent high titers or rising titers of ANCA … are often associated with relapse from remission in [microscopic polyangiitis] or [GPA]." EX1017, 11; EX1007, 3.

If not for the toxicity associated with the treatment regimens as of May 1999 (cyclophosphamide and glucocorticosteroids), treating a GPA patient with the goal of reducing ANCA levels would have been feasible. *See* EX1017, 11. Therefore,

there remained a need in the art for a less toxic treatment that was capable of safely depleting ANCA levels. EX1002 ¶¶34–35.

B. Rituximab was approved as the first monoclonal antibody that could successfully and safely deplete human B-cells.

In 1997, the FDA approved Rituxan™, the brand name for rituximab, for the treatment of patients with relapsed or refractory low-grade B-cell Non-Hodgkin's lymphoma ("NHL"). EX1006, 1; EX1012, 1; EX1035, 7. Although rituximab was approved for NHL, the FDA-approved label, Genentech's website, and the *Physicians' Desk Reference*® ("PDR") explained that this pharmaceutical product is an "antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes." EX1006, 1; EX1012, 1; EX1035, 6. As a monoclonal antibody, rituximab binds itself to the CD20 antigen found on B-cells, thus enabling the destruction of B-cells. EX1006, 1; EX1012, 1; EX1035, 6–7; EX1011, 1; EX1002 ¶36.

As the label explains, rituximab's mechanism of action is to "bind[] to the CD20 antigen on B-lymphocytes," which "has been shown to induce apoptosis [cell death]" of B-cells. EX1006, 1; EX1012, 1; EX1035, 7. Moreover, rituximab depletes both cancerous and healthy B-cells. *See* EX1006, 1; EX1012, 1; EX1035, 7; EX1011, 1. Following rituximab's initial phase I trial, Maloney reported in 1997: "Additional potential applications include … as well as possible treatment of patients with autoimmune diseases caused by autoreactive antibodies." EX1032, 11.

Rituximab was approved at a single "recommended" dose at 375 mg/m^2 consisting of four weekly intravenous infusions. *Id.* As a result of this regimen, rituximab leads to "a rapid and sustained depletion of circulating and tissue-based B cell." EX1006, 1; EX1012, 1; EX1035, 7. Indeed, in one of the trials listed on the label, 83% of the 166 patients studied had a "sustained depletion" of B-cells "within the first three doses with sustained depletion for up to 6 to 9 months post-treatment." EX1006, 1; EX1012, 1; EX1035, 7.

According to the FDA-approved Rituxan™ label, Rituxan should be taken with a corticosteroid—such as a known glucocorticosteroid like prednisone, methylprednisolone, or dexamethasone—to alleviate side effects. EX1006, 1; EX1012, 1; EX1035, 7. The Rituxan™ label explained, and the initial studies of rituximab in NHL disclosed, that although rituximab is a safe and therapeutic biologic, "Rituxan is associated with hypersensitivity reactions." EX1006, 1; EX1012, 1; EX1035, 7; EX1011, 4, Table 2.; EX1002 ¶69. These reactions occur in approximately 80% of patients during their first infusion of rituximab and in approximately 40% of patients during their subsequent infusions. EX1006, 1; EX1012, 1; EX1035, 7. "Medications for the treatment of hypersensitivity reaction, e.g., epinephrine, antihistamines *and corticosteroids* [e.g., glucocorticosteroids] should be available for immediate use in the event of a reaction during administration." EX1006, 1; EX1012, 1; EX1035, 7 (emphasis added); EX1002 ¶69.

As of May 1999, rituximab was the only approved anti-CD20 monoclonal antibody therapy on the market capable of safely and effectively depleting a human's B-cells. EX1002 ¶104.

C. Within one year of the '843 patent's provisional application, Specks separately taught that rituximab can be used to treat GPA.

In early 2000, shortly after Applicants filed the provisional application that issued as the '843 patent, Specks[3] "report[ed] on the successful, compassionate use of the anti-CD20 chimeric monoclonal antibody rituximab in a patient with chronic, relapsing cytoplasmic antineutrophil cytoplasmic antibody (cANCA)—associated [GPA]." EX1013, 1. Recognizing that rituximab was a safe and effective therapy for NHL and that four weekly infusions of 375 mg/m^2 could deplete B-cells, Specks concluded that "rituximab represents an attractive new drug for the treatment of autoimmune diseases with pathogenic autoantibodies." *Id.*

In the case study, the patient suffered from ANCA-associated GPA "in whom the use of cyclophosphamide was contraindicated and other immunosuppressive agents failed to control disease activity." *Id.* Specks chose to administer rituximab "under the hypothesis that elimination of pathogenic [proteinase 3] ANCA would allow the induction and maintenance of a lasting remission during and after tapering

[3] As indicated by Specks' disclosures, Specks and his co-authors were affiliated with and supported by only the Mayo Foundation, and not the Patent Owner. EX1013, 1.

of glucocorticoids." *Id.* Around January or February 2000, Specks decided to treat the patient with rituximab. *Id.* at 3, Figure 1; EX1002 ¶165. Specks administered four weekly infusions of 375 mg/m^2 of rituximab in combination with prednisone. EX1013, 3.

After the first dose of rituximab, the patient's GPA entered remission. *Id.* Even though the patient's GPA relapsed before the second course of rituximab was administered, Specks suggested: "*Rituximab may represent a promising new agent for mechanism-based treatment of patients with ANCA-associated vasculitis* in whom either standard therapy has failed or contraindication for standard therapy have developed." *Id.* at 5 (emphasis added). Indeed, Specks encouraged further exploration of rituximab in ANCA-associated vasculitis: "If the promise holds true, a prospective multicenter phase III trial designed to compare rituximab directly with cyclophosphamide as the primary remission-inducing agent in ANCA-associated vasculitis should be performed." *Id.*

VI. THE '843 PATENT

A. The claims

The '843 patent has 12 claims, including five independent claims. Claim 1, reproduced below, is illustrative of the claims:

> 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.

EX1001, 29:39–43.

The remaining independent claims (2, 4, 6, and 10) are substantially similar to claim 1. Claim 2 is similar to claim 1, but also requires that "more than one intravenous dose" of rituximab is administered and a glucocorticosteroid is also administered. *Id.* at 30:1–5. Claim 4 is substantially similar to claim 2 but instead requires that "more than one intravenous dose of a therapeutically effective amount of an antibody that binds to the CD20 antigen on human B lymphocytes," a class of antibodies that includes rituximab. *Id.* at 30:10–14. Claim 6 is identical to claim 4 but also adds an additional wherein clause requiring "the therapeutically effective amount of the CD20 antibody is administered intravenously, and the CD20 antibody is rituximab." *Id.* at 30:25–29. Claim 10 is identical to claim 1, but it further requires that rituximab be administered "in an amount effective to deplete B-cells in the human." *Id.* at 30:38–39.

The remaining dependent claims in the patent (3, 5, 8, 9, 11, and 12) further require that rituximab be administered in combination with glucocorticosteroids, including prednisone, methylprednisolone, or dexamethasone.

VII. CLAIM CONSTRUCTION

"A claim in an unexpired patent that will not expire before a final written decision is issued shall be given its broadest reasonable construction in light of the

specification of the patent." 37 C.F.R. §42.100(b). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016).

