

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,
Petitioner,

v.

LEPU BIOPHARMA CO. LTD.,
Patent Owner.

IPR2025-00685
Patent 10,792,370 B2

Before JEFFREY N. FREDMAN, TAWEN CHANG, and RYAN H. FLAX,
Administrative Patent Judges.

FLAX, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

I. INTRODUCTION

The claimed invention of U.S. Patent 10,792,370 B2 (“the ’370 patent,” Ex. 1001) at issue in this proceeding relates to an antibody-drug conjugate (ADC), one targeting an epidermal growth factor receptor (“EGFR,” e.g., HER1). An ADC is an antibody with a linked small-molecule drug (with cytotoxic activity). Treated diseases include colon cancer, rectal cancer, head and neck cancer, lung cancer, ovarian cancer, cervical cancer, bladder cancer and esophageal cancer. The antibody portion of the claimed ADC has a heavy chain with a variable region (V_H) having SEQ ID NOs: 5 to 7 (as disclosed in the Specification), and a light chain with a variable region (V_L) having SEQ ID NOs: 12 to 14 (as disclosed in the Specification).

Lepu Biopharma Co., Ltd. (“Patent Owner”) is the owner of the ’370 patent. Paper 20, 1 (Patent Owner Motion to Substitute Party). On March 3, 2025, CSPC Megalith Biopharmaceutical Co., Ltd. (“Petitioner”) filed a Petition for *inter partes* review challenging the patentability of claims 1–23 of the ’370 patent. Paper 1, 1 (“Pet.”). We instituted trial on October 14, 2025. Paper 10 (“Institution Decision” or “DI”).

On January 21, 2026, Patent Owner filed a Response to the Petition. (Paper 19, “Resp.”). Petitioner subsequently filed a Reply (Paper 23, “Reply”) to which Patent Owner responded with a Sur-reply (Paper 35, “Sur-reply”).

A hearing was held on July 15, 2026, where the parties presented oral argument in support of their positions. A transcript of this hearing is of record. Paper 41 (“Hr’g Tr.”).

Petitioner bears the burden of proving unpatentability of the challenged claims, and this ultimate burden of persuasion never shifts to Patent Owner. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). As we address the parties' positions, it is always in the context of this burden. To prevail, Petitioner must prove unpatentability by a preponderance of the evidence. *See* 35 U.S.C. § 316(e) (2018); 37 C.F.R. § 42.1(d) (2023).

After considering the parties' arguments and supporting evidence, as discussed in detail below, we conclude that Petitioner has proven, by a preponderance of the evidence, that the challenged claims of the '370 patent are unpatentable. We explain our decision below.

A. REAL PARTIES-IN-INTEREST

Petitioner identifies CSPC Pharmaceutical Group Limited, CSPC NBP Pharmaceutical Co., Ltd, CSPC Innovation Pharmaceutical Co., Ltd, and CSPC Megalith Biopharmaceutical Co., Ltd., as real parties-in-interest. Pet. 3.

Patent Owner initially identified Shanghai Miracogen Inc. and Lepu Biopharma Co., Ltd. as real parties-in-interest. Paper 3, 2. Subsequently, Patent Owner moved to substitute another party in this proceeding, stating, “[a]s a result of a change in corporate structure, the '370 patent is now owned by Lepu Biopharma Co. Ltd.,” which is now the only entity Patent owner identifies as a real party-in-interest. Papers 20, 34. The case caption above reflects this change.

B. RELATED MATTERS

Petitioner and Patent Owner each states that it is unaware of any judicial or administrative proceedings that would either affect or be affected by a decision in this trial. Pet. 3; Paper 3, 2; Paper 34.

C. THE '370 PATENT AND RELEVANT BACKGROUND

The '370 patent, titled "ANTIBODY-DRUG CONJUGATE," issued on October 6, 2020, from U.S. Application 15/550,995 ('995 application), which was filed on February 16, 2016. Ex. 1001, codes (10), (21), (22), (40). The '370 patent indicates priority to CN 2015 1 0085038, which was filed on February 17, 2015. *Id.* at code (30). However, Petitioner asserts, and Patent Owner does not dispute, that the claims are entitled to a filing date no earlier than the actual filing date of the '995 application. *See* Pet. 35; *see generally* Resp.

Claim 1 is the sole independent claim of the '370 patent; it recites:

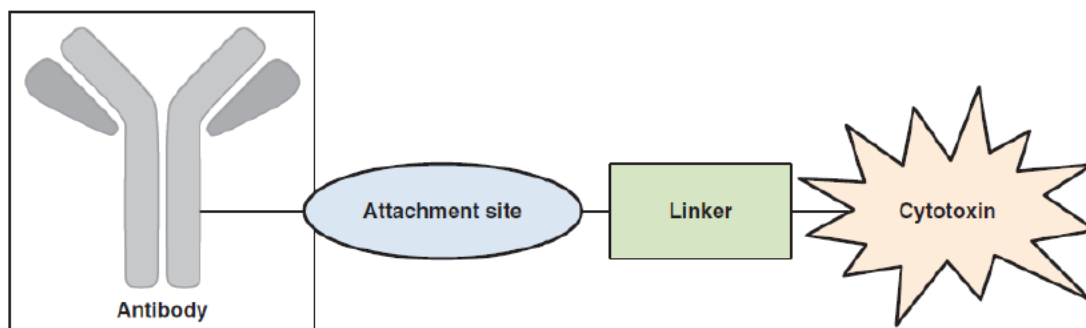
1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker, wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.

Ex. 1001, 33:2–11. The '370 patent also includes claims 2–23, which depend directly or indirectly from claim 1. *Id.* at 33:12–35:6.

As noted above, the '370 patent is directed to an antibody-drug conjugate (ADC) and, in particular, to an antibody-drug conjugate targeting an epidermal growth factor receptor (EGFR). Ex. 1001, code (57). The

'370 patent describes that its ADCs consist of three parts: “(1) a monoclonal antibody with specific binding affinity to a target; (2) a small-molecule drug with cytotoxic activity; and (3) a linker molecule linking the small molecule drug and the monoclonal antibody.” *Id.* at 2:60–65.

The Petition includes the following stylized illustration of an ADC:



The illustration above shows an antibody (grey) having an attachment site (blue oval) to which a linker (green box) is connected, which attaches a cytotoxin (peach explosion shape), i.e., the drug. *See* Ex. 1019, 4.

Some background knowledge regarding antibodies (or immunoglobulins (Ig)) is worth highlighting. Antibodies are proteins naturally made by the body, typically in response to infection, that identify and bind to antigens at epitopes (targets) thereon. Natural antibodies (e.g., IgGs, the most common type found in blood circulation, having the prototypical Y-shaped structure shown above) typically have two identical light (L) polypeptide chains (the darker grey in the figure above) and two identical heavy (H) polypeptide chains (lighter grey), each made up of amino acids. At least in IgGs, the light chains are composed of a constant domain (CL) and a variable domain (VL), and the heavy chains are composed of three constant domains (CH1, CH2, and CH3) and one variable

domain (VH), where CH2 and CH3 make up an Fc (fragment crystallizable) region, and CH1 and VH (with the light chain VL and CL domains) make up a Fab (fragment antigen-binding) region. Antibodies typically bind to antigens at the variable domains of their light and heavy chains (called a Fv (fragment variable) region).

The ADC described as the invention in the '370 patent is asserted to be a next generation antibody with respect to two FDA-approved EGFR-targeting cancer therapy products: (1) Erbitux or cetuximab, a human-mouse chimeric C225 antibody used in combination with the drugs irinotecan or fluoropyrimidine; and (2) Vectibix, a fully humanized IgG2 antibody used in combination with the drugs fluoropyrimidine, oxaliplatin and/or irinotecan. Ex. 1001, 1:57–2:32.

The '370 patent describes “the mechanism of antibody drug conjugate” as appearing to be “straightforward,” but expresses that “it is highly complex and unpredictable whether an antibody drug conjugate becomes a safe and effective drug,” which “depend[s] on a variety of factors.” *Id.* at 3:10–37.

The '370 patent describes a number of embodiments of monoclonal anti-EGFR antibodies comprising different complementarity-determining regions (CDR1, CDR2, CDR3) with specific sequences and homology to these sequences based on percentages ranging from 70% to 99%. Ex. 1001, 3:50–4:63. The '370 patent also describes various candidate cytotoxic agents that were well-known in the art, including monomethyl auristatin E (“MMAE”). *Id.* at 5:6–22. The '370 patent additionally lists well-known cleavable and non-cleavable linkers, including the cleavable linker valine-citrulline (“val-cit” or “vc”). *Id.* at 5:23–38. The '370 patent describes that

in one embodiment the linker and cytotoxic platform of the ADC is vc-MMAE—which is known in the art—and further provides the chemical structures of (1) vc-MMAE and (2) an antibody-drug conjugate comprising vc-MMAE that is also reproduced in claim 13. *Id.* at 5:39–67.

The '370 patent describes that “[t]he antibody BA03 of the present invention was BA03 as described in the Chinese invention patent application CN 103772504A, and its preparation method could be seen in Example 3 of this patent application,” and that the BA03 invention antibody includes disclosed SEQ ID NOs: 5–7 and 12–13.¹ *Id.* at 18:3–33.

Example 1 of the '370 patent is directed to the preparation of a specific ADC (called MYK-3), where the known BA03 anti-EGFR antibody is conjugated to a commercially obtained (i.e., “off the shelf”) vc-MMAE linker-cytotoxic agent platform. Ex. 1001, 19:26–29. A version of this BA03-vc-MMAE ADC is covered by the limitations of claim 1.

