Trials@uspto.gov
571-272-7822

Paper 9
Date: December 8, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO. LTD,
Petitioner,

v.

ALEXION PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-00933
Patent 9,732,149 B2

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

FLAX, *Administrative Patent Judge*.

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

I. INTRODUCTION

Alexion Pharmaceuticals, Inc. ("Patent Owner") is the owner of U.S. Patent 9,732,149 B2 ("the '149 patent"). Paper 4, 1. On May 18, 2023, Samsung Bioepis Co., Ltd. ("Petitioner") filed a Petition for *inter partes* review challenging the patentability of claim 1 (the sole claim) of the '149 patent. Paper 2, 1 ("Pet."). On September 12, 2023, Patent Owner filed a Preliminary Response to the Petition. Paper 6 ("Prelim. Resp."). With our authorization (*see* Ex. 3001), Petitioner filed a Reply to the Preliminary Response (Paper 7, "Prelim. Reply"), and Patent Owner filed a respective Sur-Reply (Paper 8, "Prelim. Sur-Reply").

Under 37 C.F.R. § 42.4(a), we have authority to determine whether to institute trial in 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 preliminary response filed under § 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 in view of the preliminary record, we conclude Petitioner demonstrates a reasonable likelihood it would prevail in showing that the challenged claim of the '149 patent is unpatentable under the presented grounds. *See* Pet.; Prelim. Resp.; Prelim. Reply; Prelim. Sur-Reply. Therefore, we grant institution of *inter partes* review. We note that there are disputed issues in this proceeding under 35 U.S.C. § 325(d) and § 314(a) concerning discretionary denial; however, we determine institution should be not be denied.

Our reasoning is discussed below.

A. REAL PARTIES-IN-INTEREST

Petitioner identifies itself, "Samsung Bioepis Co., Ltd.," as a real party-in-interest. Pet. 2. Patent Owner states, "Alexion Pharmaceuticals, Inc. is the owner of U.S. Patent No. 9,732,149 (the '149 patent") and the real-party-in-interest. Alexion Pharmaceuticals, Inc. is wholly owned by AstraZeneca PLC." Paper 4, 1.

B. RELATED MATTERS

Petitioner states, "[t]he '149 patent is not currently involved in any litigation or Patent Office proceedings. An *inter* partes review of the '149 patent filed by Amgen, Inc. was instituted as IPR2019-00741 ('Amgen IPR'). (EX1024.) No final written decision was issued in that proceeding because the Amgen IPR was terminated following settlement. (EX1026.)."[1] Pet. 2.

Patent Owner states, "[o]n May 31, 2023, Petitioner filed Petitions for *Inter Partes* Review of U.S. Patent Nos. 9,718,880 [(the '880 patent)] (IPR2023-00998) and 9,725,504 [(the '504 patent)] (IPR2023-00999) which are related to the '149 patent. An *inter partes* review of the '149 patent filed by Amgen, Inc. was instituted as IPR2019-00741. It was terminated following settlement." Paper 4, 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 October 3, 2016, which is a continuation of U.S. Patent Application 15/260,888 (now the '504 patent), filed on September 9, 2016, which is a continuation of U.S. Patent Application 15/148,839 (now the '880 patent), filed on May 6, 2016,

[1] We will refer to the Amgen IPR referenced by Petitioner by its case number IPR2019-00741, or as the "00741 IPR."

which is a continuation of U.S. Patent Application 13/426,973, filed on March 22, 2012, which is a continuation of U.S. Patent Application 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 first March 15, 2007, filing date is the priority date of the '149 patent. Pet. 15; Prelim. Resp. 2.

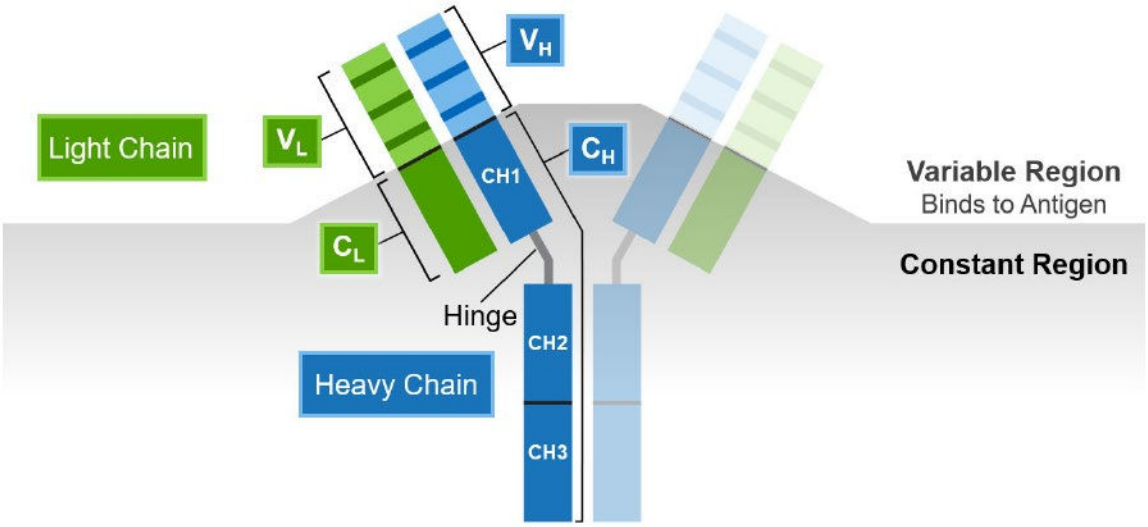
In February of 2019, Amgen, Inc. filed Petitions for *Inter Partes* Review of the '880 patent, the '504 patent, and the '149 patent in IPR2019-00740 ("00740 IPR"), IPR2019-00739 ("00739 IPR"), and IPR2019-00741 ("00741 IPR"), respectively (collectively, "the Amgen IPRs"). *See* Pet. 2 (citing Ex. 1024), Paper 4, 1; Prelim. Resp. 1 n.2. We instituted *Inter Partes* Review in each of 00740 IPR, 00739 IPR, and 00741 IPR. *See, e.g.*, Ex. 1024. In June of 2020, and following settlement between the parties, we terminated each of these proceedings without issuing a final written decision. *See* Ex. 1026. Before the filing of the instant Petition, Patent Owner submitted the records of the Amgen IPRs in the prosecution of two related applications: one that issued as U.S. Patent 10,590,189 B2 ("the '189 patent"), and another that issued as U.S. Patent 10,703,809 B2 ("the '809 patent) (collectively, "the child patents," which are challenged in IPR2023-01069 and IPR2023-01070, respectively). *See* Ex. 2102; Ex. 3002, code (56); Ex. 3003, code (56).

C. THE '149 PATENT AND RELEVANT TECHNICAL BACKGROUND

The '149 patent issued on August 15, 2017, from U.S. Application 15/284,015, which was filed on October 3, 2016. Ex. 1001, codes (10), (45), (21), (22). As noted above, the '149 patent indicates priority to an earlier

application filed on March 15, 2007, and this priority date is not contested at this stage of the proceeding. The '149 patent identifies Leonard Bell, Russel P. Rother, and Mark J. Evans as inventors and "Alexion Pharmaceuticals, Inc." as the applicant and assignee. *Id.* at codes (71), (72), (73). As noted below, these named inventors are common among several of the references asserted as prior art. The invention of the '149 patent relates to the pharmaceutical antibody "eculizumab," which is a humanized anti-C5 antibody. *See* Ex. 1001, Abstract.

For background, we reproduce a figure from the Ravetch Declaration,[2] illustrating the basic structure of an antibody:



Basic domain structure of antibody

Ex. 1003 ¶¶37–45; Pet. 5. The figure above shows a basic antibody structure having two hinged heavy chains (colored blue and labeled) and two accompanying light chains (colored green and labeled), each having constant

[2] Declaration of Jeffrey V. Ravetch, MD, PhD (Ex. 1003, "Ravetch Declaration").

regions (labeled C_H and C_L) and variable regions (labeled 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. 1003 ¶¶ 35–54. The constant regions do not bind antigens, but provide a structural framework for the antibody and coordinate the antibody's interactions with immune cells and effector molecules. *Id.* The variable regions of each chain also include three complementarity determining regions (CDR, shown as darker blue and darker green lines), which provide the antibody with antigen-binding specificity. *Id*. The constant heavy region includes sub-regions called CH1, CH2, and CH3 (the heavy chain hinge is between CH1 and CH2), separated by framework regions. *Id.* Antibodies are composed, *inter alia*, of amino acids and can be described by their particular amino acid sequences. *Id.*

There are five classes of antibodies, with IgG being the most abundant class in humans and represented by the illustration above. *Id.* IgG has been characterized as having subclass constant domains, for example, IgG1, IgG2, IgG3, and IgG4, defined by their amino acid combinations. *Id.* Each displays unique properties based on affinity for specific receptors. *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; *see also id.* at 4:60–67 (discussing SEQ ID NOS: 2 and 4), 30:16–31 ("Eculizumab Heavy chain SEQ ID NO: 2"), 30:39–47 ("Eculizumab Light chain SEQ ID NO: 4), 31–32, 35 (claimed amino acid sequences).

The complement system acts in conjunction with other immunological systems of the body to defend against intrusion of cellular and viral pathogens. *See generally* Ex. 1001, 7:11–8:56. As part of the immune system, "[c]omplement components achieve their immune defensive functions by interacting in a series of intricate but precise enzymatic cleavage and membrane binding events. The resulting complement cascade leads to the production of products with opsonic, immunoregulatory, and lytic functions." *Id.* at 7:25–30. The complement cascade progresses through the classical or alternative pathways, which "differ in their initial steps," yet "converge and share the same 'terminal complement' components (C5 through C9) responsible for the activation and destruction of target cells." *Id.* at 7:32–36. Before converging in terminal complement components, complement component "C3 is . . . regarded as the central protein in the complement reaction sequence since it is essential to both the alternative and classical pathways." *Id.* at 7:94–67. All pathways lead to the cleavage of C3 convertase and the resultant cleavage of C5 convertase into C5a and C5b. *Id.* at 7:51–53.

Blocking the cleavage of C5 with specific antibodies, however, is known to prevent complement activation. *See, e.g.*, *id.* at 11:1–6 ("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

[3] Mark J. Evans et al., US 6,355,245 B1, issued Mar. 12, 2002 (Ex. 1005, "Evans"). In addition to Mark J. Evans, this patent lists Russell P. Rother as an inventor, both of whom are listed on the '149 patent as inventors. Ex. 1005, code (75). Moreover, Evans, like the '149 patent, identifies "Alexion Pharmaceuticals, Inc." as the assignee. *Id.* at code (73).

but also the downstream complement components."); 12:6–10. According to the '149 patent:

> [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] 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 (emphasis added). 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 (emphasis added). 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. Thomas et al., *Inhibition of Complement Activity by Humanized Anti-C5 Antibody and Single-Chain Fv*, 33(17) MOL. IMMUNOL. 1389–401 (1996) (Ex. 1010, "Thomas")[4]).

[4] In addition to Thomas C. Thomas, the Thomas article lists as authors, *inter alia*, Russell P. Rother and Mark J. Evans, who are also listed as inventors on the '149 patent and of Evans. *Compare* Ex. 1001, code (72), *with* Ex. 1010, 1389, and Ex 1005, code (75).

