UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.
Petitioner,

v.

GENENTECH, INC. AND BIOGEN, INC.
Patent Owners.

Case IPR2016-01614
U.S. Patent No. 7,820,161

GENENTECH, INC. AND BIOGEN, INC.'S PATENT OWNER RESPONSE

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I. INTRODUCTION

Rheumatoid arthritis ("RA") is an incurable autoimmune disorder that can inflict severe joint pain and progressively destroy bone and cartilage, ultimately leading to permanent deformity and disability. In the late 1990s, rheumatologists and patients were dissatisfied by the lack of efficacy and long-term tolerability of the RA drugs then available. The leading textbook on rheumatology described the situation bleakly: "No single therapeutic regimen or combination of therapies has been consistently associated with marked and sustained improvement, or with a halt in progression of loss of joint structure and function." Ex. 2003 at 933.

Collaborators Genentech, Inc. and Biogen, Inc. developed new therapies for RA involving combinations of the monoclonal antibody "rituximab" (Rituxan®)—whose only approved indication at the time was to treat a form of cancer known as non-Hodgkin's lymphoma (NHL)—and an antimetabolite called "methotrexate." These combinations have unexpectedly proven to be effective at reducing the joint swelling and pain associated with RA. But the combinations achieved an even more surprising result: they have been shown to ***halt*** erosive progression—physical damage to joints—for RA patients over extended periods of time. The FDA approved the combination of rituximab and methotrexate for treatment of RA in 2006, and since then, the combination has experienced enormous commercial success.

Genentech and Biogen claim these combination therapies in U.S. Patent No. 7,820,161 (the "'161 patent"). Celltrion, Inc., a biosimilar developer, filed a petition seeking *inter partes* review of the '161 patent, and the Board instituted trial on a single ground to determine whether the four-reference combination of Edwards (Ex. 1030), "the Rituxan® Label" (Ex. 1037), O'Dell (Ex. 1015), and Kalden (Ex. 1051) renders obvious Claims 1-3, 5-7, and 9-11 of the '161 patent.

Petitioner's challenge fails for several reasons. ***First***, even assuming—contrary to the teachings of the prior art and the prevailing scientific views—that a POSA would have combined these four references to arrive at the claimed invention, the POSA would not have had a reasonable expectation of success in doing so, especially given that pharmaceutical development is an unpredictable art. Petitioner offers a single, conclusory paragraph of expert testimony to the contrary, and that testimony is contradicted by the prior art and the admissions of the expert himself, Dr. Maarten Boers. For example, as the basis for his opinion that a POSA would have had a reasonable expectation of success in treating RA patients with rituximab and methotrexate, Dr. Boers asserts in his declaration that the POSA would have expected the results of the combination to be "additive"—that is, "similar to the sum of the results achieved with each agent individually." Ex. 1002, ¶52. But that assertion is unaccompanied by any citation or explanation

whatsoever, and nowhere in his declaration does he identify even a single example of a combination therapy for RA that yielded such additive results.

Moreover, the prior art—including articles authored by Dr. Boers himself—shows that a POSA would ***not*** have expected a new combination therapy for RA like rituximab plus methotrexate to be additive because no clinical study by the priority date had demonstrated any such outcome. Shortly before the priority date, Dr. Boers published a comprehensive literature review of combination therapies for RA and he admitted at deposition that every single study that could have showed additive results failed to do so. Ex. 2016, 142:7-149:20. He also admitted that each of those studies showed "negative interaction," and that each combination therapy yielded results no better than its components administered as monotherapies. Dr. Boers admitted, in the context of no fewer than six separate examples from his own paper, that these results failed to demonstrate "a successful combination." Ex. 2016, 150:4-8. This paper by Dr. Boers is nowhere to be found in the petition.

Second, the record does not even establish that a POSA would have expected rituximab *alone* to be a successful treatment for RA. In his declaration, Dr. Boers opined that a POSA would have expected administration of rituximab at or around doses disclosed in the prior art for treatment of NHL to be successful for

RA patients. At his deposition, however, he testified that he held no such belief at any time before the priority date:

> Q. Sure. At any time before May of 1999, did you believe that the administration of rituximab at the approved dose for non-Hodgkin's lymphoma could effectively treat rheumatoid arthritis?
>
> A. I, as a person, no.

Ex. 2016, 23:7-11.

Nor would a POSA have believed that Edwards—the cornerstone reference on which Petitioner relies—provided a reasonable expectation of successfully treating RA with rituximab. Edwards described an untested hypothesis: Killing all B cells would interrupt the production of rheumatoid factors, which are responsible for causing RA. This hypothesis was contrary to the prevailing scientific view that RA was initiated and driven by T cells and pro-inflammatory cytokines. Moreover, a POSA would have been particularly skeptical of Edwards's untested hypothesis because it rested on numerous faulty premises, including that rheumatoid factors were the root cause of RA, even though decades of studies had shown no such causal link. On top of that, a POSA would have found no expectation of success based on experience with other biologics, the overwhelming majority of which had failed as RA treatments.

Third, a POSA would not have been motivated to combine Edwards, "The Rituxan® Label," O'Dell, and Kalden in the first place. Edwards is the *only* one of these references to suggest administering rituximab to an RA patient—and a POSA would not have relied on Edwards, either alone or in combination with any other reference, given its faulty premises and untested hypothesis. Indeed, history actually shows that the scientific community essentially ignored Dr. Edwards's hypothesis until he published—after the priority date—the results of a small open-label study he conducted using rituximab for treatment of RA.

Fourth, assuming a POSA would have relied on Edwards—despite its faulty premises and untested hypothesis—the POSA would have been motivated to combine rituximab, which depletes mature B cells, with an agent like cyclophosphamide that was also known to deplete B cells—not methotrexate, which has a different mechanism of action. Indeed, a POSA would have used an additional B-cell killing agent to test Dr. Edwards's hypothesis because it was known at the time that rituximab alone does not deplete all B cells. Accordingly, when Dr. Edwards tested his hypothesis in a small open-label study, he administered rituximab in combination with cyclophosphamide. Moreover, even after a randomized controlled trial revealed successful results for the combination of rituximab and methotrexate, Dr. Edwards described the suggestion "that rituximab should be used together with methotrexate" as "'completely illogical,

because the 2 treatments are unrelated, they're not doing the same thing.'" Ex. 2015, 2; Ex. 2029, 2-3.

Finally, Petitioner fails to establish that "The Rituxan® Label," Ex. 1037, is a printed publication. There is no evidence that Ex. 1037 was publicly accessible before the priority date. Consequently, the Board should not give the exhibit, or the portions of Dr. Boers declaration that rely on it, any weight.

For all these reasons, Petitioner's challenge fails and the Board should confirm claims 1-3, 5-7, and 9-11 of the '161 patent.

II. TECHNICAL BACKGROUND

A. The Immune System: T cells And B cells

The human immune system can broadly be divided into two branches: humoral immunity and cell-mediated immunity. Ex. 2085 ¶¶12-13.

Humoral immunity is mediated by molecules found in extracellular fluids such as secreted antibodies, which are also known as "immunoglobulins." *Id.* at ¶14. Antibodies specifically bind to various substances; the substances to which antibodies specifically bind are called antigens. *Id*. In a humoral immune response, antibodies travel through the bloodstream and bind to an antigen on a foreign substance, which can cause the destruction of the substance. *Id*.

Antibodies are made by B lymphocytes, also known as B cells. *Id.* at ¶¶15, 19-21. Antibodies can be secreted into the blood or can remain bound to the B cell;

the former are known as soluble antibodies. *Id*. The vast majority of soluble antibodies are secreted by B cells that have differentiated into what are called "plasma cells." *Id*.

Antibodies have constant regions, which can interact with cell surface receptors, and variable regions, which mediate the contact sites that bind to antigens. *Id.* at ¶18. Antibodies are classified according to their constant regions of different classes, which remain largely the same from antibody to antibody of the same class: IgA, IgD, IgE, IgG, IgM. *Id.* Antibodies of the IgG class are typically soluble antibodies. *Id*.

The other branch of the immune system, cell-mediated immunity, provides an immune response that does not involve antibodies, but rather involves antigen-presenting cells (such as macrophages), T cells (also known as T lymphocytes), and cytokines, which are secreted proteins that can cause inflammation and act as signals for various cellular activity. *Id*. at ¶¶16-17, 22-25.

B. Treatment of Rheumatoid Arthritis

As of the priority date, rheumatologists typically treated RA by prescribing sequential monotherapy, beginning with non-steroidal anti-inflammatory drugs (NSAIDs), followed by steroids or small-molecule second-line drugs referred to as "disease-modifying antirheumatic drugs" (DMARDs). Many DMARDs were associated with serious toxicities. Ex. 2019 at 309; Ex. 2085 ¶26.

The list of DMARDs in use at the time was large. It included anti-malarials, aminopterin, auranofin, azathioprine, bucillamine, chloroquine, chlorambucil, cyclophosphamide, cyclosporine, D-penicillamine, dapsone, gold salts, hydroxychloroquine, hydroxyurea, methotrexate, and sulfasalazine. Ex. 2085 ¶27. Clinical investigators had tested whether certain combinations of DMARDs would be more effective than monotherapy, but the vast majority of patients received monotherapy. Ex. 1015, 789; Ex. 2085 ¶¶28-31.

C. Rituximab

Rituximab is an engineered antibody that binds to a cell-surface marker called "CD20." Ex. 1001 at 2:29-31. CD20 is found—at certain stages of development—on the surfaces of certain B cells. Ex. 2009, 2825. The CD20 marker is not found during the earlier stages of B cell development, *i.e.*, on hematopoietic stem cells or on pro-B cells, but is found on the surface of mature B cells. *Id.* When activated mature B cells differentiate into plasma cells, the CD20 marker is lost. *Id.*; Ex. 2085 ¶¶32-35.