A. "vasculitis"

The broadest reasonable construction of "vasculitis" in light of the specification is any form of vasculitis known to a POSA as of May 1999. As Dr. Massarotti confirms, the plain and ordinary meaning of the term "vasculitis" to a POSA means that any form of vasculitis is being treated—with additional claim language excepting from the claim scope vasculitis in patients with RA or cancer. EX1002 ¶86.

One of the leading textbooks in the field of rheumatology, *The Textbook of Rheumatology*, described vasculitis in 1995 as "a clinical and pathologic process caused by inflammation of blood vessels" and "produces a wide variety of clinical disorders." EX1010, 60. "Vasculitis," according to its plain and ordinary meaning and as used in the '843 patent, thus includes both primary and secondary manifestations of vasculitis. *Id.*; EX1002 ¶87. This term also includes both ANCA-positive and ANCA-negative vasculitis. EX1002 ¶87. Indeed, the textbook chapter on "Vasculitis and Related Disorders" lists over a dozen diseases and disorders that manifest vasculitis: several which Applicants disclosed during prosecution (e.g.,

GPA, Kawasaki's Disease, and Churg-Strauss Syndrome) and several that were never mentioned by Applicants (e.g., Sjogren's syndrome, SLE, and Cogan's Syndrome). EX1010, 69–97. Therefore, apart from the explicit exemptions in the claims, a POSA would have understood that the meaning of "vasculitis," at a minimum, applies to every disease and disorder listed in that chapter. EX1002 ¶88.

That the claims themselves limit the definition of vasculitis by excluding two specific forms of vasculitis (but no others) along with the fact that the specification does not otherwise limit the term "vasculitis," strongly suggests that "vasculitis" should be broadly construed consistent with its scientific and plain and ordinary meaning. *Id.*; *Glaxo Wellcome, Inc. v. Andrx Pharm., Inc.*, 344 F.3d 1226, 1233 (Fed. Cir. 2003) ("When a claim term has an accepted scientific meaning, that meaning is generally not subject to restriction to the specific examples in the specification."). This is true here, where the specification does not provide a specific definition for "vasculitis," or otherwise limit the scope of what "vasculitis" covers. *Compare* EX1001, 3:47–4:19 (offering a definition of a different term, "autoimmune disease").

During prosecution, the Examiner similarly construed "vasculitis" broadly: "The claims encompass treatment of a wide variety of different forms of vasculitis

(for example RA related vasculitis) ...."[4] EX1027, 7. The Examiner made those remarks in response to Applicants' previous argument that Stone (EX1014) provided evidence of "a surprising result not predictable from the cited art." EX1026, 14. The Examiner was not persuaded by this argument because Stone "refers to the treatment of ANCA vasculitis in patients with Wegner's granulomatosis or microscopic polyangiitis" and it was "unclear whether [Stone's] studies are pertinent to other forms of vasculitis." EX1027, 7. Thus, the Examiner concluded that, by itself, "the evidence provided in [Stone] is not commensurate in scope with the claimed invention." *Id.*

Acknowledging that Stone only disclosed treatment therapies for GPA and microscopic polyangiitis, the Applicants provided evidence that "rituximab effectively treats a wide spectrum of different types of vasculitis including" eleven other examples of primary and secondary vasculitis (Behçet's Disease,[5] Churg-

[4] This statement was made before the Examiner amended and limited the claims to cover a method of treating vasculitis "in a human *who does not have rheumatoid arthritis* or cancer"—but did not otherwise limit the term "vasculitis." EX1030, 2 (emphasis added).

[5] The Kelley Textbook categorizes Behçet's Disease as a secondary vasculitis. EX1010, 95.

Strauss Syndrome, Cryoglobulinemic Vasculitis, Giant Cell Arteritis, Henoch-Schonlein Purpura, Microscopic Polyangiitis, Polyarteritis Nodosa, Takayasu's Arteritis, GPA, Kawasaki Disease, and Leukocytoclastic vasculitis[6]). EX1028, 4–5 (emphasis added). Thus, even Applicants understood that the claim language should be broadly interpreted based on their arguments. *Id.* at 6 ("In view of the failure of the cited art to suggest B-cell depletion with rituximab for treating vasculitis, the evidence previously provided [(i.e., Stone)], and the evidence provided [(i.e., the additional list of eleven examples of vasculitis)], section 103 rejections should be reconsidered or rejected.").

Accordingly, the Board should construe "vasculitis" to encompass any form of vasculitis, consistent with how a POSA would interpret the claim language, the scientific meaning of the term—as well as how the Applicants themselves and the Examiner interpreted the claims.

VIII. PRIOR ART STATUS OF CITED REFERENCES

As shown below and in the Declaration of Dr. Scott Bennett (EX1025), each of the references Petitioner relies upon for the grounds of unpatentability, with the

[6] Leukocytoclastic vasculitis is type of vasculitis that is the "commonest form" of vasculitis in patients whose SLE manifests vasculitis. EX1016, 6; *accord* EX1010, 93 (explaining that "leukocytoclastic vasculitis is common in SLE").

exception of the PDR label (EX1035), asserted in this petition is a printed publication that was publicly accessible before May 7, 1998, and therefore qualifies as prior art to the '843 patent under 35 U.S.C. §102(b). *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). The PDR label is a prior-art printed publication under 35 U.S.C. §102(a).

All of the references described below were published in journals or books that have long been cataloged or indexed in a meaningful way. EX1025 ¶¶25–124. Each reference was sufficiently accessible to the public, and ordinarily skilled artisans, exercising reasonable diligence, would have no difficulty finding copies of it. *Id.* ¶128. Moreover, each date stamp on the references has the general appearance of date stamps that libraries have long affixed to books and periodicals, and there is no reason to believe it was affixed by anyone other than library personnel, or on any other date than the date stamped on the reference. *Id.* ¶¶25–124.

A. Chan (EX1003)

As explained by Dr. Bennett, Chan is an authentic copy of a research paper published in a periodical that was first published in 1950 and is held by 871 libraries worldwide. *Id.* ¶¶107, 111. A date stamp from the University of Wisconsin Health Library indicates that the journal containing Chan was processed on December 29, 1997. *Id.* ¶112. Therefore, Chan was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶113–114.

B. Belmont (EX1004)

Belmont is an authentic copy of a research paper published in a periodical that was first published in 1958 and is held by 831 libraries worldwide. *Id.* ¶¶40, 44. A date stamp from the University of Illinois at Chicago Library indicates that the journal containing Belmont was processed on January 25, 1996. *Id.* ¶45. Therefore, Belmont was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶46–48.

C. Danning (EX1005)

Danning is an authentic copy of a research paper published a periodical that was first published in 1989 and is held by 266 libraries worldwide. *Id.* ¶¶50, 54. A date stamp from the University of Illinois at Chicago Library indicates that the journal containing Danning was processed on January 26, 1998. *Id.* ¶55. Therefore, Danning was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶56–58.

D. Rituxan™ label (EX1006 or EX1012 or EX1035)

As 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." As shown below, each of these three exhibits are prior-art printed publications under §102(a) or §102(b). Moreover, 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.

1. FDA label (EX1006) and Website label (EX1012)

The FDA label (EX1006) is a true and accurate copy of the original 1997 drug label for Rituxan™ that was approved by the FDA in November 1997 and a true an accurate copy of the "Full Prescribing Information" that appeared on the Genentech website no later January 23, 1998.[7] *Id.* ¶¶70–71. As Dr. Bennett confirms, the FDA label is available today from the FDA's website, which represents that it is the original approved label for Rituxan™ as of November 26, 1997. *Id.* ¶70.