According to Patent Owner, eculizumab, the monoclonal antibody recited in "[c]laim 1 of the '149 patent covers the non-naturally occurring, uniquely-engineered humanized antibody developed by Alexion and marketed as SOLIRIS®."[5] Prelim. Resp. 4, 8. The '149 patent 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. It is undisputed here that SEQ ID NO: 2 encodes a hybrid IgG2/IgG4 heavy chain (i.e., having a genetically engineered heavy chain constant region derived from portions of IgG2 and IgG4 isotype antibodies). *See, e.g.*, Pet. 9–10; Prelim. Resp. 9–10; Ex. 2100, 1258 (Figure 2).

The sole claim of the '149 patent 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 the recited SEQ ID NO: 2 and SEQ ID NO: 4 from the '149 patent Specification below:

[5] It is undisputed at this stage of the proceeding that "eculizumab," also marketed as Soliris, refers to a specific antibody having the primary amino acid sequence of SEQ ID NO: 2 and SEQ ID NO:4. *See*, *e.g.*, Prelim. Resp. 9–10, 14, 38; Pet. 10–11; Ex. 2022 ¶¶ 98–103, 133.

- 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. As these two reproduced sequences state, they represent the heavy and light chains of eculizumab, i.e., the antibody. *Id.* 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," a change we include, bracketed, above. *See id.* at final page.

D. PETITIONER'S ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts four (4) grounds for the unpatentability of claim 1, as follows:

Ground	Claims Challenged	35 U.S.C. §[6]	Reference(s)/Basis
1	1	102(b)	Bowdish[7]
2	1	103(a)	Bowdish, Evans, Bell,[8] Tacken,[9] Mueller PCT[10]
3	1	103(a)	Evans, Mueller PCT, Bell, Tacken
4	1	102(b)	Bell

Id. In support of these grounds for unpatentability, Petitioner submits, *inter alia*, the Ravetch Declaration. Ex. 1003. In support of its positions in the Preliminary Response, Patent Owner submits, *inter alia*, the Casadevall Declaration (Ex. 2022) and the Nussenzweig Declaration (Ex. 2026).

II. DISCUSSION

A. LEGAL STANDARDS

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is

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[6] As already noted, the parties appear to agree that the priority date to be accorded the '149 patent is March 15, 2007, which is before the AIA revisions to 35 U.S.C. §§ 102 and 103 took effect on March 16, 2013. 35 U.S.C. § 100 (note). Therefore, pre-AIA § 102 and § 103 apply.

[7] Bowdish et al., US 2003/0232972 A1, published Dec. 18, 2003 (Ex. 1004).

[8] Bell et al., US 2005/0191298 A1, published Sept. 1, 2005 (Ex. 1007).

[9] Paul J. Tacken et al., *Effective induction of naive and recall T-Cell responses by targeting antigen to human dendritic cells via a humanized anti–DC-SIGN antibody*, 106 BLOOD 1278–85 (2005) (Ex. 1008).

[10] Mueller et al., WO 97/11971, published April 3, 1997 (Ex. 1009).

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.[11] *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).

An *inter partes* review may be instituted if the information presented by a petitioner in the petition, in view of the patent owner's preliminary response and the preliminary record, shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314.

"Anticipation requires that all of the claim elements and their limitations are shown in a single prior art reference." *In re Skvorecz*, 580 F.3d 1262, 1266 (Fed. Cir. 2009). To anticipate "it is not enough that the prior art reference discloses part of the claimed invention, which an ordinary artisan might supplement to make the whole, or that it includes multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008). "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

[11] At times herein we refer to certain of Patent Owner's arguments as not persuasive; however, we do not shift the ultimate burden from Petitioner. Such unpersuasiveness is in the context of the record and the parties' arguments.

once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

A prior art reference without express reference to a claim limitation may anticipate by inherency. *See In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Id.* (quoting *MEHL/Biophile Int'l Corp. v. Milgraum,* 192 F.3d 1362, 1365 (Fed. Cir. 1999)).

Regarding obviousness, the Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), reaffirmed the framework for determining obviousness 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 unpatentable as obvious under 35 U.S.C. § 103 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 art;[12] and (4) considering objective evidence indicating obviousness or non-obviousness.[13] *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

[12] *See infra* Section II.B.

[13] *See infra* Section II.G.

"whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

B. ORDINARY LEVEL OF SKILL IN THE ART

Petitioner contends:

> A person of ordinary skill in the art ("POSA") would have knowledge of the scientific literature and have skills relating to the design and generation of antibodies, the complement system, and the application of antibodies as therapeutics before March 15, 2007. (EX1003, ¶¶16-20.) A POSA also would have knowledge of laboratory techniques and strategies used in immunology research, including practical applications of the same. (*Id.*, ¶19.) Typically, 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 discovery, development, and design of therapeutic antibodies for use as potential treatments in human disease. (*Id.*) Also, 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, a doctor of pharmacy, and a formulation chemist may have been part of a team. (*Id.*)

Pet. 12–13 (citing Ex. 1003 ¶¶ 16–19).

Patent Owner responds,

> Alexion does not dispute Samsung's POSA definition (Petition at 12-13), 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***. Under either description of a POSA, Samsung cannot prove unpatentability of claim 1 of the '149 patent under any of its four fatally flawed Grounds.

Prelim. Resp. 48.

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

At this stage in the proceedings, we accept and use Petitioner's proposed definition of the ordinarily skilled artisan, as being both generally unopposed by Patent Owner and inclusive of Patent Owner's supplemental definition. It appears that Petitioner's language "at least two years of experience in the discovery, development, and design of therapeutic antibodies for use as potential treatments in human disease" includes Patent Owner's proposed level of experience. Pet. 12–13. We also take 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 does not turn on which party's definition of the skilled artisan is used, and our determinations would be unchanged if we applied Patent Owner's supplemented 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.

C. CLAIM CONSTRUCTION

Petitioner states, "Petitioner does not believe claim construction is necessary at this time." Pet. 15. Patent Owner does not mention claim construction at this stage of the proceeding. *See generally* Prelim. Resp.

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 and there is no dispute. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))). As the case continues, we may determine that certain claim language should be interpreted.

D. PETITIONER'S ASSERTED PRIOR ART

1. Bowdish (Ex. 1004)

Bowdish is a U.S. Patent Application published on December 18, 2003.[14] Ex. 1004, code (43). At this stage of the proceeding, there is no dispute that Bowdish constitutes prior art. *See generally* Prelim. Resp. Bowdish lists Alexion Pharmaceuticals, Inc. as the official correspondence address. Ex. 1004, code (76).

Bowdish discloses "[i]mmunoglobulins or fragments thereof hav[ing] a peptide of interest inserted into a complementarity determining region (CDR) of an antibody molecule," whereupon, "[t]he antibody molecule serves as a scaffold for presentation of the peptide and confers upon the peptide enhanced stability." *Id.* ¶ 6. In certain "embodiments, the peptide replacing the amino acids of a CDR is an agonist TPO [thrombopoietin] peptide." *Id.* ¶ 17.

[14] According to Office records, Bowdish eventually issued as U.S. Patent 7,396,917 B2.

In Example 4, Bowdish describes a TPO mimetic peptide graft into the heavy chain CDR3 of antibody framework 5G1.1, described in Evans, which it incorporates by reference. *Id.* ¶¶ 191–193. According to Bowdish:

> ***Construction of 5G1.1 is described in U.S. Application. Ser. No. 08/487,283 [Evans[15]]***, incorporated herein by reference. The sequence was cloned into 5G1.1 in such a fashion as to replace the native CDR3 . . . [wherein t]he peptide graft translated into amino acids is Leu Pro Ile Glu Gly Pro Thr Leu Arg Gln Trp Leu Ala Arg Ala Pro Val (SEQ. ID. NO: 66). The 5G1+peptide was produced as a whole IgG antibody (See FIGS. 13A and 13B).

Id. ¶ 191 (emphasis added). "Purified 5G1.1+peptide antibody as well as the parental 5G1.1 were analyzed for their ability to bind to cMp1 receptor by FACS analysis." *Id.* ¶ 192.

In SEQ ID NOs: 69 and 70, respectively, Bowdish discloses the amino acid and nucleotide sequences for the "5G1.1 light chain." *Id.* ¶ 50. In SEQ ID NO: 67, Bowdish discloses the amino acid sequence of the "5G1.1–TPO heavy chain," with the substituted TPO mimetic sequence marked in bold. *Id.* ¶ 49. Bowdish discloses the corresponding nucleotide sequence in SEQ ID NO: 68. *Id.*

2. Evans (Ex. 1005)

Evans is a U.S. patent, which issued March 12, 2002, and indicates on its face as having been assigned to Alexion Pharmaceuticals, Inc. Ex. 1005 codes (45), (73). First named inventor listed on the face of Evans, Mark J. Evans, and also named inventor Russell P. Rother, appear to be inventors also listed on the '149 patent. *Compare* Ex. 1001, code (72), *with* Ex. 1005,

[15] US Application No. 08/487,283 matured into U.S. Patent 6,355,245 B1, referenced herein as Evans (Ex. 1005).

code (75). At this stage of the proceeding, there is no dispute that Evans is prior art. *See generally* Prelim. Resp.

Evans is cited in the '149 patent, as well as by other evidence of record, as teaching a "[s]uitable anti-C5 antibod[y] known to those of skill in the art" and the "antibod[y] . . . specific to human complement[,] . . . whole antibody (***now named eculizumab***)," as well as "methods of engineering such antibodies." Ex. 1001, 10:65–11:6, 12:21–29, 12:42–55 (emphasis added); *see also* Ex. 1004 ¶ 191 (Bowdish incorporating Evans by reference for teaching "[c]onstruction of 5G1.1"); Ex. 1007 ¶ 52 (Bell incorporating Evans by reference for teaching "[p]articularly useful anti-C5 antibod[y] . . . h5G1.1-mAb [or] h5G1.1-scFv," and identifying that "[t]he antibody h5G1.1-Mab is currently undergoing clinical trials under the tradename eculizumab.").

Evans discloses anti-C5 antibodies useful in the treatment of glomerulonephritis (GN) and other inflammatory diseases. Ex. 1005, Abstract, 1:14–17. Evans's Example 7 describes the isolation of anti-C5 monoclonal antibodies from mouse hybridoma designated 5G1.1. Ex. 1005, 37:34–39:30. In Figures 18 and 19, respectively, Evans discloses the amino acid sequence of the light and heavy chain variable regions of mouse antibody 5G1.1, with "[t]he complementarity determining region (CDR) residues according to the sequence variability definition or according to the structural variability definition . . . [bolded] and [underlined], respectively." *Id.* at 9:65–10:20. A representation of an excerpt of the heavy chain sequence showing the amino acid sequence of CDR3 so marked reads:

DSAVYYCAR**Y<u>FFGSSPNWYFD</u>V**WGAGTTVTVSS.

See id. at Fig. 19 (Nos. 85–112).

Evans describes making a series of different humanized 5G1.1 scFv[16] and full-length antibodies containing the CDR regions from the murine 5G1.1 antibody. Ex. 1005, 37:35–39:30, 42:59–45:33. With respect to the former, Evans discloses that "[p]articularly preferred constant regions . . . are IgG constant regions, which may be unaltered, or constructed of a mixture of constant domains from IgGs of various subtypes, e.g., IgG1 and IgG4." *Id.* at 45:29–33.

In Example 11, Evans discloses eighteen constructs "encoding . . . recombinant mAbs comprising the 5G1.1 CDRs." *Id.* at 42:56–45:33. One of these constructs, designated 5G1.1 scFv CO12, "encodes a humanized (CDR grafted and frame work sequence altered) scFv" which, according to Dr. Ravetch, "includes all six CDR sequences and variable regions of SEQ ID NOS: 2 and 4 of claim 1." Ex. 1003 ¶ 86 (citing Ex. 1005, Example 11 (No. 12)).