Examples 2–5 of the '370 patent are directed to various *in vitro* and *in vivo* assays comparing the inhibitory activities of the MYK-3 ADC *versus* the BA03 antibody (naked, without the attached drug) against various cancer cell lines and tumors, where the activity of the MYK-3 ADC was demonstrated to be generally superior. *Id.* at 19:52–22:25. In Example 6, the *in vitro* inhibitory activity of BA03-MMAE ADCs with three different linkers (BA03-vc-MMAE, BA03-MC-MMAE, and BA03-MCC-MMAE) was compared, where inhibition of tumor cell proliferation by MYK-3 (the vc variant) was demonstrated to be significantly higher than that

¹ As discussed below, Chinese application CN 103772504A is asserted prior art reference Liu, Ex. 1008, which discloses BA03.

demonstrated by the others. *Id.* at 22:26–24:5 (the chemical structures of the MMAE variants are provided).

D. PETITIONER’S ASSERTED GROUNDS FOR UNPATENTABILITY

Petitioner asserts the following grounds for unpatentability:

Ground	Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1	1–23	103	Wei ² , Liu ³
2	1–23	103	Leanna ⁴ , Wei, Liu

Pet. 5. In support of these grounds for unpatentability, Petitioner submits, *inter alia*, the Declarations of Stylianos Bournazos, Ph.D. Exs. 1002, 1200. Patent Owner submits, *inter alia*, the Declaration of Djordje Atanackovic, M.D. Ex. 2027. On this record, we find each witness competent to testify as to the subject matter of their declarations. Each party’s expert was deposed in this proceeding and the transcripts are of record. *See* Ex. 1246 (Atanackovic Depo. Tr.); Ex. 2026 (Bournazos Depo. Tr.).⁵

² G. Wei et al., US 2015/0071923 A1, pub. March 12, 2015. Ex. 1005 (“Wei”).

³ J. Liu, CN 103772504 A, pub. May 7, 2014. Ex. 1007. The Liu reference is published in Simplified Chinese and Petitioner filed a certified English translation, to which we refer herein. *See* Ex. 1008 (“Liu”). Patent Owner does not contest the accuracy of the translation. *See generally* Resp.

⁴ M.R. Leanna & C.L. Becker, WO 2014/152199 A1, pub. Sept. 25, 2014. Ex. 1006 (“Leanna”).

⁵ Based on our review of each deposition transcript in view of the record as a whole, although each witness appears competent, we are left with the impression that Dr. Bournazos’s testimony is somewhat more credible than Dr. Atanackovic’s.

This conclusion is based, *inter alia*, on each witness’s ability to recall the relevant record and respond to questions on evidentiary and technical issues.

II. DISCUSSION AND ANALYSIS

A. LEGAL STANDARDS ON PATENTABILITY

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify “with particularity . . . the evidence that supports the grounds for the challenge to each claim”)). This burden of persuasion never

See, e.g., Ex. 1246, 75:14–135:8, 243:12–252:6. Furthermore, Dr. Atanackovic’s apparent willingness (or oversight) to overlook contrary portions of evidentiary exhibits that are critical to Patent Owner’s positions and cited by Patent Owner in briefing raises credibility concerns. For example, Dr. Atanackovic: (1) relies on Tikhomirov (Ex. 1009) as concluding that a non-cleavable drug linker is required in an anti-EGFR ADC or else the therapy is overly toxic, but the reference expressly states that cleavable linkers are an option for such ADCs; and (2) relies on Crombet (Ex. 2022) in concluding that, in anti-EGFR ADCs, one desires antibodies with lower affinity to mitigate skin toxicity, although Crombet does not discuss ADCs and merely states “that higher affinity is not necessarily the best” for EGFR antagonists (naked antibodies). *See, e.g.*, Ex. 1009, 5–6; Ex. 2022, 1651; Ex. 2027 ¶¶ 13–20, 23–26, 31. Moreover, Dr. Atanackovic’s testimony that high or higher binding affinity in an anti-EGFR ADC was an undesirable or even disqualifying trait is directly at odds with public statements by Patent Owner that its own MRG003 ADC product is particularly effective *because of* its “carefully designed . . . sevenfold increased binding affinity to human EGFR, compared with cetuximab.” *See* Ex. 2032, 310 (this Exhibit reflects Patent Owner’s understanding of the invention, technology, and related product, not necessarily the perspective of the ordinarily skilled artisan at the time of the invention, but is nevertheless relevant for purposes of our credibility determination).

Our ultimate conclusions on obviousness are not, however, foundationally dependent on either witness’s testimony because the documentary evidence is generally conclusive without the need for supporting testimony.

shifts to Patent Owner. *See Dynamic Drinkware*, 800 F.3d at 1378 (discussing the burden of proof in *inter partes* review).

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. of Kansas City*, 383 U.S. 1 (1966). The *KSR* Court summarized the four factual factors 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) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the art; and (4) consider objective evidence indicating obviousness or non-obviousness. *KSR*, 550 U.S. at 406.

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *Id.* at 416. “[C]ase law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985)). “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious,” the answer depends on “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR*, 550 U.S. at 417.

KSR explains that “if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *Intel Corp. v. PACT*

XXP Schweiz AG, 61 F.4th 1373, 1380 (Fed. Cir. 2023) (quoting *KSR*, 550 U.S. at 417; and *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 797 (Fed. Cir. 2021)). If addressing a known problem, the prior art combination need not be “the *best* option, only . . . a *suitable* option.” *Id.* at 1380 (quoting *Intel*, 21 F.4th at 800 (emphasis original)).”

B. ORDINARY SKILL IN THE ART

Petitioner contends:

A person of ordinary skill in the art (“POSA”) at the time of the alleged invention would typically have had a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an MD with similar experience. A POSA would typically have had at least five years of experience with antibodies and antibody engineering, or access to other individuals with that knowledge and experience.

Pet. 32.

In our Institution Decision, we generally applied Petitioner’s definition. DI 5–6. Patent Owner does not contest Petitioner’s definition as we applied it at institution and does not propose an alternative. *See generally* Resp.

Petitioner’s proposed definition of the level of ordinary skill in the art appears to be generally consistent with the level of skill presented in the cited prior art. *See generally, e.g.*, Exs. 1005–1008; *see also Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself may reflect an appropriate level of skill in the art). However, as at institution, we reject the portion of Petitioner’s proposed definition that includes having “access to other individuals with that knowledge and experience,” as not reflecting the individual level of skill of a given skilled artisan. *See, e.g., Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962

(Fed. Cir. 1986) (holding that “[t]he person of ordinary skill is a hypothetical *person* who is presumed to be aware of all the pertinent prior art.”) (emphasis added, footnotes omitted); *but see Indivior Inc. v. Dr. Reddy’s Labys., S.A.*, 930 F.3d 1325, 1343 (Fed. Cir. 2019) (no clear error in determination that “a person of ordinary skill . . . ‘would be on a team with an engineer or scientist’”).

Consequently, we find the person of ordinary skill in the art was *a person who had a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an M.D. with similar experience, and had at least five years of experience with antibodies and antibody engineering.*

C. CLAIM CONSTRUCTION

The Board applies the same claim construction standard in trials that would be used to construe the claims in a civil action under 35 U.S.C. § 282(b). 37 C.F.R. § 100(b) (2020). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

“Petitioner submits that no term of the Challenged Claims requires construction to resolve the challenges in this Petition.” Pet. 32. We did not construe any terms in our Institution Decision. *See* DI 6–7. Patent Owner presents no express positions on claim construction. *See generally* Resp.

For the purposes of this Decision, no terms of the challenged claims require construction. *Phillips*, 415 F.3d at 1312–13.

D. PETITIONER’S ASSERTED PRIOR ART

We review and summarize the relevant portions of Petitioner’s asserted prior art references below. Petitioner asserts that each of Wei, Liu,

and Leanna is prior art under 35 U.S.C. § 102(a). Pet. 15–16, 21, 24. There is no dispute here that each asserted reference constitutes prior art. *See generally* Resp.

1. Wei (Ex. 1005)

Wei, titled “MODIFIED ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR ANTIBODIES AND METHODS OF USE THEREOF,” is the March 12, 2015, publication of U.S. Application 14/485,620, which was filed on September 12, 2014, and indicates priority to U.S. Provisional Application 61/960,253, filed on September 12, 2013. Ex. 1005, codes (12), (21), (22), (43), (54), (60). Regarding its disclosed invention, Wei states: “Provided herein are modified anti-EGFR antibodies and nucleic acid molecules encoding modified anti-EGFR antibodies. Also provided are methods of treatment and uses using modified anti-EGFR antibodies.” *Id.* at Abstr.