[7] Petitioner acknowledges that, in other IPR proceedings panels of the Board concluded that a different petitioner presented insufficient evidence to find that the "Rituxan™ label" (EX1006) was a prior-art printed publication. *See e.g.*, *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01094, Paper 12 at 10–11 (PTAB Oct. 2, 2017). The Board, however, has not had the occasion to determine whether the Rituxan™ label that was posted on Genentech's website as of January 1998 (EX1012) constitutes a §102(b) prior-art printed publication for purposes of the '843 patent. Nor has the Board addressed EX1035, the PDR label reference, which contains the same substance as the FDA label (EX1006) or the Website label (EX1012).

The well-known "Internet Archive" service shows that the Website label (EX1012) was available on the website of Genentech, which markets Rituxan™, as of January 23, 1998. *Id.* ¶71. The Internet Archive maintains an archive of webpages collected from the internet by automated "crawlers." *Id.* ¶¶27–32, 71. The archived webpages are available for search and retrieval through an interface called the "Wayback Machine," which renders accurate snapshots of webpages as they existed at the time they were captured based on the date stamp on the top of the webpage. *Id.*

Based on the Website label's appearance in the Internet Archive as of January 23, 1998, it is clear that public internet search engines at the time would have been able to find and index the Rituxan™ label, and that a POSA exercising reasonable diligence and using typical internet search tools would have readily found a copy of it. *Id.* ¶¶72–75; *see also, e.g.*, *IBM Corp. v. Intellectual Ventures II LLC*, No. IPR2015-00089, Paper 44 at 57 (PTAB Apr. 25, 2016) (relying on "Wayback Machine evidence" to "determine that Petitioner has shown that [a reference] was publicly available").

Indeed, Dr. Bennett explained that the Genentech website is organized in a convenient and hierarchical manner that a person interested in the material exercising reasonable diligence would have easily located the document with four "clicks." EX1025 ¶¶72, 77. *Suffolk Techs., LLC v. AOL, Inc.*, 752 F.3d 1358, 1365

(Fed. Cir. 2014) (holding person interested in publication can "easily locate" the material if available on a website "organized in a hierarchical manner"). Dr. Massarotti has also explained that it was an increasingly common practice for physicians in the late 1990s to locate information about a drug manufacturer's product on the drug manufacturer's website. EX1002 ¶¶64–65; *Cf. Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349 (Fed. Cir. 2016). Moreover, she was able to locate the Rituxan™ "Full Prescribing Information" quickly and easily after opening a hyperlink to the Genentech, Inc. homepage as it appeared in January 1998. EX1002 ¶65.

In addition, the FDA label (EX1006) and Website label's (EX1012) authenticity is evident from the 1999 edition of the PDR, a well-known periodical and reference that reproduces drug labels in their entirety. EX1035. The 1999 edition of the PDR (which was received by the National Library of Medicine on December 30, 1998, *see id.* at 2) contains the same labeling information as the FDA label and the Website label. *Compare* EX1006 and EX1012, *with* EX1035, 6–11.

Thus, the FDA label (EX1006) and the Website label (EX1012) are prior-art printed publications under §102(b).

2. PDR label (EX1035)

Exhibit 1035 is a true and accurate copy of the Rituxan (rituximab) entry from the 1999 edition of the PDR. EX1002 ¶66. A previous panel of the Board held that

excerpts from "the PDR" are "portions of a reference book that were published on the dates indicated on the documents" and "sufficiently establish that they constitute printed publication prior art, absent additional evidence indicating otherwise." *Frontier Therapeutics, LLC v. Medac Gesellschaft für klinishce Spezialpräparate mbH*, IPR2016-00649, Paper 10 at 21–22 & 6 n.4 (PTAB Sept. 1, 2016). The PDR label (EX1035) was date stamped by the National Library of Medicine on December 30, 1998 and is therefore a prior-art printed publication under §102(a).

E. George (EX1007)

George is an authentic copy of a research paper published in a periodical that was first published in 1994 and is held by 315 libraries worldwide. *Id.* ¶¶89, 93. A date stamp from the Southern Illinois University School of Medicine Library indicates that the journal containing George was processed on June 2, 1997. *Id.* ¶94. Therefore, George was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶95–97.

F. Mathieson (EX1008)

Mathieson is an authentic copy of a research paper published in a periodical that was first published in 1972 and is held by 328 libraries worldwide. *Id.* ¶¶79, 83. A date stamp from the Cornell University Library indicates that the journal containing Mathieson was processed on April 8, 1992. *Id.* ¶84. Therefore,

Mathieson was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶85–87.

G. Rasmussen (EX1009)

Rasmussen is an authentic copy of a research paper published in a periodical that was first published in 1988 and is held by 180 libraries worldwide. *Id.* ¶¶60, 64. A date stamp from the University of California at San Diego Library indicates that the journal containing Rasmussen was processed on April 26, 1993. *Id.* ¶65. Therefore, Rasmussen was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶66–68.

H. Kelley Textbook (EX1010)

The *Textbook of Rheumatology* is an authentic copy of a book edited by William N. Kelley et al., that was published in two volumes—a textbook that was published in 1997 and is held by 330 libraries worldwide. *Id.* ¶¶99, 102. A catalogue record from the Bibliothèque de l'Université Paris XI indicates that the Kelley Textbook, was processed on May 25, 1997. *Id.* ¶103. Therefore, the Kelley Textbook was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶103–105.

I. Maloney I (EX1011)

Maloney is an authentic copy of a research paper published in a journal that was first published in 1946 and is held by 953 libraries worldwide. *Id.* ¶¶116, 120. A date stamp from the Cornell University Library indicates that the journal

containing Maloney was processed on September 17, 1997. *Id.* ¶121. Therefore, Maloney 1997 was available to the public before May 7, 1998, and is a prior-art printed publication under §102(b). *Id.* ¶¶122–124.

IX. ANALYSIS OF GROUNDS FOR TRIAL

The claims of the ’843 patent would have been obvious to a POSA in view of multiple §102(b) prior art references that were not disclosed during prosecution. As of May 1999, the standard practice for treating patients with vasculitis in SLE or GPA was cyclophosphamide-glucocorticosteroid combination therapy. EX1010, 52, 83. While this combination was therapeutically effective, it also caused “substantial adverse side effects.” *Id.* at 83. Thus, “the general problem that confronted the inventor before the invention was made,” *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2011), was whether new therapies could be developed that could match or improve the effectiveness of existing treatments for SLE or GPA without increasing toxicity.

In light of that problem, a POSA would have been motivated to treat vasculitis in SLE and GPA by targeting the agents of the immune system that trigger vasculitis. As explained by Dr. Massarotti and as shown below, Chan, Rasmussen, and Mathieson disclosed that CD20 B-cells were the key agents in the immune response that trigger vasculitis in SLE and GPA. Therefore, it would have been obvious to treat a patient suffering with vasculitis associated with SLE or GPA by depleting the

patient's B-cells, because doing so would eliminate the key agents in the immune response that trigger the patient's vasculitis.