3. Bell (Ex. 1007)

Bell is the September 1, 2005 publication of U.S. Patent Application 11/050,543, filed February 3, 2005. Ex. 1007, codes (43), (21), (22). The first named inventor, Leonard Bell, as well as Russell P. Rother, appear to be inventors also listed on the '149 patent. *Compare* Ex. 1001, code (72) *with* Ex. 1007, code (76). There is currently no dispute that Bell is prior art. *See generally* Prelim. Resp.

Bell discloses the treatment of PNH "using a compound which binds to or otherwise blocks the generation and/or activity of one or more complement components. . . . In particularly useful embodiments, the

[16] Dr. Ravetch explains, "[a]n scFv fragment corresponds to V_L and V_H domains of an antibody joined by a short peptide linker." Ex. 1003 ¶ 39.

compound is an anti-C5 antibody selected from the group consisting of h5G1.1-mAb (***eculizumab***), h5G1.1-scFv (pexelizumab) and other functional fragments of h5G1.1." Ex. 1007 ¶ 12 (emphasis added); *see also id.* ¶ 52 ("The antibody h5G1.1-mAb is currently undergoing clinical trials under the tradename eculizumab."). Bell further discloses: "Methods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in [Evans] and [Thomas] . . . the disclosures of which are incorporated herein in their entirety." *Id.* ¶ 52. According to Bell, formulations of its anti-C5 antibodies "suitable for injection," "must be sterile," and may or may not contain preservatives. *Id.* ¶ 62.

The data disclosed in Bell includes data on studies in which eleven transfusion-dependent PNH patients received weekly 600 mg doses of eculizumab by infusion for four weeks, followed by "900 mg of eculizumab 1 week later[,] then 900 mg on a bi-weekly basis." Ex. 1007 ¶¶ 81–82. Bell characterizes the first twelve weeks of treatment as a "pilot study." *Id.* ¶ 82. "Following completion of the initial acute phase twelve week study, all patients participated in an extension study conducted to a total of 64 weeks. Ten of the eleven patients participated in an extension study conducted to a total of two years." *Id.* Bell concludes that "[p]atients in the two year study experienced a reduction in adverse symptoms associated with PNH." *Id.* ¶¶ 82, 96.

4. Tacken (Ex. 1008)

Tacken is a journal article published August 15, 2005. Ex. 1008, 1278. Tacken notes the reported research was supported by "funding from Alexion Pharmaceuticals" to the lead author, and that three of the paper's other authors "are employed by Alexion Pharmaceuticals, whose potential

product was studied in the present work." *Id.* at 1278. One of these authors, Russell P. Rother, is also an author of Thomas (Ex. 1010), and is listed as an inventor on the '149 patent (Ex. 1001, code (72)). There is currently no dispute that Tacken is prior art. *See generally* Prelim. Resp.

Tacken discloses "a humanized antibody, hD1V1G2/G4 (hD1), directed against the C-type lectin DC-specific intercellular adhesion molecule 3–grabbing nonintegrin (DC-SIGN)," and its use as a dendritic cell-based vaccine. Ex. 1008, 1278 (Abstr.). In its section describing "Recombinant antibodies," Tacken discloses the DC-SIGN construct as comprising a humanized variable heavy chain region "genetically fused with a human hybrid IgG2/IgG4 constant domain." *Id.* at 1279 (citing Mueller 1997[17]). According to Tacken, "[a]n isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [*sic*]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5." *Id.* (citing Thomas (Ex. 1010)).

5. Mueller PCT (Ex. 1009)

Mueller PCT is an international patent application published on April 3, 1997, listing Alexion Pharmaceuticals, Inc. as the applicant, and listing, *inter alia*, Mark J. Evans and Russell P. Rother as inventors (like the '149 patent and other asserted references). Ex. 1009, codes (71), (72). At this stage of the proceeding, there is no dispute that Mueller PCT is prior art. *See generally* Prelim. Resp.

[17] John P. Mueller et al., *Humanized Porcine VCAM-specific Monoclonal Antibodies with Chimeric IgG2/G4 Constant Regions Block Human Leukocyte Binding to Porcine Endothelial Cells*, 34(6) MOL. IMMUNOL. 441–52 (1997) (Ex. 1006).

Mueller PCT discloses "[a]ntibodies to porcine P-selecting protein, porcine VCAM protein and porcine CD86 protein are useful for diagnosing human rejection of porcine xenotransplants and for improving xenotransplantation of porcine, cells, tissues and organs into human recipients." Ex. 1009, Abstract. According to Mueller PCT, one object of the invention is to provide antibody molecules that neither activate complement nor bind to the FC receptor. *Id.* at 7:28–31. To achieve these and other goals, Mueller PCT points to "[r]ecombinant (chimeric and/or humanized) antibody molecules comprising the C1 and hinge regions of human IgG2 and the C2 and C3 regions of human IgG4, such antibodies being referred to hereinafter as 'HuG2/G4 mAb.'" *Id.* at 8:23–26.

Mueller PCT developed and tested "chimeric antibodies containing the C1 and hinge region of human IgG2 and the C2 and C3 regions of human IgG4 . . . (HuG2/G4 mAb)." *Id.* at 12:19–33. As controls for these experiments, Mueller PCT used "a humanized antibody directed against human C5 (h5G1.1 CO12 HuG4 mAb)." *Id.* at 11:34–12:4. 12:34–13:2, Figs. 11, 12, 15.

On pages 58–61 of Mueller PCT, the reference discloses the cDNA and amino acid sequence for the expression of "Human G2/G4."

E. GROUND 1—ANTICIPATION BY BOWDISH

1. Parties' Positions

Petitioner asserts that Bowdish, which incorporates Evans by reference, discloses the entirety of the claimed anti-C5 antibody, including both SEQ ID NO: 2 and SEQ ID NO: 4, as a starter-scaffold-antibody for making a 5G1.1 antibody with a TPO mimetic peptide. Pet. 22–26 (citing, *inter alia*, Ex. 1003 ¶¶ 100–104, 107–109; Ex. 1004, Figs. 13A, 13B, ¶ 191;

Ex. 1005, page 1 (Title), Fig. 9, Figs. 18–19, 7:60–64, 9:44–45, 9:65–10:20, 42:56–45:33 (Example 11), 143:22–144:14, claim 19). Petitioner asserts that Bowdish discloses all of claim 1's light chain sequence SEQ ID NO: 4 at its SEQ ID NO: 69, shown in Figure 13B, and all but 13 amino acids of claim 1's heavy chain sequence SEQ ID NO: 2 at its SEQ ID NO: 67, shown in Figure 13A. *Id.* at 22–23. Petitioner asserts that these missing 13 amino acids of claim 1 are due to Bowdish replacing the native CDR3 portion of Evans's antibody with a TPO mimetic peptide, but that Evans, incorporated into Bowdish by reference, discloses this native CDR3 and that this starter antibody is the claimed antibody. *Id.*

This argument is illustrated by the following figure from the Petition, incorporated from the Ravetch Declaration:

Id. at 24; *see also* Ex. 1003 ¶ 103. The figure above illustrates reverse engineering the Bowdish antibody based on its disclosure that Evans teaches the "[c]onstruction of 5G1.1" antibody, into which Bowdish's TPO mimetic peptide graft was inserted (shown in in red) "to replace the native CDR3 [represented by the middle image above—Evans's h5G1.1 scFv CO12,] with 5' ttg cca ATT GAA GGG CCG ACG CTG CGG CAA TGG CTG GCG GCG CGC GCG cct gtt 3' (SEQ. ID. NO: 65)." Ex. 1004 ¶ 191; *see also* Ex. 1003 ¶ 112. Bowdish states that "[t]he 5G1+peptide was produced as a whole IgG antibody (See **FIGS. 13A and 13B**)." Ex. 1004 ¶ 191. Thus, the

figure above shows, left-to-right, Bowdish's final antibody having a grafted TPO mimetic peptide colored red, then the substitution of that TPO mimetic peptide segment with the CDR3 segment from Evans that it replaced, and last, the full starting antibody having the amino acid sequence of Evans, which Petitioner asserts is eculizumab, i.e., the claimed antibody that binds C5, having SEQ ID NO: 2 and SEQ ID NO: 4.

Patent Owner argues that Bowdish alone does not disclose the claimed amino acid sequence and that Bowdish's incorporation by reference of Evans's 5G1.1 would have been limited to only a murine (in this case, mouse) monoclonal antibody, which, going through the reverse-engineering of Petitioner's ground, results in a different sequence than claimed. Prelim. Resp. 49. Patent Owner argues that Bowdish makes no reference to "eculizumab" or any other C5-binding antibody, and does not identify the "native CDR3" of Evans's antibody that was replaced by the TPO mimetic graft. *Id.* at 49–50. Patent Owner also argues that Petitioner's ground relies on hindsight using the claim as a roadmap. *Id.* at 50–51.

2. 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 1.

We disagree with Patent Owner's contention that Bowdish's incorporation of Evans's disclosure would have been limited to a murine antibody or framework.

As Patent Owner correctly quotes from Bowdish: "The TPO mimetic peptide graft in Fab clone X4b has been transplanted into the heavy chain CDR3 region of another antibody framework, 5G1.1. . . . ***Construction of***

5G1.1 is described in U.S. Application Ser. No. 08/487,283, incorporated herein by reference." Prelim. Resp. 49–50 (citing Ex. 1006 ¶ 191) (emphasis added). It is not disputed here that U.S. Application 08/487,283 issued as Evans. *See* Ex. 1005, code (21); *see generally* Prelim. Resp. The portion of Evans relating to "***Construction*** of 5G1.1" (*see* Ex. 1004 ¶ 191) appears to be (or at least includes) Example 11, which is titled "***Construction*** and Expression of Recombinant mAbs." Ex. 1005, 42:55–58 (emphasis added). According to Dr. Ravetch, "Evans'[s] Example 11 [ ] teaches construction of . . . humanized 5G1.1 scFv constructs." Ex. 1003 ¶ 157. None of the other Evans Examples addressing an anti-C5 antibody or a 5G1.1 antibody designate their respective disclosure as relating to "construction," as per the title of Example 11 and the sentence of Bowdish expressly incorporating Evans. *See* Ex. 1005, 33:1–42:54 (Examples 1–10); Ex. 1003 ¶ 191.

Thus, on this record, we find that Petitioner's pointing to the antibodies (or fragments) of Evans's Example 11 for use as a starting point for Bowdish's invention to be more reasonable than Patent Owner's arguments that antibodies would have been selected from some other examples.

Furthermore, Patent Owner does not dispute that, if Bowdish and Evans are read as asserted by Petitioner and its witness, Dr. Ravetch, the antibody sequences of claim 1, i.e., SEQ ID NO: 2 and SEQ ID NO: 4, are disclosed. Petitioner's reading is also consistent with the '149 patent, which states that Evans "teaches an antibody which binds to C5" and is a "[s]uitable anti-C5 antibod[y]" with respect to its invention and was "known to those of skill in the art," and, in fact, that Evans teaches the "antibod[y]

. . . specific to human complement[,] . . . whole antibody (now named eculizumab)," as well as "methods of engineering such antibodies." Ex. 1001, 10:65–11:6, 12:21–29, 12:42–55. Therefore, we do not find any error in Petitioner's assertion that Bowdish/Evans discloses the antibody of claim 1.

