UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PFIZER, INC.

Petitioner,

v.

BIOGEN INC. AND GENENTECH, INC.

Patent Owners.

Case IPR2018-00086
U.S. Patent No. 8,545,843

PATENT OWNERS' PRELIMINARY RESPONSE

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I. INTRODUCTION

The claims of U.S. Patent No. 8,545,843 ("the '843 patent") describe methods of treating vasculitis in a human patient who does not have rheumatoid arthritis or cancer by administering to the patient a therapeutically effective amount of rituximab, an anti-CD20 antibody, alone or combined with glucocorticosteroids. Because Petitioner has failed to carry its burden to show a reasonable likelihood that it will prevail with respect to any claim of the '843 patent, the Board should deny institution.

Petitioner challenges the claims of the '843 patent on four grounds, divided into two categories. Grounds I and III challenge the claims of the '843 patent based on primary references related to the presentation of vasculitis in patients with systemic lupus erythematosus ("SLE" or "lupus"). SLE is not itself a form of vasculitis. In rare instances, patients with SLE also develop vasculitis. Such vasculitis is classified as "secondary" vasculitis. Grounds II and IV challenge the claims based on primary references related to granulomatosis with polyangiitis ("GPA"), which is classified as a "primary" vasculitis.

In each of Grounds I and II, the respective primary references are combined with Exhibits 1006, 1012, and 1035 (the "Label References"), each of which Petitioner contends is a version of the rituximab label that qualifies as prior art. Institution should be denied on each of these grounds because

Petitioner fails to establish that any one of the "Label References" is a prior art printed publication on which *inter partes* review may be based.

The Petition also contains Grounds III and IV, which are substantively identical to Grounds I and II, respectively, but replace the "Label References" with Maloney I (Ex. 1011). As outlined below, each ground also fails on the merits.

"Manifestations of Vasculitis in SLE" (Grounds I and III). Relying on a primary reference, Chan, that sought to investigate the underlying mechanisms of SLE (rather than the treatment of SLE) using genetically modified mice, Petitioner cobbles together an argument that the prior art suggested that B-cell depletion would have been an effective therapy for SLE, and by extension, vasculitis secondary to SLE. None of Petitioner's cited references describe the treatment of a patient with SLE accompanied by secondary vasculitis. Instead, Petitioner appears to assume that by following Chan's research proposal for SLE, a POSA would likely also have treated a patient with secondary vasculitis; but it is well settled that inherency cannot be established by mere probabilities. Moreover, Petitioner posits that B-cell depletion would have reduced what it alleges were known triggers of vasculitis in SLE—antibodies and activated T-cells—but cites no evidence showing that rituximab's mechanism of action was known to have any effect on them.

Some of the mice studied in Chan were genetically modified to lack the ability to produce B-cells. In these mice, Chan observed lower levels of certain markers for SLE disease activity. But SLE is not a "form of vasculitis," none of the mice in Chan were reported to have vasculitis, nor does Chan discuss vasculitis. Petitioner leaps to the conclusion that a person of skill in the art ("POSA") would have expected success in treating vasculitis secondary to SLE in a human patient via therapeutic B-cell depletion, even though such an approach was never even suggested for testing in mice.

A further fundamental problem with Petitioner's argument is that the mice in Chan upon which Petitioner relies never had any B-cells. Even assuming the absence of B-cells in mice would have led to a reduction in development of SLE, and indulging Petitioner's assertion that SLE patients can in turn present with vasculitis, Chan provided no basis to assume B-cell depletion could treat, much less reverse, vasculitis in a human patient. Unlike Chan's genetically-engineered mice, human patients who present with vasculitis have B-cells from birth and have been exposed to the immune factors produced by those cells that, under Petitioner's hypothesis, lead to their vasculitis. Nothing in Chan's experiments, or any of Petitioner's other evidence, supports its theory that a POSA would have believed that B-cell depletion after diagnosis with secondary vasculitis would have been able to reverse blood vessel damage and thereby treat the patient's vasculitis.

Petitioner simply offers no evidence to bridge this gulf between Chan's B-cell-deficient mice and the treatment of vasculitis diagnosed in human patients.

In addition, even if the prior art had suggested B-cell depletion as a potential therapy for vasculitis (which it did not), Petitioner makes the further leap that a POSA would have elected to deplete B-cells using rituximab, which was known at the time only as a treatment for cancer. Petitioner ignores numerous other known therapies for autoimmune diseases and other methods of targeting B-cells, including alternative methods discussed in the very references it cites. Petitioner also never even attempts to explain why a POSA would have expected the only known rituximab dosing protocol—for cancer—to be effective in treating a patient with an autoimmune disease. This argument is driven entirely by hindsight.

Finally, several claims of the '843 patent describe the treatment of vasculitis with combination therapies of rituximab and glucocorticosteroids. Petitioner fails to establish that a POSA would have had a reason to combine these therapies in SLE patients with secondary vasculitis with any reasonable expectation of success.

"Manifestations of Vasculitis in GPA" (Grounds II and IV). In these grounds, Petitioner's primary reference, George, disclosed an alleged correlation between substances called anti-neutrophil cytoplasmic antibodies

("ANCA") and disease activity in GPA. Petitioner begins by mistaking correlation for causation, asserting that because of the correlation reported in George, a POSA would have concluded that ANCA was a cause of GPA. From this erroneous premise, Petitioner asserts that a POSA would have been motivated to treat GPA by reducing the patient's ANCA levels by using rituximab to deplete B-cells, even though its own evidence (Maloney) observed that rituximab did not reduce patients' antibody levels. Further still, none of the cited art suggested that reduced ANCA levels were even correlated with, let alone known to cause, a decrease in GPA activity.

Like in Grounds I and III, Petitioner asserts that rituximab would have been the only B-cell depleting therapy available to the POSA, and thus was a "natural choice" for GPA therapy. Again, Petitioner ignores other options that were known in the art and fails to explain why a POSA would have expected the rituximab treatment protocol for cancer to be effective in vasculitis. And again Petitioner fails to establish that a POSA would have had a reason to further combine rituximab with glucocorticosteroids in GPA patients with a reasonable expectation of success.

For at least these reasons, and the reasons explained further below, the Board should decline to institute *inter partes* review.

II. ALLEGED PRIOR ART CITED IN THE PETITION

Petitioner failed to identify any prior art that suggested treating vasculitis using rituximab, or any other anti-CD20 antibody. The only references cited that discuss rituximab are the "Label References," which are not available in this proceeding because they are not prior art printed publications, *see* Section IV, and the stand-in Maloney I article. (Ex. 1011). These references exclusively discuss the treatment of low-grade non-Hodgkin's lymphoma ("LG-NHL"). Ex. 1002, ¶ 63 ("The Rituxan™ label provided the prescribing information for rituximab's original FDA-approved use: relapsed or refractory low grade B-cell non-Hodgkin's lymphoma."). Petitioner cites no evidence of the successful treatment of any disease other than LG-NHL with rituximab before the priority date, let alone vasculitis as claimed.

Instead, Petitioner concocts two examples—secondary vasculitis in SLE and GPA—in which the art allegedly recognized that B-cells were a causative factor. From that alleged recognition, Petitioner argues that a vasculitis therapy should "target" B-cells, that targeting B-cells must mean "depleting" B-cells, and that a POSA would have elected to do so using rituximab. As explained below, the cited references do not teach what Petitioner suggests. Instead, Petitioner relies on hindsight to fill in the blanks left between the cited art and the claims.

A. The SLE References

Petitioner's primary reference, Chan, studied "a murine model of systemic autoimmune disease." Ex. 1003, 2. Specifically, Chan examined the prevailing belief in the art that "Systemic lupus erythematosus (SLE) is typically thought of as an immune complex (IC)-mediated disease." *Id*. Instead, the authors viewed "the concept of SLE as solely an IC-mediated disease . . . unlikely to explain all of lupus pathology." *Id.* In line with its goal of challenging the accepted thoughts on SLE, Chan conducted its research regarding the underlying mechanisms of SLE against this backdrop of uncertainty. Nevertheless, Chan's discussion contains a bare proposal that "B cells would be an ideal target for lupus therapy." Ex. 1003, 7.

Chan does not elaborate on what it meant by "targeting" B-cells for lupus therapy. And though it proposed this broad area of potential future study, Chan cautioned that further research was needed to determine "the effectiveness of targeting B cells in halting the progress of systemic autoimmune disease." *Id*. at 8. Notably, Chan never mentions vasculitis.

Petitioner further relies on Belmont and Danning for their descriptions of the disease process of secondary vasculitis. Secondary vasculitis is an infrequent complication associated with SLE. *See* Ex. 1005, 1 ("Vasculitis is a rather infrequent complication of SLE and may affect a variety of organs."). From these references, Petitioner cherry-picks teachings that purportedly

showed that vasculitis in SLE is "triggered by certain known antibodies" and is also "triggered by activated T-cells," thereby allegedly establishing that B-cells are critical to the disease process of vasculitis in SLE. Pet. 38. These references are chosen in an effort to connect Chan's vague suggestion that "B cells would be an ideal target for lupus therapy," with vasculitis. But neither reference suggested targeted B-cell therapy or B-cell depletion as a potential treatment for vasculitis secondary to SLE.

B. The GPA References

Petitioner cites George for its disclosure that there may be a correlation between disease activity in GPA[1] and ANCA. Ex. 1007, 3 ("The ANCA assay is of value in monitoring the activity of WG, since it correlates well with the disease activity."). Petitioner conflates this teaching with a suggestion that ANCA is an underlying *cause* of GPA. Petitioner then takes this error a step further by asserting that by targeting the purported sources of ANCA, one would have expected to treat GPA. Pet. 48-49.

