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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AMGEN, INC.,
Petitioner,

v.

ALEXION PHARMACEUTICALS,
Patent Owner.

Case IPR2019-00741
Patent 9,732,149 B2

Before TINA E. HULSE, ROBERT A. POLLOCK, and RYAN H. FLAX, *Administrative Patent Judges*.

FLAX, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
35 U.S.C. § 314

Amgen Inc. ("Petitioner" or "Amgen") filed a Petition for an *inter partes* review of claim 1, the sole claim of U.S. Patent No. 9,732,149 B2 ("the '149 patent," Ex. 1001). Paper 2 ("Pet."). Alexion Pharmaceuticals ("Patent Owner" or "Alexion") timely filed a Preliminary Response. Paper 10 ("Prelim. Resp."). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 13 ("Reply"); Paper 14 ("Sur-reply").

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute an *inter partes* review. We may institute an *inter partes* review if the information presented in the petition filed under 35 U.S.C. § 311, and any response filed under Section 313, shows that there is a reasonable likelihood that Petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314. After reviewing the parties' submissions, we conclude that Petitioner has demonstrated a reasonable likelihood that it would prevail in showing the claim of the '149 patent is unpatentable under at least one ground. Therefore, we institute *inter partes* review of the aforementioned claim on all grounds raised in the petition, pursuant to 35 U.S.C. § 314. *See SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018); *see also* Guidance on the Impact of SAS on AIA Trial Proceedings (April 26, 2018) (available at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial).

I. INTRODUCTION

A. REAL PARTIES-IN-INTEREST

Petitioner identifies itself, "Amgen Inc.," as the real party-in-interest. Pet. 58. Patent Owner also identifies itself, "Alexion Pharmaceuticals, Inc.," as the real party-in-interest. Paper 3, 2.

B. RELATED MATTERS

Petitioner has disclosed, "Amgen has concurrently filed petitions for IPR of U.S. Patent Nos. 9,718,880 ["the '880 patent] (IPR2019-00740) and 9,725,504 [the '504 patent] (IPR2019-00739), which are related to the '149 patent and also owned by Alexion." Pet. 58. Patent Owner identifies the same related *inter partes* reviews as Petitioner. Paper 3, 2.[1]

The '504, '880, and '149 patents are related as follows: the '149 patent issued from U.S. Patent Application No. 15,284,015, filed January 19, 2017, which is a continuation of U.S. Patent Application No. 15/260,888 (now the '504 Patent), filed on September 9, 2016, which is a continuation of U.S. Patent Application No. 15/148,839 (now the '880 Patent), filed on May 6, 2016, which is a continuation of U.S. Patent Application No. 13/426,973, filed on March 22, 2012, which is a continuation of U.S. Patent Application No. 12/225,040, filed as international application PCT/US2007/006606 on March 15, 2007. The parties appear to agree (they, at least, do not dispute) that this March 15, 2007 filing date is the priority date of the '149 patent.

[1] Patent Owner's Mandatory Notices begins listing its pages at page 4. This appears to be an error. We, therefore, cite to the document's pages by counting consecutively from the first page.

C. THE '149 PATENT

The invention of the '149 patent relates to the pharmaceutical antibody "eculizumab," which is a humanized anti-C5 antibody. *See* Ex. 1001, Abstract. For reference, we reproduce Figure 1 from the Balthasar Declaration,[2] illustrating the basic structure of an antibody:

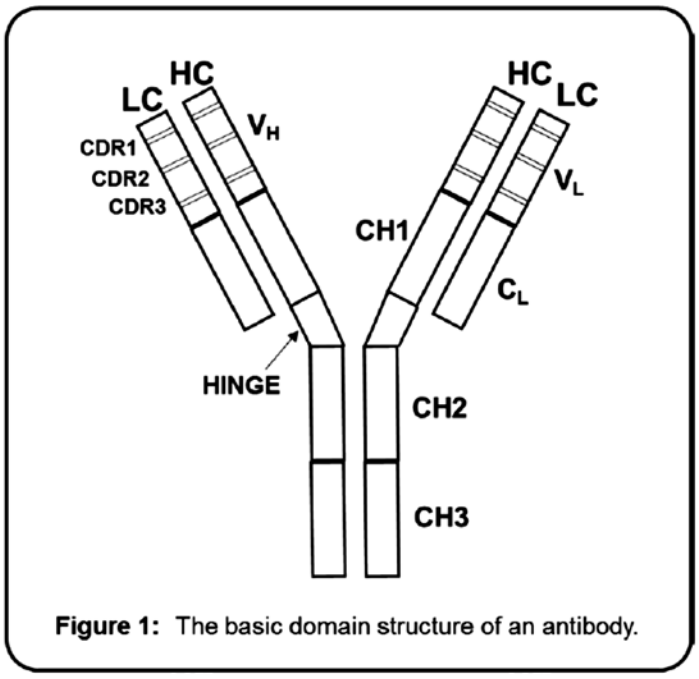


Figure 1: The basic domain structure of an antibody.

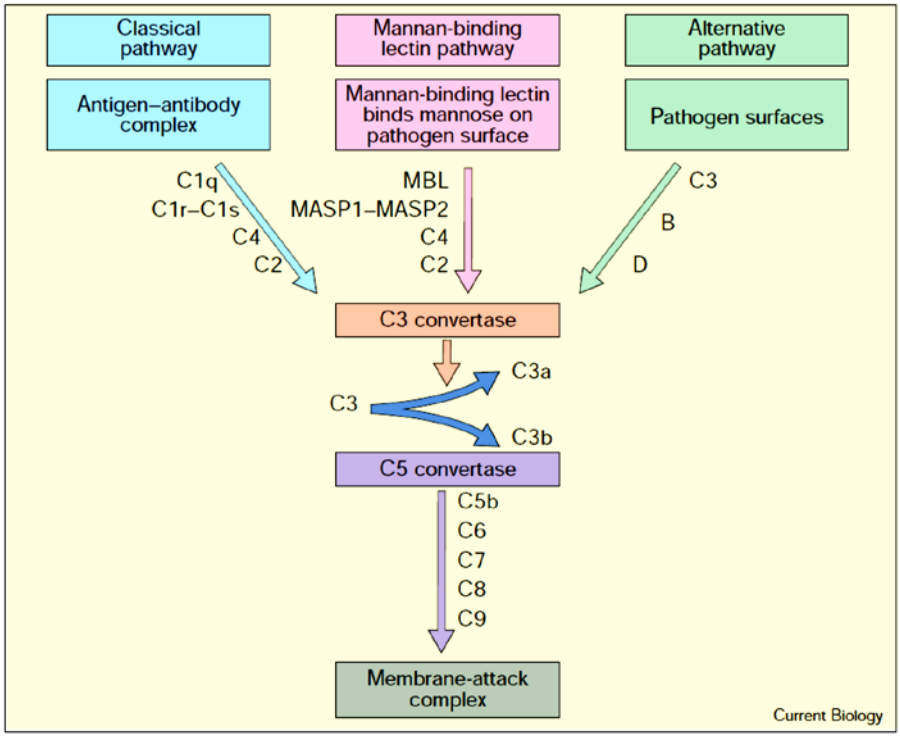
The figure above shows a basic antibody structure having hinged heavy chains (HC) and accompanying light chains (LC), each having constant regions (C_H and C_L) and variable regions (V_H and V_L), all arranged in a general "Y" shaped structure, as the variable regions and portions of the constant heavy chain regions are hinged away from one another. Ex. 1002 ¶¶ 23–24. The variable regions of each chain also include three

[2] Declaration of Dr. Joseph P. Balthasar, Ph.D. (Ex. 1002, "Balthasar Declaration").

complementarity determining regions (CDR), which provide the antibody with antigen-binding specificity. *Id*.

The sole claim of the '149 patent is directed to a C5 binding antibody having specific amino acid sequences at the heavy and light chains (SEQ ID NO: 2 and SEQ ID NO: 4, respectively), where C5 refers to the complement protein C5 convertase. Ex. 1001, 39:1–5. Complement is a "system of plasma proteins . . . so-named because it complements the activity of antibody in the lysis of bacteria." Ex. 1022 R259; *see* Ex. 1001, 7:10–8:59. As part of the immune system, complement "has a central role in host defense against many micro-organisms and in the modulation of inflammatory reactions." *Id.*; *see* Ex. 1002 ¶ 27. The figure reproduced below shows "[t]he main pathways and components of the complement activation system." Ex. 1022, R259.

Figure 1



The above figure illustrates how various complement proteins are organized into three activation pathways. Ex. 1022, R259; *see* Ex. 1001, 7:19–30. All three pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase ("C5") into C5a and C5b. Ex. 1022, Fig. 1; *see* Ex. 1002 ¶ 28. As summarized in paragraph 28 of the Balthasar Declaration, cleavage of C5 initiates the terminal complement cascade.

According to the '149 patent's Specification,

> [s]uitable anti-C5 antibodies are known to those of skill in the art. Antibodies can be made to individual components of activated complement, e.g., antibodies to C7, C9, etc. (see, e.g., U.S. Pat. No. 6,534,058; published U.S. patent application US 2003/0129187; and U.S. Pat. No. 5,660,825), U.S. Pat. No. 6,353,245 [Evans][3] teaches an antibody which binds to C5 and inhibits cleavage into C5a and C5b thereby decreasing the formation not only of C5a but also the downstream complement components.

Ex. 1001, 10:65–11:6. The Specification further states,

> A preferred method of inhibiting complement activity is to use a monoclonal antibody which binds to complement C5 and inhibits cleavage. This decreases the formation of both C5a and C5b while at the same time allowing the formation of C3a and C3b which are beneficial to the recipient. Such antibodies which are specific to human complement are known (U.S. Pat. No. 6,355,245 [Evans]). These antibodies disclosed in U.S. Pat. No. 6,355,245 [Evans] include a preferred whole antibody (now named eculizumab).

Id. at 12:21–29. The Specification also states, "[e]culizumab is a humanized monoclonal antibody directed against the terminal complement protein C5," and, thus, is intended to suppress the terminal activation cascade to prevent complement activation. Ex. 1001, Abstract, 1:63–64 (citing Thomas C.

[3] US 6,355,245 B1 (issued Mar. 12, 2002) (Ex. 1007, "Evans").

Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1023, "Thomas")).

According to Patent Owner, eculizumab, the monoclonal antibody recited in claim 1 of the '149 patent, is the non-proprietary name for its SOLIRIS product, which was approved by the FDA "for treatment of patients with PNH [paroxysmal nocturnal hemoglobinuria] on March 16, 2007." Prelim. Resp. 1–2, 6–8 (citing Ex. 1033, 1256[4]; Ex. 2005, 1[5]; Pet. 2 (citing Ex. 1009, 2).[6] The '149 patent further identifies SEQ ID NO: 2 and SEQ ID NO: 4 as the "Eculizumab Heavy [C]hain" and "Eculizumab Light [C]hain," respectively. Ex. 1001 30:16–31, 30:39–46. SEQ ID NO: 2 encodes a hybrid IgG2/IgG4 heavy chain. *See*, *e.g.*, Pet. 3; Prelim. Resp. 14.

The claim of the '149 reads as follows:

> 1. An antibody that binds C5 comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.

Id. at 39:1–5. We reproduce SEQ ID NO: 2 and SEQ ID NO: 4 from the '149 patent Specification below:

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[4] Russell P. Rother et al., *Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria*, 25(11) NAT. BIOTECH. 1256–64 (2007) (Ex. 1033, "Rother").

[5] Alexion Pharmaceuticals, Inc., Soliris™ (eculizumab), Product Label (rev. 3/2007) (Ex. 2005).

[6] Alexion Application for Extension of Patent Term Under 35 U.S.C. § 156 and 37 C.F.R. § 1.740 for Evans patent, dated May 11, 2007 (Ex. 1009).

- Eculizumab Heavy chain

SEQ ID NO: 2

QVQLVQSGAEVKKPGASVKVSCKASGYIFSNYWIQWVRQAPGQGLEWMG**[E]**

ILPGSGSTEYTENFKDRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARYF

FGSSPNWYFDVWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCL

VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGT

QTYTCNVDHKPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLFPPKPKD

TLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNST

YRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVY

TLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD

SDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK

- Eculizumab Light chain

SEQ ID NO: 4

DIQMTQSPSSLSASVGDRVTITCGASENIYGALNWYQQKPGKAPKLLIYG

ATNLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQNVLNTPLTFGQ

GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

LSSPVTKSFNRGEC

Ex. 1001, 30:16–31, 30:39–46. By way of a Certificate of Correction (dated May 15, 2018) the first line of SEQ ID NO: 2 was changed such that the final amino acid was changed from "A" to "E." *See id.* at final page.

D. PETITIONER'S ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts five (5) grounds for unpatentability, three under 35 U.S.C. § 102(b) for anticipation and the remaining two under 35 U.S.C.

§ 103 for obviousness.[7] Pet. 21–22, 24–58. Petitioner's grounds are as follows:

Ground 1: Claim 1 is anticipated under 35 U.S.C. § 102(b) by Hillmen[8];

Ground 2: Claim 1 is anticipated under 35 U.S.C. § 102(b) by Hill '05[9];

Ground 3: Claim 1 is anticipated under 35 U.S.C. § 102(b) by Bowdish[10];

Ground 4: Claim 1 would have been obvious under 35 U.S.C. § 103 over Bell,[11] Bowdish, and Evans; and

Ground 5: Claim 1 would have been obvious under 35 U.S.C. § 103 over Evans and Mueller.[12]

Id. In support of these grounds for unpatentability, Petitioner submitted, *inter alia*, the Balthasar Declaration. Ex. 1002.