Rituximab was the only available therapy for commercial sale designed to safely deplete CD20 B-cells as of May 1999. Thus, rituximab was an obvious choice for treating vasculitis. The Rituxan™ label indicates that 375 mg/m^2 of rituximab "given as an IV infusion once weekly for four doses" could safely and effectively deplete healthy or malignant CD20 B-cells. EX1006, 1; EX1012, 3; EX1035, 8. And based on the label's warnings, a POSA would have found it obvious to also add glucocorticosteroids to the regimen to treat any hypersensitivity reactions related to the rituximab infusions. EX1006, 1; EX1012, 1–2; EX1035, 7.

The rituximab-glucocorticosteroid combination therapy claimed in the '843 patent would have been an obvious choice for treating vasculitis in patients with SLE or GPA. All claims from that patent should be cancelled.

A. Ground IA—*Treatment of vasculitis manifestations in SLE*: Obviousness over Chan, the Rituxan™ label, Belmont, and Danning

1. Claim 1 recites an obvious method of treating vasculitis in SLE.

Claim 1 recites "[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." EX1001, 29:39–43. This claim

would have been obvious to a POSA over Chan and the Rituxan™ label in view of Belmont and Danning.

a. "treating vasculitis in a human patient who does not have rheumatoid arthritis or cancer"

i. The methods of claim 1 include methods of treating vasculitis in SLE.

The methods of claim 1 are directed to methods of treating any form of vasculitis that manifests in patients without RA or cancer. EX1001, 29:39–43. A POSA would know that this includes methods of treatment for vasculitis manifestations in SLE patients. EX1002 ¶98; *see supra* Part VII.A. As shown below, the method covered by claim 1 was obvious.

ii. Belmont and Danning disclosed that there were two principal triggers of vasculitis in SLE: antibodies and activated T-cells.

Belmont and Danning, which were never disclosed to the Examiner and studied only patients with vasculitis in SLE (i.e. not patients with RA or cancer).[8] Belmont and Danning taught that vasculitis in SLE is triggered by certain known antibodies and Danning taught that vasculitis in SLE is also triggered by activated T-cells. EX1004, 6, 9; EX1005, 2. Thus, a POSA developing a new treatment for

[8] Danning provides an overview of the pathogenesis of vasculitis in RA as well as the pathogenesis of vasculitis in SLE. For purposes of this Petition, only the portions of Danning relating to vasculitis in SLE are used for Petitioner's grounds.

vasculitis in SLE would have sought to target those two known pathogenic sources of vasculitis in SLE. EX1002 ¶99.

iii. Chan taught that B-cell depletion would eliminate or reduce two pathogenic triggers of vasculitis in SLE: antibodies and activated T-cells.

Chan taught that "B cells would be an ideal target for lupus therapy." EX1003, 7. Chan, which was never disclosed to the Examiner and also studied only patients without RA or cancer, stressed that B-cell targeted therapy was an ideal therapy for SLE because "[e]limination of previously activated B cells would have the dual effect of ameliorating autoantibodies *and* of eliminating the reservoir of potent [antigen presenting cells] for autoreactive T cells." *Id.* (emphasis added). In other words, Chan predicted that depleting B-cells would successfully inhibit two key triggers of vasculitis in SLE—i.e., antibodies and activated T-cells. EX1002 ¶100.

Indeed, Chan taught that the antibodies involved in SLE are created by activated B-cells, and B-cell depletion reduces the level of activated T-cells in SLE patients—the same activated T-cells that are responsible for the sustained blood vessel wall damage. EX1003, 7; EX1002 ¶42. Chan disclosed that B-cells have a key role in activating the majority of the T-cells in the immune response. EX1003, 7; EX1002 ¶¶101–102.

iv. Rituximab was the only therapy as of May 1999 that could safely and effectively deplete human B-cells.

The Rituxan™ label taught that a dosing regimen consisting of the intravenous administration of rituximab was capable of depleting the body's cells in a safe and effective manner. EX1006, 1; EX1012, 1–2; EX1035, 7; EX1002 ¶¶104–106. Indeed, the Rituxan™ label disclosed that the recommended intravenous dose for treating NHL leads to the depletion of B-cells—including non-cancerous B-cells. EX1006, 1; EX1012, 1–2; EX1035, 7.

v. It would have been obvious to treat vasculitis in SLE with rituximab because B-cell depletion would eliminate or reduce the two sources of vasculitis in SLE.

Based on the prior art, a POSA would have been motivated to combine these prior art teachings as of May 1999 in the manner recited in claim 1 with a reasonable expectation of success, 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); and (4) none of the references relies on studies of patients with RA or cancer. EX1002 ¶107. In other words, a POSA would have reasonably expected rituximab to be an effective treatment for vasculitis in SLE patients because

rituximab B-cell depletion therapy would eliminate or reduce the two primary sources of the immune response causing vasculitis in SLE. *Id.*

While Chan did not use rituximab to treat SLE, a POSA nevertheless would have reasonably expected that the effectiveness of rituximab in depleting B-cells described by the label for NHL would carry over to patients with SLE. *Id.* ¶108. That is, 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. *Id.*; EX1006, 1; EX1012, 1; EX1035, 7. Although vasculitis is not necessarily associated with cancer, rituximab targets both healthy and malignant cells. EX1006, 1; EX1012, 1; EX1035, 7; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (noting that while it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements," the obviousness "analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ").

That reasonable expectation is further supported by the known relationship between disease activity modeled in the lpr/lpr mouse[9] and the disease activity in a human patient with SLE. EX1002 ¶109. By breeding a B-cell deficient strain of mice modeling SLE, Chan demonstrated that disease activity—i.e., the measure of the immune response responsible for SLE and vasculitis in SLE—was markedly different in mice without B-cells. EX1003, 6. Mice without B-cells had less disease activity compared to those with B-cells, because B-cells were not present to form antibodies and to activate the T-cells. *Id.* at 6–7; EX1002 ¶109. Accordingly, a POSA would have expected B-cell depletion resulting from rituximab to provide a therapeutic benefit in a human patient with manifestations of vasculitis in SLE. EX1002 ¶109. *See, e.g.*, *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) ("Obviousness does not require absolute predictability of success …. [A]ll that is required is a reasonable expectation of success.").

b. "administering to the human a therapeutically effective amount of rituximab"

Claim 1 further requires "administering to the human a therapeutically effective amount of rituximab" to treat vasculitis. As explained in part IX.A.1.a, it

[9] The lpr/lpr mouse "provides a well characterized model of human SLE." EX1019, 1. The mouse is bred with a genetic design defect of the "lpr" gene, and thus is referred to as the lpr/lpr mouse. *Id.*

would have been obvious to administer rituximab with a reasonable expectation of success to treat vasculitis in patients with SLE because B-cell depletion would effectively address the two sources of vasculitis in SLE, and because rituximab was the only treatment agent in May 1999 that could safely and effectively deplete B-cells. EX1002 ¶110. A POSA looking to carry out Chan's recommendation to target B-cells would have used the recommended dose listed on the rituximab label of "375 mg/m2 given as an IV infusion once weekly for four doses" because that regimen—according to the FDA-approved Rituxan™ label—leads to "a rapid and sustained depletion of circulating and tissue-based B cell." EX1006, 1–2; EX1012, 1; EX1035, 7. And because rituximab "binds to the CD20 antigen on B-lymphocytes" irrespective of whether those B-cells are cancer cells or (as with vasculitis in SLE) healthy cells, a POSA would have had a reasonable expectation of success that this dosage would be a "therapeutically effective amount of rituximab" to deplete a patient's B-cells and in turn treat vasculitis in SLE. EX1006, 1; EX1012, 1; EX1035, 6–7; EX1002 ¶111.

c. "the administration of the rituximab consists of intravenous administration"

The limitation in claim 1 requiring that "the administration of the rituximab consists of intravenous administration" was obvious in light of the Rituxan™ label's disclosure that rituximab is a "liquid concentrate for *intravenous (IV) administration*" and the "recommended" dosage "is 375 mg/m^2 given *as an IV*

infusion once weekly for four doses." EX1006, 1–2; EX1012, 3; EX1035, 6, 8 (emphases added). There is no other administration of rituximab described in the Rituxan™ label other than intravenous administration. Thus, it would have been obvious to administer rituximab consisting of an intravenous administration in view of the Rituxan™ label's explicit instructions to do so. EX1002 ¶112.