George did not suggest that the correlation of ANCA levels and disease activity implies that ANCA causes GPA, and in fact suggests that ANCA's role, if any, in the pathogenesis of GPA was not well understood. Indeed,

[1] The literature also uses the term Wegener's Granulomatosis ("WG") to refer to GPA.

George stated that "[t]he *in vivo* evidence implicating ANCA in the pathogenesis of WG is still scant and incomplete." Ex. 1007, 3. George never suggested treating GPA by reducing ANCA or the sources of ANCA.

Petitioner further relies on Mathieson and Rasmussen as purportedly teaching that "CD20 B-cells [are] 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." Pet. 49. Neither reference cures the defect in Petitioner's foundational argument—specifically, neither supports Petitioner's theory that ANCA is a cause of GPA, and that by directly or indirectly reducing ANCA, a POSA would have expected to treat GPA. The references in fact underscore the considerable uncertainty described by George. *See, e.g.*, Ex. 1009, 8 ("We are aware that there may not be specific antigens involved in the pathogenesis in that polyclonal activation of T cells and B cells may be the result of bacterial infection often seen in the WG lesions. ***With the limited knowledge on the cellular immunological response in WG available today*** it is certainly appropriate to consider ***many more hypothetical mechanisms***.") (emphasis added).

Like George, neither of Mathieson or Rasmussen suggested B-cell depletion as a potential therapy for GPA.

C. References Related to the Treatment of Cancer with Rituximab

1. The "Label References"

The "Label References" report that rituximab, the active ingredient in Rituxan®, is an antibody directed against the CD20 antigen found on the surface of B-lymphocytes. *See, e.g.*, Ex. 1006, 1. They further report that CD20 is "expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL) but is not found on hematopoeietic stem cells, pro-B cells, normal plasma cells or other normal tissues." *Id*.

The "Label References" state that rituximab binds to the CD20 antigen on B-lymphocytes and mediates B-cell lysis *in vitro*, and specifically describe rituximab's mechanism of action as follows:

> Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

Id. ("Pre-clinical Pharmacology and Toxicology"). The "Label References" do not disclose that rituximab's mechanism of action involves decreasing the presence of antibodies, eliminating previously activated B-cells, or interfering with activated T-cells.

The "Label References" disclose that rituximab is indicated for certain ***non-Hodgkin's lymphoma*** ("NHL") patients at a recommended dose of four 375 mg/m^2 infusions, and reports on studies that administered rituximab to NHL patients in four weekly 375 mg/m^2 doses. *Id*. at 1. They further note that such an administration in NHL patients "resulted in a rapid and sustained depletion of circulating and tissue-based B-cells." *Id*.

The "Label References" do not discuss vasculitis at all. Nor do they suggest that rituximab would be safe and effective for depleting B-cells in patients other than NHL patients, whether healthy or diagnosed with a different disease.

2. Maloney 1997 (Ex. 1011)

Petitioner relies on Maloney 1997 for the same disclosures as the "Label References" and uses it as a fallback in case the Board finds (as it should) that Petitioner failed to establish that any of the "Label References" is a prior art printed publication. Like the "Label References," Maloney I contains no disclosures regarding the treatment of vasculitis, and is similarly irrelevant to the claims at issue in this proceeding. Indeed, Maloney concludes by enumerating five specific "[a]dditional areas that should be investigated using [rituximab]." Ex. 1011, 7. All five areas relate to the treatment of cancer, and none suggested investigating the use of rituximab to treat primary or secondary vasculitis.

Maloney notes that "[t]he method of tumor cell killing by [rituximab] is not completely understood and likely involves several mechanisms." *Id* at 6. Maloney posits that the mechanism may involve ADCC, "inhibit[ing] the cell cycle," and "directly induc[ing] apoptosis." *Id.* at 7. As with the "Label References," Maloney does not disclose that rituximab's mechanism of action involves decreasing the presence of antibodies, eliminating previously activated B-cells, or interfering with activated T-cells. Of particular note, Maloney observed that even following "depletion of B cells, there was minimal change in serum Ig [*i.e.* antibody] levels" in the patients studied, suggesting that rituximab was not known to decrease antibodies. *Id.* at 6.

Petitioner concedes that "Maloney I did not explicitly disclose the use of glucocorticosteroids in combination with rituximab." Pet. 56.

III. CLAIM CONSTRUCTION

Petitioner argues that the term "vasculitis" should be given its broadest reasonable construction, excepting from the claim scope vasculitis in patients with rheumatoid arthritis ("RA") or cancer. Pet. 25. Petitioner's expert contends that "[a]part from those explicit exemptions, a POSA would have understood that the phrase 'vasculitis' means inflammation of the blood vessels resulting from any disease, condition or disorder that can cause said inflammation." Ex. 1002, ¶ 87. Because no issue raised in the Petition turns on Petitioner's proposed construction of "vasculitis," Patent Owner does not

contest this interpretation for purposes of this proceeding, and the Board need not construe the term.

IV. PETITIONER FAILED TO ESTABLISH THAT THE "LABEL REFERENCES" ARE PRIOR ART TO THE '843 PATENT

A patent claim can be challenged in *inter partes* review "only on the basis of prior art consisting of patents or printed publications." 35 U.S.C. § 311(b). "'[P]ublic accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' bar under 35 U.S.C. § 102(b)." *SRI Int'l Inc. v. Internet Sec. Sys., Inc*., 511 F.3d 1186, 1194 (Fed. Cir. 2008). "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *Id*.

Petitioner has not established that any one of the "Label References" was a prior art printed publication.

A. The "FDA Label"

Petitioner fails to establish that the "FDA Label" was either disseminated before the priority date or was otherwise sufficiently accessible to the interested public. Petitioner asserts that Exhibit 1006 "is a true and accurate copy of the original 1997 drug label for Rituxan™ that was approved by the FDA in November 1997." Pet. 31. Even if this were true, Petitioner's evidence

does not establish that the document of Exhibit 1006 was actually disseminated or otherwise made available to POSAs in November 1997. Exhibit 1006 itself suggests that it is not an official FDA communication or a commercial package label since it contains what appears to be handwriting at the top of the document partially spelling "***Rit***uximab" in vertical orientation. It is highly unlikely that a document annotated with half the product name written at the top was commercially distributed with the commercial product or communicated by FDA as the "original 1997 drug label" for the Rituxan® product.

The Board's decision in *Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, No. IPR2016-01566, 2017 WL 506739 at *4 (P.T.A.B. Feb. 3, 2017) is instructive. There, the "Petitioner contend[ed] that the Glucophage® Label qualifies as prior art under 35 U.S.C. §102(b) because it was approved and published by the FDA for treating type 2 diabetes in February 2001." *Id.* at *4. In its decision denying institution, the Board held that the purported label itself, without more, was insufficient to show it was a publicly accessible printed publication. *Id.* at 11. So too here. Exhibit 1006 contains none of the hallmarks of a document published or disseminated before the priority date.

Moreover, even accepting as true Petitioner's statement that Exhibit 1006 is "the original 1997 drug label for Rituxan™ that was approved by the FDA in November 1997," Pet. 31, Petitioner offers no evidence suggesting that

the document was made publicly accessible before the priority date. Petitioner cites the declaration of its Expert Librarian, Dr. Scott Bennett, as confirming that "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.*; Ex. 1025, ¶ 70. But nothing on face of the document itself suggests that it was made available on November 26, 1997. At most, the document includes a copyright date at the bottom of page 2, which Dr. Bennett appears to recognize when he testifies only that the attachment to his declaration corresponding to Exhibit 1006, "Attachment 4b," indicates that "[Ex. 1006] was issued in November 1997." Ex. 1002, ¶ 70. But that is not evidence that the document was publicly accessible as of that date. *Pfizer Inc. v. Biogen, Inc. and Genentech, Inc.*, No. IPR2017-01115, Paper No. 65, at 15 (P.T.A.B. February 21, 2018) ("the -01115 Decision") ("Petitioners have not identified any authority for considering a copyright date on the Rituxan Label as evidence of public accessibility of the document on that date."); *See also In re Lister*, 583 F.3d 1307, 1312-13, 1317 (Fed. Cir. 2009) (holding that an official certificate of registration from the Copyright Office does not establish that a document is a printed publication).

It appears that Dr. Bennett is relying on the URL cited in his declaration to provide the November 26, 1997 date. The URL pasted in his declaration is <https://www.accessdata.fda.gov/drugsatfda_docs/label/1997/ritugen112697-

lab.pdf>. Dr. Bennett makes the bald assertion that "the drug was originally approved on 26 November 1997." Ex. 1025, ¶ 70. Even if that statement were true, it does not establish that the document was made publicly available on that date. In any event, the statement should be disregarded altogether because Dr. Bennett does not offer any foundation for his testimony or otherwise establish that he is competent to ascribe meaning to the date information present in the URL. Dr. Bennett does not purport to have firsthand knowledge about the past or present practices of the FDA. He does not claim to ever have worked there, nor does he offer any other explanation justifying his conclusion regarding the URL's meaning. *See ActiveVideo Networks, Inc. v. Verizon Communs., Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012) (discounting expert testimony where the expert "never provided any factual basis for his assertions"); *Delphix Corp. v. Actifio, Inc.*, IPR2015-01678 (Paper 8), at 20 (P.T.A.B. Feb. 10, 2016) (denying institution where Petitioner relied on "conclusory expert testimony that, itself, does not cite to evidentiary support").