[7] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '149 patent have an effective filing date before the effective date of the applicable AIA amendments, we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103 throughout this Decision.
[8] Peter Hillmen, M.B., Ph.D., et al., *Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria*, 350(6) N. ENGL. J. MED. 552–59 (2004) (Ex. 1004, "Hillmen").
[9] Anita Hill et al., *Sustained response and long-term safety of eculizumab in paroxysmal nocturnal hemoglobinuria*, 106 BLOOD 2559–65 (2005) (Ex. 1047, "Hill '05").
[10] US 2003/0232972 A1 (published Dec. 18, 2003) (Ex. 1006, "Bowdish").
[11] US 2005/0191298 A1 (published Sept. 1, 2005) (Ex. 1005, "Bell").
[12] WO 97/11971 (published Apr. 3, 1997) (Ex. 1008, "Mueller").

II. DISCUSSION

A. ORDINARY LEVEL OF SKILL IN THE ART

Petitioner contends "A POSA [person of ordinary skill in the art] in the field of the '149 patent had knowledge of the scientific literature and ha[d] skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007," and "[a] POSA also had knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same," and "[t]ypically, a POSA would have had an M.D. and/or a Ph.D. in immunology, biochemistry, cell biology, molecular biology, pharmaceutics, or a related discipline, with at least two years of experience in the field," and "[a]lso, a POSA may have worked as part of a multidisciplinary team and drawn upon not only his or her own skills, but also taken advantage of certain specialized skills of others on the team, e.g., to solve a given problem; for example, a clinician and a formulation chemist may have been part of a team." Pet. 20–21 (citing Ex. 1002 ¶ 19) (emphasis omitted).

Patent Owner responds, "Amgen does not dispute that the '149 patent concerns an antibody 'that binds C5,' defined by its specific amino acid sequence," and "Alexion does not dispute Amgen's POSA definition, except to clarify that the POSA would have ***at least two years of experience in engineering monoclonal antibodies for human therapeutic use, either in the laboratory or industry***." Prelim. Resp. 42.

The two proposed definitions of the skilled artisan are very similar, except that Patent Owner's description more-specifically defines the field of experience of the skilled artisan. However, Patent Owner concludes that

"[u]nder either description of a POSA, Amgen cannot prove unpatentability of claim 1 of the '149 patent under any of its five fatally flawed Grounds." *Id.*

At this stage in the proceedings, we accept and use Patent Owner's proposed definition of the skilled artisan, as being inclusive of Petitioner's definition, but being more specific as to what is meant by "experience in the field," taking into account the level of skill in the art reflected in the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) ("the prior art itself [may] reflect[] an appropriate level" as evidence of the ordinary level of skill in the art) (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985)). Our decision whether to institute, however, does not turn on which party's definition of the skilled artisan is used, and our determinations would be unchanged if we applied Petitioner's definition. Further, we note that evidence may be presented as the case progresses to support some other proposed definition of the skilled artisan, which may influence our determination of this issue.

B. CLAIM CONSTRUCTION

Based on the filing date of the Petition (Feb. 28, 2019), the Board interprets claim terms in an *inter partes* review ("IPR") using the same claim construction standard that is used to construe claims in a civil action in federal district court. *See* 83 Fed. Reg. 51,340 (Nov. 13, 2018) (to be codified at 37 C.F.R. pt. 42).

In construing claims, district courts give claims their ordinary and customary meaning, which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Sources for claim interpretation include "the words of the claims themselves, the remainder of the specification, the prosecution history [i.e., the intrinsic evidence], and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art." *Id.* at 1314 (quoting *Innova/Pure Water, Inc. v. Safari Water Filtration Sys., Inc.*, 381 F.3d 1111, 1116 (Fed. Cir. 2004)). "[T]he claims themselves [may] provide substantial guidance as to the meaning of particular claim terms." *Id.* However, the claims "do not stand alone," but are part of "'a fully integrated written instrument,' consisting principally of a specification that concludes with the claims," and, therefore, the claims are "read in view of the specification." *Id.* at 1315 (quoting *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 978–79 (Fed. Cir. 1995)).

Petitioner proposes "[t]he meaning of all claim terms in the '149 patent are plain on their face and require no further construction." Pet. 21 (citing Ex. 1002 ¶ 61).

Patent Owner states, "[c]laim 1 of the '149 patent recites the complete amino acid sequence for SOLIRIS®, which was not known prior to the March 15, 2007 priority date: the heavy chain consisting of SEQ ID NO: 2, and the light chain consisting of SEQ ID NO: 4," but does not contest Petitioner's claim construction position nor propose an alternative claim construction. *See generally* Prelim. Resp.; *see id.* at 15–16.

At this stage in the proceedings, and for the purposes of this decision, we find it unnecessary to construe the language of claim 1 because the claim language is readily understandable on its face, within the context of the claim, to the person of ordinary skill in the art. Should the evidence so-

demand as the case continues, we may determine that certain claim language should be interpreted.

C. *Legal Standards*

Burden in Inter Partes Review

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

Anticipation

Regarding anticipation, our reviewing court has held:

> a patent is invalid [or unpatentable] as anticipated if "the [claimed] invention was described in" a patent or published application "before the invention by" the patentee. 35 U.S.C. § 102(e). In order to anticipate the claimed invention, a prior art reference must "disclose all elements of the claim within the four corners of the document," and it must "disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)). "However, a reference can anticipate a claim even if it 'd[oes] not expressly spell out' all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal[, Inc. v. Ingersoll Cutting Tool Co.]*, 780 F.3d [1376,] [ ] 1381 (alteration in original) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)); *see also Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1344 (Fed. Cir.

> 2016) ("[A] reference may still anticipate if that reference teaches that the disclosed components or functionalities may be combined and one of skill in the art would be able to implement the combination." (citing *Kennametal*, 780 F.3d at 1383)).

Microsoft Corp. v. Biscotti, Inc., 878 F.3d 1052, 1068 (Fed. Cir. 2017). Put another way, an anticipating reference must clearly and unequivocally disclose the claimed subject matter or direct those skilled in the art to the claimed subject matter without any need for picking, choosing, and combining various disclosures of the reference not directly related to each other by its teachings. *In re Arkley*, 455 F.2d 586, 587–88 (CCPA 1972).

Further, prior art cited as anticipating may incorporate other prior art by reference.

> Incorporation by reference provides a method for integrating material from various documents into a host document—a patent or printed publication in an anticipation determination—by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein.

Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1273, 1282 (Fed. Cir. 2000) (citations omitted). Also, "[a] single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014). However, "[i]nherency may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency." *Scaltech Inc. v. Retec/Tetra L.L.C.*, 178 F.3d 1378, 1384 (Fed. Cir. 1999) (citations omitted).

OBVIOUSNESS

Regarding obviousness, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness as set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual inquiries set forth in *Graham* (383 U.S. at 17–18) that are applied in determining whether a claim is reasonably likely to be unpatentable as obvious under 35 U.S.C. § 103(a) as follows: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) considering objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. "[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious," the answer depends on "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

With these standards in mind, we address Petitioner's challenges below.

D. GROUND 1—ANTICIPATION BY HILLMEN

THE PARTIES' POSITIONS

Petitioner contends Hillmen anticipates the '149 patent's claim because "Hillmen expressly disclosed 'an antibody that binds C5[']" because Hillmen disclosed administering eculizumab to patients, which was a known anti-C5 antibody. Pet. 24–25 (citing Ex. 1004, abstract; Ex. 1002 ¶¶ 71–73).

Petitioner contends "Hillmen's antibody necessarily 'comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4' because Alexion admitted that Hillmen's eculizumab . . . necessarily possesses those very amino acid sequences." *Id.* at 25–27 (citing Ex. 1015, 738 (Boone Declaration ¶ 6)[13]; Ex. 1024, 109; Ex. 1025, 2 (these exhibits identify a trial "C02-001" as testing SOLIRIS). The Boone Declaration, cited by Petitioner, in relevant portion, states first that study C02-001 was a study of the effect of eculizumab (h5G1.1-mAb) on patients with PNH, that Dr. Boone had reviewed the eculizumab antibody used in that study and its amino acid sequence, and that Dr. Boone "concluded that the antibody (eculizumab) used in each of the studies . . . contained the heavy and light chain sequences of SEQ ID NOs: 2 and 4." Ex. 1015, 735–38 (¶¶ 5–6). As noted in n.13 *supra*, the Boone Declaration is dated May 11, 2017.

Although Petitioner does not argue that Hillmen literally expressly disclosed the claimed antibody structure with SEQ ID NOs: 2 and 4 (which, we note, it does not), Petitioner's position is that, because Hillmen disclosed a trial of the SOLIRIS eculizumab antibody, and because Patent Owner conceded that eculizumab antibody to be the claimed anti-C5 antibody, that Hillmen inherently discloses the claimed sequences. Pet. 26–27 (citing *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004)).

Petitioner's inherency rationale, based on what Petitioner calls "the general knowledge in the relevant field" (*id.* at 30), is summarized as

[13] Declaration Pursuant to 37 C.F.R. § 1.132 by Dr. Laural Boone, dated May 11, 2017 (submitted during the prosecution of U.S. Application Ser. No. 15/148,839, which became the '149 patent) (Ex. 1015, 734–41, "Boone Declaration").

follows. Contemporaneously with Hillmen's disclosure, the skilled artisan would have known that Bowdish disclosed the entire amino acid sequence of eculizumab, but for a heavy chain CDR3 region, which Bowdish disclosed as substituted with a TPO (thrombopoietin) amino acid sequence; the skilled artisan, however, would have known that Evans disclosed the amino acid sequences of eculizumab's heavy and light chain variable domains, including this CDR3 region; alternatively, understanding the above regarding Evans, the skilled artisan would have also known Mueller disclosed the hybrid IgG2/IgG4 heavy chain and light chain constant domains of eculizumab; therefore, having all this knowledge, the skilled artisan would have known that Hillmen's disclosure of a trial of "eculizumab" was necessarily the claimed anti-C5 antibody with the claimed SEQ ID NOs: 2 and 4. Pet. 29–30 (citing Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex 1007, 44:4–13; Ex. 1008, 52–53, 58–61; Ex. 1002 ¶¶ 58, 75–76).

Petitioner also relies on statements made by Patent Owner during the prosecution of related U.S. Patent Application Ser. No. 11/127,438 (expressly abandoned July 24, 2018), where, in arguing that disclosures upon which the applicant relied for priority were supportive of the then-pending claims, stated:

> Applicant respectfully disagrees and asserts that the priority applications provide ample written support for the claimed descriptions. For example, the priority documents each describe that "Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are *described in U.S. Patent No. 6,355,245* [Evans], the disclosures of which are incorporated herein in their entirely [*sic*] by this reference . . . Applicant submits that *h5G1.1* . . . [was] *well-known to one of ordinary skill in the art as eculizumab* . . . at the time of filing of priority applications.

See Pet. 12 (quoting Ex. 1049, 838–39 (emphasis Petitioner's)). Petitioner's point is that Patent Owner has taken a position that the antibody structure disclosed in Evans was well-known to the skilled artisan so that such a person of skill would have considered this structure to be the eculizumab in Hillmen, and the antibody was publically disclosed before the March 15, 2007 priority date of the '149 patent.

Patent Owner argues, "Prior to March 15, 2007, the priority date of the '149 patent, however, the unique amino acid sequence of SOLIRIS® was not publicly known or disclosed in the prior art." Prelim. Resp. 1. Patent Owner argues:

> If a POSA were searching for the sequence of "eculizumab" as described in the art, the literature as of March 15, 2007 identified an amino acid sequence and corresponding structure that is very different from what the '149 patent claims. In particular, publications describing the safety, efficacy, and clinically relevant biological activity of "eculizumab" consistently directed a POSA to the 1996 "Thomas" publication (AMG1023) for the structure and design of the antibody, which in turn described a humanized antibody constructed with a naturally-occurring "IgG4" heavy chain constant region. The claimed antibody of the '149 patent has a very different, uniquely engineered, non-naturally occurring constant region that was nowhere described in Thomas or the prior art literature showing the safety and efficacy of "eculizumab."

Id. at 2–3 (emphasis omitted).

It is Patent Owner's position that, reading Hillmen's disclosure of "eculizumab" and Hillmen's reference to Thomas, the skilled artisan would not have been directed to the version of eculizumab of the '149 patent's claim, but, as of the '149 patent's March 15, 2007 priority date, would have understood Hillmen to refer to Thomas's disclosed eculizumab, which is an IgG4 antibody, rather than a hybrid IgG2/IgG4 antibody with SEQ ID

NO: 2, as claimed. *Id.* at 3, 11–12 (referencing Ex. 1023). Patent Owner notes that Hillmen cites Thomas as *the* reference for eculizumab. *Id*. at 12 (citing Ex. 1004, 553 (which cites Ex. 1023 as reference "15")).