Claim 1 thus would have been obvious. *Id.* ¶113.

2. Claims 2, 4, 6, and 10

Claim 2 is substantially similar to claim 1, but incorporates additional limitations requiring "more than one intravenous dose" of rituximab and "administering to the human glucocorticosteroid." Neither limitation distinguishes the claimed method from the teachings of the prior art.

First, the method taught by the Rituxan™ label to deplete human B-cells by administering rituximab expressly required "four weekly intravenous infusions of 375mg/m^2 of rituximab," which is "more than one intravenous dose." EX1006, 1; EX1012, 3; EX1035, 8; EX1002 ¶115. Thus, because a POSA would have been motivated to follow (or at least start with) the treatment regimen of the Rituxan™ label to treat vasculitis manifestations in SLE with a reasonable expectation of success, this limitation would have been obvious. EX1002 ¶115. While the original "recommended" dose was approved for low-grade NHL, this dose would have been an obvious choice for treating vasculitis with SLE because the Rituxan™ label

disclosed that this dose led to the "rapid and sustained depletion" of B-cells in patients and because rituximab works by binding to the CD20 antigen that is expressed on *both* malignant and healthy B-cells. *Id.*; EX1006, 1; EX1012, 1; EX1035, 7.

Second, the Rituxan™ label taught that rituximab "is associated with hypersensitivity reactions" that afflict approximately 80% of patients in their first infusion of rituximab. EX1006, 1; EX1012, 1–2; EX1035, 7. To treat these expected reactions, the label recommended "[m]edications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines, *and corticosteroids*." EX1006, 1; EX1012, 2 (emphasis added). As a POSA would have known, glucocorticosteroids are a type of corticosteroids. EX1002 ¶118. Moreover, a POSA would have understood that glucocorticosteroids were a regular component of the standard treatment regimen for vasculitis in SLE. *Id.* ¶119; EX1010, 51. As explained by Dr. Massarotti, it would have also been obvious to combine rituximab with glucocorticosteroids to treat SLE because of their complementary mechanisms of action. EX1002 ¶116–119. Thus, claim 2 would have been obvious.

Claim 4 is identical to claim 2 except that paragraph (a) requires an "amount of an antibody that binds to the CD20 antigen on human B lymphocytes" and paragraph (b) specifically requires that "the CD20 antibody is rituximab." EX1001, 30:10–17. For the same reasons that it would have been obvious to arrive at the

method of claim 2 by using rituximab as the anti-CD20 agent, claim 4 also would have been obvious. EX1002 ¶121.

Claims 6 and 10 are identical to claims 4 and 1, respectively, but add the phrase "therapeutically effective amount" or "in an amount effective to deplete B-cells" to the limitations requiring administration of the anti-CD20 antibody. As discussed, the Rituxan™ label taught that four weekly intravenous infusions of rituximab at a dose of 375 mg/m^2 is therapeutically effective to deplete human B-cells, which a POSA would have expected to treat vasculitis in SLE. EX1006, 1; EX1012, 1; EX1035, 7; EX1002 ¶122. Thus, claims 6 and 10 would have been obvious.

3. Claims 3, 5, 7, 8, 9, 11, and 12

Dependent claims 8 and 11 depend from claims 1 and 10, respectively, and further require "administering glucocorticosteroid to the human." EX1001, 30:32–35, 41–42. And dependent claims 3, 5, 7, 9, and 12—which depend from claims 2, 4, 6, 8, and 11—further require that the glucocorticosteroid administered in combination with rituximab is specifically "prednisone, methylprednisolone, or dexamethasone." For the same reasons discussed above with respect to claim 2, claims 3, 5, 7, 8, 9, 11, and 12 would have been obvious. EX1002 ¶¶123–125. The Rituxan™ label taught the use of "corticosteroids" (e.g., glucocorticosteroids) in combination with rituximab administrations to treat "hypersensitivity reactions,"

which occurred in approximately 80% of patients. EX1006, 1; EX1012, 2; EX1035, 7.

Moreover, SLE was regularly treated with glucocorticosteroids, and it would have been obvious to combine glucocorticosteroids with rituximab because of their complementary mechanisms of action. EX1002 ¶31. Indeed, as explained by Dr. Massarotti, a POSA would have known to use methylprednisolone as the glucocorticosteroid to treat these hypersensitivity reactions because methylprednisolone was a well-known glucocorticosteroid in the art for treating general hypersensitivity or allergic reactions. Thus, claims 3, 5, 7, 8, 9, 11, and 12 would also have been obvious. *Id.* ¶125.

B. Ground IB—*Treatment of vasculitis manifestations in SLE*: Obviousness over Chan, the Rituxan™ label, Belmont, Danning, and the Kelley Textbook

Alternatively, dependent claims 3, 5, 7, 9, and 12—which depend from claims 2, 4, 6, 8, and 11, and further specify that the glucocorticosteroid administered in combination with rituximab is "prednisone, methylprednisolone, or dexamethasone"—would have been obvious in view of the Kelley Textbook when combined with the references discussed in Ground IA.

As discussed above for claims 2, 8, and 10, it would have been obvious to administer glucocorticosteroids in combination with rituximab to treat vasculitis. EX1002 ¶127. In particular, as the Kelley Textbook makes clear, vasculitis in SLE

was regularly treated with a specific glucocorticosteroid, methylprednisolone. *See* EX1010, 51. As Dr. Massarotti explains, in selecting a glucocorticosteroid to use in combination with rituximab, it would have been obvious to administer methylprednisolone because it was already part of the standard of care. EX1002 ¶127. Thus, these claims would have also been obvious for these reasons.

C. Ground IIA—*Treatment of vasculitis manifestations in GPA*: Obviousness over George, Rasmussen, Mathieson, and the Rituxan™ label.

1. Claim 1 recites an obvious method of treating vasculitis manifestations in GPA.

Independently, claim 1 would have been obvious over George, Rasmussen, Mathieson, and the Rituxan™ label. EX1002 ¶128.

a. "treating vasculitis in a human patient who does not have rheumatoid arthritis or cancer"

i. The methods of claim 1 include methods of treating vasculitis manifestations in GPA.

The method of claim 1 is directed to treating any form of vasculitis in patients without RA or cancer. EX1001, 29:39–43. A POSA would have known that this includes methods of treatment for GPA. EX1002 ¶132; *see also supra* Part V.A.2. As explained below, claim 1 was obvious.

ii. George taught that high ANCA levels correlate with increased disease activity in GPA.