We also are unpersuaded by Patent Owner's overarching argument that Petitioner's positions are fatally flawed by hindsight or that "[a] POSA as of March 15, 2007[,] would have understood that Alexion had developed a humanized antibody named 'eculizumab,' . . . [b]ut a POSA at that time would ***not*** have known that "eculizumab" had the sequence claimed in the '149 patent." *See* Prelim. Resp. 7–13, 39–43. Hindsight is inapplicable to anticipation and, moreover, it appears that Petitioner's positions consider only the disclosures of the prior art and how the person of ordinary skill in the art would have read prior art references in view of one another.

On the present record, we find the facts here to be highly analogous to those of both *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004) ("*Crish*"), and *Nichols Institute Diagnostics, Inc. v. Scantibodies Clinical Laboratory, Inc.*, 195 F. App'x 947 (Fed. Cir. 2006) ("*Nichols*"), each of which suggests claim 1 is anticipated.

In *Crish*, the claimed invention was a "[a] purified oligonucleotide comprising at least . . . the nucleotide sequence from 521 to 2473 of SEQ ID NO:1, and wherein said portion . . . has promoter activity." *Crish*, 393 F.3d at 1254. So, similar to the presently claimed pair of amino acid sequences providing an antibody (eculizumab) that binds C5, the invention of *Crish* was a sequence of oligonucleotides that had promoter activity, namely "the

hINV promoter." *Id.* Each is a sequence of biological building blocks with a function.

Further, the issue in *Crish* was whether a publication by inventor Crish that disclosed the complete structure of hINV as a plasmid, but not the sequence of the promoter region as claimed, anticipated the claim. *Id.* at 1255 *et seq*. Crish argued that those working in the relevant field had used the published plasmid and sequenced it to obtain a different promoter sequence from the claimed sequence. *Id.* at 1255. Crish argued, those of ordinary skill in the art would not have then recognized the claimed sequence in view of such results obtained by other workers. *Id.*

The similarities to this case are apparent. Here, we also have prior art disclosing the claimed composition, eculizumab, but possibly not its specific sequence. Also, here Patent Owner argues that no one could have known the claimed amino acid sequences for eculizumab and, in fact, would have looked to the wrong antibody therefor (i.e., to Thomas's disclosure of an IgG4 antibody rather than the claimed IgG2/IgG4 antibody).

Crish's claimed SEQ ID NO: 1 was obtained by sequencing the same plasmid disclosed in the prior art reference. *Id.* at 1256. Here, the '149 patent itself states that Evans teaches an antibody that binds to C5 and that it discloses a preferred whole antibody, which was later *named eculizumab.* And, here it is undisputed that the actual eculizumab antibody has the claimed sequences.

The Federal Circuit held in *Crish* that "[t]he sequence *is the identity* of the structure of the gene, not merely one of its properties." *Id.* at 1258 (emphasis added). The Court further recognized that "one cannot establish novelty by claiming a known material," in *Crish* a gene/promoter, "by its

properties," i.e., its sequence of nucleotides (which the Federal Circuit identified is the gene's identity, akin to *all* its properties) and related promoter activity. *Id.* The Court held that hINV was known and its promoter region identified in the inventor's own prior art by size and location, if not by its sequence, and "[t]he only arguable contribution to the art that Crish's [claimed invention] makes is the identification of the nucleotide sequence of the promoter region of hINV." *Id.* The Court further held that "[t]he starting material plasmid necessarily contains the gene of interest including the promoter region," thus, "the claims necessarily encompass the gene incorporated in the starting material plasmid." *Id.* at 1259.

The Federal Circuit held that, in claiming SEQ ID NO: 1, "Crish [was] claiming what Crish earlier disclosed," and "Crish cannot rely upon the inability of another worker to correctly sequence the promoter region of the hINV gene from [the] plasmid . . . when he has sequenced it accurately himself." *Id.* Thus, the Federal Circuit concluded that the Crish-published prior art and its disclosed starting materials anticipated the claim. *Id.*

Here, like *Crish*, the asserted prior art, i.e., Bowdish/Evans, is Alexion's and, at least to some degree, the '149 patent's inventor's own work.[18] Further, here, like *Crish*, the prior art discloses the claimed antibody, eculizumab, and how to construct it, even if there may have arguably been some confusion by those in the field over precisely the

[18] Both Bowdish and Evans are associated with Alexion Pharmaceuticals, Inc., and two of the named inventors of the '149 patent (Russell P. Rother and Mark J. Evans) are also named inventors of Evans. *See* Ex. 1001, code (72); Ex. 1005, codes (73), (75); Ex. 1004, code (76) (correspondence address).

structure of the antibody (i.e., IgG4 or IgG2/IgG4). Therefore, it would appear that, here, the same conclusion as in *Crish* would be appropriate.

Nichols is very similar to *Crish*, and its facts are similar to those of the present record. In *Nichols*, the claimed invention was an antibody (or fragment) that selectively binds a peptide of hPTH that has one of six peptide sequences, i.e., SEQ ID Nos. 1–6, which were hPTH 1–10, hPTH 1–9, hPTH 1–8, hPTH 1–7, hPTH 1–6, and hPTH 1–5. *Nichols*, 195 F. App'x at 949. The inventors, before their patent application, published an abstract disclosing that they developed a mixture of ten antibodies that bound to specific peptides of hPTH (i.e., hPTH 1–37); however, the true significance of the antibody mixture was not recognized at the abstract's publication.

There was no dispute in *Nichols* that the claimed antibody was present in the serum disclosed in the abstract. *Id.* at 950–51. Here, there is no dispute that the Bowdish/Evans antibody according to Petitioner's reading (and seemingly undisputed here) is eculizumab, which has the claimed amino acid sequences. As noted above, the '149 patent itself indicates that Evans discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001, 12:21–29. Further, the inventor in *Nichols* testified that the claimed antibody was isolated from the serum disclosed in the abstract using known methods. *Nichols*, 195 F. App'x at 950–51. The *Nichols* patentee also argued that the published abstract disclosed that the antibodies *predominantly* bound to the hPTH peptides, but that the claimed antibody required "selective" binding, and also that no one recognized the significance of the claimed antibody until after the abstract was published. *Id.* Here, Patent Owner's argument is that skilled artisans

would have not known eculizumab's amino acid sequence and, in fact, would have been led toward the wrong antibody (by Thomas).

The Federal Circuit held in *Nichols* that the abstract inherently anticipated the claimed antibody because, if it were isolated from the disclosed serum, using known methods, the isolated antibody would exhibit the claimed binding property, and recognition of the inherent disclosure by those of skill in the art was not needed. *Id.* Here, the prior art discloses eculizumab, including the amino acid sequences therefor. Thus, it would appear that, here, the same conclusion as in *Nichols* would be appropriate.

3. Summary

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

F. GROUND 4—ANTICIPATION BY BELL

We turn next to Petitioner's Ground 4, under which Bell is asserted to anticipate claim 1.

1. Parties' Positions

Petitioner asserts that Bell (which incorporates Evans (Ex. 1005) and Thomas (Ex. 1010) by reference) discloses the eculizumab antibody by name, unambiguously refers to the antibody as the h5G1.1 IgG2/IgG4 molecule, and teaches its use as a treatment for PNH (in clinical trials). Pet. 18, 40–41 (citing Ex. 1002, 1272, 1277–80 (¶¶ 5–6); Ex. 1003 ¶¶ 89–91, 136–137, Ex. 1005; Ex. 1007 ¶¶ 52, 82; Ex. 1010).

Petitioner asserts that an ordinarily skilled artisan would have known that eculizumab has the same sequence as the claimed SEQ ID NOS: 2 and 4

(because such an artisan would have known the amino acid sequence based on previously published Bowdish, Evans, Muller PCT, and Tacken (which discloses eculizumab's IgG2/IgG4 structure)), and that Alexion itself stated to the Office that Bell's disclosed eculizumab contained the heavy and light chain sequences as claimed. *Id.* at 42 (citing Ex. 1002, 1272, 1277–80 (¶¶ 5–6); Ex. 1003 ¶¶ 137–138; Ex. 1025, 39).

Petitioner's position is that

> Bell inherently anticipates because (1) Alexion admits that the "eculizumab" disclosed in Bell was *necessarily* of the same sequence as recited by challenged claim 1; and (2) the prior art available to a POSA fully enabled the preparation of eculizumab as of no later than the 2005 (the publication date of Tacken).

Id. (citing Ex. 1003 ¶ 139). Petitioner asserts that the production of eculizumab was disclosed in the prior art. *Id.* at 44–45.

Patent Owner argues that Bell fails to expressly or inherently disclose the claim elements because it omits "the exact amino acid sequence of eculizumab." Prelim. Resp. 59–60. Patent Owner argues that, "[w]hile Bell described administering 'eculizumab' for treating PNH, ***nothing*** in Bell taught the uniquely-engineered heavy chain reflected in 'SEQ ID NO: 2.'" *Id.* at 60. Patent Owner contends this is because Bell references Thomas's IgG4 antibody, which is not the amino sequence of SEQ ID NO: 2. *Id.* (citing Ex. 10078 ¶ 52).

Patent Owner contends that Bell's "mere naming of an investigational product (*e.g.*, 'eculizumab') . . . does ***not*** inherently anticipate later-filed patent claims detailing the specific structure or composition of that product" unless "a POSA could have ***necessarily*** determined that later claimed structure/composition from the information publicly available as of the

priority date." *Id.* at 63 (citing *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1378–83 (Fed. Cir. 2018) ("*Endo Pharms*.")). Patent Owner argues that eculizumab was not available to the public and its sequence was not disclosed as of Bell's date. *Id.* at 66.

Patent Owner also argues that Bell fails to enable the invention of claim 1 because Petitioner's theory requires consideration of Bowdish, Evans, Mueller PCT, and Tacken, and such a combination is inappropriate for anticipation. *Id.* at 61 (citing *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1335 (Fed. Cir. 2002)).

2. Analysis

On the present record we find Petitioner has met its burden of showing there is a reasonable likelihood that claim 1 is anticipated by Bell. We find the facts under Ground 4 largely in line with those under Ground 1, discussed above.

Bell uses the word "eculizumab" at least 25 times throughout its disclosure, without ever expressly explaining more than that it is an anti-C5, h5G1.1-mAb therapeutic antibody. *See generally* Ex. 1007. The record suggests "eculizumab" meant something to the person of ordinary skill in the art. *See, e.g.*, Ex. 1008, 1279 ("An isotype control antibody, h5G1.1-mAb (5G1.1, eculiz[u]mab; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5," as discussed in Mueller 1997 and Thomas).

Bell states that eculizumab is *the* "particularly useful . . . anti-C5 antibody . . . h5G1.1-mAb," discussed throughout its disclosure as a therapy for PNH patients, including, in its Examples, as a successful treatment of 11 specific PNH patients. Ex. 1007 ¶¶ 12, 21, 25, 26, 28, 30–35, 37, 52, 61,

81–96, Figs. 1A, 1B, 2, 3, 4, 5, 6a, 6b, 7, 8, 9, 10, claims 1–3, 8, 20–21, 109, 114, 119. Bell also identifies that Evans (and Thomas), which it incorporates by reference, discloses methods for eculizumab's preparation. *Id.* ¶ 52.

We find, on this record, that for the reasons discussed above regarding Bowdish/Evans under Ground 1, the facts and holdings of *Crish* and *Nichols* apply under this Ground as well. *See supra* Section II.E.2. Bell discloses the eculizumab antibody, which is the undisputed antibody of claim 1. According to *Crish*, disclosure of eculizumab is the disclosure of the identity of the antibody of claim 1. According to *Nichols*, disclosure of the existence of eculizumab, even as a generic reference to the antibody (like disclosing the preparation of sera of a mixture of unidentified antibodies), is an inherent disclosure of the claimed antibody, even if unappreciated at the time.