Patent Owner argues that:

> Thomas . . . described the design and testing of a humanized anti-C5 antibody (termed "humanized 5G1.1" or "h5G1.1") featuring an "IgG4" heavy chain constant region, which was selected because the IgG4 isotype was thought to avoid activating human complement. (AMG1023 at 1396, 1399.) Thomas reported data showing that the IgG4 humanized antibody had suitable affinity and specificity, and was as effective as the original mouse antibody (termed "murine 5G1.1" or "m5G1.1") in an *in vitro* assay showing activity blocking C5 cleavage and preventing lysis of blood cells due to complement activity. (AMG1023 at 1396.)

Id. at 12–13 (emphasis omitted).

Patent Owner states that "[t]oday, but not prior to the March 15, 2007 priority date for the '149 patent, it is known that SOLIRIS® has the specific amino acid sequence recited in claim 1 of the '149 patent, namely, 'a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" *Id*. at 13–15 (emphasis omitted). Patent Owner argues that neither

> Hillmen [n]or Hill [could] have enabled a POSA to make and use the specific antibody recited in claim 1 without undue experimentation, because both Hillmen and Hill guided a POSA as of March 15, 2007 to make and use a very different antibody – the IgG4 isotype antibody of Thomas. *See, e.g., Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1055 (Fed. Cir. 2003) (for a reference to anticipate, "[i]t is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation").

Id. at 44 (emphasis omitted). Patent Owner further argues that

> [t]he mere naming of an investigational product (e.g., "eculizumab") in a prior art publication does not inherently

> anticipate later-filed patent claims detailing the specific structure or composition of that product (i.e., SEQ ID NOs: 2 and 4), if a POSA could not have necessarily determined the later claimed structure/composition from the information publicly available as of the priority date.

Id. at 46 (emphasis omitted) (citing *Endo Pharms. Solutions, Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378–83 (Fed. Cir. 2018)).

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of the claim of the '149 patent under Ground 1.

Petitioner concedes Hillmen does not expressly disclose the claimed antibody, instead, Petitioner relies on the doctrine of inherency and a post-priority-date admission by Patent Owner that the pharmaceutical (eculizumab) referenced in Hillmen was actually the claimed antibody.

Hillmen states "[w]e tested the clinical efficacy of eculizumab, a humanized antibody that inhibits the activation of terminal complement components, in patients with PNH." Ex. 1004, 552. Hillmen further states, "[e]culizumab is a recombinant humanized monoclonal antibody that was designed to block the activation of terminal complement components.[14,15] It binds specifically to the terminal complement protein C5 . . . ." *Id.* at 553. Citation "14" of Hillmen refers to Lutz Riechmann et al., *Reshaping human antibodies for therapy*, 332 NATURE 323–27 (1988), which does not mention eculizumab; this reference is not an exhibit in this IPR. Citation "15" of Hillmen refers to Thomas (Ex. 1023), which discloses a monoclonal antibody (5G1.1) that recognizes the human complement protein C5, which was shown to effectively block C5 cleavage. *See* Ex. 1023, 1389. The parties appear to agree that Thomas does not disclose the claimed antibody.

Thomas discloses the process of developing a humanized antibody (h5G1.1 HuG4) for human C5:

> *Construction of a humanized h5G1.1 antibody*
>
> Having demonstrated the effective humanization of the 5G1.1 variable regions, an intact humanized antibody (IgG4 isotype) was constructed and produced in 293-EBNA cells. The avidity of this humanized antibody (h5G1.1 HuG4) for human C5, was compared to the murine 5G1.1 mAb by determining the ability of each to compete binding of biotinylated 5G1.1 mAb to CS (Fig. 9). The humanized h5G1.1 mAb had a two-fold lower avidity than the murine antibody. However, the humanized h5G1.1 HuG4 antibody was equipotent with the murine antibody at protecting PAEC from lysis by human serum, with a 0.5-fold molar ratio of antibody to C5 (1:1 ratio of antibody binding sites to C5) completely inhibiting lysis of the PAEC (Fig. 10).

Id. at 1396. This paragraph was the culmination of Thomas's described development of a humanized anti-C5 antibody.[14] We find nothing in Thomas that expressly discloses or alludes to a hybrid IgG2/IgG4 antibody. *See generally* Ex. 1023.

In view of the above, even with the understanding that, as argued by Petitioner, Bowdish and Evans disclosed an anti-C5 antibody or an anti-C5 antibody fragment (scFab) that taught or suggested eculizumab could be the hybrid IgG2/IgG4 antibody of the claim, we conclude that Thomas also disclosed that eculizumab was an IgG4 isotype antibody. This means that

[14] We note, Patent Owner argues that as of the '149 patent's priority date, many other references cited Thomas when referring to eculizumab. *See* Prelim. Resp. 23–25 (Table 1). Without going into detail, we find Patent Owner has accurately shown how other contemporaneous prior art references (e.g., Hill '05 (Ex. 1047) and Bell (Ex. 1005)) cited Thomas for this purpose.

"eculizumab" referred to and refers to a class or category of anti-C5 antibodies, also called 5G1.1 or h5G1.1 mAbs.

This is also supported by the portion of the prosecution history of related U.S. Patent Application Ser. No. 11/127,438 (Ex. 1049), cited by Petitioners and discussed above. Petitioner points us to the Remarks section of an Office Action Response dated August 2, 2011. In the relevant pages, Alexion states, "the priority documents each describe that 'Particularly useful anti-C5 antibodies are h5G1.1, h5G1.1-scFv and functional fragments of h5G1.1 are described in U.S. Patent No. 6,355,245 [Evans] and 'Inhibition of Complement Activity by Humanized Anti-C5 antibody and Single Chain Fv', Thomas et al., *Molecular Immunology*, Vol. 33, No. 17/18, pages 1389-1401, 1996, the disclosures of which are incorporated herein in their entirely by this reference." Ex. 1049, 838. This same portion also states, "Applicant submits that h5G1.1 and h5G1.1-scFv were well-known to one of ordinary skill in the art as eculizumab and pexelizumab, respectively, at the time of filing of priority applications." *Id.* This same portion further states,

> ***Applicant further submits that eculizumab was first constructed in the IgG4 isotype***, ***see***, e.g., the bridging paragraph of the left and right columns of page 1396 of ***Thomas*** et al. (1996), *Id.*, a copy of which is submitted herewith as Exhibit C, ***and then into the G2/G4 format, see Mueller*** et al. (1997) *Molecular Immunology*, Vol. 34, No. 6, pages 441-452, a copy of which is submitted herewith as Exhibit D, while ***in either form the h5G1.1 antibody was well known*** to be incapable to activate human complement . . .

and it was Alexion's ultimate point that "it was well-known to one of ordinary skill in the art at the time of filing of priority applications that eculizumab has a G2/G4 Fe portion, i.e., a mutated Fe portion," which

would have arguably supported the then-pending claim(s). *Id.* at 838–39 (emphasis added). Therefore, the statements above support that "eculizumab" referred to and refers to a category of antibodies, not a single antibody structure as argued by Petitioner, and also supports that Thomas's disclosure of eculizumab disclosed the first construction of eculizumab, as urged by Patent Owner here.

Upon considering the facts here in view of Petitioner's reliance on *Crish*, 393 F.3d 1253, and Patent Owner's citation to *Endo Pharms.*, 894 F.3d 1374, we find the latter case analogous to the facts here. In *Crish*, the Federal Circuit found that a claim to the specific sequence of a promoter region of the hINV gene was inherently disclosed by the prior art's disclosure of this gene, but not its promoter's sequence, and disclosure of a plasmid used to produce the gene because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Crish*, 393 F.3d at 1257–59 (also holding that evidence of use of this prior art plasmid to produce un-claimed promoters was "irrelevant"). Thus, in *Crish*, the Federal Circuit held that there could be only one necessary (correct) result from the prior art's disclosure, which was the claimed promoter sequence; hence, it was inherently disclosed and the claim anticipated. Further, in *Crish*, the Federal Circuit found that the claim to the nucleotide sequence of the hINV gene promoter region was inherently disclosed by prior art that "specifically identified [the promoter region] by size and location" because "[t]he starting material plasmid necessarily contain[ed] the gene of interest, including the promoter region." *Id.* at 1257–59. Here, however, Hillmen does not "specifically identify" an

eculizumab antibody containing the sequence of SEQ ID NO: 2, as required by claim 1.

Endo Pharms. compels a different result under the facts here. In *Endo Pharms*., the issue was again inherency (in the context of obviousness) where prior art scientific articles described clinical trials for a drug, which was later claimed as a formulation having a specific mixture of castor oil and benzyl benzoate; however, the scientific articles did not mention this mixture, but only the active component testosterone undecanoate. *Endo Pharms*., 894 F.3d at 1278. It was later confirmed that the composition of the clinical trials described in the prior art scientific articles did, indeed, have the claimed mixture of castor oil and benzyl benzoate. *Id*. The Federal Circuit held that because it was not demonstrated that a skilled artisan could extrapolate the vehicle formulation (mixture of castor oil and benzyl benzoate) used in the prior art scientific articles based on the performance data (pharmacokinetics) reported, i.e., such performance could not have only been attributed to the claimed formulation, the generic disclosure of the pharmaceutical formulation in the prior art did not inherently disclose the claimed formulation. *Id.* at 1281–83. Furthermore, *Endo Pharms*. distinguished *Crish* because that case was about the inherent properties of a known prior art product, rather than a product that was named, but not known or determinable based on the prior art disclosure of its performance characteristics. *Id.* at 1383.

Here, the prior art reference, Hillmen, discloses a clinical trial of "eculizumab." Ex. 1004, 552, 553. However, Hillmen does not explicitly identify the structure of the antibody tested, other than calling it "eculizumab" and referencing Thomas. *Id.* at 553 (citing Ex. 1023).

Thomas discloses a version of eculizumab different from that claimed (an IgG4 isotype rather than a hybrid IgG2/IgG4 antibody). Even accepting that it was possible the skilled artisan would have known of a hybrid IgG2/IgG4 antibody, as claimed (*see, e.g.*, Ex. 1002 ¶ 13), Hillmen's mere reference to "eculizumab" would have at least invoked the Thomas IgG4 isotype eculizumab, too. Thus, Hillmen's disclosure of "eculizumab" would not have necessarily led the skilled artisan to the claimed antibody with "a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Therefore, under *Endo Pharms.*, there is no inherent anticipation of claim 1 over Hillmen.

Moreover, although Hillmen cites Thomas and thereby invokes Thomas's disclosed eculizumab antibody, Bowdish, Evans, and/or Mueller are not cited in Hillmen. *See* Ex. 1004, 559. Therefore, Petitioner's discussion of Hillmen in view of Bowdish and Evans or in view of Evans and Mueller (*see* Pet. 29–30) is not relevant under an anticipation ground for unpatentability. We also disagree with Petitioner's position that such references' teaching, even if considered "general knowledge," would have somehow overridden Hillmen's direct invocation of Thomas's disclosure of eculizumab so as to point the skilled artisan to some alternative antibody structure.

Again, to summarize, based on the evidence presented at this stage in the proceedings, Petitioner has not shown that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Hillmen under Ground 1.

E. GROUND 2—ANTICIPATION BY HILL '05

THE PARTIES' POSITIONS

We note at the outset that Petitioner's Ground 2 is, as is Hill '05's disclosure with respect to Hillmen's, an extension of Ground 1 and relies on substantially the same or similar facts and bases in law. *See* Pet. 31–34. Petitioner argues "[a]s in Ground 1, the law also compels finding anticipation in Ground 2." *Id.* at 34 (again citing, *inter alia*, *Crish*, 393 F.3d at 1258).

Petitioner contends, "Hill '05 is an Alexion publication describing results from a one-year extension study involving the same 11 patients enrolled in the Hillmen Phase 2 Pilot Study." Pet. 31 (citing Ex. 1047, 2559–60). Petitioner argues Hill '05, like Hillmen, is directed to and discloses administering "eculizumab" to such patients. *Id.* (citing Ex. 1047, 2565). Petitioner's rationale for Hill '05's anticipation of the '149 patent's claim is essentially the same as discussed above for Hillmen, only replacing Hillmen's generic disclosure for "eculizumab" with Hill '05's generic disclosure for "eculizumab," paired with the same identified admissions by Patent Owner during prosecution and the same contentions that Bowdish, Evans, and Mueller, rather than Thomas, would be the skilled artisan's basis for the structure of eculizumab. *See* Pet. 31–34 (citing Ex. 1015, 736, 783; Ex. 1047, abstract, 2559–60; Ex. 1002 ¶¶ 42–58, 79–86; Ex. 1004, abstract, 554; Ex. 1042, Abstract; Ex. 1011, abstract; Ex. 1005 ¶¶ 81–96; Ex. 1012, abstract, 1235; Ex. 1013, abstract; Ex. 1006 ¶¶ 191–193, Figs. 13A, 13B; Ex. 1007, 44:4–13; Ex. 1008, 52–53, 58–61).

Patent Owner argued Grounds 1 and 2 together and, thus, makes essentially the same arguments over Ground 2 as discussed above regarding Ground 1. *See* Prelim. Resp. 42–49.

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has not carried its burden to show a reasonable likelihood of anticipation of the claim of the '149 patent under Ground 2.