George, which was never disclosed to the examiner and did not assess patients with RA or cancer, taught that ANCA levels "correlate well with the disease

activity" in GPA. EX1007, 3. Specifically, higher levels of ANCA means that the disease activity is more severe or a relapse is impending. *Id.*; EX1002 ¶133. Moreover, the presence of ANCA exacerbates the activation of neutrophils and further agitates the inflammation on the blood vessel well (i.e., the vasculitis of GPA). *Id.* at 6–7; EX1002 ¶133. Given the strong association of ANCA with GPA and its correlation with disease activity, a POSA would have been motivated to identify a therapy that targeted all sources of ANCA production (direct and indirect). *Id.* ¶133. That is, a POSA would have identified a targeted therapy that addresses the sources of ANCA production identified by Rasmussen and Mathieson—i.e., B-cells. *Id.*

iii. Mathieson and Rasmussen both taught that B-cells indirectly and directly produce ANCA.

Mathieson and Rasmussen, which were never disclosed to the Examiner and did not study patients or animals with RA or cancer, both identified CD20 B-cells as one of the primary culprits in the immune response contributing to the activation of T-cells and the production of ANCA, both of which were known to trigger GPA. EX1008, 6; EX1009, 5; EX1002 ¶134. Indeed, Mathieson taught that "the lack of a proliferative T cell response may be because T cell involvement in [primary vasculitis] is confined to the provision of B cell help" in GPA. EX1008, 5. Likewise, Rasmussen taught that the ANCA was specifically produced by CD20-expressing B-cells. EX1009, 5; EX1007, 6 (citing Rasmussen). Thus, a POSA

would have reasonably expected that depleting the B-cells using a targeted therapy would reduce both ANCA and the activated T-cells that were each known to lead to GPA. EX1002 ¶135.

iv. Rituximab was the only therapy as of May 1999 that could safely and effectively deplete human B-cells.

As the only anti-CD20 chimeric monoclonal antibody available and the only therapy that was capable of depleting the body's B-cells in a safe and effective manner as of May 1999, rituximab was the ideal and only choice to improve treatments for GPA. EX1002 ¶136. Indeed, a POSA looking for a therapy that targets B-cells, the cells that have a principal role in producing ANCA causing GPA as taught by Rasmussen and Mathieson, would have looked no further than rituximab. *Id.*

Because rituximab was known to deplete a patient's B-cells using the recommended dose as described on the Rituxan™ label, a POSA would have selected the same treatment protocol for GPA. EX1002 ¶137. The Rituxan™ label disclosed that the recommended dose for treating NHL leads to the depletion of B-cells. EX1006, 1; EX1012, 1; EX1037, 7. As such, a POSA would have administered rituximab at a dose of "375mg/m^2 given as an IV infusion once weekly for four doses" and would have had a reasonable expectation of success in depleting the

human patient's B-cells and thus treating vasculitis manifested in GPA. EX1006, 2; EX1012, 3; EX1035; 8; EX1002 ¶137.

v. It would have been obvious for a POSA to treat GPA with rituximab because it would deplete the patient's B-cells and, in turn, reduce ANCA levels.

Based on the prior art, a POSA would have been motivated to combine these prior art teachings discussed above 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. EX1002 ¶139. These teachings rendered it obvious to a POSA, with a reasonable expectation of success, to use rituximab to treat patients with vasculitis manifested in GPA by targeting the depletion of B-cells and reducing ANCA levels. *Id.*

While Rasmussen and Mathieson did not explicitly use rituximab to treat GPA, a POSA 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. *Id.* ¶140.

That reasonable expectation is further supported by the known relationship between ANCA levels and disease activity. EX1007, 3. A POSA would have reasonably expected that when ANCA levels fall following B-cell depletion, GPA disease activity would also decrease. *Id.* Accordingly, a POSA would have reasonably expected B-cell depletion resulting from rituximab to provide a therapeutic benefit in a patient with GPA. EX1002 ¶141.

b. "administering to the human a therapeutically effective amount of rituximab"

Claim 1 further requires "administering to the human a therapeutically effective amount of rituximab" to treat vasculitis. As explained in part IX.C.1.a, it would have been obvious to administer rituximab with a reasonable expectation of success to treat GPA because (1) B-cell depletion would effectively reduce ANCA production in GPA, and (2) rituximab was the only therapy available in May 1999 that could safely and effectively deplete B-cells. A POSA motivated by George to directly or indirectly target sources of ANCA production in GPA would have used the recommended dosage listed in the Rituxan™ label of "375 mg/m^2 given as an IV infusion once weekly for four doses" because that regimen leads to "a rapid and sustained depletion of circulating and tissue-based B cell." EX1006, 1–2; EX1012, 1; EX1035, 7. And because rituximab "binds to the CD20 antigen on B-lymphocytes" irrespective of whether those B-cells are cancer cells or healthy cells, a POSA would have had a reasonable expectation of success that this dosage would

be a "therapeutically effective amount of rituximab" to deplete a patient's B-cells and in turn, treat GPA. EX1006, 1; EX1012, 1; EX1035, 7; EX1002 ¶¶142–143.

c. "the administration of the rituximab consists of intravenous administration"

The limitation in claim 1 requiring that "the administration of the rituximab consists of intravenous administration" was obvious in light of the Rituxan™ label's disclosure that rituximab is a "liquid concentrate for intravenous (IV) administration" and the "recommended" dosage "is 375 mg/m^2 given *as an IV infusion* once weekly for four doses." EX1006, 1–2; EX1012, 1, 3; EX1035, 6, 8 (emphasis added). There is no other administration of rituximab described in the Rituxan™ label other than intravenous administration. Thus, it would have also been obvious to administer rituximab consisting of an intravenous administration in view of the Rituxan™ label's explicit instructions to do so. EX1002 ¶144.

Thus, Claim 1 would have been obvious. *Id.* ¶145.

2. Claims 2, 4, 6, and 10

For the same reasons mentioned above in Part IX.A.2, it would have been obvious to treat GPA using more than one intravenous infusion of rituximab and using rituximab in combination with glucocorticosteroids. EX1002 ¶146. Indeed, as described above and in Part IX.A.2, a POSA would have had a reasonable expectation of success that four intravenous infusion of rituximab would deplete a patient's B-cells and treat GPA. *Id.*

Moreover, glucocorticosteroids were part of the standard of care therapy for GPA. *Id.* ¶147. Thus, it would have also been obvious for a POSA to use glucocorticosteroids in combination with rituximab as recited in these claims. *Id.*

3. Claims 3, 5, 7, 8, 9, 11, and 12

For the same reasons discussed above in Part IX.A.3 it would have been obvious to combine glucocorticosteroids in combination with rituximab to treat GPA. *Id.* ¶148. Indeed, GPA was regularly treated with glucocorticosteroids, and it would have been obvious to combine glucocorticosteroids with rituximab because of their complementary mechanisms of action. A POSA would have also known that prednisone would have been the glucocorticosteroid of choice to treat GPA. *Id.*

D. Ground IIB—*Treatment of vasculitis manifestations in GPA*: Obviousness over George, Rasmussen, Mathieson, the Rituxan™ label, and the Kelley Textbook

For the same reasons discussed in Part IX.B, it would have been obvious to select prednisone, methylprednisolone, or dexamethasone to treat GPA. Ex 1010, 84. As Dr. Massarotti explains, in selecting a glucocorticosteroid to use in combination with rituximab, it would have been obvious to administer prednisone because it was already part of the standard of care for GPA and the Kelley Textbook disclosed that prednisone was used to treat GPA. EX1002 ¶¶149–150. Thus, these claims would have also been obvious.