We are unpersuaded by Patent Owner's citation to *Endo Pharms.*, which, on this record, we find distinguishable on its facts. In *Endo Pharms.*, the Federal Circuit found a claim to a formulation, including (1) testosterone undecanoate, in a certain mixture/ratio of (2) castor oil and (3) benzyl benzoate, was not inherently disclosed by prior art articles reporting clinical studies with testosterone undecanoate. *Endo Pharms.*, 894 F.3d at 1377–78. The prior art did not disclose the use of any co-solvent with castor oil—however, it was established that the actual formulation used in the reported studies *had* the claimed amounts of castor oil and benzyl benzoate. In *Endo Pharms.*, the evidence asserted for the inherency of the unreported benzyl benzoate claim element was pharmacokinetic performance data. *Id.* But such data/results were not argued to be attributable *only* to the claimed vehicle formulation, and the "prior art was replete with [other] potential co-

solvents" that could have been used in place of benzyl benzoate. *Id.* at 1382. Thus, benzyl benzoate and the claimed ratio of it to castor oil was not necessarily disclosed. *Id.*

The Federal Circuit held that the uncertainty in mixture composition and the possible variability in mixtures that could achieve the same reported results fell short of the facts and holding in *Crish*, where the claim was to a specific oligonucleotide, which, but for its claimed promoter sequence, was disclosed in the prior art. *Id.* at 1383. We find the facts here are more like those of *Crish* and less like those of *Endo Pharms.*, because there appears to be no dispute here that eculizumab, as disclosed by Bell, *is* the claimed antibody.

As for whether eculizumab (the claimed antibody) was enabled by Bell, we find that the present record supports that it was. Bell is explicit that Evans described "[m]ethods for the preparation of h5G1.1, h5G1.1-scFv and other functional fragments of h5G1.1." Ex. 1007 ¶ 52. Furthermore, Petitioner asserts that, in addition to Bell's explicit reference to Evans, the knowledge of those of ordinary skill in the art included that eculizumab had a human hybrid IgG2/IgG4 constant domain. *See, e.g.*, Ex. 1008, 1279. Moreover, the '149 patent, itself, states that Evans, which is a part of Bell, discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001, 12:21–29. Therefore, on the present record, we are unpersuaded regarding Patent Owner's non-enablement argument.

Regarding Patent Owner's argument that Petitioner's citation to Bowdish, Evans, Mueller PCT, and Tacken under Ground 4 alludes to obviousness and is inappropriate for an anticipation ground, we understand

that Petitioner cites these references as background. Petitioner states, "[t]he teachings of at least Bowdish and Evans, and Evans and Mueller PCT, all in view of Tacken, provided POSA with multiple direct routes to [the eculizumab amino] sequence." Pet. 41. Each of these references predates Bell, therefore, their teachings about eculizumab/5G1.1 antibodies would have been a part of the general knowledge an ordinarily skilled artisan would have brought to their reading of Bell. *See* Ex. 1004; Ex. 1005; Ex. 1008; Ex. 1009. We understand Petitioner's point to be that when Bell mentions "eculizumab," it would invoke such an understanding of the antibody in the ordinarily skilled artisan reading the reference. This is a reasonable position because, although Bell discusses eculizumab, its use, and its benefits, it never expressly describes what eculizumab is, nor did it need to do so in view of the general knowledge in the art. Under Ground 4, Petitioner does not suggest combining with Bell any teachings from these references, other than Evans, which Bell incorporates by reference.

3. Summary

Based on the evidence presented at this stage in the proceedings, it has been shown under Ground 4 that there is reasonable likelihood that the '149 patent's claim 1 is anticipated by Bell, which incorporates Evans by reference.

G. OBJECTIVE EVIDENCE INDICATING NON-OBVIOUSNESS

Before moving on to Petitioner's grounds based on obviousness, we address the parties' contentions concerning objective indicia of non-obviousness. Pet. 55–58, 70–72; Prelim. Resp. 67–69.

"Objective indicia of nonobviousness can serve as an important check against hindsight bias and 'must always when present be considered.'"

Merck & Cie v. Gnosis S.P.A., 808 F.3d 829, 837 (Fed. Cir. 2015) (citation omitted). 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 objective indicia evidencing non-obviousness. *See Graham*, 383 U.S. at 17–18. Relevant objective indicia, sometimes called secondary considerations, include commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR*, 550 U.S. at 406. Although evidence pertaining to objective indicia of non-obviousness 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).

Petitioner notes that any objective evidence of non-obviousness must have a nexus to the claimed invention. Pet. 55 (citing *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011)). Petitioner asserts that Patent Owner cannot argue commercial success of its drug Soliris, any long-felt and unrecognized need, or industry praise as objective evidence of non-obviousness, because the use of eculizumab as a treatment for PNH was expressly taught in the prior art and therefore not novel in the claim. *Id.* at 45–48 (citing Ex. 1003 ¶¶ 142–147). As for evidence of copying, Petitioner argues that its intent to develop a biosimilar of Soliris is inapposite, as biosimilar statutes and regulations require that any biosimilar of Soliris be "highly similar to the reference product." *Id.* at 48 (citing 42 U.S.C. § 262(i)(2); Ex. 1003 ¶ 165).

In response, Patent Owner asserts that commercial success, long-felt but unmet need, and industry praise all support the patentability of the challenged patent claims. Specifically, Patent Owner relies on the

commercial success of Soliris, which Patent Owner asserts has generated substantial sales in the relevant market. Prelim. Resp. 67 (citing Ex. 2018, 70). Patent Owner also asserts that Soliris fulfilled a long-felt, unmet need as the first FDA-approved treatment to reduce hemolysis in PNH patients and has received industry praise as the recipient of several awards. *Id.* at 68 (citing Ex. 2019, 1270; Ex. 2020; Ex. 2021). Moreover, Patent Owner dismisses Petitioner's copying argument, as Patent Owner contends Petitioner could have chosen to develop biosimilars of other biologic products, but instead chose to copy Soliris. *Id.* at 70. Patent Owner argues that, contrary to Petitioner's assertions, the claimed sequences were novel and nonobvious at the time of the invention. *Id.* at 68–69.

At this stage of the proceeding, we find Petitioner has shown sufficiently that Patent Owner's objective evidence of non-obviousness carries insufficient weight. "For objective indicia evidence to be accorded substantial weight, we require that a nexus must exist 'between the evidence and the merits of the claimed invention.'" *Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1330–31 (Fed. Cir. 2017) (quoting *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010)). If a patentee relies on the commercial embodiment of the claimed invention and that embodiment is the invention disclosed and claimed, a presumption of nexus exists. *See Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). That presumption is rebuttable and the evidence is not pertinent, however, "if the feature that creates the commercial success [or other secondary considerations] was known in the prior art." *See Ormco Corp. v. Align Tech. Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006).

On this record, although there is a presumption of nexus between Soliris and the challenged claims, we find Petitioner has sufficiently rebutted that presumption. In its Preliminary Response, Patent Owner relies heavily on Soliris and its treatment of PNH as evidence of commercial success, long-felt need, and industry praise. Prelim. Resp. 67–69. At this stage of the proceeding, however, we are persuaded that Bell, Hillmen 2004, and Hill 2005 all disclosed that eculizumab was a useful treatment for PNH more than a year before the '149 patent was filed. *See* Pet. 6 (citing Ex. 1007; Ex. 1013; Ex. 1011).

We also agree that the Federal Circuit's holding in *Adapt Pharma Operations Ltd. v. Teva Pharmaceuticals USA, Inc.*, 25 F.4th 1354 (Fed. Cir. 2022), is instructive with respect to Patent Owner's evidence of copying. The Court noted that "evidence of copying in the ANDA context is not probative of nonobviousness because a showing of bioequivalence is required for FDA approval." *Id.* at 1374 (quoting *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013)). Similarly, here, evidence of copying in the biosimilar context is not probative of non-obviousness because the "biological product [must be] highly similar to the reference product." *See* 42 U.S.C. § 262(k)(2)(A). That there may be "hundreds of other biologic products" that Petitioner could have developed, as Patent Owner asserts, does not outweigh the strong evidence of obviousness. Prelim. Resp. 68.

In light of the foregoing, we are not persuaded that Patent Owner's objective indicia evidence is sufficiently probative of non-obviousness at this stage of the proceeding. *See Ormco*, 463 F.3d at 1313 (finding patentee's evidence did not show commercial success where allegedly novel

features were taught by the prior art); *see also Novartis AG v. Torrent Pharms. Ltd.*, 853 F.3d 1316, 1331 (Fed. Cir. 2017) (finding objective indicia evidence not probative of non-obviousness where prior art suggested the allegedly successful feature of the claimed invention).

We recognize, however, that consideration of objective indicia of non-obviousness is highly fact dependent. We note that our determination here is preliminary, and we will re-evaluate the evidence on a full trial record in our Final Written Decision, if necessary.

H. GROUND 2—OBVIOUSNESS OVER BOWDISH, EVANS, BELL, TACKEN, MUELLER PCT

1. Parties' Positions

Under Ground 2, Petitioner challenges claim 1 as obvious over Bowdish, Evans, Bell, Tacken, and Mueller PCT. Pet. 26–35 (citing, *inter alia*, Ex. 1003 ¶¶ 110–126). Patent Owner opposes. Prelim. Resp. 51–56.

For the reasons stated with respect to Ground 1, Petitioner contends that Bowdish discloses the complete sequence of the light chain of SEQ ID NO: 4; discloses a substantial portion of the anti-C5 antibody 5G1.1; and points to Evans as evidencing the remaining amino acid sequence. Pet. 26–27 (citing Ex. 1024, 47; Ex. 1003 ¶ 110). Further referencing its arguments with respect to Ground 1, Petitioner contends that Bowdish "provides express motivation to combine its antibody framework 5G1.1 with Evans'[s] HCDR3 to arrive at Bowdish's staring antibody 5G1.1" having the claimed sequences. *Id.* at 27 (citing Ex. 1003 ¶ 111; *In re McDaniel*, 293 F.3 1379, 1385 (Fed. Cir. 2002)). For the reasons set forth in Section II.E, above, we find Petitioner's arguments sufficient to support institution.

Petitioner further points to Bell, Tacken, and Mueller PCT as providing additional motivation to combine Bowdish and Evans with a reasonable expectation of success. *Id.* at 27 (citing Ex. 1003 ¶ 112).

Petitioner contends, for example, that "Bell teaches that eculizumab, also referred to as h5G1.1, had been successful in the treatment of PNH, and expressly incorporates Evans for preparing h5G1.1. Bell discloses that a 'particularly useful' treatment for PNH is the anti-C5 antibody known as 'h5G1.1-mAb (eculizumab).'" *Id.* at 27–28 (citing Ex. 1007 ¶ 52 (stating the "h5G1.1-mAb is currently undergoing clinical trials under the trade-name eculizumab"), ¶¶ 82–83; Ex. 1003 ¶ 113). As further noted by Petitioner, Bell discloses that "[m]ethods for the preparation of h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1 are described in [Evans] and [Thomas] . . . the disclosures of which are incorporated herein in their entirety." Ex. 1007 ¶ 52; *see* Pet. 28.