Abnormal mature B cells may begin dividing uncontrollably, forming cancerous cells. Some of these cancers are called "non-Hodgkin's lymphomas" (NHLs). Ex. 2085 ¶34. The CD20 antigen is expressed on many B cell NHLs. *Id*. Accordingly, rituximab was developed, and first approved by the FDA, as a cancer therapy to deplete B cells in NHL patients.

III. THE '161 PATENT

A. Claims

All claims in U.S. Patent No. 7,820,161 require administration of rituximab with methotrexate to treat rheumatoid arthritis. *See* Ex. 2085 ¶¶36-38; Ex. 2016, 106:6-107:2. All claims also require more than one infusion of rituximab at therapeutically effective doses to treat rheumatoid arthritis. *Id.* The challenged dependent claims add dose and glucorticosteroid limitations.

B. Prosecution History

The '161 patent traces its priority back to a provisional application filed on May 7, 1999. Ex. 1001, 1:6-8. Petitioner acknowledges that the claims of the '161 patent are entitled to at least that priority date. *See* Pet. 3.

The primary reference that Petitioner relies on in this proceeding—the Edwards hypothesis paper (Ex. 1030)—was thoroughly debated during prosecution. *See* Ex. 2030 at 4.

C. Person Of Ordinary Skill In the Art

Patent Owners propose the following definition of a POSA based on the definition proposed by Petitioner Celltrion in the prior IPR on the '161 patent (Ex. 2017, IPR2015-01744, Pet. 14-15):

> [A] practicing rheumatologist with a medical degree and:
>
> (i) at least 2-3 years of experience treating RA patients;

(ii) an understanding of immunology and the pathophysiology of RA, as disclosed in the prior art; and

(iii) knowledge about the available methods of treating RA, as disclosed in the prior art.

Ex. 2085 ¶¶39-45. This definition is nearly identical to Celltrion's proposed definition from IPR2015-01744, except it clarifies that the understanding and knowledge of the POSA is based on the prior art, and that such understanding includes immunology. The clarification regarding immunology is justified because the grounds for challenge include prior art, like Edwards and Kalden, which delve deep into principles of, and research regarding, immunology. *See* Ex. 1030; Ex. 1051.

Celltrion's proposed definition in these proceedings differs radically from the definition it proposed for the very same patent in IPR2015-01744. Celltrion now seeks to imbue the person of ordinary skill with extraordinary insight into the pathophysiology of all autoimmune disorders, and into "all of the available and proposed methods of treating" those disorders, including how such proposed treatments would "work to treat such disorders." Pet. at 24-25. Celltrion offers no justification for its change in position and the Board should reject it.

Contrary to Celltrion's proposed definition, rheumatologists at the priority date did not study or treat all autoimmune disorders. Ex. 2085 ¶¶46-49 Autoimmune disorders are disparate diseases, ranging from diabetes to multiple

sclerosis, with different pathophysiologies, *id.*, as the Office recognized during prosecution. Ex. 2055 at 2 (restricting claims because RA had "different symptoms and different pathologic mechanisms" than other autoimmune disorders). As acknowledged by Celltrion's expert, more than fifty autoimmune disorders were known at the time of the invention. Ex. 2016, 92:25-93:2. Because Celltrion's expert assessed obviousness through the eyes of an unrealistically insightful POSA, *see* Ex. 2016, 244:1-5, his conclusions are unreliable and should be given little weight.

IV. PETITIONER FAILS TO ESTABLISH THAT ANY CLAIM OF THE '161 PATENT IS PRIMA FACIE OBVIOUS

"Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination." *Unigene Labs., Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011). "Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Id.* Moreover, "[a]n obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen Inc. v. F. Hoffman-La Roche, Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009).

"Importantly, the great challenge of the obviousness judgment is proceeding without any hint of hindsight." *Star Scientific, Inc., v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1375 (Fed. Cir. 2011). Obviousness "cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Cheese Sys., Inc. v. Tetra Pak Cheese & Powder Sys., Inc.*, 725 F.3d 1341, 1352 (Fed. Cir. 2013).

A POSA would not have had a reason to combine Edwards, "The Rituxan® Label," O'Dell, and Kalden so as to arrive at any of the claimed inventions, as discussed in subsection V.B. below. But even assuming otherwise, Petitioner's challenge fails because the POSA would have lacked the further required reasonable expectation of success. *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344 (Fed. Cir. 2013) (reversing a finding of obviousness because "one of ordinary skill in the art would not have reasonably predicted the successful adaptation of [the prior art] to target chromosomal DNA in eukaryotic cells," as claimed); *The Broad Inst. v. Regents of the Univ. of Cal.*, Patent Interference No. 106,048, 2017 Pat. App. LEXIS 1261, at *57 (P.T.A.B. Feb. 15, 2017) (finding that even though the prior art provided "a motivation" to combine, there was still insufficient evidence "indicat[ing that] skilled artisans would have had any expectation of success" for practicing the invention); *see* Ex. 2085 ¶¶54-57 (high-level summary

of opinions regarding non-obviousness), ¶¶81-85 (differences between the prior art and the claimed invention).

A. Assuming A POSA Would Have Had A Reason To Combine Edwards, "The Rituxan® Label," O'Dell, and Kalden, A POSA Would Not Have Had A Reasonable Expectation Of Success In Doing So.

It is well established that "pharmaceutical development is an unpredictable art." *Mylan Pharmaceuticals Inc. v. Yeda Research & Development Co. Ltd.*, IPR2015-00643 (Paper 90) at 19 (Dec. 2, 2016); *In re Efthymiopoulos*, 839 F.3d 1375, 1380 (Fed. Cir. 2016) (observing that "medicinal treatment" is one of the "unpredictable arts").

Against this legal backdrop, Petitioner offers only conclusory expert testimony in support of its argument that a POSA would have had a reasonable expectation of success for the combination of rituximab and methotrexate in RA patients, as explained below. And that conclusory testimony is contradicted by the prior art and the expert's own admissions during cross-examination. The record does not even establish an expectation that rituximab alone would successfully treat RA, much less that a combination of rituximab and methotrexate would be successful.

1. The Facts Contradict Petitioner's Expectation-Of-Success Arguments

Petitioner argues that a POSA would have had a reasonable expectation of success in treating RA patients with rituximab and methotrexate because Dr. Boers asserts, in a conclusory fashion, that:

> [a] In view of the prior art, a person of ordinary skill in the art would have had a reasonable expectation of success in treating RA patients with rituximab and methotrexate because she would have expected additive results and [b] would not have expected the two components to interfere with one another. [c] A person of ordinary skill in the art would also have been aware of the successful use of methotrexate with other biologic agents. (*See, e.g.,* Kalden, Ex. 1051.)

Ex. 1002 ¶84. Not only do these three assertions lack evidentiary support, they are contradicted by both the prior art and Dr. Boers's publications and deposition testimony, as explained below.

(a) A POSA Would Not Have Expected Additive Results From Combining Rituximab and Methotrexate

Dr. Boers's declaration defined "additive results" for a drug combination as "results that are similar to the sum of the results achieved with each agent individually." Ex. 1002 ¶52; Ex. 2016, 114:14-115:1. According to Dr. Boers, "[i]n view of the prior art, a person of ordinary skill in the art would have had a reasonable expectation of success in treating RA patients with rituximab and methotrexate because she would have expected additive results." Ex. 1002 ¶84. Dr. Boers does not try to justify that bold assertion by identifying a long list of

drug combinations that, as of the priority date, allegedly had proven additive in the treatment of RA. He does not contend that a history of additive combinations in RA created an expectation that new combinations would be additive too. In fact, nowhere in his declaration does he identify even a single example of an additive combination therapy for RA or a three-arm study showing that a combination of two agents yielded results similar to the sum of the results achieved with each agent individually. Dr. Boers never even identifies the "prior art" that, "[i]n view of" which, a POSA supposedly would have had a reasonable expectation of combining rituximab and methotrexate with additive results. Ex. 1002 ¶84.

Rather, Dr. Boers's assertion that a POSA would have had a reasonable expectation of success in treating RA patients with rituximab and methotrexate appears without any citation or explanation whatsoever. This conclusory testimony simply cannot support a finding that a POSA would have expected a combination of rituximab and methotrexate to be additive—particularly when rituximab, a cancer therapy, had not been shown before the priority date to treat RA. "Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight." 37 C.F.R. §42.65(a); *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

(Feb. 10, 2016) (denying institution where Petitioner relied on "conclusory expert testimony that, itself, does not cite to evidentiary support").

Moreover, the prior art—including Dr. Boers's own publications, not cited by Petitioner—shows that a POSA would ***not*** have expected a new combination therapy like rituximab plus methotrexate to be additive. As Dr. Boers explained in an RA paper shortly before the priority date: "To date, most drug combination trials have ***not*** shown addition or synergy (ie, benefits equal or better than the sum of benefits attributed to the single drugs)." Ex. 2019, 317 (emphasis added). In fact, Dr. Boers reviewed hundreds of studies addressing RA drug combinations for papers that he published in 1991 (Ex. 2004) and 1998 (Ex. 2008) and failed to identify even a single combination that was additive. In his 1991 literature review "compar[ing] the benefits and risks of combinations of long-acting antirhuematic drugs with those of the same drugs used singly in the treatment of rheumatoid arthritis," Ex. 2004, 316; Ex. 2016, 117:7-118:12, Dr. Boers concluded that it was not clear that any combination was even advantageous, much less additive: "In summary, the advantages of antirheumatic drug combinations over any single drug remain unproven." Ex. 2004, 323; Ex. 2016, 119:10-21; Ex. 2085 ¶¶88-90.

Three years later, another group arrived at the same conclusion after conducting its own "meta-analysis to evaluate the overall efficacy and toxicity of

combination therapy in RA." Ex. 2007, 1487. Ex. 2016, 127:6-129:18. Specifically, the group concluded:

> Combination therapy, as it has been used in recent trials, does not offer a substantial improvement in efficacy, but does have higher toxicity than single drug therapy. These combination therapy regimens are not recommended for widespread use.