Wei discloses that an impetus for its invention was the recognition that FDA-approved cetuximab, an anti-EGFR antibody, can bind EGFR in not only cancer cells, but also healthy cells, which limited its use. Ex. 1005 ¶¶ 9–10; *see also id.* ¶¶ 491–506 (reviewing details of cetuximab’s structure and function). Although acknowledging that cetuximab treats a variety of cancers and other diseases, Wei identifies potential for improvement. *Id.*

Wei identifies that:

Humanized versions of cetuximab have been generated in which the variable regions of the murine heavy and light chains have been humanized by amino acid replacements in the framework regions (see Table 5). For example, U.S. Pat. No. 7,060,808 describes H225, which contains a variable heavy chain having the sequence of amino acids set forth in SEQ ID NO: 14 and a variable light chain having the sequence of amino acids set forth in SEQ ID NO: 15. Another humanized variant,

designated Hu225, is described in U.S. Published Appl. No. US 2011/0117110, which is an antibody that contains a variable heavy chain having the sequence of amino acids set forth in SEQ ID NO: 16 and a variable light chain having the sequence of amino acids set forth in SEQ ID NO: 17. The CDRs of the *humanized variants are identical to M225* and to the C225 and other reported cetuximab antibodies as described above. *These humanized antibodies exhibit reduced immunogenicity as compared to cetuximab.*^[6] As described elsewhere herein with respect to the modified anti-EGFR variants provided herein, the humanized variants of cetuximab can be full-length antibodies or can be antigen-binding fragments thereof, including Fab', F(ab')₂, Fab, Fv, rIgG, and scFv fragments. As a full-length antibody, the humanized antibodies can possess any immunoglobulin isotype or class (e.g., IgG, IgM, IgD, IgE, IgA and IgY), any subclass (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or sub-subclass (e.g., IgG2a and IgG2b).

Ex. 1005 ¶ 501 (emphasis added).

Wei discloses modified cetuximab variants that replace the amino acid residue at position 104 “in the variable heavy chain” (e.g., example variant “Y104D” indicating replacement of tyrosine (Y) with aspartic acid (D) at residue position 104 on HC) so that the antibody exhibits greater activity under the acidic pH conditions of a tumor microenvironment as opposed to the more neutral pH of normal tissue. *Id.* ¶¶ 10, 476, 660, 728 *et seq.* Wei explains that a rationale for this modification is that a negatively charged amino acid (e.g., aspartic acid, D) replacing a neutral amino acid (e.g.,

⁶ Other asserted prior art, Liu, discloses that its therapeutic antibody was initially derived from murine antibody M225, identifies Erbitux/cetuximab as human-mouse chimeric antibody C255, and identifies that Erbitux/cetuximab, although reducing immunogenicity with respect to M255, still has immunogenicity issues leading to human anti-antibody responses and side effects. *See* Ex. 1008 ¶ 3.

maleimidocaproyl-valine-citrul[1]ine-p-aminobenzyl linker
(maleimidocaproyl-vcPAB-MMAE)” or MC-vcPAB-MMAE).

2. Liu (Ex. 1008)

Liu, titled “HUMANIZED ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR ANTIBODY AND APPLICATION THEREOF,” is the May 7, 2014, publication of Chinese Application 201210406288.3, which was filed on October 17, 2012. Ex. 1008, codes (21), (22), (43), (54).

Regarding its invention, Liu states:

The present invention relates to a humanized anti-epidermal growth factor receptor antibody. The present invention further relates to a nucleic acid molecule encoding the antibody, a vector, a host cell and a composition including the nucleic acid molecule, and a detection reagent and kit. The present invention further relates to application of the antibody to the preparation of drugs for the prevention/treatment of diseases related to an epidermal growth factor or an epidermal growth factor receptor, as well as to the preparation of the detection reagent or kit. The antibody molecule of the present invention has lower immunogenicity and higher target binding activity, resulting in stronger biological activity and anti-tumor activity in vivo and in vitro. It can be expected to have lower side effect and better curative effect in clinical application.

Id. at Abstr.

Liu explains that “[t]he therapeutic antibody against the epidermal growth factor receptor was initially derived from a murine antibody M225, . . . specifically binds to the epidermal growth factor receptor, blocking its binding with ligands, thereby inhibiting the activity of tyrosine protein kinase of the epidermal growth factor receptor, . . . [but] murine antibodies can repeatedly stimulate the human body, potentially causing hypersensitivity reactions, known as human anti-mouse antibody responses.”

Id. ¶ 3. Liu continues, “[t]herefore, the human-mouse chimeric antibody

C225 (Erbix or Cetuximab, ImClone (now in Eli Lilly) company) uses variable regions of human IgG1k and murine anti-M225, reducing the immunogenicity of the murine-derived monoclonal antibody and retaining specific affinity for the epidermal growth factor receptor.” *Id.*

Liu identifies the human-mouse chimeric antibody C225, i.e., Erbitux or cetuximab, as FDA-approved, and describes its own antibody as based thereon and improved thereover because it is humanized. *Id.* ¶¶ 3–6, 74, 144, 150, 152, 154, 160. One engineered humanized EGFR antibody according to Liu is called “BA03.” *Id.* ¶ 60. According to Liu, the heavy chain variable region of its BA03 antibody can include an amino sequence according to SEQ ID NOs: 5, 13, 42, 43, which Petitioner asserts is the same sequence as claimed for the V_H and V_L in the ’370 patent. *Id.* ¶¶ 85, 133; Pet. 24–25 (also citing Ex. 1002 ¶¶ 90–92); *see* Ex. 1001, 33:2–11 (claim 1). The ’370 patent, as well as Patent Owner’s Response, confirms Petitioner’s assertions. *See* Ex. 1001, 18:3–33 (identifying BA03 as including the claimed sequences and citing Liu as describing BA03); Resp. 1, 23 (“The anti-EGFR antibody of claim 1 is specifically defined with the six CDR sequences of antibody BA03, which is covalently linked to the cytotoxic agent via a cleavable linker. As noted in the application, BA03 was previously described in Liu as a humanized version of cetuximab having increased EGFR-binding and inhibitory activity (Ex-1008, ¶140) and reduced immunogenicity (*id.*, ¶152).”).

Liu discloses that the BA03 antibody has higher activity than Erbitux/cetuximab in terms of affinity for surface bound EGFR, blocks binding activity of EGF ligand, inhibits phosphorylation activity of EGFR, and has improved ADCC (antibody-dependent cell-mediated cytotoxicity)

effect, while also having lower immunogenicity; thus, BA03 achieves stronger biological activity and anti-tumor activity both *in vitro* and *in vivo* with expected lower side effects and better curative effect in clinical applications. Ex. 1008 ¶¶ 61, 74, 122–160 (tested examples and results).

3. Leanna (Ex. 1006)

Leanna, titled “ANTIBODY DRUG CONJUGATE (ADC) PURIFICATION,” is the September 25, 2014, published version of International Application PCT/US2014/027062, which was filed on March 14, 2014, and indicates priority as early as March 15, 2013, based on the filing of U.S. Provisional Application 61/792,834. Ex. 1006, codes (21), (22), (30), (43), (54).

Regarding its invention, Leanna states:

The invention provides methods for obtaining compositions having antibody drug conjugates (ADCs) with specified drug to antibody ratios (DARs). Included in the invention is a method for purifying an ADC mixture having ADCs with a drug loaded species of 6 or more by contacting the mixture with a hydrophobic resin such that a composition comprising less than 15% of the 6 or more drug loaded species is obtained. The invention also provides a composition wherein 70% or more of the ADCs present have a drug loaded species of 4 or less, wherein the ADC comprises an anti-EGFR antibody and an auristatin.

Id. at Abstr. One (or two) ADC disclosed by Leanna is illustrated at its Fig. 1, which is reproduced below:

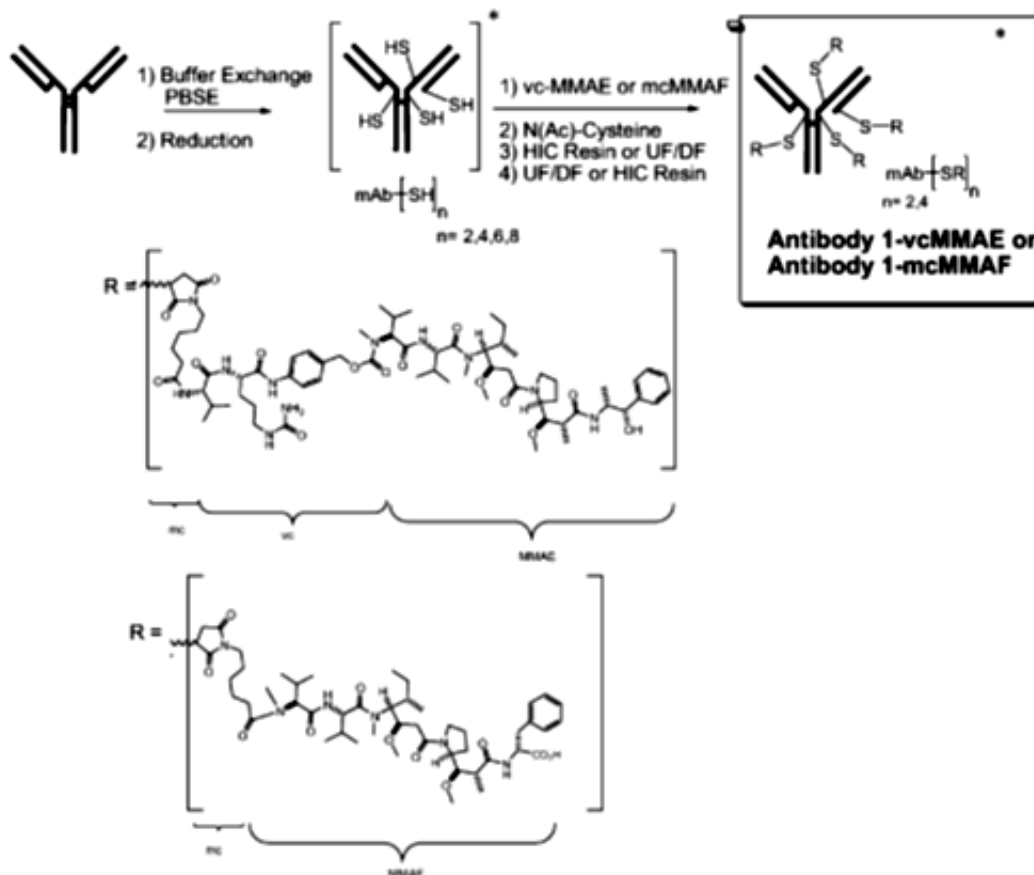


Fig. 1 illustrates, *inter alia*, the process of conjugating an antibody with vc-MMAE and purifying the ADC. *Id.* at 6. Leanna discloses this ADC to be an anti-EGFR ADC, which may be chimeric, human, or humanized, where the MMAE is conjugated to the antibody via a linker, which may be cleavable. *Id.* at 7, 11, 24–30. Leanna states, “[a]nti-EGFR antibodies suitable for use in accordance with the present compositions and methods are typically monoclonal and can include, for example, chimeric (e.g., having a human constant region and mouse variable region), humanized, or human antibodies; single chain antibodies; or the like.” *Id.* at 24. Leanna discloses that a preferred drug is the auristatin monomethylauristatin E (MMAE) and a preferred linker is a valine-citrulline (vc) linker. *Id.* at 2, 6–