Petitioner further asserts that one of ordinary skill in the art looking to obtain the amino acid sequences of Bell's "h5G1.1 (eculizumab)" would have looked to Bowdish, and understood that Bowdish's "5G1.1" antibody framework referred to the same humanized monoclonal antibody, and that SEQ ID NOS: 67 and 69 "disclose the sequences of '5G1.1' antibody framework, into which only the HCDR3 was replaced for the TPO mimetic peptide graft." *See* Pet. 28–29 (citing Ex. 1003 ¶¶ 80, 114–116, 126, 140; Ex. 1004, Figs. 13A, 13B, ¶ 192). Petitioner further contends that "[a] routine comparison of these sequences with Evans'[s] constructs in Example 11 would have quickly revealed that Evans'[s] SEQ ID NO:20 is identical to the variable regions in Bowdish's SEQ ID NO:69 & 67, except for the HCDR3 sequence," which could be readily replaced to generate the

original eculizumab antibody. *See id.* at 29–30 (citing Ex. 1003 ¶¶ 116–117).

Petitioner also points to Tacken as further confirmation that Bowdish discloses the hybrid IgG2/IgG4 heavy chain of eculizumab and as recited in challenged claim 1. Pet. 30–34 (citing, *inter alia*, Ex. 1003 ¶¶ 118–124). Petitioner contends that (like Bell) Tacken equates h5G1.1 with eculizumab and, moreover, teaches that eculizumab contains "the same IgG2/IgG4 constant region" disclosed in Mueller 1997 (Tacken's reference 17). *Id.* at 30–31 (citing Ex. 1008, 1279; Ex. 1003 ¶ 118).

Petitioner further notes that "Mueller PCT, the companion patent application for Mueller 1997, expressly discloses the full amino acid sequence for the IgG2/IgG4 constant domain heavy chain used in the 'h5G1.1 HuG2/G4' antibody," and Petitioner contends that "[a] routine alignment of the IgG2/G4 constant domain heavy chain from Mueller PCT and Bowdish would have immediately confirmed that the antibody disclosed in Bowdish has *precisely* the sequence of eculizumab," recited in claim 1. *Id.* at 31, 36–37 (citing Ex. 1009, 14, 58–59, 97; Ex. 1003 ¶¶ 119–120 (showing comparison of heavy chain constant regions)).

Petitioner again runs through the re-creation of Bowdish's starting antibody based on Evans, as discussed above regarding Ground 1. *Id.* at 32–33 (citing Ex. 1003 ¶ 121).

Patent Owner argues that Petitioner uses impermissible hindsight and its present-day knowledge of the Soliris (eculizumab) antibody to reconstruct the sequences of claim 1. *See generally*, Prelim. Resp. 51–58. Patent Owner argues, for example, that Thomas taught away from the invention and that Bowdish is non-analogous art, and one of ordinary skill in

the art seeking to develop an anti-C5 antibody composition for treating PNH "would never have started with Bowdish" because it has "nothing to do with blocking C5 cleavage or treating PNH." *Id.* at 52.

Petitioner, supported by the testimony of Dr. Ravetch, contends that Bowdish is analogous art in the field of the '149 patent. Pet. 28–29 (citing Ex. 1003 ¶ 115). In this respect, Dr. Ravetch testifies:

> A POSA looking for the amino acid sequences encoding eculizumab would have easily found Bowdish, and considered it to be analogous art to Bell and Evans for at least three reasons: (1) it provides express disclosures about the structure of the antibody "5G1.1," (2) it identifies "Alexion Pharmaceuticals" as the inventors' addressee that is the same as the assignee for Evans, and (3) it cites to the same Evans patent as does Bell for the structure of 5G1.1. Thus, a POSA would have been motivated to combine the teachings of Bowdish and Evans in view of Bell to arrive at the claimed sequence.

Ex. 1003 ¶ 115.

Patent Owner further argues that one of ordinary skill in the art would not have been motivated to combine Bowdish and Evans because Bowdish's citing to a 5G1.1 antibody is too broad and Evans discloses only fragments of anti-C5 antibodies and never uses the word "eculizumab." *Id.* at 53. Patent Owner also argues that, even were Bowdish and Evans combined per Petitioner's theory, the ordinarily skilled artisan would not have expected a resulting antibody to prevent C5 cleavage to effectively treat PNH. *Id.* at 54.

Addressing Tacken, Bell, and Mueller PCT, Patent Owner argues that the art "consistently described" eculizumab "by referencing Thomas, which disclosed an IgG4 isotype antibody." Prelim. Resp. 54–56. According to Patent Owner, "Tacken is the ***only*** document before March 15, 2007 that purportedly associated 'eculizumab' with a hybrid IgG2/IgG4 constant

region." *Id.* at 11. But, argues Patent Owner, "[n]othing in Tacken contradicted the consistent teaching of the prior art ***as a whole*** that 'eculizumab' had an IgG4 constant region." *Id.* And, considering the art as a whole, "the ***only*** plausible conclusion a POSA could have reached in view of the entire content of the art was that 'eculizumab' was Thomas's IgG4 antibody." *Id.* at 12–13 (citing Ex. 2022 ¶¶ 146, 150).

Patent Owner contends that the relevant passage from Tacken merely "point[s] to Thomas's IgG4 antibody," in the same manner as the other prior art it cites. *See* Prelim. Resp. 55; Prelim. Sur-Reply 3. Addressing the implication that Tacken, instead, teaches that eculizumab "contain[s] the same IgG2/IgG4 constant region" as a lectin-specific antibody (having "a human hybrid IgG2/IgG4 constant domain"), Patent Owner's submitted expert declaration (from IPR2019-00741) downplays the passage as just "one isolated statement," and "ambiguous," and possibly a "mistake" to be disregarded in view of "the numerous clear statements in the key publications regarding 'eculizumab' that identify it as the IgG4 antibody of Thomas." *See* Ex. 2022 ¶¶ 142, 143; Ex. 1008, 1279.

2. Analysis

Including for the reasons discussed in Section II.E, above, we do not agree with Patent Owner's assessment on the current record.

Regarding whether Bowdish is analogous art,

> Two separate tests define the scope of analogous prior art: (1) whether the art is from the same field of endeavor, regardless of the problem addressed and, (2) if the reference is not within the field of the inventor's endeavor, whether the

> reference still is reasonably pertinent to the particular problem with which the inventor is involved.

In re Bigio, 381 F.3d 1320, 1325 (Fed. Cir. 2004). On the present record before us, it appears that Bowdish is both reasonably pertinent and within the same field of endeavor of the '149 patent for the reasons identified by Dr. Ravetch, because it is directed to the construction of a humanized monoclonal antibody comprising a TPO mimetic peptide graft into the heavy chain CDR3 of antibody framework 5G1, and because it uses "the parental 5G1.1" sequence as a control for FACs analysis of the TPO mimetic antibody. *See* Ex. 1004 ¶¶ 191–193.

Regarding the Bowdish/Evans teachings, the portion of Evans relating to "***Construction*** of 5G1.1" (Ex. 1004 ¶ 191), which is what Bowdish specifically names when incorporating Evans, appears to be (or at least includes) Example 11, which is titled "***Construction*** and Expression of Recombinant mAbs." Ex. 1005, 42:55–58. None of the other Evans Examples addressing an anti-C5 antibody or a 5G1.1 antibody designate their respective disclosure as relating to "construction," as per the title of Example 11 and the sentence of Bowdish expressly incorporating Evans. *See* Ex. 1005, 33:1–42:54 (Examples 1–10); Ex. 1003 ¶ 191. Moreover, as noted by Dr. Ravetch, while Evans's Example 7 is directed to mouse antibodies, "Evans'[s] Example 11 . . . teaches construction of the *humanized* 5G1.1 scFv constructs." Ex. 1003 ¶ 157 (emphasis added). Therefore, any arguments by Patent Owner that the Bowdish/Evans disclosure would not include incorporating what Evans teaches at Example 11 into Bowdish's final antibody, to establish Bowdish's starting antibody, are not persuasive.

Regarding Bell, we find Patent Owner's position mischaracterizes the reference's incorporation of Thomas by wholly ignoring that, in the very same sentence, and preceding the cite to Thomas, Bell also incorporates Evans by reference. Ex. 1007 ¶ 52. Bell incorporates Evans as disclosing "[p]articularly useful anti-C5 antibodies . . . h5G1.1-mAb, h5G1.1-scFv and other functional fragments of h5G1.1," and "[m]ethods for the preparation" of these. *Id.* It appears that the ordinarily skilled artisan, like Bell's inventors, would not have looked solely to Thomas for eculizumab's structure. Moreover, the '149 patent itself states that Evans, which is a part of Bell, discloses "a preferred whole antibody (now named eculizumab)," and how to produce it. *See, e.g.*, Ex. 1001 12:21–29. Thus, even the '149 patent, like Bell, acknowledges that Evans is an important reference regarding eculizumab, its structure, and how to make it.

Regarding Patent Owner's arguments concerning Tacken, Dr. Ravetch testifies that,

> none of the prior art references teach that "eculizumab" has the IgG4 isotype, indeed Thomas does not refer to "eculizumab" at all. Tacken instead is the only reference that discloses any information regarding the constant domain structure of "eculizumab," and it unambiguously teaches that eculizumab has the hybrid IgG2/G4 constant domain.

Ex. 1003 ¶ 140. As noted in Section II.D.4, above, Tacken describes a lectin-specific antibody comprising a humanized variable heavy chain region "genetically fused with a human hybrid IgG2/IgG4 constant domain. [citing Mueller 1997]." Ex. 1008, 1279. Tacken used mouse IgG1 and human 5G1.1 antibodies as isotype controls in binding and internalization assays. *Id.* at 1280. With respect to the latter, Tacken states: "An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [*sic*]; Alexion Pharmaceuticals)

containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5 [citing Thomas (Ex. 1010)]." *Id.* at 1279.

On the present record, we find it plausible that Tacken's, i.e., Alexion's researchers', description of Alexion's own product suggests that eculizumab (h5G1.1) contained a "human hybrid IgG2/IgG4 constant region," making it suitable for use as an IgG2/IgG4 isotype control for the IgG2/IgG4–containing antibody under development. *See* Ex. 1003 ¶¶ 63, 68–70 (citing Ex. 1029, 10–11 (Alexion's statement in unrelated patent prosecution that in light of Evans and Mueller 1997, it was well known as of 2002 "that eculizumab has a G2/G4 Fc portion")).

On the present record, we do not favor Patent Owner's interpretation of Tacken, particularly in view of what appears to be the close association between Alexion and the authors of Tacken. *See* Ex. 1008, 1278 (footnote). Specifically, Tacken discloses that the reported lectin-specific antibody research was supported by "funding from Alexion Pharmaceuticals" to the lead author, and that three of the other authors were "employed by Alexion Pharmaceuticals, whose potential product was studied in the present work." *Id.* Notably, one of the Tacken authors, Russell P. Rother, is also an author of Thomas, published some nine years earlier. *See* Ex. 1010, 1389. If it would have been reasonable for anyone to have known that eculizumab had a human hybrid IgG2/IgG4 constant domain and was an h5G1.1-mAb, specific for the human terminal complement protein C5, as reported in Tacken, the Tacken authors would have been such people.

On the present record, we find it unlikely that Mr. Rother and the other Tacken authors mistakenly referred to eculizumab as having an IgG2/IgG4 constant region. We find it more plausible that Tacken cites to

Thomas as describing eculizumab's C5-specific CDRs, and refers to Mueller 1997 (Ex. 1006) for the IgG2/IgG4 heavy chain sequence common to both eculizumab and the anti-lectin antibody under development. We also find it plausible that other documents Patent Owner points to as citing to Thomas also do so in reference to the C5-specific variable domain, rather than to the constant region or other non-antigen binding features of the molecule. *See* Prelim. Resp. 12–13, 55.