E. Grounds III and IV—*Treatment of vasculitis manifestations in both SLE and GPA*: Substituting Maloney I instead of the Rituxan™ label in the combination of references used in grounds I and II.

For 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). In IPR2016-01064, Patent Owner is challenging the authenticity and prior art status that the parties in that proceeding also call "the Rituxan™ label." In view of this dispute, and out of an abundance of caution, Petitioner offers these two grounds to assert that claims 1–12 of the '843 patent would have been obvious to a POSA as of May 1999 without reliance on the Rituxan™ label (EX1006 or EX1012 or EX1035) because Maloney I provided the same disclosures as the Rituxan™ label. As explained by Dr. Massarotti, Maloney I disclosed the same teachings as the Rituxan™ label she relied upon in formulating her opinions regarding the obviousness of the claims of the '843 patent. EX1002 ¶¶152–161.

Maloney I disclosed that rituximab is a chimeric monoclonal antibody that is administered intravenously. EX1011, 1. Maloney also disclosed that four weekly intravenous infusions of 375mg/m^2 of rituximab caused "normal B cells [to] rapidly deplet[e] from the peripheral blood of nearly all patients and remained depleted until 6 months posttreatment, followed by a slow recovery." *Id.* at 6. Thus, Maloney I

disclosed that multiple infusions of rituximab can successfully deplete the "normal"—i.e., non-malignant—B-cells of a human patient. EX1002 ¶¶ 154, 161.

Moreover, Maloney I taught that: "[t]he adverse events observed in this trial were predominantly infusion related …." EX1011, 6. Along with these adverse events and others reported in Table 2, a POSA would have understood that these are allergic or hypersensitivity reactions caused by rituximab. EX1011, 4, Table 2; EX1002 ¶¶155, 161. Such reactions, as explained by Dr. Massarotti, are the typical kinds of allergic or hypersensitivity reactions that could be treated using glucocorticosteroids when treated with a chimeric monoclonal antibody. EX1002 ¶¶156–157, 161. Thus, although Maloney I did not explicitly disclose the use of glucocorticosteroids in combination with rituximab, a POSA would have known that the type of adverse events reports by Maloney I are easily treatable using glucocorticosteroids, and thus it would have been obvious to use glucocorticosteroids in combination with rituximab. *Id.*

Therefore, claims 1–12 would have been obvious irrespective of the prior-art status of the Rituxan™ label (EX1006 or EX1012, or EX1035) because Maloney I, as a §102(b) prior-art printed publication, provided the same teachings relied upon in this petition that were disclosed in the Rituxan™ label.

F. Specks' near-simultaneous invention of the claimed methods is strong objective evidence of obviousness.

Objective evidence of near-simultaneous invention further confirms that the challenged claims would have been obvious. "Independently made, simultaneous inventions, made with a comparatively short space of time, are persuasive evidence that the claimed [invention] was the product only of ordinary … skill." *Geo. M. Martin Co. v. Alliance Mach. Sys. Int'l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (quotations omitted). Moreover, alleged inventions reduced to practice even after the filing of the provisional application qualify as a near-simultaneous invention that is probative of obviousness. *See id.* at 1306.

The Specks publication, which was also never disclosed to the Examiner, provides objective evidence of near-simultaneous invention. Just eight months after the provisional application that led to the '843 patent was filed, Specks reported that independent practitioners (who do not appear to be affiliated with Patent Owner or the named inventors) treated a patient with GPA using four weekly intravenous infusions of rituximab in combination with prednisone (a glucocorticosteroid). EX1013, 3, Figure 1; EX1002 ¶¶164, 167. Specks explained that the decision to treat the patient with rituximab was based on the relatively "few side effects" associated with rituximab's approved dosing regimen, and because B-cell depletion was expected to reduce the ANCA that was known to contribute to GPA. EX1013, 4.

After administering four intravenous infusions of rituximab in combination with prednisone, the patient's B-cells were depleted and GPA went into remission. *Id.* at 3. In view of these results, Specks concluded that "[r]ituximab may represent a promising new agent for mechanism-based treatment of patients with ANCA-associated vasculitis in whom either standard therapy has failed or contraindications for standard therapy have developed." *Id.* at 5; EX1002 ¶166.

Specks therefore provides strong evidence of simultaneous invention that corroborates the obviousness of using multiple intravenous infusions of rituximab to treat vasculitis in combination with glucocorticosteroids, as claimed in the challenged claims of the '843 patent. *See Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000) ("The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art" and may be "an indication of obviousness when considered in light of all the circumstances.") (quotations omitted).

G. The alleged secondary considerations asserted during prosecution fail to demonstrate that claims 1–12 are nonobvious.

Petitioner is not aware of any probative evidence of secondary considerations that would undermine the evidence of *prima facie* obviousness discussed above—particularly in view of the objective evidence of near-simultaneous invention. EX1002 ¶169. In any event, "objective evidence of nonobviousness simply cannot

overcome such a strong *prima facie* case of obviousness." *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008).

At this stage, Petitioner has no burden to identify and rebut secondary considerations. Patent Owner must first present a *prima facie* case for such considerations, which Petitioner may then rebut. *Sega of Am., Inc. v. Uniloc USA Inc.*, IPR2014–01453, Paper 11 at 20 (PTAB Mar. 10, 2015). Thus, panels routinely reject arguments against institution based on secondary considerations. *See e.g.*, *Mylan Pharm. Inc. v. Allergan, Inc.*, IPR2016–01127, Paper 8 at 18 n.4 (PTAB Dec. 8, 2016).

Nevertheless, out of an abundance of caution, Petitioner preliminary addresses (1) the alleged "unexpected results" asserted during prosecution (which were the sole basis for allowance); and (2) the alleged "failure of others and long-felt but unmet need" that were also asserted (but which the Examiner did not credit). EX1030, 7–9. Petitioner further reserves the right to address any evidence of secondary considerations that Patent Owner may present in this proceeding.

1. The claimed methods produce no "unexpected results."

The '843 patent issued only because the Examiner's obviousness rejections were "withdrawn in view of [the Examiner's] amended claims and applicant[']s arguments regarding unexpected results." EX1030, 7–9. Those arguments were based on the 2010 Stone article (EX1014), which reports on the effectiveness of the

claimed invention to treat patients with ANCA-positive GPA without causing the side effects of cancer or infertility. However, as shown below, Stone fails to provide evidence of nonobviousness because (1) a POSA would have expected the results reported in Stone; (2) the evidence provided by Stone is not commensurate in scope with the claims; and (3) at most, the results show a mere difference in degree rather than a probative difference in kind.

a. Stone stated that the results of rituximab glucocorticosteroid therapy were expected, thus confirming that the claimed invention was obvious.