7, 14, 26, 29, 32. Leanna discloses using an ADC to treat cancer by administering a therapeutically effective amount. *Id.* at 6, 13. Leanna discloses that anti-EGFR ADCs can be co-administered with cetuximab. *Id.* at 40, 42.

Leanna discloses that ADCs are “an emerging class of potent anti-cancer agents, which have recently demonstrated remarkable clinical benefit.” *Id.* at 1. Leanna discloses that deleterious effects of high drug loaded ADCs are known and can be mitigated by controlling and optimizing drug load, e.g., a lower percentage of the therapeutic composition may comprise a drug-loaded species or the drug-to-antibody ratio may be lowered. *Id.* at 1–3.

E. OBJECTIVE INDICIA OF NON-OBVIOUSNESS

Both of Petitioner’s grounds for unpatentability are based on obviousness and Patent Owner asserts that evidence of objective indicia of non-obviousness, in the form of a long-felt and unmet need and copying, supports the patentability of the challenged claims. *See* Pet. 5; Resp. 56–66.

“[O]bjective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis,” and “may often be the most probative and cogent evidence in the record.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016); *see also Graham*, 383 U.S. at 36 (“[Objective indicia] may also serve to guard against slipping into use of hindsight, and to resist the temptation to read into the prior art the teachings of the invention in issue.” (internal quotation marks and citation omitted)). Therefore, we consider this issue from the outset.

“In order to accord substantial weight to [objective indicia of non-obviousness, also called] secondary considerations[,] in an obviousness analysis, ‘the evidence of secondary considerations must have a ‘nexus’ to the claims, *i.e.*, there must be ‘a legally and factually sufficient connection’ between the evidence and the patented invention.’” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (citing *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d 1324, 1332 (Fed. Cir. 2019)). “The patentee bears the burden of showing that a nexus exists,” whether such a showing is established as a rebuttable presumption or “by showing that the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’” *Id.* at 1373–74 (further citing, *inter alia*, *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)).

However, “a strong showing of obviousness may stand ‘even in the face of considerable evidence’” of objective indicia of non-obviousness. *Adapt Pharma Operations Limited v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1372 (Fed. Cir. 2022) (quoting both *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1374 (Fed. Cir. 2018) and *Rothman v. Target Corp.*, 556 F.3d 1310, 1322 (Fed. Cir. 2009)); *see also Pfizer*, 480 F.3d at 1372 (“Although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion.”).

1. Long-Felt and Unmet Need

“Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious.” *Apple Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1055 (Fed. Cir. 2016). Establishing long-felt need requires objective evidence that an art recognized problem

existed in the art for a long period of time without solution; the need must have been a persistent one that was recognized by those of ordinary skill in the art. *In re Gershon*, 372 F.2d 535, 539 (CCPA 1967). “[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.” *Tex. Instruments v. U.S. Int’l Trade Comm’n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

Patent Owner identifies the alleged long-felt and unresolved need as a “need for a clinically viable anti-EGFR ADC.” Resp. 56. Patent Owner asserts that the claimed invention meets this need because it “[led] to the first ever regulatory approved anti-EGFR ADC.” Resp. 57 (citing Ex. 2027 ¶¶ 13, 85). Patent Owner asserts that, since the 2004 FDA-approval of the anti-EGFR pharmaceutical antibody cetuximab, no anti-EGFR ADC has been approved anywhere in the world (as of the Petition-date); but notes that there are currently at least four more regulatory approved pharmaceutical EGFR-targeting antibodies, i.e., panitumumab, nimotuzumab, necitumumab, and amivantamab, somewhere worldwide. Resp. 57 (citing Ex. 2027 ¶¶ 13, 85). These other four pharmaceutical products are not ADCs, however; they are naked antibodies like cetuximab.

As evidence that there was an unmet need for an anti-EGFR ADC, Patent Owner identifies several initiated (beginning in 2012), but terminated, clinical trials of anti-EGFR ADCs (named ABT-414, ABBV-221, ABBV-321, and HTI-1511), arguing that the antibody product has been an attractive target for potential therapies and the industry has had a strong interest for years, but has found no success in producing a clinically viable anti-EGFR

ADC. *Id.* at 57–59 (citing Ex. 2027 ¶¶ 86–87; Ex. 2012, 1;⁷ Ex. 2013, 4;⁸ Ex. 2014, 2;⁹ Ex. 2016, 1¹⁰). Neither Patent Owner nor its expert,

⁷ Exhibit 2012 discloses preclinical evaluation of anti-EGFR ADC using a newly engineered mAb (monoclonal antibody) with “similar intensity to cetuximab,” conjugated to MMAE with a novel bis-alkylating linker. Ex. 2012, Abstr. The article identifies “[a] clear dose dependent anti-tumor response was observed with complete tumor regressions observed at the 15 mg/kg dose in both models, which were resistant to treatment by cetuximab.” *Id.* However, considering the entire article, although the article compares its antibody of focus with cetuximab, we do not discern that the article identifies cetuximab or its regulatory approval as the impetus for developing or clinically testing an ADC, or that there was a long-felt need therefor. *See generally id.*

⁸ Exhibit 2013 indicates that a clinically-tested ADC (called depatux-m or ABT-414) “demonstrated promising clinical activity in glioblastoma multiforme (GBM) patients,” but was limited by corneal side effects common to the conjugated drug, MMAE; thus, the article compares depatux-m/ABT-414 to an anti-EFGR antibody conjugated to MMAE (ABBV-221), which it reports had “advanced to a phase 1 clinical trial[s]” as of publication. Ex. 2013, Abstr. Considering the entire article, although the article compares its antibody of focus with cetuximab, we do not discern that the article identifies cetuximab or its regulatory approval as the impetus for developing or clinically testing an ADC, or that there was a long-felt need therefor. *See generally id.*

⁹ Exhibit 2014 discusses clinical testing an ADC called serclutamab talirine (Ser-T or ABBV-321) and reports “tolerable safety profile with minimal antitumor activity observed in patients with glioblastoma. The glioblastoma dose-expansion cohort was closed due to a lack of efficacy.” Ex. 2014, Abstr. Considering the entire article, we do not discern that it identifies cetuximab or its regulatory approval as the impetus for developing or clinically testing an ADC, or that there was a long-felt need therefor. *See generally id.*

¹⁰ This exhibit discloses a safety and PK study of “ABBV-221,” but considering the entire exhibit, we do not discern that it identifies cetuximab

Dr. Atanackovic, however, identifies why these trials were terminated (with the possible exception of Exhibit 2014, *see supra* note 9) and

Dr. Atanackovic testifies that there could be many possible reasons for termination. *See* Resp. 57–59; *see* Ex. 2027 ¶¶ 85–89; *see* Ex. 1246, 264:5–268:6; 270:13–14.

Neither Patent Owner nor Dr. Atanackovic asserts, much less identifies, where or even that the alleged unmet need was ever *articulated* by anyone.

Patent Owner asserts that the claimed invention met the alleged long-felt need in 2025 when it received Chinese government approval for its anti-EGFR ADC drug, called MRG003, which it asserts embodies the claims of the '370 patent by using the BA03 antibody cleavably linked (using a valine-citrulline linker) with a cytotoxic payload (MMAE), and that this pharmaceutical is now “fast tracked” by the U.S. FDA as a breakthrough. *Id.* at 60 (citing Ex. 2021, 1 (press release identifying “an innovative antibody drug conjugate . . . targeting . . . EGFR,” conjugated with MMAE); Ex. 2003, 1 (press release discussing the drug and regulatory approval)).

Patent Owner also asserts that Petitioner has its own anti-EGFR ADC candidate in clinical testing (called “CPO301” or “SYS6010”—indicated to use an antibody derived from cetuximab); and also that Petitioner disclosed an ADC in a patent application that appears to utilize BA03 (called “SWY2110”), which Patent Owner asserts “matches” SYS6010 based on Petitioner’s patent application. Resp. 61 (citing Ex. 2008 ¶¶ 80–87; Ex. 2009, 1–2; Ex. 2010, 1).

or its regulatory approval as the impetus for developing or clinically testing an ADC, or that there was a long-felt need therefor. *See generally* Ex. 2016.