We invite the parties to further address this issue at trial.

On the limited record before us, we find it reasonable that one of ordinary skill in the art would have been motivated with a reasonable expectation of success, to produce eculizumab, as claimed, by replacing the CDR3 region of Bowdish's "5G1.1+peptide antibody" with Evans's CDR3 sequence to arrive at Bowdish's "parental 5G1.1," having the sequences set forth in claim 1. *See* Ex. 1004, ¶¶ 191–193.

3. Summary

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 Bowdish, Evans, Bell, Tacken, and Mueller PCT, under Ground 2.

I. GROUND 3—OBVIOUSNESS OVER EVANS, MUELLER PCT, BELL, TACKEN

1. Parties' Positions

Petitioner's Ground 3 is quite similar to Petitioner's Ground 2, but without including Bowdish, which Petitioner asserts is not needed to have rendered claim 1 obvious in view of Evans, Mueller PCT, Bell, and Tacken. Pet. 35–40 (citing, *inter alia*, Ex. 1003 ¶¶ 127–135).

Petitioner begins with Bell's disclosure, which it asserts would have motivated an ordinarily skilled artisan to determine the amino acid sequence of its disclosed anti-C5 antibody eculizumab. *Id.* at 35. Regarding this, Petitioner asserts that Bell points directly to Evans and Thomas, each being incorporated by reference. *Id.* (citing Ex. 1003 ¶ 127). Upon examining Evans, such an artisan would have understood (readily so, as asserted by Petitioner) that the critical CDR sequences for the heavy and light chains of an original mouse antibody 5G1.1 that binds C5 was disclosed, as were variable domain sequences for humanized forms of 5G1.1. *Id.* (citing Ex. 1005, 1:1–3, 9:65–10:20, 42:56–45:23, Figs. 18–19, Claim 19; Ex. 1003 ¶¶ 128–129). Petitioner again points to Evans's Example 11, which provides nine humanized scFv structures corresponding to the V_H and V_L domains of an antibody joined by a short peptide linker. *Id.* at 35–36 (citing Ex. 1005, 42:56–45:33; Ex. 1003 ¶ 128). Petitioner asserts that,

> Evans then explains that "one each of the various L1, L2, and L3 CDRs" and "one each of the various H1, H2, and H3 CDRs" disclosed in Example 11, assembled into "matched pairs of the variable regions (e.g. a VL and a VH region) . . . may be combined with constant region domains by recombinant DNA or other methods known in the art to form full length antibodies *of the invention*."

Id. at 36 (citing Ex. 1005, 45:5–33; Ex. 1003 ¶ 128). Petitioner's point is that, without naming any of such antibodies "eculizumab," Evans taught artisans how to build each of these 5G1.1 antibodies and eculizumab would result. *Id.*

Petitioner points to Bell as support for Evans teaching the structure of 5G1.1 antibodies, and eculizumab, specifically. *Id.* Petitioner asserts that a limited (finite) number of antibodies are taught in this scenario and that the

artisan would have had good reason to pursue them (Bell says to do so, for example), meaning each was obvious to try; hence, producing eculizumab was obvious to try. *Id.* at 36–37 (citing, *inter alia*, *KSR*, 550 U.S. at 421; Ex. 1003 ¶ 130).

Petitioner points to Mueller PCT as focusing such an ordinarily skilled artisan upon an antibody construct identified as CO12, because Mueller PCT discusses an h5G1.1 *CO12* HuG2/G4 antibody, which would point to Evans's CO12 Example, which would result in "a perfect match to SEQ ID NOS:2 and 4 recited in challenged claim 1." *Id.* at 37–38 (citing Ex. 1009, 14; Ex. 1003 ¶¶ 131–132).

Petitioner also points to Tacken as specifically teaching that eculizumab has an IgG2/IgG4 constant region (refers to Mueller 1997), and also would have motivated the ordinarily skilled artisan to create an antibody as in Evans with such a constant region (as discussed in both Mueller 1997 and Mueller PCT). *Id.* at 39–40 (citing Ex. 1003 ¶¶ 48, 133–134).

Patent Owner again argues that Evans's only "actual antibody" is a 5G1.1 murine antibody, which is unrelated to the antibody of Mueller PCT. Prelim. Resp. 56–57. Patent Owner argues there would have been no motivation for the skilled artisan to have combined sequences from Evans and Mueller PCT and, even if one were to make such an antibody, the prior art pointed towards Thomas's "incorrect" HuG4 sequence for eculizumab. *Id.* at 57. Patent Owner argues that only with hindsight would a person of ordinary skill in the art reasonably have expected to successfully produce an antibody by combining a variable region of Evans with an IgG2/G4 heavy chain constant region of Mueller PCT, or would have expected it to cleave C5 and safely and effectively treat PNH. *Id.* at 58.

2. Analysis

We find Petitioner has met its burden for institution and do not find Patent Owner's arguments persuasive largely for the reasons discussed above over similar arguments relating to Grounds 1, 2, and 4.

We find compelling Petitioner's assertion that Bell and Tacken provide a starting point for an ordinarily skilled artisan to develop eculizumab as an h5G1.1-mAb, anti-C5 antibody, and also as to what eculizumab's structure would be – an h5G1.1-mAb with an IgG2/IgG4 constant region. Ex. 1007 ¶¶ 12, 52; Ex. 1008, 1279. We also find compelling Petitioner's assertion that an ordinarily skilled artisan would have looked to Evans for a humanized variable domain of 5G1.1 (Bell tells one to do so to produce eculizumab for treating PNH in humans), and that, upon focusing on an antibody like that identified by Tacken (also identified as eculizumab, specific for the human terminal complement protein C5), such a skilled artisan would have produced one having SEQ ID NOS: 2 and 4, as claimed. Mueller PCT discloses the amino acid sequence of such a human G2/G4 constant region, thus, a skilled artisan would have also found it useful in such an endeavor. Thus, at this stage of the proceeding, we find no fatal flaw to Petitioner's case under Ground 3.

3. Summary

Based on the evidence presented at this stage in the proceedings, it has been shown that there is a reasonable likelihood that the '149 patent's claim 1 would have been obvious over Evans, Bell, Tacken, and Mueller PCT, under Ground 3.

III. DISCRETIONARY DENIAL

Patent Owner presents arguments that we should exercise our discretion to deny institution in this proceeding. Prelim. Resp. 17–32. As explained below, we are not persuaded by any of these arguments and will not deny institution.

A. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner contends that we should exercise our discretion to deny the Petition under 35 U.S.C. § 325(d). Prelim. Resp. 1–2, 17–32; Prelim. Sur-Reply 1–6. According to Patent Owner, prior art asserted and arguments presented in the Petition are the same as, or cumulative of, art and arguments previously presented to the Office. Prelim. Resp. 17–26. Patent Owner also argues that Petitioner has not shown the Office erred in a manner material to patentability of challenged claims. *Id.* at 26–32. Petitioner disagrees as to both points. Pet. 49–61; Prelim. Reply 1–6; Ex. 1003 ¶¶ 110–135, 140, 149–159.

In determining whether to deny institution under § 325(d), we use the following two-part framework:

> (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). The *Becton, Dickinson* factors provide useful insight into how to apply the

framework under 35 U.S.C. § 325(d). *Id.* at 9 (referencing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph)).

Under § 325(d), the art and arguments must have been previously presented to the Office during proceedings, such as examination of the underlying patent application, pertaining to the challenged patent. *Advanced Bionics*, Paper 6 at 7. Previously presented art includes art made of record by the Examiner, and art provided to the Office by an applicant, such as on an Information Disclosure Statement ("IDS"), in the prosecution history of the challenged patent. *Id.* at 7–8.

1. Whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office

Under the first part of the *Advanced Bionics* framework, we consider "whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office." *Id.* at 8. We evaluate *Becton, Dickinson* factors (a), (b), and (d) to determine whether Petitioner has demonstrated material error. *Id.* at 10. Those factors are:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination; and
>
> (d) 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.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

With respect to the first part of the *Advanced Bionics* analysis, we address "whether the same or substantially the same art . . . w[as] previously presented to the Office." *Advanced Bionics*, 7–8 (stating that "[p]reviously presented art includes . . . art provided to the Office, such as on an Information Disclosure Statement (IDS)").[19] Patent Owner contends that Evans and Mueller 1997 (asserted to be cumulative to Mueller PCT), as well as counterpart references for Bowdish ("U.S. Patent No. 7,482,435—also published as U.S. Pub. No. 2003/0049683—is the parent patent to Bowdish") and Bell ("published six different times as U.S. 2005/169921; U.S. 2010/068202; U.S. 2011/086040; U.S. 2012/308559; WO 2005/074607; and EP1720571"), were disclosed in the prosecution leading to the issuance of the '149 patent. Prelim. Resp. 18, 20–22.

In response, Petitioner notes that Evans was, indeed, cited by the Examiner in a rejection, agrees that Bell was cited in an IDS, and characterizes the '435 patent as a "parent of Bowdish," but argues that Mueller PCT was neither before the Office nor cumulative to Mueller 1997 because only the former "discloses the complete IgG2/G4 constant domain used in eculizumab." Pet. 50–51; Prelim. Reply 2 (citing Pet. 51 n5).[20]

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[19] Although the parties also address the alternative question of whether the same or substantially the same *arguments* were previously presented to the Office, that analysis is not necessary here, but is subsumed, in relevant part, in our discussion of the second prong of *Advanced Bionics*.

[20] Petitioner's contention is undercut somewhat by "Dr. Ravetch's characterization of Mueller PCT as "a '***companion*** patent application

Petitioner further points out that Patent Owner identifies no citation to Tacken in the prosecution leading to the issuance of the '149 patent "despite Tacken's express teaching that eculizumab contains the IgG2/G4 constant region." Prelim. Reply 2.[21]

Patent Owner also points to the prosecution history of the later-filed and -issued '189 and '809 child patents, wherein Patent Owner

> submitted the entire history of each of Amgen's IPRs against the '880, '504, and '149 patents, including all the references cited in those IPRs including Bowdish, Evans, Bell, Tacken, and Mueller PCT as well as all briefs, expert reports, and testimony, early in the prosecution to be considered by the Examiners.

Prelim. Resp. 22; *see also* Ex. 1032, 48 (IDS in '189 prosecution disclosing IPR petitions); Ex. 1032, 27, 38 (IDS in '189 prosecution disclosing Mueller PCT and Tacken, respectively). Patent Owner also asserts that "[t]he arguments were the same too," but the Examiner allowed the claims. *See* Prelim. Resp. 22 (citing Ex. 2101, 341, 416–18, 1222–23, 1227–29, 1370, 1374–80).

Like the claims at issue here, the claims of the child patents recite, in relevant part, an antibody that "comprises a heavy chain consisting of SEQ ID NO: 2 and a light chain consisting of SEQ ID NO: 4." *See, e.g.*, Ex. 3002, 39:15–24; Ex. 3003, 39:14–20. Moreover, as with the present IPR, an issue addressed by the Examiner in the child patents was whether

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describing the ***same work*** published in the Mueller 1997 article." *See* Sur-Reply 4 (citing Ex. 1003 ¶¶ 62, 128).

[21] Although Petitioner argues that mere citation of references in an IDS may not be sufficient to satisfy the first element of *Advanced Bionics*, that line of inquiry is not necessary here. *See* Reply 1–2.

the hybrid IgG4/IgG2 heavy chain described by claimed SEQ ID NO: 2 was known or obvious over the prior art. *See*, *e.g.*, Ex. 1002, 14840–43 (Alexion's argument in the '019 prosecution that the prior art "repeatedly and consistently described 'eculizumab' as having an IgG4 heavy chain constant region" (capitalization normalized)), 14854–55 (similar), Examiner's Reasons for Allowance for the '019 patent stating, e.g., that Evans, identified as the closest prior art, "does not teach an antibody that binds C5 which have a H and L chain with SEQ ID Nos: 2 and 4, respectively").