Moreover, that the document of Exhibit 1006 "is available today from the FDA's website," Pet. 31, does not establish that it was available to a POSA before the priority date of the '843 patent. -01115 Decision at 15 (Petitioner has not "shown that the Rituxan Label it retrieved from the FDA website in 2016 was available on that site prior to the critical date of the [patent]."). Nor does Petitioner cite any evidence that it was. In any event, Petitioner never

contends that a POSA actually viewed or would have been able to discover the "FDA Label" before the priority date. Petitioner thus fails to meet its burden to prove that Exhibit 1006 is a prior art printed publication.

B. The "Website Label"

Petitioner also contends that "[t]he 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." Pet. 32. Petitioner contends that because of "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*. This argument fails because Petitioner failed to establish by competent evidence that the "Internet Archive" actually captured the "Website Label" on January 23, 1998.

Petitioner contends that Exhibit 1012 was captured by the Internet Archive, and thus available on Genentech's website, as of January 23, 1998. Pet. 32. To establish this alleged publication date, Petitioner again relies on the testimony of Dr. Bennett. Dr. Bennett testifies that the document alleged to be the "Website Label," "Attachment 4c," is a "copy of an Internet Archive capture, made on 23 January 1998, of a Genentech Webpage that presents an HTML version of Document 4 and is described as the 'Full Prescribing

Information for Rituxan™." *Id.* at ¶ 71. The only support that Dr. Bennett offers for the proposition that the capture was "made on 23 January 1998" is general testimony regarding the alleged operation of the Internet Archive's "Wayback Machine." *Id*. at ¶¶ 27-32. However, Dr. Bennett does not offer any foundation for such testimony or otherwise establish that he is competent to offer it. Dr. Bennett does not purport to have firsthand knowledge about the past or present activities or capabilities of the Internet Archive organization, nor does he claim to ever have worked there. He cites no source or support for his bald assertion that "[c]rawlers automatically create a snapshot of webpages as they existed at a certain point in time" and that "[t]he Wayback Machine is an application using a crawler created by the Internet Archive to search its archive of Web page URLs and to represent, graphically, the date of each crawler capture." *Id.*, ¶ 28. Nor does he cite any source or support for his assertion that "the URL for the capture begins with the identification of the Internet Archive page (e.g., http://web.archive.org/web/) followed by information that dates and time stamps the capture as follows: year in yyyy, month in mm, day in dd, time code in hh:mm:ss (e.g., 20041208081749, or 8 December 2004 at 8:17:49 a.m.) . . . followed by the URL of the original capture site." *Id.* at ¶ 30. Notably, Exhibit 1012 bears no "URL for the capture." Ex. 1012. Dr. Bennett claims that "[t]he Internet Archive is a resource that is well known to library professionals and is used by many such

professionals." *Id.* at ¶ 32. But even assuming that is true, it does not establish library professionals as competent to testify as to what goes on—or allegedly has gone on—at the Internet Archive organization, including the alleged activities or capabilities of Internet Archive crawlers. Dr. Bennett can offer only speculation about the operation of the Internet Archive's "crawlers," and does not purport to have any knowledge about the alleged webpage of Exhibit 1012. Thus, Petitioner has failed to meet its burden of establishing that the "Website Label" is prior art to the '843 patent. *See ActiveVideo Networks, Inc.* 694 F.3d at 1327.

Petitioner relies on *IBM Corp. v. Intellectual Ventures II LLC*, No. IPR2015-00089, Paper 44, at 57 (P.T.A.B. Apr. 25, 2016) as allegedly holding that "Wayback Machine evidence" is sufficient to "determine that a Petitioner has shown that [a reference] was publicly available." Pet. 34. But that case is inapposite for at least two reasons. First, the "Wayback Machine evidence" in *IBM Corp.* was a "Butler Affidavit" from "the Office Manager of the Internet Archive, which includes the Wayback Machine service." *IBM Corp.*, IPR2015-00089, Paper No. 44 at 54. Here, by contrast, Petitioner offers only an unsupported declaration by Dr. Bennett, an individual unassociated with the Internet Archive. Second, the holding on which Petitioner relies addresses the ***admissibility*** of evidence in the context of a Motion to Exclude, not whether "Wayback Machine evidence" is ***sufficient*** to establish a particular publication

date. *See Id.* at 50-57. Accordingly, Petitioner fails to establish that Exhibit 1012 is a prior art printed publication.

Petitioner's arguments regarding Dr. Massarotti's purported ability "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," Pet. 33, also fail. Petitioner did not submit any exhibit allegedly showing the Genentech Homepage as it appeared in January 1998, and for the same reasons discussed above, Dr. Bennett's testimony failed to establish that any such hyperlink, viewed today, accurately display's the content that was displayed at the hyperlink before the priority date.

Similar to its failure to establish the "Website Label" as a printed publication in IPR2017-01166, Petitioner here too did not "endeavor to establish that the Rituxan Webpage, or the Genentech website of which it was a part, was well-known to the community interested in the subject matter of the reference, indexed, or that it included numerous related articles." *See Pfizer, Inc. v. Biogen, Inc.*, No. IPR2017-01166, Paper No. 9 at 15 (P.TA.B. Nov. 13, 2017) ("the -01166 Decision"). Dr. Bennett's assertion that "[t]he reasonable conclusion is that (1) Internet search engines in 1997 and 1998 would have been able to find and index document 4, and (2) that a reasonable diligent researcher or member of the public interested in this subject in 1997 and 1998 using typical Internet search tools would have readily found a copy of

Document 4 by at least 23 January 1998," Ex. 1025, ¶ 71, is substantively identical to Dr. Bennett's testimony in the prior proceeding, which the Board called "unsupported and conclusory testimony [that is entitled to] little weight." -01166 Decision at 15.

Petitioner's further reliance on Dr. Massarotti's testimony does not cure these deficiencies. Her testimony fails to establish that the Genentech website was well-known in the community interested in the subject matter of the reference. *See* -01115 Decision at 19 (finding that Petitioner failed to "offer[] evidence indicating that persons skilled in treating rheumatoid arthritis would have identified and visited Genentech's website before the critical date, and in doing so, would have searched for rituximab drug information, a product newly manufactured and ***indicated for the treatment of non-Hodgkin's lymphoma.***") (emphasis added). Her ability to allegedly discover the relevant document after being spoon-fed by counsel the starting point—the purported 1998 homepage—fails to establish that, in 1998, the website would have been known to POSAs or otherwise discoverable using search tools.

C. The "PDR Label"

Petitioner contends that 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)." Pet. 34. Petitioner cites no evidence supporting its claim that that the document of Exhibit 1035 "was date

stamped by the National Library of Medicine on December 30, 1998." Pet. 34. It simply asserts that it was. *Cf. In re Hall*, 781 F.2d at 897, 900 (Fed. Cir. 1986) (Librarian's affidavit establishing normal time frame and practice of indexing, cataloging and shelving doctoral theses established that the thesis in question would have been accessible by the public before the critical date); *Samsung Elec. Co. v. Image Proc. Techs. LLC*, No. IPR2017-00336, Paper No. 15, at 31-37 (P.T.A.B. May 25, 2017) (presenting testimony of librarian based on ***her own personal knowledge and experiences*** regarding the public accessibility date of a contested reference).

There is no evidence supporting Petitioner's assertion that the purported date stamp was placed there, by an unknown person, on the date it states. Petitioner provides only a photocopy that appears to show a date-sticker placed over a page of the document from which it copied. *See* Ex. 1035, 2. The sticker on its own is insufficient to establish the document's date of availability. On a separate portion of the page, there is another mark that appears to show a sticker or other label bearing the text "Property of the National Library of Medicine." *Id.* This sticker does not bear any date, nor is there any evidence connecting it to the "date" sticker appearing above it on the page.

Dr. Bennett, Petitioner's "expert librarian," does not opine on this document. In particular, though Petitioner offers Dr. Bennett's testimony regarding the veracity of library date stamps placed on numerous other cited

references, *see* Pet. 34-36, it does not do so for the "PDR Label." Petitioner cites paragraph 66 of Dr. Massarotti's declaration to purportedly establish the authenticity of the document, but at most she states that "after reviewing the document that has been marked as exhibit 1035, it is my opinion that this is a true and accurate copy of the rituximab entry from the 1999 edition of the PDR." Ex. 1002, ¶ 66. Even if true, Dr. Massarotti's testimony fails to establish that the 1999 edition of the PDR was made available to the interested public before the priority date. Indeed, Dr. Massarotti herself does not offer any opinion on the alleged date stamp of December 30, 1998.

Petitioner states that in *Frontier Therapeutics, LLC v. Medac Gesellschaft für klinische Spezialpraparate mbH*, No. IPR 2016-00649, Paper 10 at 21-22 & 6 n.4 (P.T.A.B. Sept. 1, 2016), a 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." Pet. 34. In that case, the petitioner relied upon the 39th edition of the PDR from 1985, which is not the version at issue here. The 1985 edition also would have been published over 20 years before the earliest priority date of the patent at issue in *Frontier Therapeutics*. *See* Ex. 2001, 1.

Here, the only date actually "indicated ***on*** the document" of Exhibit 1035, as opposed to stickers applied to the document by some

unknown means, on some unknown date, by some unknown person, is the 1999 copyright date. *See* Ex. 1035. This at best supports a publication date of December 31, 1999, which is after the priority date of the '843 patent.[2] Accordingly, Petitioner has failed to meet its burden of proving that the "PDR Label" was publicly available before the priority date.

V. GROUND I: THE CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER THE "SLE REFERENCES" IN VIEW OF THE "LABEL REFERENCES"

Petitioner asserts in the alternative that the claims of the '843 patent would have been obvious over either the combination of Chan, the "Label References," Belmont, and Danning (Ground "IA"), or Chan, the "Label References," Belmont, Danning, and the Kelley Textbook (Ground "IB"). Each sub-ground fails.