Upon reviewing Hill '05, we find its disclosure to be no more specific as to the structure of eculizumab than that of Hillmen. *See generally* Ex. 1047. Hill '05 states, "[w]e previously reported the outcome of an open-label study of eculizumab in patients with PNH.[2]" Ex. 1047, 2559 (reference "2" is Hillmen (Ex. 1004)). Hill '05 further states, "[e]culizumab is a humanized monoclonal antibody that specifically targets the complement protein C5 and prevents its cleavage.[9]" *Id.* (reference "9" is Thomas (Ex. 1023)). Thus, Hill '05, like Hillmen, invokes Thomas as a reference for eculizumab.

For the same reasons discussed above regarding Ground 1, based on the evidence presented at this stage in the proceedings, Petitioner has not shown that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Hill '05 under Ground 2.

F. GROUND 3—ANTICIPATION BY BOWDISH

THE PARTIES' POSITIONS

It is Petitioner's position that Bowdish, which incorporates Evans by reference, discloses the entirety of the claimed anti-C5 antibody as a starter scaffold antibody.

Petitioner contends that Bowdish disclosed "a 5G1.1 antibody as the starter 'scaffold' antibody sequence for creating a recombinant TPO-mimetic+h5G1.1 antibody." Pet. 35 (citing Ex. 1006 ¶ 191). Petitioner argues Bowdish disclosed "the full 5G1.1 antibody amino acid sequence [i.e., an anti-C5 antibody, as claimed,] except for the heavy chain CDR3 (HCDR3) sequence, which Bowdish replaced with the TPO-mimetic peptide sequence, LPIEGPTLRQWLAARAPV." *Id.* (citing Ex. 1006 ¶¶ 191–193, Figs. 13A (SEQ ID NO: 67; "5G1.1 – TPO Heavy Chain (Bold Denotes TPO mimetic) Amino acid sequence"), 13B (SEQ ID NO: 69; "5G1.1 Light Chain Amino Acid Sequence")).

Petitioner argues:

> A POSA would have understood that the only portion of the "scaffold" 5G1.1 antibody sequence not expressly disclosed in Bowdish is the HCDR3 sequence because Bowdish taught that "[t]he TPO mimetic peptide graft in Fab clone X4b has been *transplanted into the heavy chain CDR3* of another antibody framework, *5G1.1* . . . The sequence was *cloned into 5G1.1* in such a fashion as to *replace the native CDR3*."

Pet. 37–38 (citing Ex. 1006 ¶ 191; Ex. 1002 ¶¶ 91–93). Petitioner also argues, "Bowdish disclosed that the starter scaffold antibody 5G1.1 was produced according to Evans, stating that '[c]onstruction of 5G1.1 is described in [Evans], incorporated herein by reference.'" *Id.* at 38 (citing Ex. 1006 ¶ 191). Thus, it is Petitioner's contention that "a POSA would have known that the heavy chain of Bowdish's 5G1.1 starter antibody contained the YFFGSSPNWYFDV CDR3 sequence [of Evans], regardless of which 'version' of Evans' humanized 5G1.1 the POSA considered." *Id.* at 38–39 (citing Ex. 1002 ¶ 95).

Petitioner points to the Balthasar Declaration (¶¶ 49–54, 58, 88–103) as support for and for an explanation as to how Bowdish discloses the claimed antibody. Pet. 35–41. The Balthasar Declaration states, "[a] POSA would have understood that Bowdish's '5G1.1' antibody is an anti-C5 antibody based on Bowdish's citation to Evans—which describes the anti-C5 antibody 5G1.1—for information about '[c]onstruction of 5G1.1' . . . [and], Bowdish's '5G1.1' antibody necessarily comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." Ex. 1002 ¶ 89. The Balthasar Declaration states, "a POSA would have known that the only portion of the sequence disclosed in Bowdish's Figures 13A-13B that is different from the original h5G1.1 'scaffold' antibody disclosed in Bowdish is the portion of [its] SEQ ID NO: 67 that corresponds to the TPO peptide." *Id.* ¶ 92. The Balthasar Declaration explains, at length, how and why the Bowdish anti-C5 antibody starter scaffold and the Evans 5G1.1 antibody or antibody fragment with CDR3 amino acid sequence fit together (*see, e.g.*, Ex. 1002 ¶¶ 91–102), however, the combination and its relevance to the claimed antibody is perhaps best illustrated by the Balthasar Declaration's Figures 4, 5, 6, 7, and 13, which show Bowdish's SEQ ID NO: 67 as compared to the claimed SEQ ID NO: 2, Bowdish's SEQ ID NO: 69 as compared to the claimed SEQ ID NO: 4, Evans exemplary SEQ ID NO: 20 as compared to the claimed SEQ ID NOs: 2 and 4, and Bowdish's SEQ ID NO: 67 with Evan's heavy chain CDR3 sequence replacing the TPO peptide sequence as compared to the claimed SEQ ID NO: 2. We reproduce these figures below:

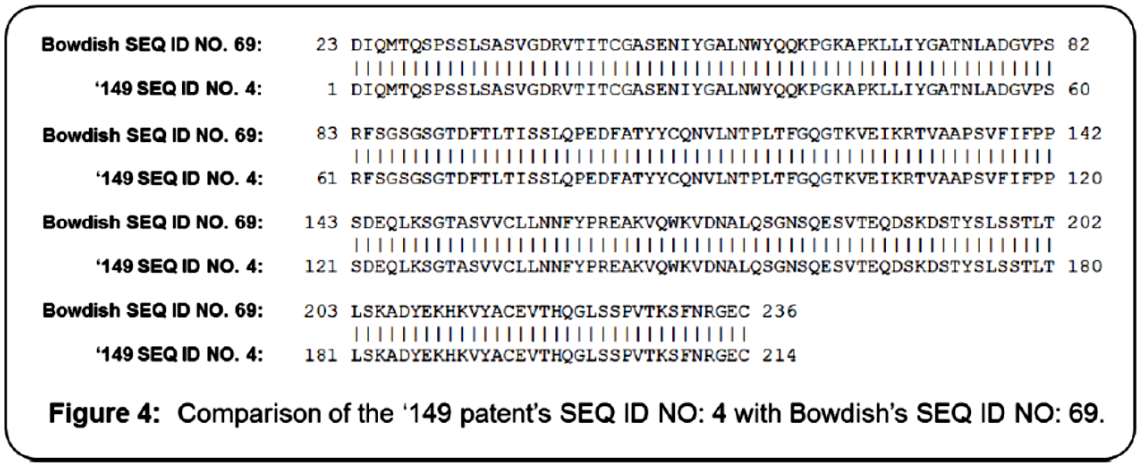

Figure 4: Comparison of the '149 patent's SEQ ID NO: 4 with Bowdish's SEQ ID NO: 69.

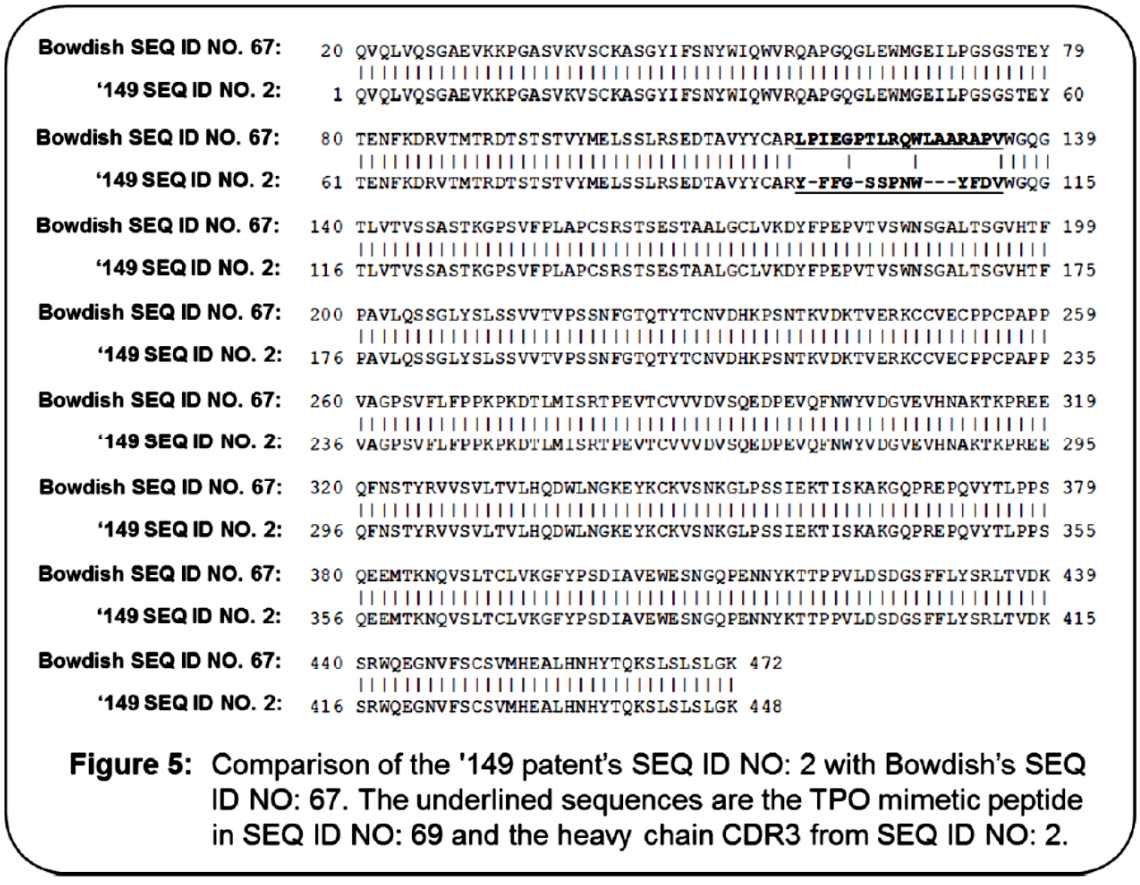

Figure 5: Comparison of the '149 patent's SEQ ID NO: 2 with Bowdish's SEQ ID NO: 67. The underlined sequences are the TPO mimetic peptide in SEQ ID NO: 69 and the heavy chain CDR3 from SEQ ID NO: 2.

Balthasar Declaration Figure 4 (above-top) shows that Bowdish's disclosed antibody amino acid sequence SEQ ID NO: 69 (minus leader sequences, which would be cleaved off as part of the maturation of the antibody) matches with the claimed antibody amino acid sequence SEQ ID NO: 4. Ex.

1002 ¶ 51. Balthasar Declaration Figure 5 (above-bottom) shows that Bowdish's disclosed antibody amino acid sequence SEQ ID NO: 67 (minus leader sequences) matches with the claimed antibody amino acid sequence SEQ ID NO: 2, except for the portion including the TPO mimetic amino acid sequence (underlined). *Id.*

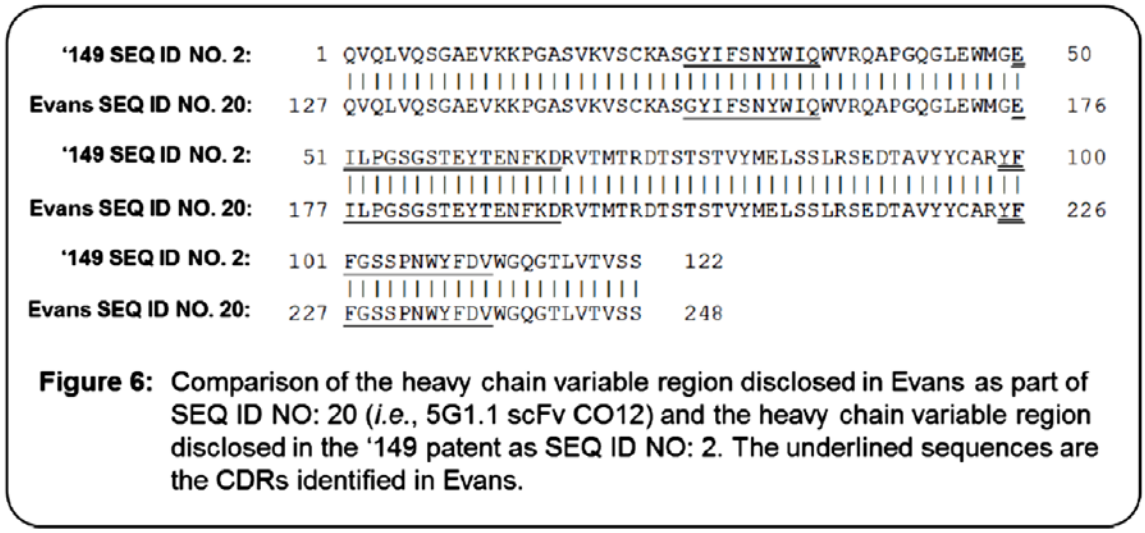

Figure 6: Comparison of the heavy chain variable region disclosed in Evans as part of SEQ ID NO: 20 (*i.e.*, 5G1.1 scFv CO12) and the heavy chain variable region disclosed in the '149 patent as SEQ ID NO: 2. The underlined sequences are the CDRs identified in Evans.