Ex. 2007 at 1487; *id.* at 1491 ("Combination therapy as it has been used in clinical trials is not a valuable therapeutic alternative for most patients with RA."); Ex. 2085 ¶91.

In 1998, Dr. Boers published a second comprehensive literature review, adding studies published after his first review. Ex. 2008, 612. His research for the update "yielded 231 new citations," which "[t]ogether with previous reviews," brought "the total to 611 titles scanned." *Id.* at 613; Ex. 2016, 136:12-20, 139:15-140:10. Of those, Dr. Boers determined that 20 studies provided "strong" or "moderately strong" evidence, based on randomization and blinding, of combination therapy in RA. Ex. 2008, 612. Dr. Boers summarized his analysis of those studies in Table I. *Id.* at 614.

Six of the studies (Faarvang, Gibson, Haar, Williams, Willkens, and Haagsma) had the capacity to demonstrate additive results, if they existed, because they were three-arm trials with one arm administering a combination of two agents

and the other two arms each administering one of the two agents as monotherapy. *Id.*; Ex. 2016, 140:11-24. For each of these studies, Dr. Boers found that there was no difference in efficacy between the combination and its components taken alone, and there was either no difference in toxicity or a "'trend of more toxicity'" for the combination relative to its components as monotherapies. Ex. 2008, 613-14; Ex. 2016, 141:21-142:3 (Faarvang), 143:5-12 (Gibson), 144:11-18 (Haar), 148:12-149:13 (Williams, Willkens, and Haagsma). Thus, every single one of the studies failed to show additive results, Ex. 2008 at 614, Ex. 2085 ¶¶92-94; as Dr. Boers confirmed at deposition:

> Q. And the combination in Faarvang failed to show additive results; is that correct?
>
> A. Correct.. . .
>
> Q. And the results for the combination in Gibson were not additive, correct?
>
> A. Correct.. . .
>
> Q. And the results for the combination in Haar were not additive, correct?
>
> A. Correct.. . .
>
> Q. Exactly. And so for these three studies, Williams, Willkens, and Haagsma, the results for the combination in -- were not synergistic, correct?
>
> A. Correct.

Q. And the results for those three studies were not additive, correct?

A. Correct.

Ex. 2016, 142:7-149:20. Notably, the non-additive combinations of Williams, Willkens, and Haagsma each included methotrexate as one of the agents. *Id.*

Given this track record of combinations that did not produce additive results, including for combinations with methotrexate, a POSA would have had no reason to expect additive results from a combination of rituximab and methotrexate. Ex. 2085 ¶¶88-94.

(b) If Anything, A POSA Would Have Expected Rituximab And Methotrexate To Interfere, Yielding Results No Better Than Either Agent As Monotherapy

Dr. Boers confirmed at deposition that not only did all six of the three-arm studies above fail to show additive results, all six actually demonstrated "negative interaction." Ex. 2016, 142:10-13 (Faarvang); 143:19-21 (Gibson); 144:25-145:2 (Haar); 149:14-20 (Williams, Willkens, and Haagsma). As he generally explained in his 1998 paper and also confirmed at deposition, "negative interaction" means that the "results of the combination are the same or only slightly better than the single drugs." Ex. 2008, 617; Ex. 2016, 136:4-138:12. In other words, "negative interaction" is "interference" between the drugs of the combination. Because all six of the prior-art studies comparing combinations to each of their individual

components demonstrated such interference, a POSA would have expected, if anything, that rituximab and methotrexate would interfere too, contrary to Dr. Boers's conclusory assertions. Ex. 1002 ¶84; *id.* ¶52; Ex. 2085 ¶¶95-97.

In his declaration, Dr. Boers asserts that methotrexate "had a different mechanism of action than rituximab." Ex. 1002 ¶52. But he does not accompany that assertion with any discussion or explanation whatsoever. And his own testimony forecloses any inference that a POSA would have expected only agents with the same mechanism of action to have negative interactions. For example, at deposition he denied that "negative interaction -- is a phrase that you only use when the combination therapy is addressing two agents that are directed to the same target" and he volunteered that "[t]here may be many reason[s] for negative interaction." Ex. 2016, 138:4-12.

(c) The Prior Art Demonstrated That RA Combinations, Including Combinations Of Methotrexate And Biologic Agents, Were Either Unsuccessful Or Unproven.

In reference to his 1998 paper, Dr. Boers confirmed at deposition that in each of the six prior-art studies comparing combinations to their individual components, the results for the combinations were no better than the results for the respective components as monotherapies. Ex. 2016, 142:14-17 (Faarvang), 143:22-25 (Gibson), 145:3-6 (Haar), 149:14-150:3 (Williams, Willkens, and Haagsma);

Ex. 2085 ¶98. He agreed that, consequently, not a single one of those six studies identified a successful combination therapy:

> Q. And so none of the three-armed studies that I've identified from column one identified a successful combination for the treatment of rheumatoid arthritis; is that correct?
>
> A. That is correct.

Ex. 2016, 150:4-8; Ex. 2085 ¶98.

Applying this same standard, it is apparent that several other combinations reviewed in Dr. Boers's 1998 paper also proved unsuccessful. For example, in a two-arm study by Moreland (Ref. [7]) comparing the combination of methotrexate plus a biologic (a monoclonal anti-CD4 antibody) to methotrexate alone, Dr. Boers found that there was no difference in efficacy or toxicity, meaning that taking the combination was no better than taking one of the components as monotherapy. Ex. 2008, 614. Similarly, Dr. Boers found that the combinations in the two-arm trials of Bendix (Ref. [9]), Porter (Ref. [11]), and Ciconelli (Ref. [25]) all had efficacy equal to and toxicity equal to or trending greater than those for one of their components. *Id.*; Ex. 2085 ¶¶99-100. Thus, the prior art showed that none of these combinations were successful either, according to Dr. Boers's own analysis.

The rest of the combinations in Dr. Boers's 1998 paper remained unproven. With one exception, all were two-drug combinations that had been studied in two-

arm trials comparing the combination to only one of its components individually, Ex. 2008, 614, making it impossible to assess whether the combination was better than either drug alone. The exception to the two-drug combinations was a triple combination studied in a three-arm trial comparing the combination, one of the components individually, and a sub-combination of the two other components. But here too, at least one component of each combination was not tested individually. Thus, in all of these studies, it was impossible to discern whether the result observed for the combination was any better than the result that would have been observed for the omitted component alone. Because the result for each combination might have been no better than result for the omitted component individually, it was unclear whether or not the combination was successful. Ex. 2085 ¶101.

In his declaration, Dr. Boers asserts that "[a] person of ordinary skill in the art would also have been aware of the successful use of methotrexate with other biologic agents. (*See, e.g.,* Kalden, Ex. 1051.)." Ex. 1002 ¶84; *id.* ¶52. But no such successful combinations had in fact been shown as of the priority date. Kalden does not identify any combination of methotrexate and a biologic as a successful combination. Ex. 2085 ¶102; *see id.* ¶¶70-74. Kalden simply says that "[c]ombining methotrexate and the repeated administration of anti-TNF-α MAb cA2, Kavanaugh *et al.* (41) demonstrated that combination therapy ***might be*** an

important therapeutic approach for RA patients whose disease is not completely controlled by MTX alone." Ex. 1051, S-96 (emphasis added). Petitioner did not include the cited Kavanaugh reference as part of the record, and does not argue that Kavanaugh established any treatment as a successful combination. Notably, Kavanaugh is a 1996 abstract that Dr. Boers apparently did not even consider "strong" enough to include in his 1998 literature review.

Elsewhere in his declaration, Dr. Boers mentions a 1999 article by Weinblatt reporting a two-arm trial comparing the combination of etanercept and methotrexate to methotrexate alone. Ex. 1002 ¶53. But Weinblatt did not test etanercept monotherapy and therefore was unable to address whether the result of the combination was any better than the result that would have been observed from etanercept monotherapy. Ex. 1021, 253 (Abstract). Thus, a POSA would not have concluded that Weinblatt demonstrated a successful combination. Ex. 2085 ¶¶103-104.

Not only did the literature fail to demonstrate that any combination of a biologic and methotrexate was successful as of the priority date, there existed evidence establishing that such a combination was not successful. As discussed above, a study by Moreland comparing methotrexate alone to the combination of methotrexate plus an anti-CD4 antibody showed that the combination was

unsuccessful—even though anti-CD4 and methotrexate had different mechanisms of action. *Id.* at ¶104.

2. Petitioner Does Not Even Argue, Much Less Offer Evidence, That A POSA Would Have Had Any Expectation Of Success With Respect To The Inventions Of Claims 3, 7, and 11.

Dependent claims 3, 7, and 11 require not only administering to a human more than one intravenous dose of a therapeutically effective amount of rituximab and methotrexate, but also "administering to the human a glucocorticosteroid." Petitioner and its expert do not even attempt to establish that a POSA would have had a reasonable expectation of success in treating RA in a human with the triple combination of rituximab, methotrexate and a glucocorticosteroid. Petitioner therefore fails to establish that claims 3, 7, and 11 are prima facie obvious.

3. The Record Does Not Even Establish An Expectation That Rituximab Alone Would Successfully Treat RA, Much Less That A Combination Of Rituximab and Methotrexate Would Be Successful.

A POSA would have had no expectation of success for a combination of rituximab and methotrexate without also having an expectation that rituximab alone would be effective to treat RA.[1] If rituximab alone was not effective to treat

[1] This would be so even if a POSA would have expected the combination to be additive. A combination of two drugs can be additive even if one or both of the drugs has zero success individually because 0 + X = X and 0 + 0 = 0. But in those

RA, then the combination of rituximab and methotrexate could be no better than methotrexate monotherapy, which means it could not possibly be a successful combination.

The record here does not establish an expectation that rituximab alone would successfully treat RA. Quite the opposite. Dr. Boers admitted that, as of the priority date, he did not believe that administering rituximab at the NHL dose—the dose that he opines a POSA would have tried—could effectively treat RA:

> Q. Sure. At any time before May of 1999, did you believe that the administration of rituximab at the approved dose for non-Hodgkin's lymphoma could effectively treat rheumatoid arthritis?
>
> A. I, as a person, no.