The records shows that SYS6010/CPO301 has received FDA fast-track review by the U.S. FDA. Ex. 2009. It is not clear on this record that Petitioner's SWY2110 ADC including BA03 is undergoing clinical trials or that Petitioner's other SYS6010 ADC includes BA03. Thus, we do not discern that the record supports that Petitioner has selected an ADC according to the challenged claims for clinical trials. Nonetheless, Patent Owner asserts that its evidence that MRG003 (Patent Owner's ADC) and CPO301 (Petitioner's ADC) "both use the BA03 antibody and a cleavable linker" "supports a finding of nexus between the claimed invention and the secondary consideration evidence . . . [because both] MRG003 and CPO301 both use the BA03 antibody and a cleavable linker." *Id.* at 62.

To summarize Patent Owner's positions on this issue, Patent Owner asserts that, once cetuximab was FDA-approved in 2004, the industry found a need to conjugate a drug to this antibody or one like it, which went unmet as evidenced by several clinical trials of anti-EGFR ADCs commenced and terminated in the years between 2012 and 2022, until Patent Owner gained Chinese approval of a pharmaceutical including BA03-vc-MMAE (also under consideration by FDA) and Petitioner tested and sought regulatory approval for a cetuximab-derived ADC with a glycine-based linker and an unidentified drug.

Petitioner responds that Patent Owner has failed to establish a nexus between its evidence of objective indicia and the claimed invention.¹¹

¹¹ Petitioner focuses on Patent Owner's MRG003 product and argues no nexus with "commercial success and industry recognition"; however, Patent Owner did not assert such indicia, but rather asserted long felt need and copying. *See* Reply 23.

Reply 22. Petitioner argues that the claims cover a broad genus (ADCs with anti-EGFR antibodies cleavably linked to any cytotoxic agent)¹² and Patent Owner has not shown that MRG003's regulatory approval, success, or industry recognition can be attributed to the features claimed in the '370 patent rather than, for example, clinical development expertise, manufacturing capability, regulatory strategy, or clinical trial dosing and schedule. *Id.* at 23 (citing Ex. 1246, 142:2–144:18 (Dr. Atanackovic testifying that the claims cover millions of different antibodies)).

Petitioner argues that, although others have not developed and marketed anti-EGFR ADC products, those others were dealing with ADCs having different antibodies, linkers, or payloads than claimed in the '370 patent and did not use a cetuximab-class antibody. *Id.* at 24. Petitioner argues that, as to the alleged failures, i.e., terminated clinical trials, Patent Owner's evidence does not identify the "specific reasons for terminations" and, according to Dr. Atanackovic, "there could be a number of reasons." *Id.* (citing Ex. 1246, 264:15–265:17, 265:19–270:14; Ex. 1200 ¶ 72). Petitioner argues that the terminations of clinical trials were essentially product failures, but that ADCs were produced in the prior art and succeeded in demonstrating anti-tumor activity, e.g., Wei's huY104D-vc-MMAE and Leanna's 1-vc-MMAE. *Id.* (citing Ex. 1002 ¶¶ 32–58; Ex. 1005 ¶¶ 1116–1127; Ex. 1006 50–60).

¹² Petitioner over-generalizes slightly because the claims are directed to antibodies with certain amino acid sequences, e.g., those included in BA03. However, such antibodies could otherwise differ significantly in their sequence.

We have considered the record and the parties' positions on the issue of long-felt and unmet need and, as discussed below, find that, if Patent Owner's evidence is entitled to any weight at all to support non-obviousness, it is entitled to very little weight.

As an initial matter, considering this issue, our reviewing court has stated that "long-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." *Tex. Instruments*, 988 F.2d at 1178. No evidence here shows that, other than Patent Owner's statements in this proceeding, anyone *articulated* there was a need for "a clinically viable anti-EGFR ADC," expressly or implicitly. There is simply no direct evidence of this of record. Without any past articulation of the alleged need, it is difficult to analyze the evidence to identify whether a need was, indeed, long-felt and persistent, and whether it remained unmet until the claimed invention.¹³

Patent Owner presents only indirect, circumstantial evidence that there was a need for "a clinically viable anti-EGFR ADC" in the form of four initiated and terminated (from 2012–2022) trials of such pharmaceuticals. However, on this record, it is not possible to know why these products did not make it through a regulatory process or to market.

¹³ We also note that Patent Owner stated in its 2022 investor report that, as of that date, "ADCs represent an emerging class of anti-tumor targeted therapies that combine a mAb with a potent tumor cell-killing payload via a linker." Ex. 2032, 291. This document also identifies that, as of that date, another anti-EGFR ADC was part of "the competitive landscape," called Akalux, as well as four other anti-EGFR ADCs called M1231, EGVR(v)-EDV-Dox, ZV0203, BL-B01D1 that were in clinical trials since as early as 2016. *Id.* at 297–99. Thus, it is not apparent that the alleged need had been long-felt or that it had not been met.

Exhibit 2012 discloses its anti-EGFR ADC *produced an anti-tumor response*, Exhibit 2013 indicates that an anti-EGFR ADC *demonstrated promising clinical activity*, Exhibit 2014 reported a tolerable safety profile but minimal antitumor activity for its anti-EGFR ADC, and Exhibit 2016 indicates only the existence and testing of its anti-EGFR ADC. Exs. 2012–2014, 2016; *see also* Sur-reply 26–27 (renewing the same argument). So, there appears to have been some success in these trials in producing an anti-EGFR ADC with a therapeutic effect, and there is little or no evidence explaining why such products were not further pursued. None of this evidence satisfies Patent Owner’s burden to show the advocated long-felt need existed or that such a need was not met.

In addition to these evidentiary shortcomings, on this record it is unclear that Patent Owner has established the required nexus between the invention defined by the ’370 patent’s claims and the evidence that Patent Owner’s pharmaceutical product has satisfied a long-felt need. To show a product has a presumed nexus with a claimed invention (or that a presumption of nexus is established) the two must be “coextensive,” which “requires the patentee to demonstrate that ‘the product is essentially the claimed invention.’” *Teva Pharms. Int’l GmbH v. Eli Lilly and Co.*, 8 F.4th 1349, 1361 (Fed. Cir. 2021). To otherwise establish a nexus, a party must show the objective indicia evidence is the “direct result of the unique characteristics of the claimed invention.” *Fox Factory*, 944 F.3d at 1373–74 (quoting *In re Huang*, 100 F.3d at 140). Unclaimed features of the product and external business or industrial factors must be considered. *See Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1418 (Fed. Cir. 2022).

Patent Owner contends that its own MRG003 ADC and Petitioner's CPO301 (aka SWY6010) both use the BA03 antibody and that this supports there is a nexus. It is unclear that the record fully supports Patent Owner's contention.

MRG003 may include BA03, but it is less clear that CPO301 uses the BA03 antibody. As noted above, Patent Owner cites Exhibits 2009 and 2010 for this proposition. *See* Resp. 61. Exhibit 2009 identifies that CPO301/SY6010 is an anti-EGFR antibody drug conjugate undergoing fast track review by the FDA and states "CPO301 is a humanized monoclonal antibody, optimized from cetuximab, and conjugated with a topoisomerase I inhibitor." Nowhere does this Exhibit state that the antibody is BA03. Exhibit 2010 states the product "is a novel ADC comprising of an anti-epidermal growth factor receptor (EGFR) humanized IgG1 monoclonal antibody conjugated to topoisomerase I inhibitor JS-1 via a cleavable glycine-glycine-phenylalanine-glycine tetrapeptide linker." Nowhere does this Exhibit state the antibody is BA03. Patent Owner asserts, without evidentiary citation, that CPO301 somehow *matches* SWY2110-ADC described in Petitioner's patent application—we do not discern they are the same. *See* Resp. 61. However, in its Reply, Petitioner asserts that CP301 uses a different linker and cytotoxic payload than Patent Owner's product, not necessarily that CPO301 does not include the BA03 antibody; thus, we lack certainty on this fact. Reply 25.

To summarize, MRG003 likely includes BA03, but CPO301 may or may not. For these reasons, Patent Owner's nexus contentions commence on questionable grounds.

Patent Owner’s assertion that a long-felt and unmet need existed and was met by the invention focuses on the ’370 patent’s invention generally (no claims are specifically argued) and evidence that the BA03 antibody, valine-citrulline linker, and MMAE payload of MRG003 embodies the claimed invention. Resp. 60–62; *see also* Sur-reply 27–28. Patent Owner argues that “the specific BA03 antibody for use in an ADC was not obvious.” Resp. 60. However, the scope of claim 1 may include MRG003’s BA03, but it also broadly includes countless other antibodies, and the scope of claim 1 may include MRG003’s valine-citrulline linker, but it also includes any cleavable linker, and further, claim 1’s scope includes any cytotoxic agent, not just MMAE. *See, e.g.*, Ex. 1001, 5:7–20, 5:25–36, 9:1–10:53, 11:36–67, 12:4–64 (describing a multitude of options for antibodies, which potentially vary in countless ways other than the specific recited variable region portions, linker options, and cytotoxic agent options); *see also* Resp. 38 (Patent Owner asserting there were “millions of ways to modify cetuximab.”); Ex. 1002 ¶¶ 196–199 (Dr. Bournazos discussing the scope of linkers and cytotoxic agents claimed). Therefore, we question whether a nexus, presumed or otherwise, is established by Patent Owner’s evidence that one specific embodiment within the much broader scope of the invention has allegedly succeeded or met a need.