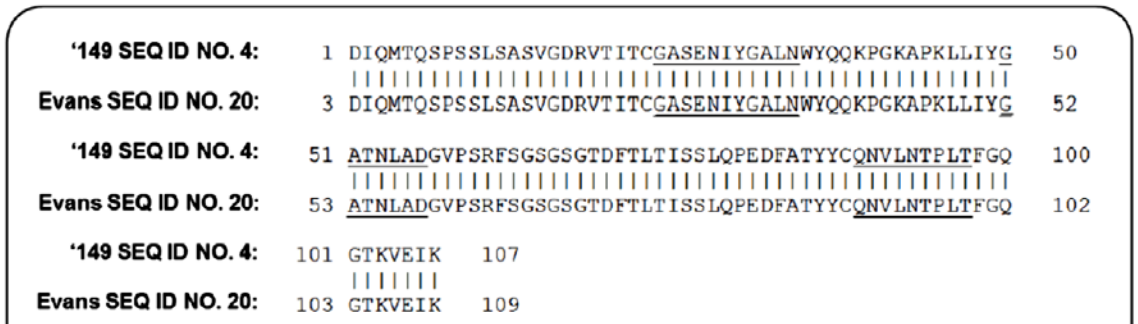

Figure 7: Comparison of the light chain variable region disclosed in Evans as part of SEQ ID NO: 20 (*i.e.*, 5G1.1 scFv CO12) and the light chain variable region disclosed in the '149 patent as SEQ ID NO: 4. The underlined portions are the CDRs identified in Evans.

Balthasar Declaration Figure 6 (above-top) shows that Evans's disclosed antibody amino acid heavy chain variable region sequence SEQ ID NO: 20 matches with the claimed antibody amino acid sequence SEQ ID NO: 2. Ex.

1002 ¶ 53. The underlined sequences are the CDRs identified in Evans. Balthasar Figure 7 (above-bottom) shows that Evans' disclosed antibody amino acid light chain variable region sequence SEQ ID NO: 20 (i.e., 5G1.1 scFv CO12) matches with the claimed antibody amino acid sequence SEQ ID NO: 4. *Id.* Again, the underlined portions being Evans's CDRs.

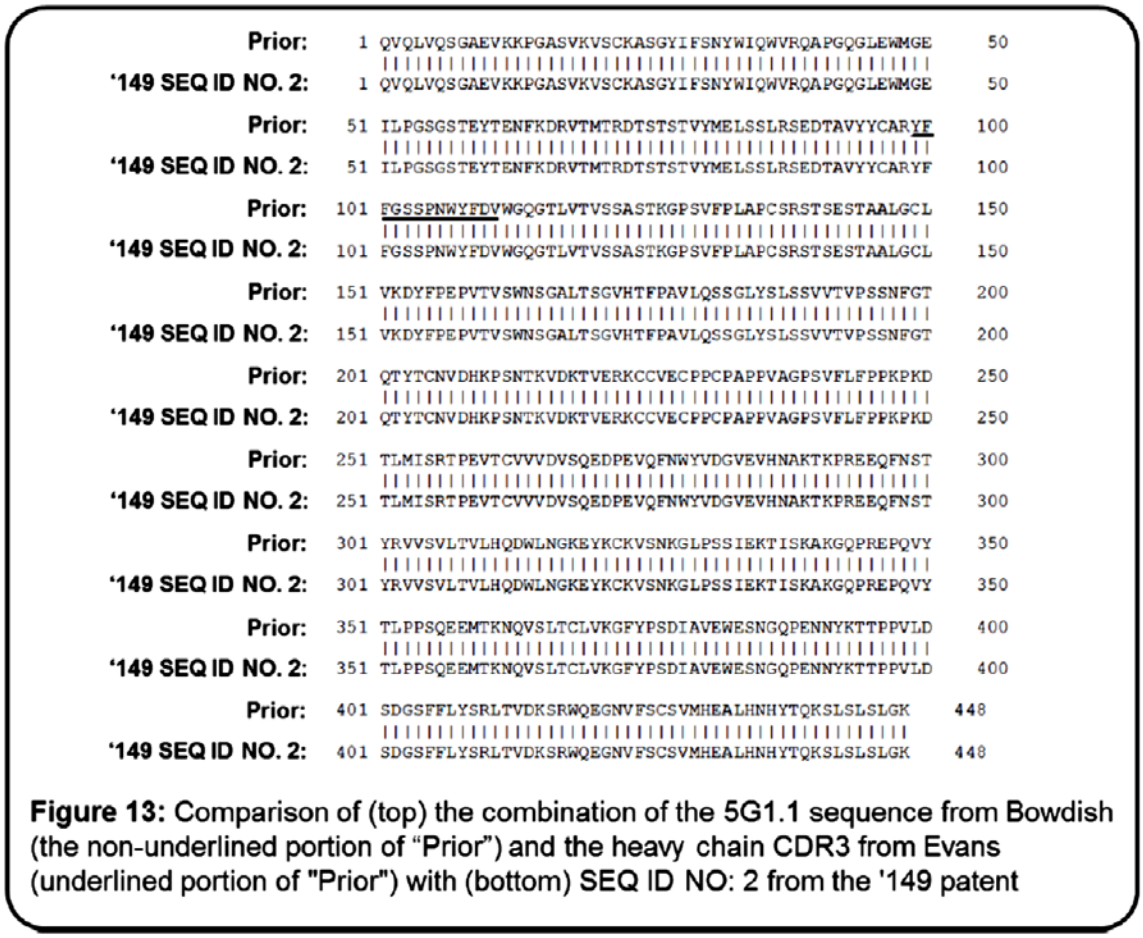

Figure 13: Comparison of (top) the combination of the 5G1.1 sequence from Bowdish (the non-underlined portion of "Prior") and the heavy chain CDR3 from Evans (underlined portion of "Prior") with (bottom) SEQ ID NO: 2 from the '149 patent

Balthasar Declaration Figure 13 (above) shows how, once Evans's disclosed antibody amino acid heavy chain variable region sequence (underlined) is provided in Bowdish's anti-C5 antibody scaffold structure, as it would have been before its replacement with the TPO sequence, the antibody sequence matches with the claimed antibody amino acid sequence SEQ ID NO: 2. Ex.

1002 ¶ 53. Having already shown in the Balthasar Declaration Figure 4, above, that Bowdish's SEQ ID NO: 69 matches the claimed SEQ ID NO: 4, Balthasar Declaration's Figure 13, above, accounts for the remainder of the claimed antibody.

Further to the above, the Balthasar Declaration further illustrates how the Bowdish, and its incorporated-by-reference Evans, antibody amino acid sequences fit together as the Bowdish starting 5G1.1, anti-C5 antibody scaffold at Figure 12, reproduced below:

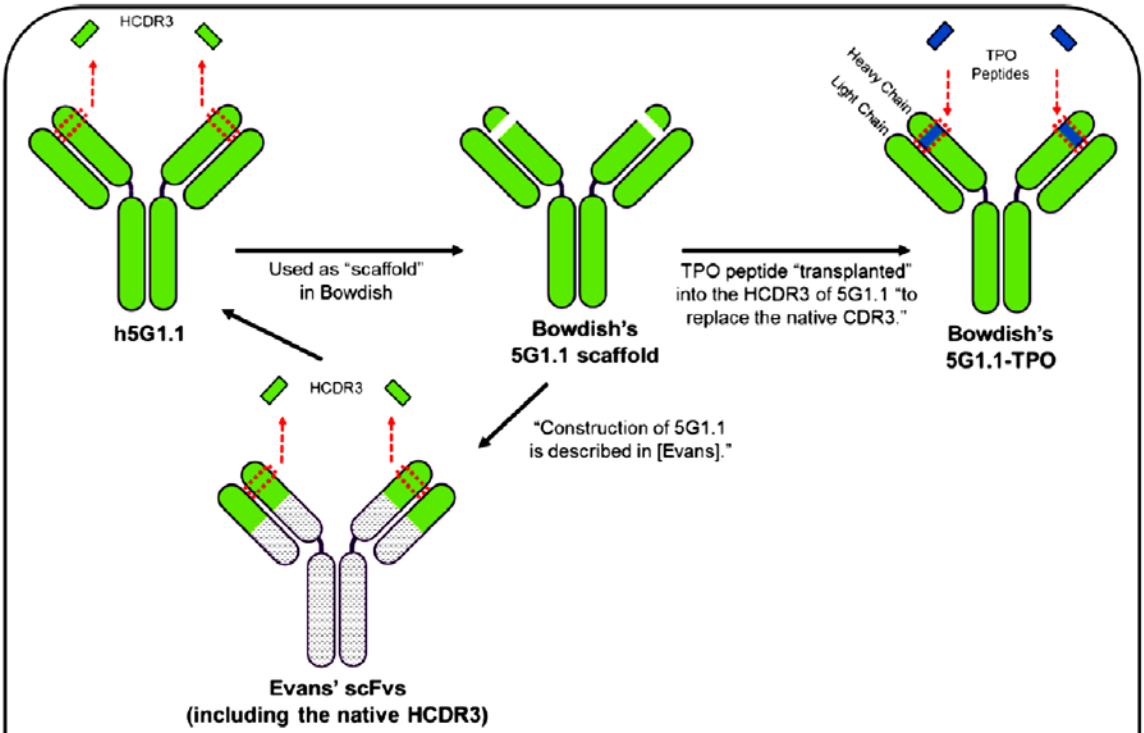

Figure 12: Diagram showing how the 5G1.1 sequence in Bowdish was used as a scaffold into which a TPO mimetic peptide was inserted to generate the 5G1.1-TPO construct (top row). The diagram also shows how the original 5G1.1 sequence could have been generated by inserting the heavy chain CDR3 region from Evans' svFvs into the 5G1.1 scaffold sequence (bottom row)

Balthasar Declaration Figure 12 (above) shows the original Bowdish scaffold antibody, the portion of that antibody removed and replaced with the TPO amino acid sequence, and how Evans's HCDR3-portion amino acid

sequence was that original amino acid portion replaced by the TPO amino acid sequence. Ex. 1002 ¶ 96.

The Balthasar Declaration states, "[a] POSA would have known that Bowdish explicitly disclosed the entire amino acid sequence of 5G1.1 with the exception of the heavy chain CDR3 region, and that the incorporated reference Evans provided the sequence of that missing heavy chain CDR3 region" and that "[c]onstructing the sequence of the source 5G1.1 antibody—which aligns perfectly with the [ ] claimed antibody—would have required only standard molecular and cellular biology methods that were well known in the art to provide predictable results." *Id.* ¶ 102 (citing Ex. 1006 ¶¶ 191–93, Figs. 13A, 13B; Ex. 1007, 21:4–24:61, 44:4–13; Ex. 1008, 37:37–39). Furthermore, although the Balthasar Declaration focuses on Evans's SEQ ID NO: 20 as evidence that its CDR3 sequence would be found in the original Bowdish antibody, the Balthasar Declaration states:

> a POSA would have seen that all of the 5G1.1 heavy chains in Evans contain the same CDR3 sequence: YFFGSSPNWYFDV. AMG1007, e.g., Fig. 19, 43:13-14, 43:26-27, 43:33-34, 43:60-61, 44:2-3, 44:12-13, 44:21-22, 44:30-31, 44:39-40, 44:49-50, 44:59-60, 45:3-4. A POSA therefore would have understood that Bowdish (via its incorporation of Evans) teaches that YFFGSSPNWYFDV is the sequence of the 5G1.1 heavy chain CDR3 (i.e., the heavy chain CDR3 of eculizumab).

Ex. 1002 ¶ 95 (emphasis omitted).

Patent Owner argues Bowdish is "a non-analogous reference" and "would not have disclosed or enabled the uniquely-engineered anti-C5 antibody of claim 1." Prelim. Resp. 3, 49. Patent Owner argues, at various points in its Preliminary Response, that neither Bowdish nor Evans uses the term "eculizumab." *Id*. at 4, 29.

Patent Owner also argues that,

> neither Bowdish's reference to using "5G1.1" as a scaffold for a TPO-mimetic peptide (AMG1006 ¶ [0066], [0191]), nor Bowdish's citation to Evans (*id*. ¶ [0191]), would have explained to a POSA how Bowdish's TPO-mimetic construct relates to the structure of "eculizumab," including the structure of its heavy chain constant region.

Prelim. Resp. 33–34. Patent Owner's point being that the skilled artisan would not read Bowdish, which incorporates Evans by reference, as disclosing the starting antibody structure that ultimately resulted in the TPO-mimetic construct.

Patent Owner also argues Bowdish does not expressly disclose "an antibody 'comprising a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4.'" Prelim. Resp. 49. Patent Owner argues that it is error to look to Evans's disclosure as it relates to Bowdish for anticipation because "the law makes clear that anticipation cannot be shown by combining portions of the claimed invention from multiple references." *Id.* at 50 (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002).

Patent Owner also argues that, even considering Bowdish and Evans together, "Amgen fails to show how Bowdish and Evans together would have disclosed '[a]n antibody that binds C5' comprising the specific, uniquely-engineered amino acid sequence of claim 1 of the '149 patent." Prelim. Resp. 50. Patent Owner's argument is that Bowdish is focused on its TPO-mimetic construct and has nothing to do with C5 binding. Patent Owner contends that Bowdish's use of the term "5G1.1" in reference to its antibody scaffold would not have taught an anti-C5 antibody. *Id.* at 51. Patent Owner also argues that Evans would not have taught the skilled

artisan that an antibody with its variable region sequences would be an anti-C5 antibody. *Id.*

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood of anticipation of the claim of the '149 patent under Ground 3.