Petitioner contends that Chan would have motivated a POSA to treat SLE patients with rituximab to deplete their B-cells. Pet. 38. According to Petitioner, this would have allowed a POSA to treat secondary vasculitis in SLE patients because such B-cell depletion would also mitigate the pathogenic triggers of vasculitis in SLE. Pet. 38-39. The argument fails for multiple reasons, including the following broad categories: (i) the art did not suggest

[2] Even so, Patent Owner does not concede that the copyright notice establishes that the document was publicly accessible in 1999. *See In re Lister*, 583 F.3d at 1317.

that a POSA reasonably would have expected success in treating SLE by depleting the patients' B-cells with rituximab; and (ii) even if the art had suggested the administration of rituximab to SLE patients, there was no suggestion that rituximab would have been able to treat vasculitis—damage to blood vessels—that may occur in some unidentified and rare subset of SLE patients.

A. Petitioner Failed To Establish That Any Of The "Label References" Is A Prior Art Printed Publication.

Petitioner failed to establish that any one of the "Label References" was publicly available before the priority date, as discussed in Section IV. Accordingly, those references do not "fall[] within the proper scope of an *inter partes* review," *Cisco Sys. v. Constellation Techs.*, No. IPR2014-01085. Paper No. 11, at 9 (P.T.A.B. Jan. 9, 2015), and Grounds IA and IB fail.

B. There Was No Suggestion To Use Rituximab To Treat SLE And No Reasonable Expectation Of Success.

To prove that a claim is obvious, Petitioner must show "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). "[I]n the unpredictable arts such as medicinal treatment, for a method to be obvious to try, there must be some

suggestion in the prior art that the method would have a reasonable likelihood of success." *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016).

1. The Art Did Not Suggest The Use Of Rituximab To Treat SLE.

(a) Chan Did Not Suggest B-Cell Depletion As A Treatment For SLE.

Petitioner bases each ground relying upon "Treatment of vasculitis manifestations in SLE"[3] on Chan's sweeping and vague hypothesis that "B cells would be an ideal target for lupus therapy." Ex. 1003, 7. From this snippet, Petitioner and Dr. Massarotti reach the conclusion that "Chan taught that B-cell depletion would eliminate or reduce the two triggers of vasculitis in SLE: antibodies and activated T cells." Ex. 1002, ¶ 100. Chan contains no such teaching, explicit or implicit. Nor does anything in the record suggest that "targeting" B-cells is synonymous with "depleting" B-cells. But that is exactly what Petitioner's sleight-of-hand implies. At most, Chan suggested the "[e]limination of ***previously activated*** B cells," and not the non-specific depletion of all B-cells. Ex. 1003, 7.

Petitioner hones in on Chan's suggestion to explore B-cells as a target for SLE therapy only to fabricate a tenuous link between SLE and the "Label References"' description of rituximab's mechanism of action. Specifically, the "Label References"—which relate exclusively to the use of rituximab to treat

[3] Grounds I and III.

NHL—allegedly disclosed that rituximab is able to "deplete healthy or malignant CD20 B-cells." Pet. 37. But this fails for at least two reasons. First, as discussed in § II.C below, there is no evidence that rituximab's mechanism of action involved eliminating or reducing antibodies and activated T-cells, which are the purported "two triggers of vasculitis" in SLE according to Petitioner and its expert. Ex. 1002, ¶ 100. Second, to suit its proposed combination, Petitioner assumes that in order to "target" B-cells (as it claims Chan teaches), a POSA necessarily would have "depleted" them. This subtle leap serves to "define[] the problem"—identifying a therapy that would moderate the effects of B-cells in lupus patients—"in terms of its solution"—depleting the B-cells using rituximab, which "reveals improper hindsight in the selection of the prior art relevant to obviousness." *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) (quotations and citations omitted).

(b) The "Label References" Did Not Suggest Administering Rituximab To Deplete The B-Cells Of SLE Patients.

Petitioner does not (and could not) cite any passage in the "Label References" that actually suggested that rituximab would safely and effectively deplete the B-cells of an SLE patient, or any patient other than an NHL patient. It simply asserts that rituximab would do so, based solely on data that was derived from studies in NHL. *See, e.g.*, Ex. 1006. The "Label References" are completely silent as to whether rituximab would be safe and effective in

depleting the B-cells of an SLE patient. At most, Petitioner's characterizations of the disclosures of the "Label References" amount to a "hope" that depleting B-cells using rituximab would provide a possible therapeutic benefit, but provides no proof that this would be the case in SLE. *Coalition for Affordable Drugs V LLC v. Biogen MA Inc.*, No. IPR2015-01136, Paper 23, at 13-14 (P.T.A.B. Sept. 2, 2015) (when the connection between two diseases is "speculative," a reference that "at best, describes a possible therapeutic efficacy" in a yet-to-be tested disease at most "support[s] a finding that one skilled in the art 'hopes' [the drug] will be useful[, h]owever . . . a 'hope' may or may not come to pass.").

(c) Petitioner Misleadingly Suggests That Rituximab Was The Only Therapy As Of May 1999 That Could Target B-Cells.

Petitioner's obviousness theory also depends on its contention that "[r]ituximab was the only therapy as of May 1999 that could safely and effectively deplete human B-cells." Pet. 40. But this contention is unsupported by the record. The cited "Label References" contain no such suggestion, and publications available at the priority date suggested otherwise. In essence, Petitioner attempts to camouflage its hindsight selection of rituximab by suggesting that it was the only B-cell depleting therapy known at the time of the invention. Petitioner's expert does not go this far and states only that "rituximab was the only commercially available therapy that could safely and

effectively deplete a patient's B-cells." Ex. 1002, ¶ 106. Even if Dr. Massarotti's suggestion were correct (which it is not), the options available to a POSA seeking to develop a new treatment for vasculitis were not limited strictly to those therapies that were "commercially available."[4] This is particularly true given the art's uncertainty regarding the mechanisms responsible for causing SLE, and a step further, the mechanisms responsible for causing vasculitis secondary to SLE.

Indeed, in the same paragraph of Chan that Petitioner cites for the proposition that "B cells would be an ideal target for lupus therapy," Chan states that "[a] recently described treatment approach that does target autoantibodies and B cells (and probably T cells) is the combination of plasmapheresis and cyclophosphamide. Preliminary results suggest that this is indeed a disease-modifying therapy. We speculate that the heart of the efficacy of this therapy is elimination of autoreactive B cells and their APC function." Ex. 1003, 7. At the time of Chan's statement, the equipment and know-how to perform plasmapheresis were clinically available, and cyclophosphamide was

[4] Were this the standard, Petitioner's argument fails by its own admission, since it concedes that rituximab was not commercially available for vasculitis. *See* Ex. 1002, ¶ 36 (describing LG-NHL as the only FDA-approved use for rituximab before the priority date).

commercially available. Ex. 2002, 001 (treating SLE patients with plasmapheresis); Ex. 2003, 003 (referring to FDA-approved Cytoxan® (cyclophosphamide) product labeling). Yet Petitioner ignores Chan's express suggestion of plasmapheresis/cyclophosphamide—not rituximab—as a possible disease-modifying therapy. This omission simply underscores that Petitioner's combination is driven by hindsight.

Cupps further explained that cyclophosphamide (identified by Chan) was known to be an effective treatment in "nonneoplastic immune mediated diseases." Ex. 1021, 5; Ex. 1002, ¶ 29. In particular the Cupps study demonstrated that cyclophosphamide ("CY") provided a "profound suppression of B-cell function in patients treated with chronic low-dose CY for inflammatory or immunologically mediated, nonneoplastic diseases." Ex. 1021, 5; Ex. 1002, ¶ 29. Dr. Massarotti further notes that Cupps showed that cyclophosphamide "either stops or slows the growth and development of B-cells and T-cells, and it slows down or halts the B-cell antibody production." Ex. 1002, ¶ 29 (citing Ex. 1021, 3 (Fig.1)). Thus, unlike rituximab, which had only been tested in cancer (*i.e.* neoplastic disease), Cupps disclosed the use of cyclophosphamide to target B-cells in inflammatory or immunologically mediated diseases. And Dr. Massarotti confirms that "[a]ll of this would have been known to a POSA in 1998 or 1999." *Id.* Cupps therefore described the approach proposed by Chan—targeting B-cells. Ex. 1021, 5-6 ("[L]ow-dose

[cyclophosphamide] therapy has been shown to have profound and selective suppressive effects on human B cell function. The demonstration of this selective suppression may help explain the ***dramatic efficacy of this type of therapy in certain nonneoplastic diseases characterized by hyperreactivity at the B cell level expressed either by aberrant antibody production [and] circulating and deposited immune complexes.***").

Other examples in the art cast further doubt on Petitioner's contention that rituximab was the only known therapy a POSA could turn to, assuming one would have been motivated to target the B-cells of an SLE patient (one would not have been). Multani 1998 disclosed that the monoclonal antibody CAMPATH-1 and its humanized form, CAMPATH-1H, which targeted CD52, "an antigen expressed by both B and T cells" were known to deplete both B and T cells. Ex. 2004, 006. Thus, Campath-1/1H would further address Petitioner's second alleged "principal trigger[]of vasculitis" in SLE (*i.e.*, T cells).