Ex. 2016, 23:7-11; *see* Ex. 2085 ¶105. In other words, as of the priority date, even Dr. Boers himself had no expectation that RA could be successfully treated with rituximab at the dose he believes a POSA would have been motivated to try.

A POSA would have been especially pessimistic about rituximab's prospects of success—assuming that the POSA would have been motivated by Edwards to

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circumstances, the result for the combination is no better than the result for one of its components taken individually, which means that the combination is unsuccessful. *See* Ex. 2016, 150:4-8.

try rituximab in RA patients in the first place—because Edwards described a theoretical hypothesis based on flawed premises. The POSA also would have been pessimistic because the field was littered with failed biologic monotherapies.

(a) A POSA Would Have Been Especially Pessimistic About Rituximab's Prospects Of Success Because Edwards Described An Untested Hypothesis Based On Faulty Premises.

Edwards hypothesized a cure for RA. Ex. 1030, 126, 129. The hypothesis was built on two fundamental premises. The first premise was that certain autoantibodies called "rheumatoid factors" (RFs) actually cause RA. Ex. 1030, 126 ("[The] hypothesis . . . point[s] to a central role for immune complexes, and specifically for IgG RF, in the pathogenesis of RA"). The second premise was that an anti-CD20 antibody like rituximab would interrupt production of pathogenic RFs by killing all B cells. *Id.* at 126, 129 (proposing "interruption of autoantibody production" by "destroy[ing] all mature B cells," including "pathogenic IgG RF-producing clones," and stating that "destruction of mature B cells can be achieved with an anti-B-cell (CD20) antibody"). The hypothesis posited that B cells that give rise to pathogenic RFs arise by random mutations, which are unlikely to repeat, and therefore killing them could interrupt production of such RFs permanently, thereby curing the disease. Ex. 1030, 129; Ex. 2085 ¶¶58-67, 106.

The Edwards hypothesis acknowledged that "[s]everal detailed aspects of the hypothesis need to be tested." Ex. 1030, 129. But even without such testing, a

POSA would have rejected both premises of the Edwards hypothesis because each was inconsistent with the scientific literature as of the priority date, as explained in the subsections below. Patent Owners submitted evidence of this to the Office during prosecution (*see* Ex. 1023 ¶¶19-27) and in the prior IPR proceeding (*see* Ex. 2017, 26-35), but Petitioner and its expert ignore that evidence and offer no reason why a POSA would have accepted the hypothesis despite its scientific infirmities. Thus, even assuming that a POSA would have been motivated by Edwards to try rituximab in RA patients, the POSA would not have had a reasonable expectation of success in doing so.

(i) A POSA Would Have Rejected The Premise That RFs Cause Rheumatoid Arthritis

By 1998, the scientific community had considered and rejected the idea that RA was initiated and driven by RFs. Rather, a POSA at the time would have viewed RA as initiated and driven by T cells and pro-inflammatory cytokines. Ex. 2085 ¶107.

In the 1940s, RFs were detected in the blood of certain RA patients, Ex. 1030, 126, leading some scientists to conceive of RA as an antibody-mediated process caused by RFs and immune complexes. Researchers began investigating whether RFs were a byproduct of the disease, or whether they were the cause of it. *Id*. ¶¶108-109.

Over the years, research showed that the relationship between RFs and RA is not one-to-one, suggesting that RFs are not causative: some patients with RA do not have RFs, and some people with RFs do not have RA. *See* Ex. 2013, 1 (finding IgG RF titers of 9 in 9% of healthy adults), Ex. 2014, 65 (reporting IgG RF in only 66% of RA patients); Ex. 1030, 126 ("[T]he relationship between RF and disease is not one to one."); Ex. 2016, 177:14-178:8 (stating that "there's people with rheumatoid arthritis who have no rheumatoid factor," and confirming that "there are people who would test positive for rheumatoid factor and not have rheumatoid arthritis"); Ex. 2085 ¶¶110-113.

Dr. Boers admitted at deposition that even in RA "patients with rheumatoid factor, the severity or the progression of disease is not one on one linked to rheumatoid factor titers [levels]." Ex. 2016, 177:19-22. He added that "in general it can be said that people with high titers have more severe disease and also more chance of extraarticular manifestations," *Id.* at 177:22-24, but that is consistent with RF as a correlated byproduct, rather than a cause, of the disease.

A study published in 1961 in the official journal of the American College of Rheumatology, which Dr. Boers confirmed "was a respected journal among persons skilled in the art," Ex. 2016, 19:5-20, showed that injecting RFs and B cells from RA patients into healthy patients did not give the healthy patients RA. Ex. 2012 at abstract ("There was no indication in these studies that transfusion of

the rheumatoid factor complex has had ability to produce disease in the recipients . . . ."). Ex. 2016, 174:21-176:3; Ex. 2085 ¶¶114-117.

A placebo-controlled trial published in the prestigious New England Journal of Medicine in 1983 showed that even in chronic RA patients in which RFs could be found, removing RFs from the blood (using a process called "plasmapheresis") did not provide a clinical benefit. Ex. 2011, 1124 (Concluding that despite producing "[s]ignificant reductions" in "rheumatoid factor titer" and other laboratory measures, "plasmapheresis does not have clinical benefit in chronic rheumatoid arthritis.").[2] If "self-associated dimeric complexes of IgG RF found in the blood of RA subjects are small enough both to evade clearance by complement receptors and to cross endothelium to reach the extravascular space," as proposed in the Edwards hypothesis, Ex. 1030 at 126, then a POSA would have expected

[2] The article notes that there was "no statistically significant difference between the clinical responses to true and sham plasmapheresis therapy" and that "[o]verall, the patients improved on both types of treatment, suggesting that a placebo effect was the most likely explanation for the observed transient improvement." Ex. 2011, 1127-28. As an alternative explanation for the improvement in both patient groups, the article speculated that "[t]he disposable plasticware used may have absorbed low-molecular-weight inflammatory mediators during both cycles of therapy." *Id.* at 1128.

that such complexes would also migrate from the extravascular space back across the endothelium into the blood where they would be depleted by plasmapheresis. Ex. 2085 ¶¶118-122.

In view of this, and other research pointing to a non-causative role for RFs, Dr. Edwards notes at the beginning of his article that "[i]nterest in RF-based immune complexes waned." Ex. 1030, 126. Dr. Boers agreed: "I think the interest went down, yes. To be fair, yes." Ex. 2016, 52:16-17.

By 1992, a "major revolution" had taken place: "Synovitis [was] no longer conceived as an antibody-mediated process involving rheumatoid factors and immune complexes, but rather as a cell-mediated process involving T cells, antigen-presenting cells (APC), macrophages, synoviocytes, and cytokines." Ex. 2002, 729; Ex. 2085 ¶¶123-127.

"Considerable evidence support[ed] the role of T cells in the initiation and perpetuation of rheumatoid synovitis." Ex. 2018, 239. As Dr. Boers confirmed at deposition, prior art reported that "in animal models inflammatory arthritis could be transferred from one animal to another by transferring T-cells." Ex. 2016, 36:10-14; *see* Ex. 2018, 238 ("[P]articular T cells responding to specific epitopes from the disease-inducing antigen are able to transfer the disease in question to naïve animals."); Ex. 2002, 732 ("More direct evidence comes from experiments in

which adjuvant arthritis can be transferred, in the absence of antigen, by T cell lines or clones . . . .").

Dr. Boers also confirmed that the prior art taught "inflammatory arthritis could be treated in such an animal by blocking the T-cell receptor." Ex. 2016, 36:15-18; *see* Ex. 2018, 238 ("Furthermore, the disease can be treated by specific immunotherapeutic maneuvers directed against the antigenic peptide or against the T-cell receptor specific to the disease-inducing T cell."). Prior art also showed that inflammatory arthritis could be treated in animals by removing the thymus, where T cells originate. Ex. 2002, 732 ("Bursectomy in the chicken, which ablates the B lymphocyte system, has no effect on DGA [Dumonde-Glynn arthritis], but thymectomy severely inhibits or even abolishes it (39).").

As explained in Kalden, researchers had discovered a genetic link between "T cell receptor genes" and patients with RA. Ex. 1051, S-91; Ex. 2018, 236. And clinical studies aimed at eliminating T cells had shown success. *Id.* (citing "clinical trials aimed at elimination of T cells by thoracic duct drainage, T cell apheresis or by treatment with cyclosporine A"); Ex. 2002, 732 (identifying "physical (thoracic duct drainage, total lymphoid irradiation, and lymphocytapheresis), chemical (cyclosporine A), and biological (monoclonal antibodies directed against the T cell structures such as CD4 and IL-2 receptor) forms of therapy" as "hav[ing] a beneficial effect on RA").

As Dr. Boers agreed at deposition, "T-cells were viewed . . . as having a central role in rheumatoid arthritis." Ex. 2016, 30:7-10; *Id.* at 212:18-20 (describing "all the other scientists being, you know, crystal clear about what they thought was the key player in the inflammation, which was the T-cell"). Accordingly, "researchers were developing new drugs, new RA drugs, based on the central role that T-cells were thought to play in rheumatoid arthritis." Ex. 2016, 32:4-9; *see* Ex. 1051 at S-91. "By 1990, cytokines such as tumour necrosis factor alpha (TNF-α) had come to be considered the more important mediators in the joint, and therapeutic trials using cytokine blockade [had] reinforced that view." Ex. 1030, 126; Ex. 1051, S-91 ("Based on our increasing knowledge of the pathogenic mechanisms underlying tissue destruction in RA, two main targets for monoclonal antibodies and other biological agents have been identified: T cells and proinflammatory cytokines.").