We are satisfied on the record before us, as discussed above, that Bowdish, which incorporates Evans, discloses a 5G1.1 antibody with a structure as disclosed by Bowdish's Figures 13A and 13B, but, rather than having a TPO mimetic peptide grafted therein at the heavy chain CDR3 portion, having the CDR3 amino acid sequence disclosed by Evans. *See* Ex. 1006 ¶ 191, Figs. 13A, 13B; Ex. 1007, 7:62–63, 10:9–10, 42:55–45:33, 121–123 (SEQ ID NO: 20), Figs. 18, 19; *see also* Ex. 1002 ¶¶ 49–54, 58, 88–103, Figs. 4, 5, 6, 7, 12, 13 (Balthasar Declaration explaining Bowdish's disclosure). On this record, Bowdish's disclosed starting 5G1.1 antibody is disclosed to be identical to the claimed anti-C5 antibody (Evans confirms that its 5G1.1 antibody, referenced by Bowdish, is anti-C5).

Furthermore, the Balthasar Declaration supports that only standard, well-known, molecular and cellular biology methods would have be required to both identify the starting 5G1.1 antibody structure of Bowdish (based on Evans) and that the skilled artisan would have been able to make such an anti-C5 antibody with the claimed amino acid sequences based on this disclosure. Ex. 1002 ¶¶ 102–103. This conclusion is bolstered by Bowdish's disclosure, which states "[t]hose of ordinary skill in the art using known techniques would be able to synthesize antibodies." Ex. 1006 ¶ 131.

Regarding Patent Owner's opening volley that Bowdish is not analogous art,

> [T]he question whether a reference is analogous art is irrelevant to whether that reference anticipates. A reference may be from an entirely different field of endeavor than that of the claimed invention or may be directed to an entirely different problem from the one addressed by the inventor, yet the reference will still anticipate if it explicitly or inherently discloses every limitation recited in the claims.

In re Schreiber, 128 F.3d 1473, 1478 (Fed. Cir. 1997). Further, although Patent Owner is correct that the word "eculizumab" does not appear in the disclosures of Bowdish or Evans, neither does it appear in the claim of the '149 patent, and Bowdish and Evans clearly disclose anti-C5 antibodies and/or fragments thereof, i.e., 5G1.1 mAb, 5G1.1 scFv CO12. *See, e.g.*, Ex. 1006 ¶ 191 (antibody framework 5G1.1, as constructed by Evans); Ex. 1007, 7:62–63 (5G1.1 is most preferred anti-C5 antibody), 44:4–13. In any event, even though the ultimate objectives of Bowdish are not to produce a therapeutic anti-C5 antibody, as is the focus of the '149 patent (and Evans), Bowdish is nonetheless directed, in part, to such an antibody and requires it as a starting point for other uses (as a scaffold), and Bowdish expressly integrates the disclosure of Evans, which *is* directed to such therapeutic anti-C5 antibodies. Thus, Bowdish "is from the same field of endeavor, regardless of the problem addressed" or "is reasonably pertinent to the particular problem with which the inventor is involved," even if it is not within the inventor's field of endeavor. *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000–01 (Fed. Cir. 2016) (quoting *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992)).

As for Patent Owner's contention that Bowdish does not expressly disclose the claimed amino acid sequences, Bowdish incorporates Evans by reference (Ex. 1006 ¶ 191), which means that Evans's disclosure, in particular that portion describing the construction of a 5G1.1 antibody, is integrated from Evans into the Bowdish host document; Bowdish makes clear that Evans is effectively part of Bowdish as if it were explicitly contained therein. *See Advanced Display Sys.*, 212 F.3d at 1282. Petitioner is not "combining" Bowdish and Evans. Bowdish has already combined the two as an integrated document.

Regarding Patent Owner's argument that Bowdish has nothing to do with an anti-C5 antibody and its use of the term "5G1.1" would not refer to such, we disagree. Bowdish is clear that its starting antibody is the antibody with a structure as shown in its Figures 13A and 13B, but constructed as Evans taught to construct a 5G1.1 antibody, which Evans confirmed is an anti-C5 antibody. *See* Ex. 1006 ¶ 191; Ex. 1007, cols. 7–8.

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Bowdish, which incorporates Evans by reference, under Ground 3.

G. OBJECTIVE EVIDENCE INDICATING NON-OBVIOUSNESS

Factual considerations that underlie the obviousness inquiry include the scope and content of the prior art, the differences between the prior art and the claimed invention, the level of ordinary skill in the art, and any relevant secondary considerations, or objective indicia, evidencing non-obviousness. *See Graham*, 383 U.S. at 17–18. Relevant secondary considerations include commercial success, long-felt but unsolved needs,

failure of others, and unexpected results. *KSR*, 550 U.S. at 406, (2007). Although evidence pertaining to secondary considerations must be taken into account whenever present, it does not necessarily control the obviousness conclusion. *See, e.g.*, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007).

Before moving on to Petitioner's grounds based on obviousness, we address Petitioner's contention that "[t]here are no objective indicia of nonobviousness." Pet. 41, 47, 48, 57–58. In particular, Petitioner notes that during the prosecution of the '149 patent's parent application (the '504 patent), Alexion argued that the claimed heavy chain of eculizumab, i.e., the hybrid IgG2/IgG4 constant domain, provided surprising and unpredictable results, such as decreased effect or function, reduced immunogenicity, and increased half-life. Pet. 57 (citing Ex. 1014, 588, 593 (¶ 8)). Petitioner contends the claimed sequence of eculizumab was well-known in the art and that the alleged surprising and unpredictable features of the antibody were not shown to have a nexus with the claim limitations. *Id.* (citing Ex. 1034, 1279). Petitioner further contends that, in view of Mueller II, antibodies with the claimed hybrid IgG2/IgG4 heavy chain were known not to bind FcR and to be less immunogenic, and that it would have been known that antibodies with this claimed hybrid heavy chain would have an increased half-life. *Id.* at 57–58 (citing Ex. 1031, 488, 451; Ex. 1032, 5, 19; Ex. 1002 ¶ 140).

Patent Owner contends that evidence of commercial success, long-felt, but unmet need, and industry praise supports the non-obviousness of the challenged claim. Prelim. Resp. 60.

Patent Owner argues that SOLIRIS, the product embodying the claimed antibody, is a commercial success, having produced annual net product sales in excess of $1 billion in 2018. *Id*. (citing Ex. 2018, 70). Patent Owner contends that this commercial success "has a direct nexus to the patented features of the '149 patent, which claims the uniquely-engineered, non-naturally occurring antibody responsible for the drug's clinical (and therefore commercial) success as a treatment for PNH, as well as the complement-mediated hemolytic condition aHUS." *Id.* at 61.

At this stage in the proceedings, based on the evidence presented by Patent Owner, it is apparent that SOLIRIS is a successful product. "[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." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016). This "presumption of nexus is rebuttable: a patent challenger may respond by presenting evidence that shows the proffered objective evidence was 'due to extraneous factors other than the patented invention.'" *Id.* Here, the parties appear to agree that the claim of the '149 patent is directed to the commercial product SOLIRIS. However, commercial success "is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention – as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996).

Patent Owner argues that because SOLIRIS is "the first FDA-approved treatment to reduce hemolysis in patents with PNH," there is

evidence that the claimed antibody fulfilled a long-felt, unmet need in the market. Prelim. Resp. 61 (citing Ex. 2019, 1270).

At this stage in the proceeding, the available evidence supports that anti-C5 antibodies were considered potential therapeutic options for "many years" before 2007, and that Alexion's eculizumab product "is currently the only complement-specific antibody on the market" and is the "first and only approved therapy for PNH." Ex. 2019, 1270. Again, it may be presumed that there is a nexus between the claimed and novel elements of the SOLIRIS product and the meeting of the long-felt need. However, "[w]here the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Patent Owner also contends "SOLIRIS® also received industry praise as the recipient of multiple Prix Galien awards (the industry's highest accolade . . . ." Prelim. Resp. 61 (citing Ex. 2020; Ex. 2021).

As with the other two contended bases for indicia of non-obviousness, although it is apparent there was high praise for the SOLIRIS product from the relevant industry, there is a rebuttable presumption that this praise has a nexus with the claimed subject matter. *Cf. In re Kao*, 639 F.3d at 1068.

With the above-discussed arguments and evidence in mind when considering obviousness, we consider Petitioner's grounds for unpatentability below. However, given the early stage of these proceedings, we decline to accord much weight to Patent Owner's substantially untested evidence of objective indicia of non-obviousness. The parties will have the

opportunity to further develop the relevant facts during trial, and the Board will evaluate the fully-developed record at the close of the evidence.

H. Ground 4—Obviousness Over Bell, Bowdish, and Evans

The Parties' Positions

Petitioner's Ground 4, although based in obviousness, is substantially similar in many respects to the anticipation Ground 3, discussed above. Ground 4, like Ground 3, cites Bowdish and Evans, but combines their relevant disclosure with the Bell reference. Petitioner's arguments on Ground 4 also echo those of Ground 3 to the extent they discuss Bowdish and Evans. *See* Pet. 41–44. Thus, the discussion above for Ground 3 also applies here to Ground 4 and we supplement this discussion as needed to identify and address the parties' additional arguments unique to this ground.

Petitioner additionally contends:

> Bell taught that targeting complement protein C5 with eculizumab (h5G1.1) is safe and effective for treating PNH patients, providing ample reason for a POSA to make a humanized anti-C5 antibody such as eculizumab. AMG1005, ¶¶[0083]-[0096]. Because Bell does not expressly provide the amino acid sequence of its anti-C5 antibody, a POSA would have looked to other known teachings in the art pertaining to eculizumab (5G1.1), like Bowdish and Evans.

Pet. 45. Petitioner argues that this would have led the skilled artisan to combine Bowdish and Evans with Bell. *Id.* Petitioner's premise is that, having Bell in hand and knowing an anti-C5 antibody (eculizumab) was a desirable product, the skilled artisan would have consulted Bowdish and Evans, each of which refers to its antibody as 5G1.1, in order to identify the structure (amino acid sequence) of eculizumab. *See* Ex. 1005 ¶¶ 12, 52 ("Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other

functional fragments of h5G1.1 are described in U.S. Pat. No. 6,355,245 [Evans] and . . . Thomas et al., . . . the disclosures of which are incorporated herein in their entirety by this reference."), ¶¶ 81–96 (discussing eculizumab as the anti-C5 antibody h5G1.1-mAb); Ex. 1006 ¶ 191 (identifying a 5G1.1 antibody constructed as in Evans); Ex. 1007 cols. 7–8 (discussing antibodies to human complement component C5, i.e., anti-C5 antibodies, as 5G1.1); *see also* Ex. 1002 ¶ 107 ("Bell discloses 'an antibody that binds C5' as required by claim 1 in its disclosure of eculizumab, and provides a reason to make that antibody.").

Petitioner cites the Balthasar Declaration (¶¶ 101–119) as explaining how and why the skilled artisan would have combined Bell, Bowdish, and Evans so as to achieve the claimed anti-C5 antibody (the Declaration's rationale for obviousness is, as expected, very similar to the rationale set forth for anticipation under Ground 3). The Balthasar Declaration states:

> a POSA would have had reason to combine the disclosures of Bell, Bowdish and Evans to arrive at the antibody of claim 1, and would have had a reasonable expectation of doing so because these three references provide complementary information relating to an anti-C5 antibody that would have required only routine techniques to combine.

Ex. 1002 ¶ 106. The Balthasar Declaration states that "Bell concluded that '[p]atients in the two year study experienced a reduction in adverse symptoms associated with PNH'" and "Bell's report of successfully treating PNH with eculizumab would have provided reason for a POSA to make eculizumab for the same purposes." *Id.* ¶ 107 (quoting Ex. 1005 ¶ 96). The Balthasar Declaration notes that Bell identifies that the anti-C5 antibody eculizumab is useful, but does not expressly disclose its structure, in particular the heavy chain with SEQ ID NO: 2 and the light chain with SEQ

ID NO: 4, but the Declaration indicates that Bowdish and Evans disclose as much and that Bowdish and Evans would be referenced by the skilled artisan wanting to obtain this antibody. Ex. 1002 ¶¶ 108–117. As such, Petitioner's rationale for motivation to combine these references is supported.

Petitioner argues that the skilled artisan would have had a reasonable expectation of successfully combining the cited prior art to achieve an anti-C5 antibody as claimed because, as with Ground 3, "only basic molecular biology techniques" were required. Pet. 47 (citing Ex. 1002 ¶ 118 ("A POSA would have had a reasonable expectation of success in making the antibody of claim 1 from the disclosures of Bell, Bowdish, and Evans because doing so would have required only basic molecular and cellular biology techniques.")). As further support for this, as already noted above, Bowdish expresses that "[t]hose of ordinary skill in the art using known techniques would be able to synthesize antibodies" and Evans describes such techniques for producing an anti-C5 antibody as a pharmaceutical agent for humans. Ex. 1006 ¶ 131; Ex. 1007, 7:6–13, 19:46–67, 21:4–24:64, 37:35–45:33; 121–123 (SEQ ID NO: 20).