Further, U.S. Patent No. 5,484,892 to Tedder *et al*. discloses types of anti-CD22 antibodies that "can be useful therapeutic methods for treatment of patients to treat or block B cell activation, particularly in autoimmune disease." Ex. 2005, 3:8-10. It further explains that "[a]ll antibodies are produced by B cells following antigen stimulation and activation. Therefore, blocking CD22 function, which may be critical for normal B cell adhesion activities, may

inhibit the production of antibodies including autoreactive antibodies." *Id.* 3:14-17.

Petitioner completely ignores these alternative therapies and therapeutic targets (which are merely exemplary and non-exhaustive), which were known in the art to target B-cells or otherwise address the purported pathogenic triggers of vasculitis in SLE on which it focuses its analysis: antibodies and activated T-cells. Instead, Petitioner concludes that "a POSA developing a new treatment of vasculitis in SLE would have sought to target [the] two known sources of vasculitis in SLE [antibodies and activated T cells]" using rituximab. Pet. 38-39. But again, Petitioner identifies no art expressly suggesting use of rituximab for SLE treatment, nor suggesting that rituximab's mechanism of action was known to target either antibodies or activated T-cells. *See* § II.C. In sum, Petitioner's hindsight bias is underscored by its jump to the conclusion that a POSA would have chosen rituximab, to the exclusion of any other potential therapies.

2. A POSA Would Not Have Expected Success Using Rituximab To Treat SLE In A Human Patient.

Petitioner contends that "[w]hile 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." Pet. 41. This argument fails at least

because Petitioner did not establish that rituximab would be able to successfully bind the B-cells of an SLE patient and also failed to establish that Chan's study in mice would have informed a POSA that B-cell depletion (using rituximab or any other drug), would be an effective treatment for SLE in a human patient.[5]

(a) Petitioner Does Not Even Allege, And No Cited Evidence Suggests, That Rituximab Could Bind And Deplete The B-Cells Of An SLE Patient.

Even if Chan had suggested B-cell depletion as a treatment for SLE, which, as explained above, it did not, Petitioner failed to establish that rituximab would successfully deplete the B-cells responsible for causing a patient's SLE. Petitioner alleges that "Chan, Rasmussen, and Mathieson disclosed that CD20 B-cells were the key agents in the immune response that trigger[s] vasculitis in SLE and GPA," Pet. 36, and that since "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 rituximab would be able to deplete B-cells in an SLE patient. Pet. 43. Of the three references mentioned in

[5] Later clinical trials of rituximab in SLE patients "demonstrated no difference in primary or secondary end points between the placebo group and the rituximab group over 52 weeks of treatment." Ex. 2009, 010.

the aforementioned quote, only Chan is cited in the grounds relying on SLE-associated vasculitis (Grounds I and III).[6] But Chan does not characterize the B-cells at issue in SLE as CD20 positive—CD20 is never mentioned in the article—and Petitioner does not allege that any reference taught that the B-cells specifically involved in SLE's pathogenesis were known to be CD20 positive. *Compare to* Ground II, Pet. 49 ("Rasmussen taught that the ANCA [in GPA patients] was specifically produced by CD20-expressing cells.").

The "Label References" do not support Petitioner's conclusion that rituximab would be effective in SLE. Notably, Petitioner states that the "Label References" taught that "over 90 percent of the human's B-cells express the target antigen of rituximab," (*i.e.* CD20). Pet. 41. But this is mere speculation. The "Label References" only refer to 90 percent when stating that CD20 is expressed on ">90% of B-cell non-Hodgkin's lymphomas (NHL) but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues." Ex. 1006, 1; Ex. 1012, 1; Ex. 1035, 6.

Moreover, the art did not suggest that rituximab would successfully bind and deplete the B-cells involved in the pathogenesis of SLE. In another proceeding, Petitioner acknowledged that even amongst different types of

[6] Petitioner relies on Rasmussen and Mathieson in Grounds II and IV, which address "Treatment of vasculitis manifestations in GPA."

cancer cells, the manner in which the CD20 antigen physically presents on the surface of B-cells can differ significantly, having an effect on rituximab's expected success. *See* Ex. 2006, 054-055 ("[A] POSA would have understood that the weaker density of CD20 [on a particular type of cancer cell] is akin to having a smaller 'target' for rituximab to hit, making it less likely that any given unit of rituximab successfully binds to the CD20 antigen."). In other words, by Petitioner's admission, the mere presence of CD20 on a particular B-cell alone would not have predicted rituximab's success in killing it. Accordingly, Petitioner failed to establish that rituximab would even be able to effectively bind and destroy the B-cells of an SLE patient.

(b) Chan's Studies In Genetically Modified Mice Would Not Have Predicted Success In Treating Human SLE Patients With Rituximab.

Petitioner argues that a POSA would have been motivated to pursue rituximab as a treatment for SLE based on Chan's studies in lpr/lpr mice, including in "a B-cell deficient strain" of lpr/lpr mice. Pet. 42. Petitioner alleges that the lpr/lpr mouse model studied in Chan "was well-known in the art as an excellent animal model for human SLE." Ex. 1002, ¶ 40. To the extent that the cited art establishes that the lpr/lpr mouse is a good model of SLE, it is because "the *lpr* mutation appears to have a role in the genesis of autoantibodies," allowing the mice to "develop[] anti-DNA antibodies and a lupuslike nephritis." Ex. 1019, 1.

According to Petitioner, "Chan demonstrated that disease activity i.e., the measure of the immune response responsible for SLE and vasculitis in SLE—was markedly different in [lpr/lpr] mice without B-cells." Pet. 42. Petitioner goes on to allege that "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" because Chan demonstrated that "[m]ice without B-cells had less disease activity compared to those with B-cells." *Id.* This observation is entirely unsurprising since B-cells are the cells that produce the autoantibodies that allowed the mice to model SLE in the first place. *See* Ex. 1019, 1 ("Autoantibodies, specifically anti-DNA antibodies, are the serological hallmark of SLE."). In short, the attributes of the MRL-lpr/lpr mouse that lead to its recognition as "an excellent animal model for human SLE," Ex. 1002, ¶ 40, in the cited art are not present in Chan's B-cell deficient version of the mice because they were ***bred without the ability to produce B-cells*** in the first place.

Accordingly, Chan fails to inform how unmodified lpr/lpr mice (*i.e.*, mice born with the ability to produce B-cells) would respond to B-cell depleting therapies generally, or rituximab specifically. Indeed, Chan even identified a need for further testing to determine what would happen in the B-cell deficient mice following "[r]econstitution of B-deficient MRL-*lpr/lpr* mice with various types of B cells." Ex. 1003, 7. *Id.* As discussed further below

in Section V.D, the "Label References" did not establish that it would have been safe and effective to permanently deplete a patient's B-cells as required by Petitioner's reliance on Chan. Rituximab was approved only for temporary B-cell depletion, with B-cells reported to return to their median levels following treatment. *See id.*

C. Even If A POSA Would Have Expected Rituximab To Treat SLE, One Would Not Have Expected Success In Treating Secondary Vasculitis.

As explained above, the art did not suggest the use of rituximab to treat SLE with a reasonable expectation of success. To arrive at the claimed invention—treatment of vasculitis—Petitioner further contends that the teachings of Chan, Belmont, and Danning would have led a POSA to expect success in treating a rare subset of SLE patients who also have secondary vasculitis. But even if the art suggested that rituximab should have been used in SLE (which it did not), it did not go so far as to suggest that rituximab would also have been effective in treating vasculitis secondary to such SLE.

1. The Cited References Did Not Suggest Targeted B-Cell Therapy For An SLE Patient With Secondary Vasculitis.

Petitioner argues that "Chan demonstrated that disease activity—i.e., the measure of the immune response for SLE and vasculitis in SLE—was markedly different in mice without B-cells," and thus "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." Pet. 42. This misstates the teachings of Chan, because Chan never discusses vasculitis.

Other cited art observed that "[i]t is a widely held notion that patients with [SLE] often have vasculitis," but that "[i]ts frequency and characteristics [] have not been determined." Ex. 1016, 1-2 (finding a 35.9% rate of occurrence of symptoms "suggestive of vasculitis" in cohort of 540 SLE patients). Even if Petitioner were correct that Chan's findings suggested that rituximab would treat SLE (which, as discussed above, it did not), Petitioner also appears to assume that rituximab would treat some subset of those patients with SLE-associated vasculitis. In other words, Petitioner suggests that the art would have lead a POSA to treat SLE patients with rituximab, and in turn, some of those patients would have had secondary vasculitis. Even if there was a "high" likelihood that some of those patients had vasculitis, inherency does not follow from any such likelihood. *In re Montgomery*, 677 F.3d. 1375, 1384 (Fed. Cir. 2012) ("[I]nherency does not follow even from a very high likelihood that a prior art method will result in the claimed invention."). Petitioner must show the treatment of a patient with vasculitis (in this ground, vasculitis secondary to SLE), as evidenced by the references, in order to inherently satisfy the claim limitation. Petitioner fails to do so.

2. Chan's Studies In B-Cell Deficient Mice Would Not Have Informed The Treatment Of Vasculitis.

Petitioner argues that, since Chan's "[m]ice without B-cells had less disease activity than those with B-cells, because B-cells were not present to form antibodies and to activate the T-cells," that a POSA would have expected success in treating SLE, and by extension vasculitis secondary to SLE, through B-cell depletion. Pet. 42. Putting aside the deficiencies in Petitioner's argument *vis-à-vis* Chan's applicability to the treatment of SLE with rituximab described in Section V.B, Petitioner never even contends that the Chan's mice would have modeled ***vasculitis*** in SLE. *See, e.g.*, Ex. 1002, ¶ 40 (describing Chan's mice as "an excellent animal model for human ***SLE***.") (emphasis added).