Accordingly, when the Edwards hypothesis published in the late 1990s, a POSA would have approached its premise that RFs cause RA with significant skepticism, knowing that the scientific community already had considered and discarded that theory. Ex. 2085 ¶128. Even one of Petitioner's own experts admitted in another proceeding that "most rheumatologists considered that rheumatoid factors were not central to the pathogenesis of RA," and Dr. Edwards' theory "that RA might in fact be (primarily) a B-cell mediated disease . . . went

against the prevailing medical opinion at the time." Ex. 2042, ¶¶7-8. In 2005, Dr. Elena Massarotti (who Pfizer, Inc. offers as an expert in support of IPR2017-01115 against the '161 patent) wrote that "[u]ntil recently, the main focus in RA pathogenesis has been on T cells and cytokines." Ex. 2044, 788; *see id.* at 787 (noting after the priority date that "the use of rituximab has expanded to diseases where B cells have traditionally not been thought to be pivotal in pathogenesis (such as rheumatoid arthritis).").

Neither Petitioner nor its expert articulate any reason why a POSA supposedly would have been inclined, after reading the Edwards hypothesis, to revisit the abandoned theory that RFs cause RA. The Edwards hypothesis does not identify any scientific breakthrough in the study of RFs. It does not describe any *in vitro* or animal model suggesting that RFs cause RA. It does not point to an RF-based therapy that had shown success, or even promise, in treating RA. Rather, according to the hypothesis, the "new information" on which the hypothesis was based consisted of abstract research that supposedly "[elucidated] the structure and function of [FcγR] receptors" and "established that synovial intima is a highly specialized immunological microenvironment which includes an unusual pattern of FcγR expression." Ex. 1030, 126 ("Armed with this new information, we are now in a position to construct a hypothesis . . . .").

The record fails to show—and neither Petitioner nor its expert even argue—that a POSA would have found this "new information" to be persuasive evidence that RFs cause RA, contrary to the consensus view among rheumatologists after decades of research. Ex. 2085 ¶¶128-129. Petitioner points to no prior art before or after Edwards suggesting that this "new information" may be tied to the pathogenesis of RA.

(ii) A POSA Also Would Have Rejected The Premise That An Anti-CD20 Antibody Like Rituximab Would Interrupt Production Of IgG RF Immunoglobulins

Assuming that a POSA, as of the priority date, would have accepted the premise that RF immunoglobulins cause RA, the POSA would have rejected the premise that an anti-CD20 antibody like rituximab would actually interrupt production of RFs. Experience had shown that immunoglobulin levels remained within normal limits after administration of rituximab. Even without the benefit of that experience, a POSA would not have expected that rituximab would interrupt RF production because the POSA would have understood that immunoglobulins are produced by plasma cells, which are long-lived and not depleted by rituximab. And even assuming that rituximab would kill B cells expressing IgG RF, a POSA would have expected such B cells to reappear rapidly because they were known to be produced by routine gene expression.

(1) Experience Showed That Immunoglobulin Levels Remained Within Normal Limits After Administration Of Rituximab

The Edwards hypothesis focused on RFs of the IgG class, Ex. 1030, 126 ("[The] hypothesis . . . point[s] to a central role for immune complexes, and specifically for IgG RF, in the pathogenesis of RA"), and proposed interrupting production of these IgG RFs by administering "an anti-B-cell (CD20) antibody," like rituximab. *Id.* at 129. But all phases of rituximab testing in the oncology setting demonstrated that rituximab did not significantly change mean IgG levels.

The Phase I trial examined immunoglobulin levels in patients "monthly during a 3-month follow-up period" after administration of rituximab and reported in 1994 that "there was no significant change in the serum IgG (Fig 3A) or IgM (Fig 3B) levels over this period." Ex. 1025, 2462. Edwards cited this trial and acknowledged that "Ig levels are maintained" after administration of rituximab. Ex. 1030, 129.

Edwards noted that the Phase I trial measured Ig levels only "in the short term." *Id*. But longer trials were already under way, and after Edwards was submitted for publication—but before the priority date—those trials had shown that IgG levels are maintained in the long term as well. In the Phase II trial published in 1997, investigators tested immunoglobulin levels in patients for more

than a year and found that "[t]here were no significant changes in mean IgG levels" after rituximab administration. Ex. 1026, 2188.

A Phase III trial published in 1998 monitored patients even longer—more than two years—and determined at a median follow-up time of 11.8 months that "[m]ean serum IgG and IgA levels remained within normal limits throughout the study." Ex. 2009, 2826-27, 2829. As Dr. Boers explained, "whatever change occurred did not decrease the levels of those Ig's below a level which would be interpreted as being normal." Ex. 2016 at 157:22-24.

Thus, by the priority date, experience with rituximab showed that IgG immunoglobulins remained within normal limits after administration of rituximab, contrary to the premise that an anti-CD20 antibody like rituximab would interrupt IgG RF levels. Ex. 2085 ¶¶131-137.

(2) A POSA Would Have Understood That Immunoglobulins Are Produced By Plasma Cells, Which Are Long-Lived And Not Depleted By Rituximab

Even without the benefit of the experience from rituximab trials, a POSA as of the priority date would not have expected an anti-CD20 antibody like rituximab to interrupt production of immunoglobulins, including IgG RF. Rather, a POSA would have known:

(i) that immunoglobulins are produced in bulk by plasma cells, Ex. 2010, 363 ("The majority of serum antibody is produced by terminally

differentiated plasma cells."); Ex. 2016, 160:5-161:6 (characterizing this as "[b]asic immunology. . . . from medical school"), and

(ii) that "[t]he CD20 antigen is expressed on early B cells but not upon differentiation to antibody secreting plasma cell." Ex. 1026, 2191; Ex. 2009, 2825 ("The cell-surface antigen CD20 . . . . is expressed on normal B cells from the pre-B cell stage to the activated B-cell stage, but is not expressed on stem cells, plasma cells, or cells of other lineages.").

In other words, a POSA would have known that rituximab does not kill the cells that produce immunoglobulins like IgG RF, and therefore would not have expected rituximab to interrupt the production of IgG RFs directly.

Nor would a POSA have expected rituximab to interrupt production of IgG RFs indirectly. Although rituximab may kill B cells that otherwise would differentiate into new IgG RF-producing plasma cells, a POSA would have known that existing IgG RF-producing plasma cells would be long-lived. It was once assumed that plasma cells were not long-lived, but that assumption had been dispelled by the priority date. Indeed, papers published in 1997 and 1998 in journals like NATURE and CELL reported that "antibody-secreting plasma cells from bone marrow are as long-lived as memory B cells," Ex. 2021, 133, which were believed to live for decades, Ex. 2065, 39 ("The fact that immunological memory can last for many years (in humans, memory to certain viral infections can

be lifelong) has led to the widely held belief that memory cells are extremely long lived."); Ex. 2010, 363 (reporting that "a substantial fraction of plasma cells can survive and continue to secrete antibody for extended period of time (>1 year) in the absence of any detectable memory B cells."); *see* Ex. 2022, 1703 ("Recently, it has been demonstrated that persistent antibody titers are provided by long-lived plasma cells."); Ex. 2085 ¶¶138-145.

In a 2002 paper, the authors of Edwards acknowledged that "removal of the cellular source of pathogenic autoantibodies. . . . should perhaps not have been expected" by them because "B-lymphocytes do not secrete large amounts of antibody;" rather "[a]ntibody is produced in bulk by daughter plasma cells," which do not express CD20. Ex. 2024, 825; Ex. 2085 ¶¶146-149. The authors attributed their own misguided expectations to "a largely erroneous assumption, *i.e.* that plasma cells are short-lived and dissipate rapidly." *Id.* They suggested that they were not the only ones who made such an assumption, and stated that the assumption appears to be erroneous "now," but the prior art shows that a POSA would have known that the assumption was erroneous even before the priority date, as discussed above. As even the authors acknowledge with respect to their assumption "that plasma cells are short-lived and dissipate rapidly," *id.*, "[e]vidence that this was not so was already available from lymphoma subjects treated with rituximab, in whom total immunoglobulin levels changed little,

despite the absence of circulating B-lymphocytes for many months," *id.*, as discussed in Section IV.A.3(a)(ii)(1) above.

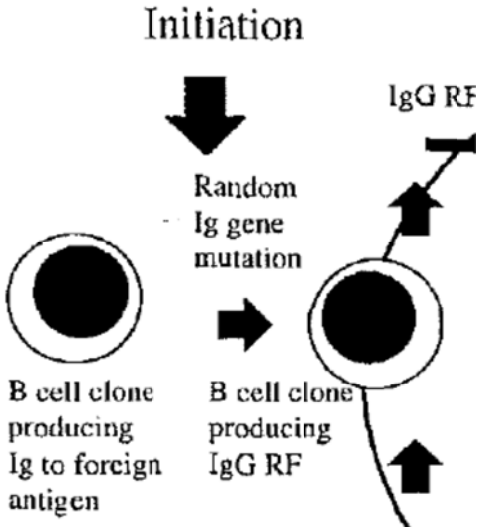
(3) A POSA Would Have Expected B Cells Expressing IgG RF To Reappear Rapidly Because They Were Known To Arise By Routine Gene Expression.

By the priority date, a POSA would have known that B cells expressing RFs are generated by routine V(D)J rearrangements of "germline" sequences found in a person's hereditary DNA. Ex. 2035, 1320 ("These studies have suggested that germline genes with little if any somatic mutation can generate RF specificity."); Exhibit 2036, 2119 ("These results show that the light chain variable regions of some human RF autoantibodies can be generated without somatic mutation, and that genes capable of encoding RF light chains are present in normal people."); Ex. 2085 ¶¶150-153.

A POSA also would have known that "B cells are produced rapidly." Ex. 1030, 129. Thus, assuming that rituximab would kill B cells expressing IgG RF, a POSA would have expected that new B cells expressing IgG RF would appear quickly—perhaps in a matter of weeks—resulting in no meaningful interruption of IgG RF production even if pre-existing IgG-RF producing plasma cells were short-lived. Ex. 2085 ¶154.