Patent Owner argues that, absent impermissible hindsight, the skilled artisan would not have combined, or reasonably expected success in combining, Bowdish, Evans, and Bell. Prelim. Resp. 5, 52–55. Patent Owner argues that Bell, like Hillmen, taught eculizumab was the antibody of Thomas, i.e., an IgG4 constant-region-antibody, and nothing in the other references would point the skilled artisan toward a different antibody, e.g., the antibody covered by the claim. *Id.* As a tertiary part of this hindsight argument, Patent Owner also argues Thomas taught away from the claimed

invention because Thomas described an "eculizumab" with an IgG4 constant region. *Id.* at 53.

Patent Owner argues that Petitioner has overlooked "the complexity and unpredictability involved in designing monoclonal antibodies for human clinical therapy, where even small changes to the amino acid sequence (including in the "constant" regions) could significantly impact the antigen-binding affinity and specificity of the antibody, as well as the antibody's clinical efficacy and safety." Prelim. Resp. 39 (citing Ex. 2015, 506, 508; Ex. 2017, 961–62). Patent Owner's contention is that, in view of this complexity and unpredictability, the skilled artisan would not have ventured away from Thomas's known antibody; i.e., would not have looked to Bowdish and Evans (or Mueller) to teach such an antibody. *Id.* at 41.

Patent Owner also argues that "[e]ven if Bowdish and Evans were combined as per Amgen's hindsight-driven theory, a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating conditions such as PNH." *Id.* at 56. Patent Owner's rationale is that even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration. *Id.* Patent Owner also argues that Bell, in citing Thomas for preparation of h5G1.1-mAb, taught away from the prior art combination or changing the antibody to be the claimed structure. *Id.* at 56–57.

ANALYSIS

At this stage in the proceedings and for the reasons discussed below, we find Petitioner has carried its burden to show a reasonable likelihood of that the claim of the '149 patent would have been obvious under Ground 4.

"It is well settled that 'anticipation is the epitome of obviousness.'" *In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); accord *Cohesive Tech., Inc. v. Waters Corp.*, 543 F.3d 1351, 1364 (Fed. Cir. 2008). Here, on the facts before us, there is no reason to depart from this well-settled principle of law. As we have noted above in this and the preceding section, we have found on the record before us at this preliminary stage that there is a reasonable likelihood that claim 1 is anticipated by Bowdish, which incorporates, i.e., is necessarily combined with, Evans. Thus, likewise, there is a reasonable likelihood that the claim would have been obvious over these references for the same reasons under the legal standards for obviousness set forth above. Adding the disclosure of Bell to the combination of Bowdish and Evans serves to reinforce the proposition that a 5G1.1 antibody as taught by Bowdish and Evans would be desirable to the skilled artisan.[15]

[15] Patent Owner at one point notes that "Amgen suggests that 'eculizumab' was somehow disclosed or claimed by the Evans patent (AMG1007) (e.g., Petition 2, 46, 49-50) – but it is undisputed that Evans neither used the term 'eculizumab,' nor disclosed the heavy chain constant region or full sequence of the claimed antibody of the '149 patent." Prelim. Resp. 29–30 (footnote and emphasis omitted). Patent Owner accurately identifies that Evans does not expressly disclose the term eculizumab, this heavy chain constant region, or full antibody sequence; however, as noted above, Bowdish both discloses the antibody structure and expressly invokes its own combination with Evans for the express purpose of constructing a 5G.1.1 antibody. This provides further support that Bowdish and Evans would have been combined with Bell by the skilled artisan for the purpose of identifying eculizumab's (5G1.1) structure.

Regarding Patent Owner's argument that Bowdish, Evans, and Bell's combination would require improper hindsight and that Bell's disclosed antibody would necessarily be that of Thomas's disclosure, we are not convinced. As noted above, Bell extols the virtues of the anti-C5 antibody, eculizumab, but does not identify its structure. Bell does cite to and incorporates by reference Thomas, thus, Thomas's IgG4 isotype antibody would be one type of eculizumab contemplated by Bell. However, Bell *also* cites to and incorporates by reference Evans, which is cited by and incorporated by referenced by Bowdish. As discussed above regarding Ground 3, Bowdish discloses and requires the anti-C5 antibody 5G1.1 and points to Evans for to how to make it. Thus, Petitioner's arguments rely on the disclosures of the prior art and no improper hindsight is necessarily invoked under Petitioner's rationale.

As for Patent Owner's contention that Thomas taught away from the claimed invention (or, somehow taught away from the prior art combination), we disagree. A "teaching away" requires a reference to actually criticize, discredit, or otherwise discourage the claimed solution. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). "[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* at 1200 (citation and emphasis omitted). Thomas does not criticize, discredit, or discourage the claimed invention or the prior art combination. Thomas, at worst, teaches the original eculizumab construction, an alternative to the version as taught by Bowdish and Evans. Teaching an alternative, however,

is not sufficient to show a reference teaches away from the claimed invention. *See id.* at 1201 ("The prior art's mere disclosure of more than one alternative does not constitute a teaching away from . . . alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.").

Regarding Patent Owner's argument that the complexity and unpredictability of antibody engineering for clinical therapy would mean that only Thomas's antibody would have been used in the prior art, we find the evidence of record does not support this. First, the claim of the '149 patent does not recite using the anti-C5 antibody for a clinical therapy. Second Petitioner has argued and this argument is supported by the evidence, as noted above, that the antibody could be prepared using the skill and techniques known in the art.

Regarding Patent Owner's argument that "[e]ven if Bowdish and Evans were combined . . . , a POSA would not have reasonably expected the resulting compound to work in binding to C5 or safely and effectively treating conditions such as PNH" because even small changes could substantially impact an antibody's binding properties, safety, and efficacy for human administration, we disagree. Prelim. Resp. 56. As noted above, the claim of the '149 patent covers only the antibody, and does not recite any particular use thereof (other than functionally being anti-C5). Thus, whether a therapeutic use of the claimed or prior-art-disclosed antibody would or would not be safe or effective is not material here. Further, Regarding Patent Owner's related argument that Bell taught away from the claim and combination with Bowdish and Evans, we also disagree. Bell does, indeed, cite Thomas as disclosing "[m]ethods for the preparation of h5G1.1-mAb,

h5G1.1-scFv and other functional fragments of h5G1.1," but it also cites Evans in the very same sentence. *See* Ex. 1005 ¶ 52. Thus, Thomas and Evans each teaches a version of Bell's antibody and how to make it.

We take note of Patent Owner's arguments relating to and evidence of objective indicia of non-obviousness, discussed above at Section II.G. Although we noted that there was some evidence to support Patent Owner's contentions of commercial success, long-felt but unmet need, and industry praise, we also noted that the relevant facts are likely not fully developed and Patent Owner's contentions may be rebutted. Therefore, at this stage in the proceedings, we find that Petitioner should be given the opportunity to rebut Patent Owner's evidence during trial where the parties can develop the record further.

Again, to summarize, based on the evidence presented at this stage in the proceedings, it has been shown that there is reasonable likelihood that the '149 patent's claim 1 would have been obvious over Bell, Bowdish, and Evans under Ground 4.

I. GROUND 5—OBVIOUSNESS OVER EVANS AND MUELLER

THE PARTIES' POSITIONS

Petitioner contends, "[c]laim 1 also would have been obvious in view of Evans and Mueller" and "a POSA would have had a reason to combine these references with a reasonable expectation of successfully making the claimed antibody." Pet. 48 (citing Ex. 1002 ¶¶ 120–137). Petitioner argues that "Mueller disclosed the amino acid sequence of an anti-C5 antibody's light chain constant domain and the hybrid IgG2/IgG4 heavy chain constant domain" and "Evans disclosed the complete amino acid sequences of the heavy and light chain variable domains of anti-C5 antibodies" and

"described combining the antibody variable regions with constant domains—including hybrid IgG constant domains—to make a complete anti-C5 antibody." Pet. 48–50 (citing Ex. 1007, 44:4–13, 45:24–33, SEQ ID NO: 20; Ex. 1008, 58-61; Ex. 1002 ¶¶ 121, 123–125, 129–133, Fig. 16).

Petitioner argues:

> In looking for a constant domain to pair with Evans' variable regions, a POSA would have looked to Mueller because Mueller taught antibody constant regions designed with a lower propensity to activate the immune system (and complement)—a desirable feature for a complement inhibiting antibody. AMG1008, 7:28-31, 8:23-26, 12:27-30; AMG1002, ¶¶125-128. A POSA reading Evans also would have looked to Mueller for "h5G1.1" sequence information because Mueller disclosed a 5G1.1 antibody with a hybrid IgG2/IgG4 constant domain. AMG1002, ¶¶125-128.

Pet. 50. Petitioner notes, "Dr. Balthasar explains, Mueller disclosed the amino acid sequence of a hybrid IgG2/IgG4 heavy chain constant domain when Mueller disclosed the sequence of the chimeric anti-VCAM '3F4' antibody." *Id.* at 51 (citing Ex. 1002 ¶¶ 129, 132; Ex. 1008, 58–61).

Petitioner's rationale for combining Mueller and Evans is that Mueller disclosed chimeric 3F4 HuG2/G4 heavy chain, and mature 3F4 heavy and light chain variable regions such that, a skilled artisan aligning the two would identify the 3F4 variable regions (at Figure 9) as amino acids 20–137 of the 3F4 HuG2/G4 heavy chain and amino acids 20–131 of the 3F4 light chain. Pet. 51 (citing Ex. 1008, 51–53, 58–61, Fig. 9). Petitioner contends that, seeing this, a skilled artisan "would have immediately known that the remainder of the 3F4 HuG2/G4 heavy chain (amino acids 138-463 is the hybrid IgG2/IgG4 constant region of that antibody, and that the remainder of the 3F4 light chain (amino acids 132–238) is the light chain constant region

of that antibody." *Id.* at 51–52 (citing Ex. 1002 ¶ 132, Fig. 15; Ex. 1008, 52–53, 56–57). With this understanding of the heavy and light chain constant domain sequences in mind, Petitioner contends, the skilled artisan would look to Evans to complete the whole antibody using Evans's variable regions identified from its SEQ ID NO: 20, particularly because Evans uses the same "CO12" nomenclature to refer to its 5G1.1 scFv as Mueller does in referring to h5G1.1. *Id.* at 52–53.

Petitioner's argued rationale for combining Mueller and Evans is that Mueller taught antibodies with lower immune response and identified an antibody as h5G1.1 CO12 HuG2/G4 mAb, which the skilled artisan would have known is eculizumab. Further, Petitioner argued, Evans taught the complementary parts of this anti-C5 antibody, so, by combining the elements of the two references a complete antibody would be created having the SEQ ID NO: 2 and SEQ ID NO: 4 of the claim. *Id.* at 55–56.

Patent Owner argues that, without improper hindsight, Mueller and Evans would not have been combined by the skilled artisan. Prelim. Resp. 58. Patent Owner argues "[a] POSA as of March 15, 2007 considering the problem addressed by the '149 patent – designing an anti-C5 antibody that would be safe and effective to treat conditions such as PNH – would have had no reason to look at Mueller, which had nothing to do with that problem." *Id.* (citing *Broadcom Corp. v. Emulex Corp.*, 732 F.3d 1325, 1334 (Fed. Cir. 2013) ("While a prior art reference may support any finding apparent to a person of ordinary skill in the art, prior art references that address different problems may not, depending on the art and circumstances, support an inference that the skilled artisan would consult both of them simultaneously.").

Patent Owner argues "[a] POSA would have understood that Mueller could have used ***any*** antibody with an IgG4 or IgG2/G4 isotype as a 'negative control' for its *in vitro* experiments, as long as it did not bind to VCAM," meaning, there would be no reason to incorporate the variable regions taught by Evans. *Id.* at 59.

ANALYSIS

Unlike the case with Bowdish and Evans, here, Mueller and Evans do not reference one another. Would their combination be impossible? Certainly not. However, the mere fact that prior art can be combined does not establish that one of ordinary skill would have done so. *See, e.g.*, *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (The "mere fact that the prior art may be modified in the manner suggested . . . does not make the modification obvious unless the prior art suggested the desirability of the modification.").

Ground 5 presents a close question on whether there would have been motivation to combine Mueller and Evans in the manner argued by Petitioner. Upon review of the Balthasar Declaration, it is apparent that Mueller's 3F4 heavy chain provides a match for part of the claimed SEQ ID NO: 2. *See* Ex. 1002 ¶ 56, Fig. 8. Further, Mueller's 3F4 light chain provides a match for part of the claims SEQ ID NO: 4. *Id.* ¶ 57, Fig. 9.