Petitioner's contentions regarding Chan's findings in B-cell-deficient mice also do not address whether depleting B-cells would have had any effect on vasculitis in a human patient. Even if a POSA would have expected rituximab to successfully deplete the B-cells of a human patient with secondary vasculitis, the patient would have produced B-cells his or her entire life, up to the point of depletion, unlike the B-cell deficient mice in Petitioner's counterfactual. In particular, under Petitioner's theory, those B-cells would have been a key contributing factor to the presentation of vasculitis in such a patient, necessary both to trigger the underlying SLE, as well as to purportedly cause the secondary vasculitis's characteristic blood vessel damage. The B-cell

deficient mice in Chan would never have faced either problem, as they were bred without the ability to produce the requisite B-cells in the first place.

Moreover, Chan, Belmont, and Danning are entirely uninformative as to whether depleting B-cells ***after*** the onset of vasculitis secondary to SLE would have been an effective treatment. At best, Chan's findings in B-cell deficient mice suggest that B-cell depletion before the onset of vasculitis (which would be impossible to recreate in a human vasculitis patient) might be prophylactic. But this is not the solution that Petitioner proposes, nor would it be safe, effective, or feasible in a human patient. No cited art suggested that depleting B-cells of a patient with vasculitic damage to his or her veins and arteries would reverse such damage and result in effective treatment. Similarly, as discussed in further detail in section V.D, below, the use of rituximab described in the "Label References" was for ***temporary*** depletion of B-cells. Nothing in the art suggested that such a temporary depletion could effectively treat vasculitis.

3. The Art Did Not Provide A POSA With A Reasonable Expectation That Rituximab Would Treat Vasculitis.

Vasculitis comprises a "diverse group of disorders characterized by inflammation of the blood vessel wall," and "may involve arteries of any size; therefore, different vasculitic syndromes may have a spectrum of clinical and pathologic features." Pet. 9-10. Under Petitioner's construction, "the phrase

'vasculitis' means inflammation of the blood vessels." Ex. 1002, ¶ 87; Pet. 25. Petitioner argues that Belmont and Danning taught that "there were two principal triggers of vasculitis in SLE: antibodies and activated T-cells." Pet. 38. Even if Petitioner established that administering rituximab to patients with vasculitis secondary to SLE would deplete their B-cells and control these triggers (it has not, *see* §§ V.B-V.C.1), it does not even allege that rituximab would treat the "inflammation of the blood vessels," which Petitioner concedes characterizes vasculitis. Pet. 25.

Moreover, Belmont states that "[v]asculitis in SLE is most commonly due to the local deposition of immune complexes, particularly those containing antibodies to DNA, in blood vessel walls." Ex. 1004, 3-4. Vasculitis results from chemical reactions which generate toxins that in turn infiltrate blood vessel walls and result in the blood vessel damage characteristic of vasculitis. *Id*. at 4. Petitioner alleges only that "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." Pet 40-41. But this ignores Petitioner's evidence that the immune response is only one step in the pathogenesis of vasculitis in SLE. As further explained by Danning, following the immune responses and deposition of immune complexes in the blood

vessels, the complexes undergo further chemical reactions, and those substances in turn damage the blood vessels. Ex. 1005, 2.

Petitioner does not allege, let alone offer evidence from the prior art, establishing that B-cell depletion therapy, initiated in a patient already presenting with vasculitis secondary to SLE, would successfully treat the patient. Chan's B-cell deficient mice never had B-cells and thus were incapable of generating the immune complexes that react to form vasculitis-causing toxins in the first place. In contrast, any human patient presenting with vasculitis and thus targeted by Petitioner's proposed therapies would already have generated the pathogenic immune cells, and they would already have reacted so as to cause inflammation and damage to the blood vessels. Even if depleting B-cells would shrink the supply of potential triggers, there is no indication that doing so would have had any effect on the vasculitic symptoms already presenting in the patient. As noted above, Belmont attributed vasculitis in SLE to the deposition of immune complexes on the blood vessel walls. While B-cells may be involved in the creation of these complexes, the complexes themselves are not B-cells. Nothing in the art suggested that a POSA would have assumed that these complexes—and the blood vessel damage for which they are responsible—would vanish as a result depleting a vasculitis patient's B-cells.

D. A POSA Would Not Have Expected To Achieve The Permanent Depletion Of B-Cells Required By Petitioner's Theory Using The Rituximab Dosing Regimen For NHL.

Petitioner contends that Chan's observation of reduced SLE "disease activity" in MRL-lpr/lpr mice bred without B-cells is predictive of the efficacy of rituximab in SLE patients, including those presenting with secondary vasculitis. As explained above, this is not the case. Even so, Petitioner's proposal presupposes a therapy that results in a ***permanent*** depletion of B-cells, so as to cause immune system conditions that most closely mimic the mice bred without B-cells upon which its approach is based. Yet Petitioner contends that "[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/m^2 given as an IV infusion once weekly for four doses' because that regimen—according to the FDA-approved Ritxuan™ label—leads to 'a rapid and sustained depletion of circulating and tissue-based B cell[s].'" Pet. 43.

The dosages disclosed in the "Label References," however, were not designed to, and did not result in, a permanent depletion of B-cells. Indeed, the "Label References" recognized that "B-cell recovery began at approximately six months following completion of treatment," and that "[m]edian B-cell levels returned to normal by twelve months following completion of treatment." *See, e.g.,* Ex. 1006, 1. Petitioner cites no evidence that the treatment regimens in the "Label References" would have led a POSA to

believe that their goal was to maintain a complete depletion of B-cells. Indeed, the dosing regimen in the "Label References" suggested that rituximab was administered to NHL patients in four weekly doses of 375 mg/m^2, within the window of depletion that would be expected from the first dose, for example to ensure a complete depletion of ***cancerous*** B-cells once and for all before allowing healthy B-cells to grow back. This is a key distinction between NHL therapy, in which rituximab binds and kills the malignant (cancerous) B-cells, and therapy for chronic autoimmune diseases like SLE, in which the B-cells themselves allegedly are "healthy cells", Pet. 43, but play a role in the manifestation of the disease. Ex. 1005, 1. In NHL treatment, the goal is to eliminate the patient's B-cells with the hope that only healthy B-cells will regenerate and replace the cancerous ones.

Put simply, nothing in the "Label References" suggested that rituximab would be safe and effective to maintain a permanent and complete depletion of a patient's B-cells. Nor does Petitioner suggest a dosing regimen that would have done so. Yet its only purported evidence of a method of treating SLE (one step removed from SLE-associated vasculitis) is that Chan observed some comparative reduction in ***SLE*** (not vasculitis) disease activity in mice that never had B-cells in the first place. There is simply no evidence that the "Label References"' dosing regimen, which taught the regeneration of healthy B-cells

following the eradication of the cancerous ones, is equivalent to the life-long B-cell deficiency of Chan's mice.

In short, none of Chan, Danning, and Belmont support Petitioner's assertion that a temporary depletion of B-cells would be effective "to deplete a patient's B-cells and in turn treat vasculitis in SLE." Pet. 43. This is particularly true given that Petitioner's only evidence of reduced disease activity occurred in mice that were bred without the ability to produce B-cells in the first place. Even assuming that the dosing regimen for NHL would achieve a six month depletion of an SLE-vasculitis patient's B-cells, Petitioner does little more than offer a guess, untethered to anything in the prior art, that such a temporary depletion would treat the patient's vasculitis. This shortcoming is particularly stark given that, whatever it might say about the genesis of SLE, none of Petitioner's evidence addresses whether B-cell depletion (of any duration) could in any way treat vascular injury. *See* § V.C.2.

E. There Was No Reason To Combine Rituximab With Glucocorticosteroids (Claims 2-9, 11-12).

Petitioner contends that the "Label References" further taught that "rituximab 'is associated with hypersensitivity reactions' that afflict approximately 80% of patients in their first infusion of rituximab," and that "[t]o treat these expected reactions, the label recommended '[m]edications for the treatment of hypersensitivity reactions e.g., epinephrine, antihistamines,

and corticosteroids.'" Pet. 45. Petitioner's selective parsing of the quotations from the "Label References" is misleading. The "Label References" discuss hypersensitivity reactions and corticosteroids under the heading "Warnings." *See* Ex. 1006, 1. This section does not state that 80% of patients experienced hypersensitivity reactions. The 80% figure is only mentioned under the heading "Adverse Reactions" and subheading "Infusion-Related Events," approximately ten paragraphs below the discussion of hypersensitivity reactions. *See id.* These infusion-related events were not described as "hypersensitivity reactions" and were "resolved with slowing or interruption of the RITUXAN infusion and with supportive care (IV saline, diphenhydramine, and acetaminophen)." *Id.* The supportive care for these patients did not include glucocorticosteroids. *See id.* Accordingly, Petitioner's suggestion that the label recommended glucocorticosteroids for these patients is unsupported by its cited evidence. Nor has Petitioner established that a POSA would have been concerned with hypersensitivity reactions when administering rituximab to an SLE patient or any patient other than the NHL patients discussed in the "Label References."

Petitioner further argues that "a POSA would have understood that glucocorticosteroids were a regular ***component*** of the standard treatment regimen for vasculitis in SLE." Pet. 45 (citing Ex. 1010, 51) (emphasis added). None of the combinations disclosed in the Kelly textbook include rituximab or

any other biologic, and Petitioner fails to explain why a POSA would have elected to pluck the glucocorticosteroids from the combination therapies disclosed in Kelly to combine them with rituximab, to the exclusion of the other components. Nor does Petitioner establish that a POSA would reasonably have expected such combinations to be safe and effective.