The Edwards hypothesis proposed that "pathogenic autoantibodies such as IgG RF develop by chance mutations," causing disease. Ex. 1030, 128; Ex. 2016,

217:14-18. But not even Dr. Boers was willing to defend that proposal at deposition. Instead, in connection with a discussion of part of Fig. 1 of the Edwards hypothesis,



Ex. 1030, 128. Dr. Boers characterized the proposal as "very silly":

> So he's ignoring -- I mean, this is -- this is a very silly part of the cartoon saying initiation, you know how rheumatoid arthritis starts? Oh, it's just a random Ig gene mutation. Here we have these B cell clones. And there you go off, we have explained rheumatoid arthritis. No. No.

Ex. 2016, 213:3-9. As Dr. Boers admitted, a POSA was "not going to lean on Dr. Edwards' expertise to really understand how those rheumatoid factors got there, you know, got into existence in the first place, because that part of the cartoon is a big, wide empty space that the other experts were filling in with their expertise." *Id.* at 213:22-214:2.

(iii) Edwards Stated That Aspects Of The Hypothesis Needed To Be Tested, With The Ultimate Test Being Administration of Anti-CD20 To RA Patients.

Edwards repeatedly states that it is describing only a hypothesis. Ex. 1030, 126 (stating "we are now in a position to construct a hypothesis"); *id.* ("Perhaps the most important aspect of this hypothesis . . . ."); *id.* ("Much of the hypothesis . . . ."). And it warns that "[s]everal detailed aspects of the hypothesis need to be tested." *Id.* at 129. As Dr. Boers admitted, the hypothesis made "some very big leaps of, ***not present evidence***, but ideas leading to another idea, that if true would lead to another idea," and so on. Ex. 2016, 219:7-11 (emphasis added). The hypothesis specifically identifies at least the following aspects that require testing:

- the "precise role of FcγRIIIa in the cytokine response to immune complexes of different sizes and steric characteristics," Ex. 1030 at 129;
- the "relationship between the clinical evolution of RA and circulating IgG RF dimers capable of inducing TNF-α release from FcγRIIIa+ macrophages *in vitro*," *id.*; and
- the "link between mechanical stress, growth factor production and FcγRIIIa expression." *Id.*

The record is devoid of evidence that any of this testing had been done by the priority date, much less that any results of such testing were consistent with the hypothesis. Consequently, a POSA would not have had a reasonable expectation

that what Edwards acknowledged to be the "ultimate test of the hypothesis"—"the efficacy of destruction of RF-producing B-cell clones by anti-CD20 antibodies and/or other agents"—would have been successful. Ex. 2085 ¶¶155-156. A reasonable expectation of success cannot be provided by "some very big leaps of, not present evidence." Ex. 2016, 219:7-11.

Petitioner and its expert argue that a POSA would have had a reasonable expectation of success using "doses at or around those disclosed in the Rituxan® label for treating NHL" because "that dose had been shown to deplete B-cells successfully, the same goal for treating RA." Ex. 1002 ¶84. But the question is not whether rituximab would have been expected to kill B cells in RA patients. The claims of the '161 patent are not directed to methods of killing B cells in RA patients, they are directed to methods of treating RA.

(b) The Field Was Littered With Failed Biologic Agents, Many With Strong Scientific Foundations

In the decade leading up to the priority date, many researchers were developing biologics for the treatment of RA. As Dr. Boers confirmed at deposition, "[t]here were many failures." Ex. 2016, 185:12-14. In fact, there were only two successes, infliximab and etanercept, and they both worked by blocking the pro-inflammatory cytokine anti-TNFα. Ex. 2085 ¶¶157-163.

In 1997, O'Dell observed that "much publicity about biologic agents and their application to the treatment of RA has appeared" but "[u]nfortunately, the

results of these interventions, when studied in controlled trials (with the possible exception of therapies directed against tumor necrosis factor alpha [TNFα]), have been ***singularly unimpressive***." Ex. 1015, 792 (emphasis added, footnotes omitted); *see* Ex. 2085 ¶¶75-80.

The list of failed biologics for RA included a monoclonal antibody known as CAMPATH-1H, Ex. 2016, 190:7-11, which targeted the CD52 antigen found on the surfaces of mature B cells and T cells. Ex. 2032 at 1589. Clinical studies using CAMAPTH-1H showed that it was able to deplete B cells (as well as T cells) when given to RA patients. *Id.* at 1592, Fig. 2 (showing substantial depletion of "CD19+ (B cells)"). Despite the decrease in B cells, however, CAMPATH-1H did not result in "a sustained clinical response." *Id.* at 1594. Given the failure of CAMPATH-1H, a B cell (and T cell) depleting antibody, a POSA would not have had a reasonable expectation of success for another B cell depleting antibody like rituximab. Ex. 2085 ¶¶130, 164.

Another biologic failure in RA was anti-CD4, an antibody directed against the T cell surface marker CD4, as evidenced by the Moreland article (Ref. [7]) reviewed by Dr. Boers in 1998. Ex. 2008, 614; Ex. 2016, 185:15-17; *supra* Section IV.A.1(c) above. Other biologic failures before the priority date included:

- anti-CD5, anti-CD7, anti-CD25, and anti-ig64 antibodies
- cytokine inhibitors, including IL-8 and IL-12

- cytokines such as IL4, IL10, and IL11
- antibodies targeting adhesion molecules, including anti-ICAM-1
- interferons alpha and beta-1b

Ex. 2048; Ex. 2049; Ex. 2085 ¶¶59-162 (identifying additional failures).[3] The long list of failures underscores the unpredictability of this field of art. *Id.* ¶¶86-87.

Moreover, many of these failed biologics had strong scientific foundations as potential treatments for RA. For example, experimental models suggested that inhibiting T cells, e.g., with anti-CD4, could be effective to treat RA, *see supra* Section IV.A.3(a)(i) above, and knowledge that IL-4 was an anti-inflammatory cytokine in animals models suggested that synthetic IL-4 might be effective. Ex. 2079. In contrast, no *in vitro* or animal studies existed that supported use of a B cell killer like rituximab to treat RA.

* * *

Accordingly, the record does not even establish an expectation that rituximab alone would successfully treat RA, much less that a combination of rituximab and methotrexate would be successful.

[3] These review articles were published shortly after the priority date, but they cite prior art studies evidencing each of the biologic failures in the list.

B. The POSA Would Not Have Combined Edwards, "The Rituxan® Label," O'Dell, and Kalden In The First Place

A POSA would not have relied on the teachings of Edwards, either alone or in combination with any other references, given the faulty premises on which it was based. Indeed, history actually shows that the scientific community declined to rely on the Edwards hypothesis, as discussed below.

However, even assuming a POSA would have relied on the Edwards hypothesis, the POSA would not have been motivated to combine it with a reference disclosing methotrexate. A POSA believing the Edwards hypothesis instead would have combined it with a reference disclosing an agent that killed B cells.

As for "The Rituxan® Label," Ex. 1037, Petitioner fails to establish that Ex. 1037 was a prior art printed publication. Accordingly, the Board should not give any weight to Ex. 1037 or the section of Dr. Boers's declaration that relies on it.

1. A POSA Would Not Have Relied On The Edwards Hypothesis, Given The Faulty Premises On Which It Was Based.

As discussed in Section IV.A.3(a) above, Edwards described an untested hypothesis based on premises that were inconsistent with the scientific literature as of the priority date. Accordingly, a POSA would not have relied on the Edwards hypothesis as the foundation for any combination of references.

History actually shows that the scientific community declined to rely on the Edwards hypothesis at the time. As Dr. Silverman sets forth in his declaration, more than half a dozen review articles describing potential biologic agents for the treatment of RA were published after the Edward hypothesis, between 1998 and 2000. Not one of them cited the Edwards hypothesis, let alone endorsed it. Ex. 2085 ¶¶166-169. Nor did a single one even mention rituximab. *Id.* Moreover, several of these review articles were published before the priority date. *Id.* The conspicuous absence of any reference to the Edwards hypothesis, rituximab, or B cell depletion in any review articles circulating at the time would have further discouraged a POSA from relying on the Edwards hypothesis.

Moreover, according to Petitioner's Exhibit 1039, Dr. Edwards reportedly started his own open-label study ***without using methotrexate.*** Dr. Edwards administered a modified form of a cancer regimen used to kill B cells in NHL patients—rituximab, cyclophosphamide, and prednisone—to a handful of patients at University College London Hospitals. Ex. 1039 at ¶¶11-17. But even armed with resulting data that he characterized as "consistent with the concept that RA is critically dependent on B lymphocytes," Ex. 2028, 205 (Abstract), Dr. Edwards struggled to find a journal willing to publish his study. His manuscript was "rejected by at least 5 international journals" before the Journal of the British Society of Rheumatology finally agreed to publish it. Ex. 2043, 215.

Only after these and other results, including results from a randomized controlled clinical trial, were published after the priority date did people in the scientific community begin to take interest in the possibility of using rituximab to treat RA. As Dr. Massarotti observed, "[f]ocus turned to the role of B cells in RA when a small open-label trial reported the use of rituximab on 5 patients with refractory RA." Ex. 2045, 758 (citing the paper submitted here as Exhibit 2028). As one of Petitioner's experts admitted in another proceeding against Patent Owners, "skepticism remained until clinical research done by Edwards and others showed in the early 2000s that Edwards' hypothesis that depletion of mature B cells would be efficacious, was in fact correct." Ex. 2042 ¶9 (conceding that "[t]he most important publication in this regard is Edwards' 2004 article in the leading general clinical journal *New England Journal of Medicine*").

The scientific community's lack of reliance on the untested Edwards hypothesis is consistent with a view of the hypothesis as simply a paper that "uses strong language" in an effort to "get[] real attention," and that gets "there by, you know, some very big leaps of, not present evidence, but ideas leading to another idea, that if true would lead to another idea, that if true, would cure the disease," as Dr. Boers testified. Ex. 2016, 219:2-11. It is also consistent with a view of Dr. Edwards as simply having "constructed the hypothesis to be provocative," and "[w]hether or not the hypothesis was correct, [] want[ing] to be provocative to the

community of rheumatologists," as Dr. Boers confirmed at deposition. *Id.* at 232:17-23.