During this proceeding, each party has pointed us to Patent Owner’s Exhibit 2032, which is a “Global Offering” prospectus understood to be directed to investors or potential investors. This evidence was produced after the invention date and does not reflect, for example, the understanding of ordinarily skilled artisans as of the invention, but does indicate Patent Owner’s understanding of the related product and technology. It discusses

Patent Owner's MRG003 ADC product and, although Patent Owner's counsel indicated at our final hearing that Patent Owner had not "really developed a very good understanding why [it] worked," (*see* Hr'g Tr. 55:8–15), Patent Owner's public statement in Exhibit 2032 is that the MGR003 product was successful because of the following advantages, which were "carefully designed": (1) the antibody was humanized and had a sevenfold increase in binding affinity to human EGFR compared to cetuximab; (2) the MMAE payload was well-validated and widely used, with a potency and bystander effect demonstrated in a variety of cancer models; (3) the cleavable linker helps to release the MMAE quickly into cytoplasm; and (4) the DAR (drug-to-antibody ratio) of MRG003 was "one of the critical factors . . . to optimize . . . safety and efficacy." Ex. 2032, 310. Even if we might find that features 1–3 (above) *are* in some way part of claim 1 of the '370 patent, the final "critical" drug-to-antibody ratio is *not*. Therefore, there appears to be evidence that at least one technical, unclaimed feature of Patent Owner's product led to its success (allegedly meeting the asserted long-felt need). This alone likely forecloses a finding of nexus for the broadest invention, as Patent Owner argues here.

Having considered the parties' positions on long-felt need, we are unpersuaded that the need existed—it was not articulated by anyone before this proceeding. We are not persuaded that others necessarily failed to meet the alleged need merely by failing to market a product; some efforts appear to have had some success and we do not know why (or even that) the products were abandoned. We are also unpersuaded that a nexus has been established between Patent Owner's evidence and the invention—at best,

only one species among many covered by the broadest claim has matured into a regulatory approved product.

For these reasons, we give Patent Owner's evidence concerning a long-felt and unmet need very little weight when considering whether the challenged claims were obvious.

2. Copying

"Copying requires duplication of features of the patentee's work based on access to that work Evidence of copying may include internal documents, direct evidence such as photos of patented features or disassembly of products, or access and similarity to a patented product." *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019) (citation and quotation marks omitted). *Liqwd* cautioned against "collapsing the separate infringement and copying inquiries into a single analysis." *Id.*

In this regard, our reviewing court held that "if the only evidence of copying was a competitor's abandonment of one product design and subsequent adoption of a design similar to that of a patented product after issuance of the patent, that did 'not establish that [the competitor] engaged in copying,'" and "more is needed than merely showing that similarity exists between the patent and the competitor's accused product." *Liqwd*, 941 F.3d at 1137. However, the court also noted that "initial attempts at one design together with the 'prompt adoption of the claimed feature soon after the patent issued, are relevant indicia of nonobviousness.'" *Id.* at 1138.

Patent Owner asserts that its MRG003 anti-EGFR ADC and Petitioner's CPO301 anti-EGFR ADCs are each encompassed by claim 1, and that public records evidence that Petitioner copied "core features" of MRG003. Resp. 63 (citing Ex. 2032, 53; Ex. 2033, 129). Patent Owner

asserts that it exclusively licensed the Liu¹⁴ patent for developing ADCs, then developed and received approval for the MRG003 product, and that Petitioner then acquired the owner of Liu (Shanghai JMT-Bio, Inc. or “JMT”). *Id.* at 63–64. Patent Owner asserts that Petitioner was aware of the MRG003 product and had access to the technology of BA03 (mentioning them in a patent application). *Id.*

Patent Owner asserts that, in developing its product, Petitioner followed the teachings of Wei to produce pH-selective derivatives of BA03 (referred to as SWY2110). *Id.* at 64–65. Patent Owner asserts that, despite data showing these derivatives were superior to BA03, Petitioner ultimately produced SYS6010, which “contains the BA03 antibody” (which includes the claimed amino sequences of the ’370 patent). *Id.* Patent Owner asserts that this *logically means* Petitioner copied the claimed invention (BA03) because it observed the success of MRG003. *Id.* at 65.

Petitioner argues that its allegedly copied product, CPO301, uses at least a different linker and a different cytotoxic payload than the vc-MMAE of the ’370 patent’s focus. Reply 25 (citing Ex. 2008, 2; Ex. 1100, 1–2; Ex. 1103, 1; Ex. 1001, claim 13).

After considering the parties’ positions, we find scant (if any) evidence of copying. There is no direct evidence of copying on this record. If the MRG003 product was the product Petitioner allegedly copied, Patent Owner itself identifies that Petitioner’s CPO301 product differs in material ways, e.g., “differ[s] in terms of the specific linker and payload used.” Resp. 62. Evidence that Petitioner used the BA03 antibody, one to which it owned

¹⁴ Liu, Exhibit 1008, is a patent application filed in China. It is not clear on this record what patent issued from this application.

intellectual property rights and had been publicly known since at least 2014 as an effective humanized anti-EGFR antibody clinically superior in several important ways to cetuximab (*see* Ex. 1008 ¶¶ 122–160), when developing an ADC, is not sufficient to show that Petitioner copied the invention of the ’370 patent.

Here, Patent Owner’s proof of copying distills down to a theory as to why Petitioner chose to use its own BA03 antibody technology over other options and an allegation that Petitioner’s product infringes the ’370 patent. We find the evidence insufficient to give any weight to Patent Owner’s allegations of copying.

3. Summary on Objective Indicia of Non-Obviousness

Having considered each party’s positions and the evidence of record, in accordance with the analysis and conclusions above, we give very little weight to evidence concerning long-felt and unmet need and no weight to evidence of copying when considering the record regarding obviousness. We now turn to the merits of Petitioner’s challenges of unpatentability.

F. GROUND 1—ASSERTED OBVIOUSNESS OVER WEI AND LIU

Legal writing often addresses the logical fallacy of the “strawman,” where a scenario that *can* be argued against is conjured and attacked, while facts and arguments that *should* be challenged are ignored. This is the circumstance we find here, where Patent Owner bases its arguments on such a strawman, which we address below.

To generally summarize, there is no dispute that the preferred embodiment of the invention of the ’370 patent, and covered by its claims, (1) is a known, humanized version of the FDA-approved, anti-EGFR, cancer-treating cetuximab antibody (BA03); (2) to which is conjugated a

known and off-the-shelf cancer-treating platform (MMAE drug and valine-citrulline linker); (3) i.e., “BA03-vc-MMAE ADC.” *See* Ex. 1001, 18:3–5,¹⁵ 18:61–19:30,¹⁶ 33:2–11; *see also* Resp. 1–2 (introduction summarizing this invention); Ex. 1005 ¶¶ 434, 687–688 (vc-MMAE was known); Ex. 1006, 7, 14 (vc-MMAE was known); Ex. 1008 (BA03 was known); Ex. 1009; Ex. 2027 ¶¶ 7–8, 13; Ex. 2032,¹⁷ 310.

When analyzing obviousness, “if there’s a known technique to address a known problem using ‘prior art elements according to their established functions,’ then there is a motivation to combine,” because *KSR* explains that, “if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.” *Intel Corp.*, 61 F.4th at 1380.

The ’370 patent confirms that there was a problem to be addressed: a “need in the art to have humanized anti-epidermal growth factor receptor antibody drugs . . . to further improve therapeutic efficacy and reduce side effects,” and a need for an ADC utilizing such an antibody to provide “target

¹⁵ This portion of the Specification states, “[t]he antibody BA03 of the present invention was BA03 as described in the Chinese invention patent application CN 103772504A,” which identifies Liu (Ex. 1008).

¹⁶ This portion of the Specification, describing “Example 1: Preparation of Antibody-Drug Conjugate,” states, “[t]o the [BA03] antibody was added . . . vc-MMAE (purchased from Haoyuan Chemical Technology Co., Ltd., No. HY-15575).”

¹⁷ Exhibit 2032 is Patent Owner’s (2022) investor statement, which discusses this embodiment as its pharmaceutical product. Patent Owner states that MMAE was “a well-validated and widely used cytotoxic payload for clinical-stage as well as marketed ADCs.” *Id.* at 300.

specificity” for “the cytotoxicity of the chemical drug.” Ex. 1001, 2:50–3:1. The ’370 patent also confirms that BA03 and vc-MMAE were known compositions/techniques with established functions: a humanized anti-EGFR antibody, a cleavable linker, and a cytotoxic agent. *Id.* at 5:8–37, 18:3–7, 18:61–19:39. As Patent Owner’s Response identifies, Patent Owner simply made the “*choice*” to use the prior art BA03 antibody, and known-candidate cytotoxic payload MMAE (having acceptable safety and stability and potency). Resp. 1, 5–6, 23 (emphasis added).

As discussed in more detail below, Petitioner has identified that the anti-EGFR antibody cetuximab existed in the prior art; that a humanized (i.e., clinically better) version of cetuximab (BA03) existed in the prior art; and that ADCs using cetuximab variants and the same linker-drug combination claimed (vc-MMAE) were also disclosed in the prior art. None of this is in dispute. Petitioner asserts that the logical (and obvious) progression from the FDA-approved cetuximab would have been to humanize it to mitigate immunogenicity, and to add a conjugated cancer-treating drug thereto, because each step progresses cancer therapy, which Petitioner asserts would have led the ordinarily skilled artisan to the claimed invention of the ’370 patent. We agree.