Petitioner further makes the bare assertion that "it would have been obvious to combine rituximab with glucocorticosteroids to treat SLE because of their complementary mechanisms of action." Pet. 45. Even if this statement were true (it is not), it is insufficient to render any claim of the '843 patent obvious, because each one requires the treatment of ***vasculitis*** and not just SLE. To the extent that Petitioner is contending that some SLE patients would likely also have vasculitis, such an improper inherency argument should be rejected. *See* § V.C.1.

Moreover, before the priority date, the art suggested that the mechanisms of action of steroids and rituximab may interfere with one another—the antithesis of "complementary mechanisms of action." Specifically, it was known that steroids might prevent the recruitment of immune effector functions to mediate B-cell lysis including antibody dependent cellular cytotoxicity. *See* Ex. 2007, 017 ("Glucocorticoids inhibit NK-mediated cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC)."). ADCC

was one of the mechanisms by which rituximab was known to destroy B-cells. *See* § II.C.

Thus, Petitioner failed to establish that a POSA would have had any reason to combine rituximab with glucocorticosteroids to treat a vasculitis patient with a reasonable expectation of success.

VI. GROUND II: THE CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER THE "GPA REFERENCES" IN VIEW OF THE "LABEL REFERENCES"

Petitioner also contends that the claims of the '843 patent would have been rendered obvious by the "GPA References" in view of the "Label References." Petitioner contends that George (Ex. 1007) disclosed that there was a "strong association of ANCA with GPA and its correlation with [GPA] disease activity" which would have motivated a POSA "to identify a therapy that targeted all sources of ANCA production (direct and indirect)" in order to treat GPA. Pet. 49. Petitioner then turns to Rasmussen and Mathieson as purportedly identifying the direct and indirect sources of ANCA production. Specifically, Petitioner contends that Rasmussen and Mathieson identified B-cells as "the sources of ANCA production," and that "a POSA would have identified a targeted therapy" in order to address those sources. Pet. 49. Though no reference suggested doing so, Petitioner contends that reducing or eliminating ANCA would be effective to treat GPA, and that a POSA would have done so using B-cell depletion therapy. Specifically, Petitioner jumps to

the conclusion that a POSA "would have looked no further than rituximab." Pet. 51. The Board should reject these arguments.

Petitioner also fails to establish in either of Grounds IIA or IIB that any of the claimed combination therapies of rituximab and glucocorticosteroids would have been obvious.

A. Petitioner Failed To Establish That Any Of The "Label References" Is A Prior Art Printed Publication.

Petitioner failed to establish that any one of the "Label References" was publicly available before the priority date, as discussed in Section IV. Accordingly, those references do not "fall[] within the proper scope of an *inter partes* review," *Cisco Sys.*, Paper 11, at 9, and Ground II fails.

B. The Art Did Not Suggest That Depleting B-Cells Would Treat GPA.

Petitioner contends that the "GPA References" contained teachings that would have led a POSA to conclude that GPA should be treated by targeting B-cells, specifically by administering a therapy that would deplete B-cells. The "GPA References" would not have led a POSA to such a conclusion.

1. George Did Not Teach That ANCA Was Known To Cause GPA.

Petitioner relies on George, which discloses a "correlation" between ANCA levels and GPA disease activity, to argue that "a POSA would have been motivated to identify a therapy that targeted all sources of ANCA (direct

and indirect)" in order to treat GPA. Pet. 49. This reveals Petitioner's unstated and fallacious assumption that this correlation implies causation, that is, that ANCAs cause GPA and that GPA disease activity could therefore be reduced by decreasing ANCA levels. But George only disclosed "that ANCA levels '***correlate*** well with the disease activity' in GPA." Pet. 48 (quoting Ex. 1007, 3) (emphasis added). George does not suggest that this correlation implicated ANCA as a cause of GPA or a target for treatment, and Petitioner's attribution of this suggestion to George should be rejected. *Norfolk & W. Ry. Co. v. Ayers*, 538 U.S. 135, 173 (2003) ("Correlation is not causation."); *USEC Inc. v. United States*, 34 F. App'x 725, 729, n.* (Fed. Cir. 2002) (conflating correlation with causation "is obviously fallacious"); Ex. 2008 (The fact that a "measure correlates with a biological event does not mean that it is caused by this event, because correlation does not imply causation.").

Petitioner relies on Dr. Massarotti's testimony, Ex. 1002 at ¶ 133, to justify its interpretation that George taught that "higher levels of ANCA means that the disease activity is more severe or a relapse is impending" and that "the presence of ANCA exacerbates the activation of neutrophils and further agitates the inflammation on the blood vessel wall." Pet 49. This overstates George's disclosures. At most, George taught that POSAs observed that the presence of ANCA often increased at times when GPA activity was at its highest. This does not at all suggest or provide a motivation to "target[] all

sources of ANCA production" in order to treat GPA because George did not suggest that by reducing ANCA levels (either directly or indirectly), the patient's GPA could be treated.

In fact, George taught that a POSA would not have expected there to have been the causal relationship between ANCA and GPA that Petitioner implies existed. Though it recognized a correlation between ANCA and disease activity, George stated that "[t]he *in vivo* evidence implicating ANCA in the pathogenesis of WG [GPA] ***is still scant and incomplete***." Ex. 1007, 3 (emphasis added). Given this admitted uncertainty regarding the mechanisms causing GPA, a POSA would not have jumped to the conclusion, as Petitioner does, that controlling the production of ANCA would lead to success in treating GPA. Underscoring the uncertainty a POSA would have had regarding the disease process of GPA, George went on to suggest that "[a]ctivation of the neutrophils by ANCA could [] be ***partly responsible for enhancement*** of the inflammatory processes observed in WG" but notes that POSAs did not understand "how infections eventually lead to the local damage observed within the vessel walls and the renal system." Ex. 1007, 4 (emphasis added).

At best, George disclosed a series of bare hypotheses regarding the role ANCA in the pathogenesis of GPA. It never expressly suggested that targeting the sources of ANCA production (whether directly or indirectly) would treat GPA. It certainly does not suggest doing so by depleting B-cells, whether with

rituximab or otherwise. Petitioner's citation of Rasmussen and Mathieson as allegedly teaching that "CD20 B-cells [are] one of the primary culprits in the immune response contributing to the activation of T-cells and the production if ANCA, both of which were known to trigger GPA," Pet. 49, is simply irrelevant, because, as set forth above, Petitioner builds from the faulty premise that the George taught that ANCA caused GPA. Accordingly, a POSA would not have had any reason to expect success in treating GPA by reducing ANCA levels.

2. None Of The Cited References Suggested Reducing ANCA Levels With B-Cell Depletion Therapy To Treat GPA.

None of the cited references suggested that a POSA would have expected B-cell depletion to provide a therapeutic benefit in GPA patients. Despite this lack of evidence, Petitioner concludes that "a POSA would have reasonably expected that depleting the B-cells using a targeted therapy would reduce [] ANCA" that was "known to lead to GPA." Pet. 49-50. But, as explained above, the evidence does not suggest that ANCA was "known to lead to GPA." Pet. 50. Moreover, there is no evidence that rituximab's mechanism of action involved reducing any antibody levels, let alone ANCA levels in particular. *See* § II.C; Ex. 1011, 6 (observing that even following "depletion of B cells, there was minimal change in serum Ig [*i.e.* antibody] levels[.]").

Petitioner also contends that B-cell depletion with a targeted therapy would "reduce … the activated T-cells that were [] known to lead to GPA." Pet. 49-50. Petitioner does not point to any evidence that suggests that activated T-cells were known to lead to GPA (or that B-cell depletion can reduce activated T-cells). Petitioner and Dr. Massarotti reach the conclusion that "'activated T-cells … were known to lead to GPA" based on Mathieson's disclosure that "the lack of a proliferative T cell response may be because T cell involvement in [vasculitis] is confined to the provision of B cell help' in GPA." Ex. 1002, ¶ 135 (citing Ex. 1008, 6) (brackets Dr. Massarotti's). The cited passage contains no suggestion that activated T-cells were known to lead to GPA. In fact, the sentence preceding Dr. Massarotti's quotation describes new research that shows "functional differences within T cell subsets," and shows that one subset "is responsible for providing B cell help and that a different subset is involved in proliferative T cell responses." Ex. 1008, 6. Because the Mathieson study "could only detect the latter subset," they concluded that "the lack of a proliferative T cell response ***may*** be because T cell involvement in SV is confined to the provision of B cell help." *Id*. (emphasis added). Neither Mathieson nor Petitioner elaborate on what "the provision of B cell help" means, though it certainly cannot mean, as Petitioner suggests, "causes GPA." Certainly, Petitioner's suggestion that depleting B-

cells would reduce T-cells does not follow from Mathieson's suggestion that the T-cells are confined to "the provision of B cell help."

Far from suggesting that activated T-cells were known to lead to GPA, Mathieson taught uncertainty as to their role in GPA's pathogenesis. Ex. 1008, 1 ("The role of T cells in S[ystemic] V[asculitides] is uncertain."). Indeed, in the paragraph that Dr. Massarotti quotes, Mathieson states that a "possible explanation of our failure to demonstrate autoreactive T cells is that such cells may not be directly involved in the pathogenesis of" vasculitis, and further that their studies provided further evidence that "T cells are not of major importance" in the pathogenesis of vasculitis. Ex. 1008, 6.

In sum, the art did not in any manner suggest that B-cell depletion would be an effective therapy in GPA. None of the cited references expressly suggested such a therapy. Nor do they support Petitioner's contrived rationale that B-cell depletion would reduce levels of ANCA and activated T-cells, and in turn treat GPA. The disclosures of the cited art and the absence of any logical connection between those disclosures and Petitioner's rationale reveals that Petitioner simply worked backwards from the claimed invention to pick snippets of the prior art that nominally support its argument. This is textbook hindsight reconstruction. *See Purdue Pharma L.P. v. Depomed, Inc.*, 643 F. App'x 960, 966 (Fed. Cir. 2016).