Petitioner argues that the proposal in the Edwards hypothesis to administer an anti-CD20 antibody like rituximab to RA patients "was well received by POSAs" based on private letters that do not themselves qualify as printed publications. Pet. 28. Based on one letter, Petitioner argues that Dr. Edwards "succeeded in securing funding from [his employer] the University College London to conduct a trial to treat subjects with RA with rituximab in October 1998." Based on another letter, Petitioner argues that "[h]e also succeeded in securing approval from that University's ethics committee (Ex. 1034), and permission to use rituximab off-label during that trial to treat RA from the UK Medicines Control Agency." Pet. 28-29.

But there is no evidence that the corresponding decision makers at University College or the UK Medicines Control Agency were even rheumatologists, much less that they satisfied the other aspects of Petitioner's definition of a POSA. Nor is there evidence that their decisions reflect that the proposal was actually "well received" by them. Moreover, there is no evidence describing the criteria that were applied by these decision makers, though the letter from the UK Medicines Control Agency makes clear that the agency made no evaluation of the merits: "In coming to its decision, the Licensing Authority has

not evaluated the safety, quality and efficacy of the product." Ex. 1035. Even assuming that the proposal to administer rituximab to RA patients was, in fact, "well received" by these decision makers, it would not follow that the Edwards hypothesis (Ex. 1030) itself was "well received" such that a POSA would have combined it with other references to arrive at the claimed invention.

2. Assuming A POSA Would Have Relied On Edwards, The POSA Would Have Been Motivated To Combine Rituximab With Another B Cell Killer, Not With Methotrexate.

Petitioner and Patent Owner agree that the Edwards hypothesis envisions a possible cure for RA but disagree as to whether it also envisions anything less—e.g., mere treatment.[4] Either way, there can be no dispute that the strategy proposed by the Edwards hypothesis was "to kill all B cells." Ex. 1030, 129; *id.* (proposing that "the logical thing to do is destroy all mature B cells"). Thus, assuming a POSA

[4] It does not. The article itself states that "[p]erhaps ***the most important aspect of this hypothesis*** is that it refocuses attention on the possibility that permanent interruption of autoantibody production might effectively cure the disease" and expressly "propose[s] that this might be possible." Ex. 1030, 126 (emphasis added); *id.*, 129 ("The chance that RF B-cell clones can be abrogated permanently is uncertain, but perhaps for the first time there is a strategy that would logically lead to disease cure.").

would have relied on the teachings of the Edwards hypothesis, the POSA would have tried to design a regimen to kill all B cells. Ex. 2085 ¶¶170-171.

A POSA would have known that rituximab alone would not "kill all B cells." In a pre-clinical animal model, repeated doses of rituximab were shown to kill only 80% of mature B cells in the body. Ex. 1025, 2458. Rituximab also was not able to deplete all B cells in cancerous human lymph nodes. *Id.* at 2462, Table 4 (showing remaining B cells in biopsies of lymph nodes). Dr. Boers confirmed that these studies demonstrate that rituximab alone did not kill all B cells. Ex. 2016, 165:21-166:15.

The Edwards hypothesis cites the paper reporting these studies, Ex. 1030, 129 (Reference [37]), and even acknowledges that rituximab alone will not kill all B cells when it describes the "ultimate test of the hypothesis" as "the efficacy of destruction of RF-producing B-cell clones by anti-CD20 antibodies ***and/or*** other agents." *Id.* (emphasis added). Thus, if a POSA would have tried to design a regimen to kill all B cells, as the Edwards hypothesis taught, and if the POSA would have included rituximab in such a regimen, then the POSA would have combined rituximab with another B cell killer, such as cyclophosphamide. Ex. 2085 ¶¶172-177.

In fact, that is precisely what Dr. Edwards himself did when he set out to test his hypothesis in an open-label study. He combined rituximab with

cyclophosphamide and prednisolone "based on the type of combination therapy used in B-cell lymphoma." Ex. 2028, 206; Ex. 1039, ¶17. A rituximab plus cyclophosphamide arm also was included in the subsequent randomized controlled trial in which Dr. Edwards participated. Ex. 1045, 2572.

Even the Edwards hypothesis itself suggests the use of cyclophosphamide to kill B cells to "allow anti-non-self B-cell clones, but not pathogenic IgG RF-producing clones, to re-emerge." Ex. 1030, 129. The article states that "[t]his may well be what happens when subjects with RA treated with high-dose cyclophosphamide prior to bone marrow transplantation go into long-term remission." *Id.* Moreover, cyclophosphamide was already in the arsenals of rheumatologists, and significant lymphocyte depletion had been reported when RA patients were treated with cyclophosphamide. Ex. 2027, 791 (Table 2).

In contrast, none of the instituted references (or any other prior art cited by Petitioner) taught using methotrexate to kill B cells. Ex. 2085 ¶176. Dr. Edwards himself rejected the notion of treating RA with the combination of rituximab and methotrexate even after observing successful results for that very combination in the above-mentioned randomized controlled trial, which also included a rituximab-plus-cyclophosphamide arm showing "no appreciable difference" by comparison. Ex. 2044, 789. Dr. Edwards described the suggestion "that rituximab should be used together with methotrexate" as "'completely illogical, because the 2

treatments are unrelated, they're not doing the same thing.'" Ex. 2015, 2. As Dr. Boers confirmed, "when Dr. Edwards is saying that methotrexate is not doing the same thing, his point is that methotrexate, unlike rituximab, is not depleting B-cells." Ex. 2016, 241:1-5. A POSA subscribing to the teachings of the Edwards hypothesis simply would not have tried a combination of rituximab and methotrexate.

Moreover, a POSA would not have added methotrexate on top of a combination of rituximab and another B cell killer like cyclophosphamide because of concerns about overlapping toxicities. For example, a POSA would have known that both methotrexate and cyclophosphamide can cause bone marrow suppression, Ex. 2046, 234 (reporting that methotrexate "can cause hepatic toxicity, bone marrow suppression, sterility, and severe gastrointestinal ulceration"); *id.*, 235 (reporting that cyclophosphamide "can cause a number of severe adverse effects, including hemorrhagic cystitis, severe bone marrow suppression," and other complications). Bone marrow suppression impairs the development of new blood cells, including new B cells (as opposed depleting existing B cells). Ex. 2085 ¶176. Increasing the risk of bone marrow suppression by administering two agents known to suppress bone marrow, in combination with rituximab, would have been of particular concern to a POSA, given that the rituximab kills B cells, making the development of new B cells all the more important. *Id.*

Dr. Boers argues that a POSA would have taken a pick-and-choose approach to the teachings of the Edwards hypothesis and "perhaps reject part of the proposition and find another part compelling." Ex. 2016, 229:6-7. According to Dr. Boers, "if even only 25 percent of what [Dr. Edwards] was proposing in this paper were true, we would have a new mechanism of action to treat rheumatoid arthritis, maybe not to cure, but to treat." *Id.* at 219:19-23. This is textbook hindsight. "'It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.'" *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 448 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)). Here, as discussed above, no one *in fact* paid attention to any part of the Edwards hypothesis until after Dr. Edwards published the results of his small open-label study.

3. Petitioner Fails To Establish That Ex. 1037 Is A Printed Publication.

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 argues that Ex. 1037 "was a publicly available printed publication as of December 1997" on the ground that (i) it "bears a copyright date of 1997," (ii) it "and its associated Approval Letter, Ex. 1052, are available on the FDA's website as part of the November 26, 1997 approval package," and (iii) "[p]ursuant to FDA regulations, Genentech was required to include this with its Rituxan® product as of December 1997, when Genentech began selling Rituxan® in the U.S." Pet. 17 n.2 (citing 21 C.F.R. §201.59 (1997)). None of these assertions withstands scrutiny:

(i) That Ex. 1037 bears a copyright date of 1997 says nothing about whether it was ever actually publicly accessible. Petitioner fails to cite a single case holding that a copyright date is sufficient indicia of public accessibility under the patent laws. And the Federal Circuit has held that not even an official certificate of registration from the Copyright Office establishes that a document is a printed publication. *In re Lister*, 583 F.3d 1307, 1312-13, 1317 (Fed. Cir. 2009).

(ii) That Ex. 1037 may be available on the FDA's website now, or was available when Petitioner "last visited July 6, 2016" (more than 17 years after the

priority date), *id.*, says nothing about whether it was publicly accessible—on an FDA website or otherwise—as of December 1997. Petitioner describes Ex. 1037 "as part of the November 26, 1997 approval package," but offers no evidence to support that characterization or explain what it means.

(iii) The 1997 version of 21 C.F.R. §201.59 did not provide that "Genentech was required to include [Ex. 1037] with its Rituxan® product." Pet. 17 n.2. Rather, it simply provided that "no person may initially introduce or initially deliver for introduction into interstate commerce any drug to which §§201.56, 201.57, 201.100(d)(3) apply unless the drug's labeling complies with the requirements set forth in the regulations, with the following exceptions . . . ." Ex. 2047, 29. Petitioner fails to offer any evidence that Rituxan® was a drug to which "§§201.56, 201.57, 201.100(d)(3)" applied, and that none of the listed exceptions made §201.59 inapplicable. Even assuming that Rituxan's labeling had to "compl[y] with the requirements set forth in the regulations" and that Ex. 1037 is a copy of the label reviewed by the FDA in November 1997, Petitioner fails to submit any evidence that the regulations prohibited Genentech from making any changes to the label before selling Rituxan®. Even the regulations in force today allow post-approval label changes, many of which do not require further FDA approval. *See, e.g.*, 21 C.F.R. 601.12(f)(3). Petitioner also fails to submit evidence that the FDA did not approve a revised label for Rituxan® before it was sold.