The Balthasar Declaration provides an illustration as its Figure 10 showing the extent each of Evans and Mueller (and Bowdish) disclose the claimed SEQ ID NOs: 2 and 4; this figure is reproduced below:

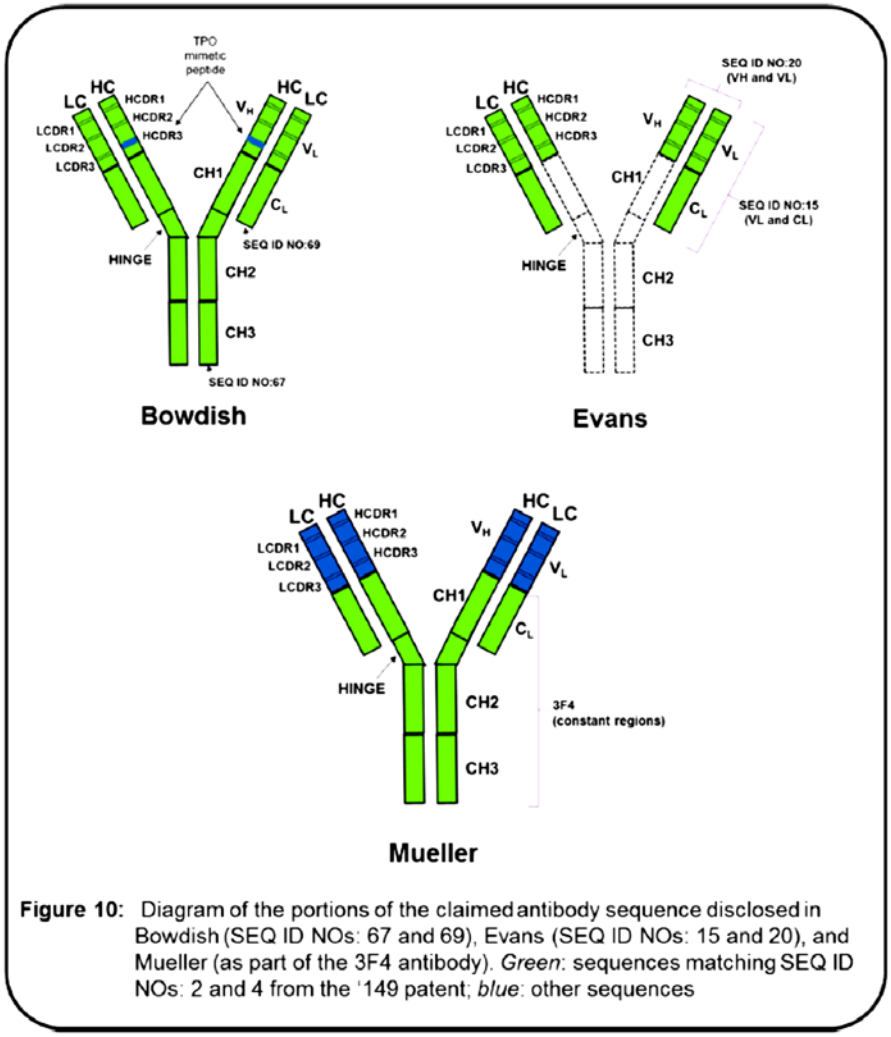

Figure 10: Diagram of the portions of the claimed antibody sequence disclosed in Bowdish (SEQ ID NOs: 67 and 69), Evans (SEQ ID NOs: 15 and 20), and Mueller (as part of the 3F4 antibody). *Green*: sequences matching SEQ ID NOs: 2 and 4 from the '149 patent; *blue*: other sequences

Ex. 1002 ¶ 58. The Balthasar Declaration's Figure 10 shows three antibody structures: Bowdish top-left, Evans top-right, and Mueller bottom; with the sequence portions disclosed by each matching the claimed sequences in green and their other sequence portions in blue.

Based, in part, on this figure, it appears that Petitioner's rationale for combining Mueller and Evans is somewhat tenuous. We are left asking why

would the skilled artisan pair Evans with Mueller, and then chose precisely the portions of Evans's and Mueller's disclosed amino acid sequences to use and which to discard so as to arrive at a final antibody that perfectly matched the claimed antibody? At this stage in the proceedings, based on the evidence before us, the answer is not entirely clear.

In view of this, Patent Owner's argument regarding improper hindsight makes some sense. True, Mueller mentions "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)," but beyond mentioning it, Mueller does not provide much other disclosure. *See* Ex. 1008, 12. It is not apparent that the skilled artisan, knowing of Evans, would look to Mueller, or vice versa.

Based on the evidence presented at this stage in the proceedings, it has not been shown that there is reasonable likelihood that the '149 patent's claim 1 would have been obvious over Mueller and Evans under Ground 5.

J. BOARD'S DISCRETION TO DENY INSTITUTION UNDER 35 U.S.C. §§ 325(D) AND 314(A)

THE PARTIES' POSITIONS

Patent Owner argues that the "Petition should also be denied institution under 35 U.S.C. §§ 325(d) and 314(a), because Amgen's Grounds rely on the 'same or substantially the same prior art or arguments' previously presented to the PTO." Prelim. Resp. 61. Patent Owner argues that during prosecution the Examiner "extensively considered" Hillmen (Ex. 1004) (which is cumulative of Hill '05 (Ex. 1047)), Evans (Ex. 1007), Bell (Ex. 1005), U.S. Patent 7,482,435 cumulative of Bowdish (Ex. 1006), and Mueller II (Ex. 1031) cumulative of Mueller (Ex. 1008), as well as having considered the arguments presented thereover as Grounds 1–5. Prelim. Resp. 62–63.

Patent Owner contends "[i]n the course of patent prosecution leading to issuance of the '149 patent, as well as prosecution of related U.S. Patent Nos. 9,725,504 ('the '504 patent') and 9,719,880 ('the '880 patent'), the Examiner considered the same, or substantially the same, prior art that Amgen now asserts in its Petition." Prelim. Resp. 16. Patent Owner states:

> For example, in finding claim 1 of the '149 patent to be novel and nonobvious, the Examiner:
>
> - Expressly discussed Amgen's asserted references Hillmen 2004 (AMG1004), Evans (AMG1007), and Wang (AMG1028) as a basis for rejection, before ultimately finding claim 1 to be allowable over the art (*see*, *e.g.*, AMG1015 at 486-487, 596-598);
> - Considered Amgen's asserted references Hill 2005 (AMG1047) and Bell (AMG1005), which Alexion submitted to the PTO (*see*, *e.g.*, AMG1015 at 490, 497, 504);
> - Considered U.S. Patent No. 7,482,435 (ALXN2016), which is the parent to and cumulative of Amgen's cited "Bowdish" application (AMG1006), disclosing the same information on which Amgen relies here (*see*, *e.g.*, AMG1015 at 489); and
> - Considered the "Mueller II" article (AMG1031), which is cumulative of Amgen's asserted "Mueller" reference (AMG1008) because, as Amgen's declarant recognized in connection with Amgen's Petition regarding the related '880 patent, Mueller II "discloses the same antibodies" as Mueller. (*See*, *e.g.*, AMG1015 at 506; IPR2019-00740, AMG1002 ¶ 169 & n.12.)

Prelim. Resp. 17.

Petitioner's position on this issue is that:

> The arguments and evidence presented herein were not before the examiner during prosecution and, therefore, do not

> constitute "the same or substantially the same prior art or arguments" under 35 U.S.C. §325(d).
>
> During prosecution, the examiner rejected Alexion's claims as (i) anticipated by Hillmen in view of Thomas; (ii) anticipated by Appel; and (iii) anticipated by Wang. AMG1015, 598-600. Those rejections rested solely on disclosures in Thomas and Evans for eculizumab sequence information. *Id.* The examiner later allowed the '149 patent claims mistakenly believing—because of Alexion's mischaracterization of the art—that the sequence and structure of eculizumab were not already known.
>
> Though Hillmen was referenced by the examiner during prosecution, this Petition presents it in a different light, along with new references—Bell, Bowdish, and Mueller, which teach the IgG2/IgG4 constant domain missing from the art raised during prosecution.
>
> Bell and a parent application to Bowdish (US 2003/0049683 A1) was cited but not relied upon during prosecution, and Mueller was not cited at all. Thus, this Petition presents important information that the examiner failed to appreciate or consider, including information never even presented to the examiner. Consequently, this Petition is not the same as, substantially the same as, or cumulative of any previous arguments. Rather, the art combinations here, which were not raised by the examiner during prosecution, provide the complete sequence of eculizumab, thereby teaching the very thing the examiner mistakenly concluded was missing from the prior art.

Pet. 23–24.

ANALYSIS

Regarding the Board's discretion under 35 U.S.C. § 325(d), in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, the Board enumerated non-exhaustive factors to be considered in exercising discretion under 35 U.S.C. § 325(d) on whether to institute *inter partes* review. Case IPR2017-01586,

slip op. at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (precedential as to § III.C.5, first paragraph). The non-exhaustive *Becton* factors are:

> 1. the similarities and material differences between the asserted art and the prior art involved during examination;
>
> 2. the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> 3. the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> 4. the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> 5. whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> 6. the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Id. (numbers added). The *Becton* factors are not dispositive, but are part of a balanced assessment of the relevant circumstances in a particular case and we do not simply default to a tally of each factor to determine whether or not an IPR should be instituted.

Here, Patent Owner has not clearly identified how its arguments fall under the above-noted factors, but Patent Owner has, generally, argued that the prior art before us now was considered by the prosecuting Examiner either directly or as being cumulative of references that were so considered, and has further argued that the unpatentability issues presented in the Petition are the same as those at issue before the Examiner.

Patent Owner has specifically cited the prosecution history of the ’149 patent (application ser. no. 15/284,015) in support of its arguments under section 325(d). Prelim. Resp. 17 (citing Ex. 1015, 486–87, 489, 490, 497,

504, 506, 596–98)); *see also id.* at 62–63. Upon review of this evidence, what we find is that the Examiner actually considered Hillmen in rejecting the claim for obviousness-type double patenting and for anticipation. *See* Ex. 1015, 488, 596. As discussed above, at this stage in the proceedings, the anticipation Ground 1 over Hillmen, on its own, is not considered sufficient to institute IPR; therefore, Hillmen's consideration during prosecution is not determinative here.

However, the other identified references were listed in Information Disclosure Statements signed by the Examiner, but we are not pointed to evidence that they were expressly considered during prosecution; we cannot draw any particular inference from the mere inclusion of the reference on an Information Disclosure Statement. The Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution. *See, e.g.*, *Amneal Pharmaceuticals LLC v. Alkermes Pharma Ireland Ltd.*, IPR2018-00943, Paper 8 at 40 (PTAB Nov. 7, 2018) (declining to deny institution based on Section 325(d) where the reference was listed on the face of the patent, but Patent Owner provided no evidence "about the extent to which the Examiner evaluated" the reference during prosecution); *Digital Check Corp. d/b/a ST Imaging v. E-Imagedata Corp.*, IPR2017-00178, Paper 6 at 12–13 (PTAB Apr. 25, 2017) (acknowledging that a prior art reference was cited in an IDS, but granting institution because there was no indication that the claims were rejected based on those references or that the Examiner substantively discussed those references during prosecution); *Fox Factory, Inc. v. SRAM, LLC*, IPR2016-01876, Paper 8 at 7–9 (PTAB Apr. 3, 2017) (refusing to deny institution based on

Section 325(d) for grounds based on a prior art reference that was simply cited in an IDS and not considered at any length); *Praxair Distribution, Inc. v. INO Therapeutics, LLC*, IPR2015-00893, Paper 14 at 8 (PTAB Sept. 22, 2015) (granting institution even though the references were previously cited in an IDS because patent owner failed to identify with specificity where the references were considered); *HyperBranch Medical Technology, Inc. v. Confluent Surgical, Inc*., IPR2018-01099, Paper 14 at 17 (PTAB Nov. 27, 2018) (instituting IPR because, *inter alia*, "[t]he Examiner does not appear to have considered the combined teachings of Spero and Haber during examination of the '021 patent.").

Based on the evidence presented by Patent Owner, *Becton* factors 1–6 weigh in favor of not exercising our discretion not to institute here. Therefore, based on the evidence cited by Patent Owner and for the reasons above, we decline to exercise our discretion under Section 325(d) to deny institution here.

Other than the heading of Section VI of the Preliminary Response and that section's first sentence invoking the statute, Patent Owner presents no arguments or evidence directed to the Board's discretion under 35 U.S.C. § 314(a). *See* Prelim. Resp. 61–63. Therefore, we also decline to exercise our discretion under Section 314(a) to deny institution.

III. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of prevailing on Grounds 3 and 4 in showing that claim 1 of the '149 patent is either anticipated by Bowdish or would have been obvious over Bell, Bowdish, and Evans. Our decision at this stage derives from our preliminary review of the challenged claims, the

asserted prior art, and the opinions set forth in the as-yet-unrebutted Balthasar Declaration.

In accordance with the Court's decision in *SAS Institute, Inc.*, 138 S. Ct. at 1359–60 and Office guidance,[16] we institute an *inter partes* review of the challenged claim of the '149 patent on all grounds alleged by Petitioner.[17] Nevertheless, this decision does not reflect a final determination on the patentability of the claim. We further note that the burden remains on Petitioner to prove unpatentability of each challenged claim. *Dynamic Drinkware*, 800 F.3d at 1378.

ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review of claim 1 of the '149 patent, in accordance with each ground on which the challenge to each claim is based in the Petition, is hereby *instituted*; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), *inter partes* review of the '149 patent will commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

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[16] Guidance on the Impact of SAS on AIA trial proceedings (Apr. 26, 2018), accessible at https://www.uspto.gov/patents-application-process/patent-trial-and-appeal-board/trials/guidance-impact-sas-aia-trial (last accessed Oct. 2, 2018) ("At this time, if the PTAB institutes a trial, the PTAB will institute on all challenges raised in the petition," and "for pending trials . . . , the panel may issue an order supplementing the institution decision to institute on all challenges raised in the petition.").

[17] In view of the complexity of the art and arguments presented, the parties are, nevertheless, invited to negotiate an agreement to focus on some subset of the asserted Grounds.

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