In view of the unique record before us, we agree with Patent Owner that all of the references relied on by Petitioner here, "were previously presented to the Office" as required by § 325(d) and *Advanced Bionics*. Prelim. Resp. 19. Accordingly, we proceed to part two of the analysis.

2. Whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims

Under the second part of the *Advanced Bionics* framework, we consider "whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics*, Paper 6 at 8. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Id.* at 8 n.9. We evaluate *Becton, Dickinson* factors (c), (e), and (f) to determine whether Petitioner has demonstrated material error. *Id.* at 10. Those factors are:

> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection; . . .

> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
>
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18.

Petitioner raises at least four non-trivial arguments for why the Examiner allegedly erred in the prosecution of '149 patent and the identified child patents. *See* Pet. 52–61; Prelim. Reply 2–6. For the purpose of our analysis, we find it sufficient to address only two of those arguments.

Tacken

Petitioner argues that the Examiner of the child patents overlooked or misapprehended the significance of Tacken's statement that eculizumab contains an IgG2/G4 constant region and, thus, did not appreciate the significance of the IgG2/G4 sequence disclosed in Mueller PCT. *See* Pet. 65–67; Prelim. Reply 5–6; Ex. 1003 ¶¶ 170, 172–174. In this respect, Petitioner points to Alexion's Response to an Office Action in the prosecution of the '189 patent, which avers that

> [T]he literature as of March 15, 2007 . . . consistently identified "eculizumab" as the antibody described in the "Thomas" publication . . . which has a naturally-occurring "IgG4" heavy chain constant region. Accordingly, a person of ordinary skill in the art as of March 15, 2007 would have had ***no doubt*** that "eculizumab" was Thomas's IgG4-isotpe humanized antibody, because the pertinent literature ***consistently and unambiguously*** said so[.]

Pet. 55 (citing Ex. 1036, 6). As noted by Petitioner, Alexion "went on to list several references that purportedly referred to eculizumab as an IgG4 antibody," via citation to Thomas. *Id.* at 55–56; Ex. 1036, 6–8. Petitioner

argues that Alexion's characterization of the art was incomplete and inaccurate for failing to account for Tacken. Pet. 67. We agree with Petitioner.

As noted in Sections II.D.4 and II.H, above, Tacken describes a lectin-specific antibody comprising a humanized variable heavy chain region "genetically fused with a human hybrid IgG2/IgG4 constant domain [citing Mueller 1997]." *Id.* at 1279. Tacken used mouse IgG1 and 5G1.1 antibodies as isotype controls in binding and internalization assays. *Id.* at 1280. With respect to the latter, Tacken states: "An isotype control antibody, h5G1.1-mAb (5G1.1, eculizamab [*sic*]; Alexion Pharmaceuticals) containing the same IgG2/IgG4 constant region, is specific for the human terminal complement protein C5 [citing Thomas (Ex. 1010)]." *Id.* at 1279.

On its face, we find it plausible that Tacken understood and reported that eculizumab (h5G1.1) contained a "human hybrid IgG2/IgG4 constant region," making it suitable for use as an IgG2/IgG4 isotype control for the IgG2/IgG4–containing antibody under development. *See* Ex. 1003 ¶¶ 64, 69, 70 (citing Ex. 1029, 10–11 (Alexion's statement in unrelated patent prosecution that in light of Evans and Mueller 1997, it was well known as of 2002 "that eculizumab has a G2/G4 Fc portion").

Patent Owner, in contrast, contends that the above passage from Tacken merely "point[s] to Thomas's IgG4 antibody," in the same manner as the prior art it raised with the Examiner. Prelim. Sur-Reply 3. Addressing the implication that Tacken instead teaches that eculizumab "contain[s] the same IgG2/IgG4 constant region" as Tacken's lectin-specific antibody (having "a human hybrid IgG2/IgG4 constant domain"), Patent Owner's expert downplays the passage as "a single sentence taken out of

context from a single publication," and which the skilled artisan would have found "ambiguous," "confusing," and possibly a "mistake" to be disregarded in view of "the numerous clear statements in the key publications regarding 'eculizumab' that identify it as the IgG4 antibody of Thomas." Ex. 2022 ¶¶ 142, 143; Ex. 1008, 1279.

On the present record, we do not favor this interpretation, particularly in view of what appears to be the close association between Alexion and the authors of Tacken. In this respect, Tacken discloses that the lectin-specific antibody research was supported by "funding from Alexion Pharmaceuticals" to the lead author, and that three of the paper's other authors were "employed by Alexion Pharmaceuticals, whose potential product was studied in the present work." Ex. 1008, 1278. Notably, one of these authors, Russell P. Rother, is also an author of Thomas, published some nine years earlier.

On the present record, we find it unlikely that Mr. Rother and the other Tacken authors mistakenly referred to eculizumab as having an IgG2/IgG4 constant region. We find more plausible that Tacken cites to Thomas as describing eculizumab's C5-specific CDRs, and refers to Mueller 1997 for the IgG2/IgG4 heavy chain sequence common to both eculizumab and the anti-lectin antibody under development.

As such, we find it error for the Examiner of the child patents to have not expressly considered Tacken in the context of the other references Alexion pointed to as allegedly demonstrating the "consistent teachings as of March 15, 2007 that 'eculizumab was the IgG4 antibody of Thomas.'" Ex. 1002, 14840–14843, 14854. But for this error, the Examiner would have

better appreciated the disclosure of Mueller PCT. *See* Ex. 1003 ¶¶ 170, 172–174.

Bowdish and Evans

Petitioner further argues that, during the examination of the child patents, the Examiner erred in evaluating Bowdish and Evans by relying on Alexion's comparison between of Bowdish's *humanized* IgG2/G4 TPO-mimetic antibody (5G1.1+peptide antibody), with sequences of Evans's *mouse* 5G1.1 sequence, instead of using Evan's *humanized* 5G1.1 sequence as the comparator, which would have shown "no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert." Pet. 57; Prelim. Reply 6; Ex. 1036, 13–16. "This, unsurprisingly revealed a mismatch in the sequences." Pet. 57; *see* Ex. 1036, 14 (showing alignment between Bowdish SEQ ID NO: 67 (Ex. 1004 ¶ 49) and the "heavy chain variable region of [mouse] antibody 5G1.1" (Evans Fig. 19 (Ex. 1005, 10:9–21, Fig. 19)).

But, according to Petitioner and its technical expert, Dr. Ravetch, one of ordinary skill in the art would have understood that the humanized nature of Bowdish's 5G1.1+peptide antibody, and that a comparison using Evans's humanized 5G1.1 sequence would have shown "no mismatch beyond the HCDR3 region of the TPO mimetic peptide insert." Pet. 57; Ex. 1003 ¶¶ 83 (citing Ex. 1004 ¶ 192 as disclosing that Bowdish used "anti-human IgG" to detect 5G1.1), 85.

According to Petitioner, the comparison presented during prosecution was predicated on Alexion's representation to the examiner that Bowdish's "[c]onstruction of 5G1.1" would have directed a POSA only to Evans's mouse antibody in Examples 7–10. *Id.* (citing Ex. 1036, 13). Petitioner

contends that Alexion's argument to the Examiner ignored the express description of other, more pertinent, examples in Evans. In particular,

> Evans'[s] Example 11 expressly teaches humanized 5G1.1 scFv **constructs** and is entitled "**Construction** and Expression of Recombinant mAbs." (EX1005, 42:56-45:33 (emphasis added).) Example 11 also states: "Recombinant DNA **constructions** encoding the recombinant mAbs comprising the 5G1.1 CDRs are prepared by conventional recombinant DNA methods[.]" (EX1005, 42:59-62 (emphasis added).) Evans also discloses "CDR sequences that are useful in the **construction** of the humanized antibodies of the invention[.]" (EX1005, 8:50-54 (emphasis added).)

Pet. 58–59. Instead, Petitioner argues, "Alexion focused the Examiner on [Evans's] Example 7, entitled 'Preparation of anti-C5 Monoclonal Antibodies,' which discloses preparing (not constructing) the parent 5G1.1 mouse antibody from the mouse hybridomas of the prior art." *Id.* at 59 (citing Ex. 1005, 37:34–39:30).[22]

We agree with Petitioner that, "[t]he Examiner was persuaded by the Alexion's comparison," as evidenced by the Reason for Allowance:

> Evan's [*sic*] scaffold 5G1.1 mouse antibody variable regions or the whole 5G1.1 mouse antibody with the sequences for Bowdish's TPO mimetic compound would still have revealed a mismatch in amino acids beyond those that Bowdish identified as the TPO mimetic peptide insert.

Pet. 57 (citing Ex. 1035, 006–07; Ex. 1003 ¶ 175).

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[22] Although not necessary to our finding of error sufficient to satisfy the second prong of *Advanced Bionics*, Petitioner plausibly argues that the Examiner was also misled by Alexion's incorrect characterization of Evans as disclosing "multiple options" for heavy chain CDR3—whereas, "all nine humanized scFv sequences of Evans have only one unique HCDR3 sequence (YFFGSSPNWYFDV), not 'multiple options.' (*See* EX1005, 42:56-45:33; *see also supra* VIII.C; EX1003, ¶178, Appendix A.)." Pet. 60.

Patent Owner presents no specific rebuttal, merely asserting that Petitioner's "purported errors are the same flawed arguments Samsung asserts in its Petition, which are fully accounted for in Alexion's POPR." Prelim. Sur-Reply 6. We address the teachings of Bowdish and Evans in Sections II.D and II.E, above.

Considering the record before us, we agree with Petitioner that the Examiner erred in crediting Alexion's comparison between Bowdish's humanized IgG2/G4 TPO-mimetic antibody and Evans's mouse 5G1.1 sequence, without considering the more pertinent comparison between Bowdish's sequence and Evans's humanized 5G1.1 sequence.

3. Summary

For the reasons discussed above, we decline to exercise our discretion under 35 U.S.C. § 325(d) to deny the Petition.

B. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 314(a) AND *FINTIV*

Patent Owner points to § 314(a) as a basis for denying institution, but provides no substantive argument or evidence on this point. *See* Prelim. Resp. 17–32; *see generally* Prelim. Sur-Reply 6. Under certain circumstances, the Board may apply our discretion under 35 U.S.C. § 314(a) to deny institution in light of a parallel district court proceeding involving the same patent. *See, e.g.*, *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential). But, as noted by Petitioner, the patent at issue here "has never been asserted in any litigation." Pet. 49. Accordingly, we also decline to exercise our discretion under Section 314(a) to deny institution.

IV. CONCLUSION

On the record before us at this stage in the proceeding, Petitioner has demonstrated a reasonable likelihood of showing that claim 1 of the '149 patent is unpatentable under at least one ground. Accordingly, we institute an *inter partes* review of the challenged claim of the '149 patent on all grounds alleged by Petitioner. This decision does not reflect a final determination on the patentability of the claim.

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.

For PETITIONER:

Michelle Rhyu
Daniel Knauss
COOLEY LLP
rhyums@cooley.com
dknauss@cooley.com

For PATENT OWNER:

Gerald Flattmann
Andrew Cochran
CAHILL GORDON & REINDEL LLP
gflattmann@cahill.com
acochran@cahill.com