C. Petitioner Misleadingly Suggests That Rituximab Was The Only Therapy As Of May 1999 That Could Target B-Cells.

Assuming that a POSA would have sought to reduce a GPA patient's levels of ANCA and activated T-cells by B-cell depletion, Petitioner next contends that "[a]s 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." Pet. 50. The record suggests otherwise. The election of rituximab as a therapy for GPA was not a forgone conclusion, evidenced by Petitioner's concession that "Rasmussen and Mathieson did not explicitly use rituximab to treat GPA." Pet. 51. Petitioner does not attempt to offer any reasoning or rational underpinning that would have led a POSA to conclude that a POSA would have "looked no further than rituximab." Pet. 50. To the extent that the combination of George, Rasmussen, and Mathieson suggested that targeting B-cells would reduce ANCA, they did not contain any suggestion that a POSA should have done so using an "anti-CD20 chimeric monoclonal antibody." *Id.* Petitioner's "reasoning seems to say no more than that a skilled artisan, once presented with the [] references, would have understood that they *could be* combined. And that is not enough: it does not imply a motivation to pick out those [] references and combine them to arrive

at the claimed invention." *PersonalWeb Techs., LLC v. Apple, Inc.*, 848 F.3d 987, 993 (Fed. Cir. 2017).

Moreover, Petitioner ignores numerous therapies known-in-the-art to target B-cells, self-servingly arriving at a list of potential solutions that included only rituximab. *See* § V.B.1.(c). Petitioner uses only hindsight, and not logic derived from the prior art, to arrive at the claimed invention.

D. There Was No Suggestion In The Art To Target B-Cells In GPA Patients Using Rituximab With A Reasonable Expectation Of Success.

Petitioner contends that because of "the known relationship between ANCA levels and disease activity … [a] POSA would have reasonably expected that when ANCA levels fall following B-cell depletion, GPA disease activity would also decrease." Pet. 52. Thus, Petitioner contends that "a POSA would have reasonably expected B-cell depletion resulting from rituximab to provide a therapeutic benefit in a patient with GPA." *Id.*

1. The prior art suggested that rituximab would not reduce antibody levels.

Petitioner's premise that B-cell depletion with rituximab would reduce a patient's ANCA (antibody) levels is controverted by its own evidence. Specifically, Maloney reported that following B-cell depletion with rituximab, patients experienced "minimal change in serum Ig [*i.e.* antibody] levels." Ex. 1011, 6. This finding directly contradicts Petitioner's guess that "ANCA

levels [would] fall following B-cell depletion." Pet. 52. Accordingly, a POSA would not have reasonably expected success in treating GPA by administering rituximab to decrease ANCA levels.

2. There is no evidence that one would have expected to treat GPA merely by controlling ANCA levels.

As explained above in Section VI.B.1, the "known relationship" that Petitioner contends existed between ANCA levels and disease activity at most shows that ANCA levels ***correlated*** with disease activity. Petitioner provides no evidence that suggests that ANCA caused GPA and that reducing ANCA levels would have any effect on GPA disease activity. This is particularly so given that it is well established that "medicinal treatment" is one of the "unpredictable arts." *In re Efthymiopoulos*, 839 F.3d at 1380.

3. Petitioner fails to explain why a POSA would have expected to successfully treat GPA using the NHL dosing regimen.

Petitioner contends that the "Label References"' dosing regimen of "375 mg/m^2 given as an IV infusion once weekly for four doses" would have been obvious "because that regimen leads to 'a rapid and sustained depletion of circulating and tissue-based B cell[s]." Pet. 52. Petitioner further contends that "a POSA would have had a reasonable expectation of success that this dosage would be a 'therapeutically effective amount of rituximab' to deplete the patient's B-cells and in turn, treat GPA." Pet. 52-53.

While Petitioner's theory that eliminating ANCA and activated T cells is deficient for the reasons discussed above, to the extent that such a theory is correct, then a POSA would not have expected success using the NHL dosing regimen. As Petitioner notes in its formulation of reasonable expectation of success, the "therapeutically effective amount of rituximab" must deplete the patients' B-cells in order to treat GPA. Pet. 50-51. According to Petitioner, if the purported triggers of GPA (ANCA and activated T-cells) are present, then GPA activity will be higher. Thus, under Petitioner's hypothesized mechanism, a permanent depletion of B-cells would be required for treatment of GPA. But, as explained above in Section V.D, the NHL dosing regimen contemplates the regeneration of B-cells, particularly given the differing therapeutic objectives in treating cancer as opposed to autoimmune disorders. The evidence did not suggest that such a temporary B-cell depletion would have any effect in treating a GPA patient. At the very least, Petitioner failed to establish how quickly the disease manifests from its alleged triggers, whether the vasculitic damage is reversible, and if it was, how long it would take for B-cell depletion to result in a clinical benefit. Accordingly, a POSA would not have expected success in using an NHL dosing regimen to treat GPA in the manner suggested by Petitioner.

E. There Was No Reason To Combine Rituximab With Glucocorticosteroids (Claims 2-9, 11-12).

Petitioner contends that it would have been obvious to combine rituximab with glucocorticosteroids in GPA patients for the same reasons discussed in its arguments relating to vasculitis manifestations in SLE mentioned in Ground I. *See* Pet. 52-53. Accordingly, for the same reasons discussed above in Section V.E, it would not have been obvious to combine rituximab with glucocorticosteroids to treat GPA.

VII. GROUNDS III AND IV: SUBSTITUTING MALONEY I FOR THE "LABEL REFERENCES" IN GROUND I OR GROUND II DOES NOT CURE THE DEFICIENCIES OF EITHER GROUND

Petitioner offers Grounds III and IV as substitutes for Grounds I and II "because Maloney I provided the same disclosures as the Rituxan™ label." Pet. 55. Resultantly, these substitute grounds fail for the same substantive reasons that Grounds I and II fail. *See* §§ V.B-E; VI.B-E. Moreover, a POSA concerned with autoimmune diseases (including vasculitis) would not have turned to Maloney to inform the treatment of SLE or GPA because Maloney exclusively discusses the treatment of cancer, even when proposing avenues of future study. *See* § II.C.2.

Finally, Grounds III and IV fail to render obvious the claimed combination therapies using rituximab and glucocorticosteroids (claims 2-9,11-12) because Maloney never suggested such combinations. Indeed, Petitioner

concedes that "Maloney I did not explicitly disclose the use of glucocorticosteroids in combination with rituximab." Pet. 56. Petitioner contends that Maloney observed that "adverse events observed in this trial were predominantly infusion related" and asserts that "a POSA would have understood these are allergic or hypersensitivity reactions caused by rituximab." *Id.* From this unsupported premise, Petitioner then contends that "[s]uch reactions . . . are the typical kinds of allergic or hypersensitivity reactions that could be treated using glucocorticosteroids when treated with a chimeric monoclonal antibody." *Id.*

Yet Maloney never reported the administration of steroids, and in fact expressly stated that "[t]he [rituximab] treatment was well tolerated, causing only ***minimal*** infusion-related symptoms." Ex. 1011, 2 (emphasis added). This rendered the prophylactic administration of steroids unnecessary to combat any side effects, and Petitioner identifies no other reference in these grounds that suggested its proposed prophylactic administration of steroids with rituximab. Moreover, as explained in Section V.E, POSAs had reason to believe that steroids would interfere with rituximab's mechanism of action, which would have further led one away from adding them to the rituximab protocol described by Maloney.

VIII. THE BOARD NEED NOT ADDRESS PETITIONER'S ARGUMENTS REGARDING OBJECTIVE INDICIA OF NON-OBVIOUSNESS

Because Petitioner failed to set forth a *prima facie* case that the claims of the '843 patent were obvious, Patent Owner declines to address Petitioner's arguments relating to objective indicia of non-obviousness at this time, but reserves its rights to address objective indicia at a later stage should the Board institute IPR.[7]

IX. CONCLUSION

The Board should not institute *inter partes* review under any of Petitioner's proposed Grounds.

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[7] Petitioner's contention that purported near-simultaneous invention is secondary, non-statutory evidence of obviousness ignores this Board's prior decisions. *See Costco Wholesale Corp. v. Robert Bosch LLC*, IPR2016-00039, 2016 WL 2866222, at *5 *(*P.T.A.B. Apr. 25, 2016*)* ("[W]e do not agree with Petitioner's characterization that it is 'well-settled' that simultaneous invention is strong evidence that the claimed apparatus was the product of ordinary mechanical or engineering skill. *See Geo. M. Martin,* 618 F.3d at 1304–05 (noting that the secondary consideration of simultaneous invention ***might*** supply indicia of obviousness ***in some rare instances***, and acknowledging a proposition to the contrary in *Lindemann Maschinenfabrick GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1460.") (emphasis added).

Dated: March 7, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

Pursuant to 37 C.F.R. § 42.24 (d), I certify that the present paper contains 13,940 words as counted by the word-processing program used to generate the brief. This total does not include the tables of contents and authorities, the caption page, table of exhibits, certificate of service, or this certificate of word count.

Dated: March 7, 2018

Respectfully submitted,

/s/ *Michael R. Fleming*
Michael R. Fleming

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. 42.6, the undersigned certifies that on March 7, 2018, a copy of the foregoing document and Patent Owners' Exhibits 2001-2009 were served by electronic mail upon the following:

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