Patent Owner, as a response to both of Petitioner’s unpatentability grounds, tweaks these facts and assertions to build the proverbial strawman, which at its core argues that we must begin an evaluation of the prior art not with the FDA-approved cetuximab antibody ripe for humanizing and its humanized BA03, but with Wei’s cetuximab-based antibody and ADC already improved in a specific, different way; one which may be but is not necessarily humanized; one that should not be modified. We do not find that

Petitioner's challenges are limited in this way and do not agree with Patent Owner's strawman argument. For at least this reason, Patent Owner's arguments are not persuasive.

We discuss these issues further below.

1. Petitioner's Positions

As noted above, Petitioner bears the ultimate burden of proof here and, under Ground 1, asserts that the combination of Wei and Liu teaches all elements of claims 1–23 and renders the claims obvious and unpatentable. Pet. 37–65 (citing, *inter alia*, Ex. 1001, 3:10–37, 5:25–6:65, 18:1–36; Ex. 1002 ¶¶ 102–106, 187–188, 191–193, 195; Ex. 1003, 406–7; Ex. 1004, 200, 298; Ex. 1005 ¶¶ 229, 238–239, 328, 434, 441–458, 558–559, 660, 666, 740, 742, 903, 1086–1141, claims 27–40, 48–55, 58; Ex. 1006, 8, 15, 34–51, Examples 1, 4, claim 8; Ex. 1008 ¶¶ 37, 60, 85, 108, 123–124, 141–146, 148–160, Figs. 4–5; Ex. 1009, 4, 10–11; Ex. 1010, 3–6; Ex. 1015, 6; Ex. 1016, 5–6; Ex. 1017, 1–2; Ex. 1018, 939, 942).

Petitioner asserts that the ordinarily skilled artisan had reasons to combine Wei and Liu because Liu discloses a humanized version of cetuximab (i.e., BA03) and identifies its advantages over cetuximab; Wei also teaches a humanized version of cetuximab (“substantially identical” to BA03, or at least a related clone-sibling thereto) and advantages of humanization; and each of Wei and Liu discloses using such antibodies as anti-EGFR, cancer therapy antibodies.¹⁸ Pet. 40–42 (citing, *inter alia*,

¹⁸ Petitioner was not so explicit on expectations for success in the Petition, but in response to Patent Owner's arguments, Petitioner asserts that the record establishes that, by the date of the '370 patent, those working in the field had already successfully received FDA approval for ADCs with

Ex. 1002 ¶¶ 187–188; Ex. 1003, 406–07; Ex. 1005 ¶¶ 1103, 1116–1127, 1139; Ex. 1008 ¶¶ 148–152); *see also* Reply 9 (citing Ex. 2026, 101:19–23, 103:23–106:19 (Dr. Boumazos’s cross-examination testimony)). Petitioner asserts that the trend in the field of antibody therapy development is always towards humanized antibodies from murine or chimeric ones. Pet. 7–8, 42.

With respect to Liu’s BA03 humanized version of cetuximab, Petitioner identifies that Liu states it is superior to cetuximab because it has stronger EGFR phosphorylation inhibition, higher ADCC activity, and significantly lower immunogenicity. *Id.* at 2, 40. Petitioner asserts that Wei teaches producing cancer-therapy ADCs by attaching a vc-MMAE platform (cytotoxic payload with cleavable linker) to a cetuximab variant differing by one substituted amino acid, and also to a humanized cetuximab variant (again, for lower immunogenicity). *Id.* at 40–42. Petitioner asserts that using the BA03 antibody rather than (the FDA-approved) cetuximab, alone (per Liu) or in an ADC (per Wei), would have been understood to result in

cleavable linkers and even the vc-MMAE platforms, specifically. Reply 15–16 (citing Ex. 1002 ¶¶ 51–55; Ex. 1010, 3; Ex. 1019, 2; Ex. 1020, 6; Ex. 1021, 1–2; Ex. 1026, 1–2). Moreover, Petitioner asserts that Wei demonstrated that this platform could be predictably used with cetuximab variants, including humanized ones like Liu’s BA03. *Id.* at 16–17 (citing Ex. 1002 ¶¶ 181–201; Ex. 1005 ¶¶ 1116–117; Ex. 1008 ¶¶ 141–160; Ex. 1015, 6–8; Ex. 1020, 2–7; Ex. 1026; Ex. 2026, 89:11–91:10, 101:9–108:15). Petitioner asserts that this evidence establishes the reasonable expectation of success for the ordinarily skilled artisan in achieving the claimed invention based on the prior art combination. *Id.* at 15; *see also Electa Ltd. v. ZAP Surgical Sys, Inc.*, 81 F.4th 1368, 1376–78 (Fed. Cir. 2023) (“a finding of reasonable expectation of success can be implicit,” and that finding “may flow from the prior art references themselves . . .”).

higher binding affinity and ligand blocking abilities, and cause less hypersensitivity reactions in human subjects. *Id.* at 42.

Petitioner covers all challenged claims as taught by the Wei-Liu combination, but as to claim 1 (*see supra* Section I.C quoting the claim), Petitioner asserts that Wei teaches an ADC with an anti-EGFR antibody that is covalently linked to a cytotoxic agent via a cleavable linker in disclosing Y104D-MC-vcPAB-MMAE and huY104D-MMAE, which include a modified and humanized version of cetuximab cleavably linked to the cytotoxic payload MMAE with valine-citrulline. Pet. 37–40 (citing, *inter alia*, Ex. 1005 ¶¶ 229, 660, 742, 1092–1141). As for the specifically recited amino acid sequences of V_H and V_L , Petitioner cites Liu as disclosing a humanized anti-EGFR antibody, i.e., the humanized cetuximab antibody BA03, which indisputably has those sequences. *Id.* (citing, *inter alia*, Ex. 1001, 18:3–6; Ex. 1008 ¶¶ 60, 85, 108, 123–124, 141–146, 148, 150, 152–160, Figs. 4–5). Both Wei’s and Liu’s antibodies are disclosed to be effective cancer therapies that improve over the FDA-approved cetuximab. *Id.* (citing, e.g., Ex. 1005 ¶¶ 1122–1127; Ex. 1008 ¶¶ 148, 150, 152–160, Figs. 4–5).

Claim 2 depends from claim 1 and adds “FR1, FR2, FR3, FR4 of the variable region of the heavy chain of the anti-epidermal growth factor receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 8 to 11,” which Petitioner asserts is disclosed by Liu because these sequences are part of the BA03 antibody. Pet. 51 (citing, *inter alia*, Ex. 1001, 18:1–36; Ex. 1008).

Claim 3 also depends from claim 1; it recites “FR1, FR2, FR3, FR4 of the variable region of the light chain of the anti-epidermal growth factor

receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 15 to 18,” which, like claim 2, Petitioner asserts is disclosed by Liu because these sequences are part of the BA03 antibody. Pet. 52 (citing, *inter alia*, Ex. 1001, 18:1–36; Ex. 1008).

As for claim 4, which also depends from claim 1 and adds “the heavy chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human IgG constant region, a human IgM constant region, a human IgA constant region, and a human IgD constant region,” Petitioner asserts that this is disclosed by Liu and by Wei because the BA03 antibody and Wei’s Y104D antibody have a human IgG1 constant region. Pet. 52–53 (citing Ex. 1005 ¶¶ 558–559; Ex. 1008 ¶ 37).

Claim 5 depends from claim 4 and recites “the IgG is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4,” which, like claim 4, Petitioner asserts is taught by Wei’s and Liu’s antibodies that have a human IgG1 constant region. Pet. 53 (citing Ex. 1005 ¶ 328; Ex. 1008 ¶ 37).

Claim 6 also depends from claim 4 and adds that “the constant region of the heavy chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 3,” which Petitioner asserts is taught by Liu because the BA03 antibody includes the sequence of amino acids. Pet. 53–54 (citing, *inter alia*, Ex. 1001, 18:3–6; Ex. 1008).

Claim 7 depends from claim 1 and recites “the light chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human lambda constant region, and a human kappa constant region,” which Petitioner asserts is taught by Liu because the

BA03 antibody has a human kappa light chain constant region, as does Wei's antibody. Pet. 54 (citing Ex. 1005 ¶¶ 558–559; Ex. 1008 ¶ 37).

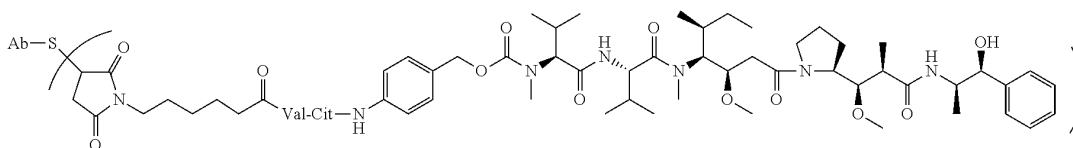
Claim 8 depends from claim 7 and adds that “the constant region of the light chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 4,” which Petitioner again asserts is disclosed by Liu's BA03 antibody, which includes the claimed amino acid sequence. Pet. 54–55 (citing, *inter alia*, Ex. 1001, 18:3–6; Ex. 1008).

Claim 9 depends from claim 1 and recites that the ADC “has a structure as shown in Formula I, Ab-(L-D)_p Formula I wherein: Ab represents the anti-epidermal growth factor receptor antibody; L represents a cleavable linker; D represents the cytotoxic agent; p represents 1-9,” which Petitioner asserts is obvious in view of Wei's Y104D-MMAE ADC (having, e.g., a val-cit linker) and DAR of 4 (i.e., p between 1–9). Pet. 55–56 (citing Ex. 1005 ¶ 1103).