A printed publication is a particular document, not just information. Thus, the evidence must show that a particular document was "publicly accessible." *SRI Int'l*, 511 F.3d at 1194. It is not enough to merely show that certain information was disseminated or made available in some form or another. Nor is it enough to assert that a document is an FDA-approved label. *Mylan Pharms. v. Boehringer Ingelheim Int'l GmbH*, IPR2016-01566 (Paper 15) at 11-12 (Feb. 3, 2017).

Here, Petitioner does not contend that Ex. 1037 is a copy of a document that was actually enclosed with a vial of Rituxan® sold before the priority date. Rather, Petitioner represents that Ex. 1037 is a copy of a document downloaded from the FDA website on July 6, 2016, with otherwise unspecified provenance. Accordingly, Petitioner has not established that Ex. 1037 is a printed publication upon which unpatentability may be established in an *inter partes* review, *Cisco Sys., Inc. v. Constellation Techs. LLC*, IPR2014-01085 (Paper 11) at 9 (Jan. 9, 2015) ("Petitioner has not made a sufficient showing that Rosenberg qualifies as a printed publication under 35 U.S.C. § 102(b) and, thus, falls within the proper scope of an *inter partes* review."), and the Board should not give Ex. 1037, or the portions of Dr. Boers' declaration that rely on it, any weight.

V. UNREBUTTED OBJECTIVE INDICIA OF NON-OBVIOUSNESS DEMONSTRATE THAT THE CLAIMS OF THE '161 PATENT ARE NOT OBVIOUS.

"[O]bjective indicia of nonobviousness are crucial in avoiding the trap of hindsight when reviewing, what otherwise seems like, a combination of known

elements." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Such objective indicia include long-felt need, unexpected results, and commercial success. *Id.* at 1358-59.

A. The Claimed Treatments Unexpectedly Halted Erosive Progression, Satisfying A Long-Felt Need.

Rheumatoid arthritis is a crippling disease because it can progressively erode joints to the point of severe deformity and disability. Ex. 2085 ¶¶10, 178. Investigators measure progressive erosion of joints using x-rays or radiographs. *Id*. ¶178. At the time of the invention, "no single therapy regimen or combination of therapies ha[d] been consistently associated . . . with a halt in progression of loss of joint structure and function." Ex. 2003, 933. Although several DMARDs had been shown to ***slow*** erosive progression, the scientific community was still searching for a therapy that could ***halt*** erosive progression—ideally for an extended period.[5]

[5] At deposition, Dr. Boers asserted that four DMARDs had been shown by reliable evidence to be capable of halting erosive progression from RA. But he failed to cite any evidence, much less reliable evidence, in support of that assertion, and his testimony was inconsistent with the record. For example, Dr. Boers identified methotrexate as one such DMARD, Ex. 2016, 68:7-18, but O'Dell unequivocally states that "[m]ethotrexate does not halt erosive disease," citing no fewer than ten supporting articles. Ex. 1015, 782. In any event, Dr. Boers later confirmed that "even for the DMARDs, which [he had said] had been shown to

Ex. 2016, at 78:2-5 (agreeing that "a halt in radiographic [erosive] progression is a better outcome than retarding radiographic progression"). As a scientific director at the National Institutes of Health remarked six months after the priority date: "For decades, rheumatologists have searched for a medical therapy that can actually stop progression of rheumatoid arthritis." Ex. 2052, 2; Ex. 2085 ¶¶178-181.

Treatment with the combination of rituximab and methotrexate, as described in all the claims of the '161 patent, unexpectedly satisfied this long-felt need for a therapy to halt erosive progression in RA patients. Large clinical trials show that the combination of rituximab and methotrexate has halted erosive (radiographic) progression for many years in a significantly higher proportion of patients than methotrexate alone. Ex. 2005; Ex. 2006. These clinical trials have been conducted in RA patients with early, untreated disease as well as in those with later, hard-to-treat disease that has not adequately responded to several prior therapies. *See, e.g.*, Ex. 2005, 353 (describing a study in methotrexate-naïve patients with early active RA and reporting that "a significantly higher proportion of patients receiving rituximab 2x1000 mg+MTX showed no radiographic progression (defined as

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be—to have some efficaciousness for preventing or retarding erosive progression, there was a major problem with toxicity," and "that's one reason why rheumatologists continued to search for new and better therapies." Ex. 2016, 70:3-11. Dr. Boers's testimony simply underscores the long-felt need.

change in mTSS ≤0) over 2 years compared with those receiving placebo+MTX"); Ex. 2016, at 75:13-25 (confirming that the authors of Ex. 2005 fairly characterized their results); Ex. 2006 at 1159-1160 (describing a study in patients with active RA who had previously experienced an inadequate response to TNF inhibitors and reporting that "[t]he proportion of patients with no progression in joint damage over 2 years was significantly higher in the rituximab group than in the placebo group," with both groups receiving methotrexate, and that "[o]f those patients randomised to rituximab who did not progress during the first year, 87% did not progress during the second year either"); Ex. 2085 ¶¶182-186.

The amounts of rituximab administered in these clinical trials along with methotrexate was either two infusions of 500mg, or two infusions of 1000mg, separated by two weeks. Ex. 2005; Ex. 2006. Each of these infusions falls within the 250 mg/m^2 to about 1000 mg/m^2 range of doses required by claims 2, 6, and 10 of the '161 claims.[6] Ex. 2085 ¶¶183-184. Thus, the evidence shows that the methods claimed in the '161 patent are able to halt erosive progression for at least two years in a range of patients and at a range of doses. "Objective evidence of nonobviousness need only be 'reasonably commensurate with the scope of the claims.'" *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257 (Fed. Cir. 2013) (vacating

[6] The average body surface area of a patient is about 1.7 m^2, making the claimed range approximately 425 mg to 1700 mg. Ex. 2085 ¶ 183.

Board's decision of obviousness for overly "strict" application of nexus requirement). In any event, "there is a presumption of nexus" here, given that Patent Owner has shown that the methods practiced in the studies that establish rituximab halts erosive progression are embodiments of the '161 patent claims. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) ("[T]here is a presumption of nexus for objective considerations when the patentee shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'").

Petitioner argues that the invention did not satisfy any long-felt need because two TNF inhibitors, infliximab and etanercept, were available by the priority date. But Petitioner cites no evidence that a POSA knew, as of the priority date, that these TNF inhibitors could halt erosive progression, let alone for extended periods of time. Therefore, at the time of the invention, there was still a long-felt need for such RA treatment. *See* Ex. 2085 ¶187.

The claimed combinations of rituximab and methotrexate not only satisfied that long-felt need, they did so unexpectedly, particularly given that methotrexate was known not to halt erosive progression, Ex. 1015 at 782, and a POSA would not have expected a B cell killer like rituximab to halt erosive progression given what was known about the pathophysiology of RA at the time. It was known that bone erosion is caused by specialized cells call osteoclasts, and that these cells are

activated by cytokines such as RANKL, TNF-alpha, and IL-6. Ex. 2085 ¶188-192 Neither B cells nor immune complexes were (or are) believed to be directly involved in the formation, survival, and activity of osteoclasts. *Id.* It remains unclear, even today, how rituximab can so effectively halt erosive progression. *Id.*

B. The Claimed Treatment Has Been An Enormous Commercial Success.

During prosecution, Patent Owners pointed out that "[w]orldwide sales of rituximab for use in combination with methotrexate to treat RA have been significant since its approval in 2006." Ex. 2020 at 27. Indeed, as reported in Genentech's SEC filings for the first two full years following approval, net U.S. sales of rituximab for 2007 were $2.285 billion, with approximately 8% to 10% estimated to be sales in the immunology setting, and net U.S. sales for 2008 were $2.587 billion, with approximately 11% to 13% estimated to be immunology sales. Ex. 2051, 47. In 2007 and 2008, RA was the only immunology indication for which rituximab was approved, and the approval was only for rituximab "in combination with methotrexate." Ex. 2026, 1223; Ex. 2085 ¶¶192-193. Thus, Rituxan® sales for the RA indication, which required the claimed combination of rituximab and methotrexate, totaled nearly a half of a billion dollars over that two-year period alone.

Sales of rituximab for RA since the patent issued demonstrate even greater commercial success. As explained by economist Dr. Ryan Sullivan, sales of

rituximab to treat RA in combination with methotrexate, as claimed by the '161 patent, [redacted] Ex. 2084 ¶¶33-35.

The FDA approved label for Rituxan® indicates that Rituxan® is rituximab, and that Rituxan® is indicated for treatment of RA only "in combination with methotrexate," Ex. 2026, 1223, as required by all of the claims of the '161 patent. Ex. 1001, 26. Moreover, the label specifies that the FDA approved dose is "two-1000 mg intravenous infusions separated by 2 weeks." Ex. 2026, 1224. Again, each of these 1000 mg infusions is within the 250 mg/m^2 to about 1000 mg/m^2 range of doses required by claims 2, 6, and 10. Ex. 1001, 26. Ex. 2085 ¶¶183, 193. Thus, there can be no dispute that the Rituxan® product marketed by Genentech embodies the inventions claimed in the '161 patent and that there is therefore a presumption of nexus to the demonstrated commercial success. *WBIP,* 829 F.3d at 1330 n.4. In any event, as Dr. Sullivan determined, "the commercial success of rituximab for RA, as used in combination with methotrexate, is due to the claimed technology of the '161 patent and not due to unrelated factors such as excessive marketing or promotion." Ex. 2084 ¶46.

VI. CONCLUSION

The Board should reject Petitioner's obviousness arguments, which are based on hindsight, and confirm all of the challenged claims.

Dated: June 2, 2017

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6, the undersigned certifies that on June 2, 2017, a copy of the foregoing document **GENENTECH, INC. AND BIOGEN, INC.'S PATENT OWNER RESPONSE** and **Exhibits 2002-2085** have been served in its entirety via e-mail/FTP site, as agreed, on counsel of record for petitioners at the following address:

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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 13,978 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, signature blocks, certificate of service, or this certificate of word count.

Dated: June 2, 2017

Respectfully submitted,

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