As Stone itself reports, a POSA would have expected the results reported in Stone based on what was publicly available to a POSA as of May 1999. That expectation was based on the same knowledge that would have been available to a POSA as of May 1999. Stone explained that "B lymphocytes play an important role in the pathogenesis of autoimmune disease including ANCA-associated vasculitis. In ANCA-associated vasculitis, the percentage of activated peripheral blood B lymphocytes correlates with disease activity, and certain effects of cyclophosphamide on B lymphocytes."[10] EX1014, 2. That is, Stone reported that a POSA would have expected to treat ANCA-associated vasculitis by targeting B-

[10] All the references that Stone cited for that proposition are prior art to the '843 patent.

cells. As discussed above in parts IX.A and IX.C, and as explained by Dr. Massarotti, the prior art disclosed that B-cell depletion therapy would eliminate and reduce two different pathogenic sources of vasculitis in at least two diseases. EX1002 ¶172. Thus, Stone confirms that a POSA as of May 1999 would have reasonably expected that rituximab combined with glucocorticosteroids would effectively treat vasculitis. *Id.* ¶173.

Applicants also argued during prosecution that "the skilled person would not have expected from the art that rituximab … would not cause the side effects (cancer or infertility) associated with the standard of care." EX1029, 7. However, there was nothing unexpected about rituximab's lack of side effects because the Rituxan™ label only disclosed that rituximab was associated with minor hypersensitivity reactions. EX1006, 1; EX1012, 1–2; EX1035, 7. As explained by Dr. Massarotti a POSA would not have expected that rituximab would lead to cancer or infertility. EX1002 ¶174. Thus, a POSA would not have expected that rituximab would have serious side effects as of May 1999 in view of the prior art.

b. Any alleged unexpected results obtain for GPA patients are not commensurate in scope with the claimed invention.

During prosecution, Applicants alleged that the combination of rituximab and glucocorticosteroids provided unexpectedly superior results as compared to the combination of cyclophosphamide and glucocorticosteroids in patients with

relapsing GPA as demonstrated by Stone. EX1029, 7. Moreover, Applicants also alleged that "the skilled person would not have expected from the art that rituximab would be effective in vasculitis." *Id.* But even if that were true (it is not), the scope of these alleged unexpected results is limited only to a patient sub-group having ANCA-positive GPA and is not commensurate in scope with the claimed methods, because the claims were intended to treat a much larger population—i.e., patients with ANCA-negative GPA and all other forms of vasculitis with the exception of vasculitis in RA or cancer. That is fatal to Applicant's assertion because "objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Asyst Techs. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Here, the alleged unexpected results, do not encompass all forms of GPA as Applicants originally asserted during prosecution. Indeed, Stone acknowledged that these results are not commensurate with all forms of GPA: "We enrolled only patients with severe ANCA-associated vasculitis who were ANCA-positive. Thus, it is *not clear* whether the treatment effects extend to patents with limited [GPA] or those where are *ANCA-negative*." EX1014, 9 (emphases added). Accordingly, the results obtained with respect to ANCA-positive GPA patients are not commensurate in scope with the claimed invention because both forms of GPA are covered by the claims. EX1002 ¶175.

c. The asserted "unexpected" results show, at most, a mere difference in degree, not a probative difference in kind.

"Unexpected results that are probative of nonobviousness are those that are different in kind and not merely in degree from the results of the prior art." *Galderma Labs., L.P.*, 737 F.3d at 739. Here, at most, Stone shows only a difference in the *degree* of B-cell depletion between cyclophosphamide and rituximab—not a new difference in the *kind* of effects produced by the art. EX1002 ¶176. Stone reported that both cyclophosphamide and rituximab deplete B-cells, and the only difference between the two therapies is that rituximab depletes B-cells at a slightly faster rate. EX1014, 9, Figure 3; EX1002 ¶177. Thus, with respect to the novelty of using rituximab to treat vasculitis, Stone does not establish a "significant difference in degree of the same property" that "amount[s] to a marked superiority for purposes of evaluating unexpected results." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (quotation omitted).

2. The claimed methods did not meet any "long-felt need" or overcome any "failure of others."

During prosecution, Patent Owner raised—unsuccessfully—allegations of both long-felt need and failure of others based on results reported in Stone and the NIH Article that "cyclophosphamide was the standard of care for vasculitis for more than 40 years but was associated with serious side effects including increased risk of

cancer and infertility and there was a high rate of relapse." EX1029, 6 (emphasis omitted). For at least two reasons, these arguments do not support nonobviousness.

First, even assuming "a long-felt need is established, evidence must show that the claimed invention satisfied that need." *In re Gardner*, 449 F. App'x 914, 918 (Fed. Cir. 2011) (citing *In re Cavanagh*, 436 F.2d 491, 496 (C.C.P.A. 1971)). Patent Owner, citing an NIH article (EX1015) that reported on the results of Stone (EX1014), asserted that the need was for a treatment to address "a high rate of relapse and a need for retreatment." EX1029, 6–7 (citing EX1015). Stone, however, "*focused exclusively* on remission induction *but did not address* the question of retreatment with rituximab." EX1014, 9 (emphases added). Moreover, Stone reported that "it is not clear whether the treatment effects extend to patients with limited Wegener's granulomatosis or those who are ANCA-negative." *Id.* Thus, the need for treating all forms of GPA vasculitis without retreatment, whether ANCA positive or not, remained unmet. EX1002 ¶181.

Second, the claimed invention merely combines standard glucocorticosteroid therapy with rituximab, which had just become available for the first time in November 1997 with the FDA's approval of Rituxan™. Because rituximab was not available before 1997, any "failure of others" or "long-felt need" does not suggest that combining glucocorticosteroid therapy with rituximab was nonobvious. Indeed, "once another supplied the key element [of the combination], there was no long-felt

need," and "'unsuccessful attempts to reach a solution … before that time became wholly irrelevant.'" *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1998) (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966)).

X. CONCLUSION

For the foregoing reasons, the Board should institute *inter partes* review and cancel claims 1–12 of the '843 patent as unpatentable.

Dated: November 2, 2017

Respectfully submitted,

/Jovial Wong/
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner

WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Telephone: 202-282-5000
Fax: 202-282-5100
Email: rituximabIPR@winston.com

Charles B. Klein
(to seek *pro hac vice* admission)
Eimeric Reig-Plessis
(to seek *pro hac vice* admission)

Back-Up Counsel for Petitioner

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION

Pursuant to 37 C.F.R. §42.24, I certify that the foregoing PETITION FOR *INTER PARTES* REVIEW contains 13,902 words (as calculated by the word processing system used to prepare the Petition), excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1).

Dated: November 2, 2017

Respectfully submitted,

WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Telephone: 202-282-5000
Fax: 202-282-5100
Email: rituximabIPR@winston.com

/Jovial Wong/
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner

CERTIFICATE OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), I certify that, on November 2, 2017, true and correct copies of the foregoing PETITION FOR *INTER PARTES* REVIEW, and all Exhibits thereto, were served by overnight courier service on Patent Owner at the correspondence address of record for U.S. Patent No. 8,545,843 B2, and at another address known as likely to effect service, as follows:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080

Michael R. Fleming (Reg. No. 67,933)
IRELL & MANELLA LLP
1800 Avenue of the Stars, Suite 900
Los Angeles, CA 90067

Dated: November 2, 2017

Respectfully submitted,

WINSTON & STRAWN LLP
1700 K Street NW
Washington, DC 20006
Telephone: 202-282-5000
Fax: 202-282-5100
Email: rituximabIPR@winston.com

/Jovial Wong/
Jovial Wong
Reg. No. 60,115

Lead Counsel for Petitioner