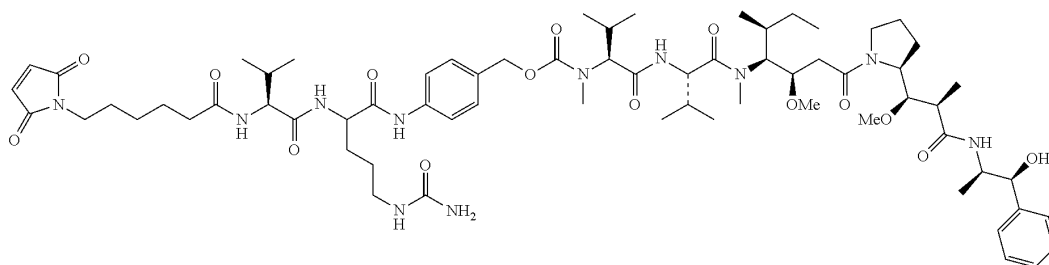
Claim 10 depends from claim 9 and adds that “the cytotoxic agent is selected from the group consisting of chemotherapeutic agents, radioisotopes, antibiotics, enzymes, and biologically active peptides,” and, claim 11 depends from claim 10 and further adds that “the cytotoxic agent is selected from the group consisting of Monomethyl auristatin E (MMAE), Monomethyl auristatin F (MMAF), maytansinoid alkaloids, Calicheamicin, duocarmycin MGBA, doxorubicin, ricin, diphtheria toxin, I131, and tumor necrosis factors,” which Petitioner asserts is taught by Wei's Y104D-MMAE ADC because the MMAE payload is a chemotherapeutic agent that interferes with microtubule dynamics and GTP hydrolysis. Pet. 56–57 (citing Ex. 1005 ¶ 434).

Claim 12 depends from claim 9 and adds that “the linker is selected from the group consisting of valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), N-succinimidyl 4-(2-pyridylthio)valerate (SPP), and 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB),” which Petitioner asserts is taught by Wei’s ADC because it contains a val-cit cleavable linker. Pet. 57 (citing Ex. 1005 ¶ 1103).

Claim 13 also depends from claim 9 and it recites that the ADC “is:



wherein Ab represents the anti-epidermal growth factor receptor antibody, p is 1-8,” which Petitioner asserts is taught by Wei in disclosing an ADC including a linker and payload with the following chemical structure:



and because Wei’s exemplary ADC has a DAR of 4, which teaches the requisite *p* value. Pet. 58–59 (citing Ex. 1005 ¶¶ 740, 742, 1102–1103, claim 40).

Claim 14 also depends from claim 9 and recites “the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB),” which Petitioner asserts is taught by Wei where its Y104D-MMAE ADC uses a cleavable linker “maleimidocaproyl-valine- citrullinep-

aminobenzyl linker (maleimidocaproyl-vcPAB-MMAE) as described in Francisco et al. Blood 102:1458-1465 (2003).” Pet. 59 (citing Ex. 1005 ¶ 1103).

Claim 15 depends from claim 1 and adds that the ADC composition, “optionally, further comprises at least one pharmaceutically acceptable carrier, diluent or excipient,” which, although only optional and therefore not limiting, Petitioner asserts is taught by Wei in disclosing ADCs can be part of pharmaceutical formulations with a carrier or excipient. Pet. 59–60 (citing Ex. 1005 ¶¶ 238, 861–875).

Claim 16 also depends from claim 1 and recites “[a] method for treatment of a disease associated with epidermal growth factor receptor (EGFR), comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1,” and claim 17 depends from claim 16 and adds that “the disease associated with epidermal growth factor receptor (EGFR) is a tumor associated with overexpression of EGFR,” which Petitioner asserts is taught by Wei’s anti-EGFR ADC, disclosed as used for targeted delivery of cytotoxic or cytostatic agents for cancer treatment (tumors over-expressing EGFR), formulated to achieve maximal efficacy, minimal toxicity, and reduced side effects. Pet. 60–61 (citing Ex. 1005 ¶¶ 239, 442, 666).

Claim 18 depends from claim 1 and recites “[a] method for inhibiting tumor angiogenesis, delaying tumor progression, inhibiting tumor growth, or inhibiting tumor cell proliferation, comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1,” which

Petitioner asserts is taught by Wei where its ADC is used to treat cancers. Pet. 61–62 (citing Ex. 1005 ¶¶ 441–458, 1086–1127, claims 48, 58).

Claim 19 depends from claim 18 and adds that “the tumor is selected from colon cancer, rectal cancer, head and neck cancer, lung cancer, ovarian cancer, cervical cancer, bladder cancer, esophageal cancer, breast cancer, renal cancer, prostate cancer, gastric cancer, pancreatic cancer and brain glioma,” which Petitioner asserts is taught by Wei in disclosing using its ADC to treat, e.g., glioblastomas, prostate, and breast cancers, among others. Pet. 62–63 (citing Ex. 1005 ¶ 903).

Claim 20 depends from claim 17 and recites “the tumor is a tumor with KRAS gene mutation,” and claim 22 depends from claim 19 and adds “the tumor is a tumor with KRAS gene mutation,” which Petitioner asserts is taught by Wei’s ADC, which was tested and shown to effectively treat breast cancer with KRAS-mutated tumors. Pet. 63, 64–65 (citing Ex. 1005 ¶¶ 1116–1127).

Claim 21 also depends from claim 17 and it recites “the tumor is a tumor with BRAF gene mutation,” and claim 23 depends from claim 19 and adds that “the tumor is a tumor with BRAF gene mutation,” which Petitioner asserts is taught by Wei’s ADC, which was tested and shown to effectively treat breast cancer with BRAF-mutated tumors. Pet. 63–65 (citing Ex. 1005 ¶¶ 939, 942).

Reviewing Petitioner’s assertions and the evidence of record, we find that Petitioner has accounted for the teaching of each element of each challenged claim as taught by the Wei-Liu combination. Petitioner has shown each of Wei and Liu to be prior art and has established a reason with

rational underpinning why the person of ordinary skill in the art would have combined these references with a reasonable expectation of success.

We now turn Patent Owner's arguments and any responses thereto offered by Petitioner.

2. Patent Owner's Positions (and Petitioner's Replies Thereto)

Patent Owner argues that the ordinarily skilled artisan would not have been motivated to combine Wei and Liu (to modify Wei—*see* “strawman” discussion above—Petitioner does not argue that Wei must be modified) because Wei's solution to cetuximab's lack of tumor-specificity is engineering (acidic) pH-selectivity into a cetuximab variant via a Y104D residue modification (changing tyrosine, Y, to aspartic acid, D), and, because Liu's BA03 antibody lacks such pH selectivity, replacing Wei's antibody with Liu's would abandon Wei's benefits. Resp. 24–30 (citing, *inter alia*, Ex. 1005 ¶¶ 9, 994, 1130–1131, 1139; Ex. 2008, 19, 34–35, 65; Ex. 2026, 88:23–89:10; Ex. 2027 ¶¶ 48, 52, 54–58). Patent Owner argues that BA03 would have appeared to be an inferior choice for modifying Wei's ADC because of its lack of pH-selectivity.

Patent Owner argues that Wei teaches away from using Liu's BA03 in an ADC because, without pH-selectivity, BA03 would have “equal binding activities in tumor and non-tumor environments,” which Wei discourages. Resp. 30–32 (citing, *inter alia*, Ex. 1005 ¶ 9; Ex. 2027 ¶ 59).

Patent Owner argues that Wei already teaches a residue-104 mutated and humanized antibody in huY104D and, therefore, there would have been no reason to replace that with the BA03 humanized antibody of Liu. Resp. 30–34 (citing Ex. 2026, 25:11–19, 110:4–111:17, 112:1–113:6).

Patent Owner argues there is no evidence that such a replacement would have any benefits. *Id.* at 34–35 (citing, *inter alia*, Ex. 2027 ¶¶ 62–63, 65).

Patent Owner also argues that it was not obvious to try replacing Wei’s humanized antibody with BA03 because there were millions of possibilities in modifying/humanizing cetuximab and there is no evidence of a likelihood (or reasonable expectation) of success in using BA03 in an ADC. Resp. 35–39 (citing, *inter alia*, Ex. 1002 ¶ 187; Ex. 1008; Ex. 2026, 27:7–14, 78:19–22, 101:19–102:12, 102:12–19, 105:4–13, 108:2–15, 109:6–111:17, 112:1–113:21, 116:8–11; Ex. 2027 ¶¶ 45–46, 78–80).

Patent Owner argues (against both Grounds 1 and 2) that the ordinarily skilled artisan “would have avoided the BA03-VC-MMAE ADC” (the result of combining Wei and Liu) because the conventional ADC design strategy was to decrease antibody binding affinity, but BA03 has a higher binding affinity than cetuximab (which was already too high, according to Patent Owner), making it unattractive.¹⁹ Resp. 46–50 (citing, *inter alia*, Ex. 2026, 122:25–123:1). Patent Owner identifies this convention as “strategy B4” (understood to reference “B4” in Sections II.B.3–4 of the Response) and points to Tikhomirov (citing Ex. 1009, 3–4, 10–11 (these

¹⁹ In more than one office action, the USPTO examiner indicated the opposite of this conclusion—that higher binding affinity of BA03 was advantageous. *See* Ex. 1003, 394 *et seq.*; Ex. 1004, 146 *et seq.*, 240 *et seq.* Patent Owner (then applicant) filed responses, one amending the claim to limit the recited ADC to have a cleavable linker, but never argued that BA03’s higher affinity was a problem or unexpected benefit, instead arguing that the recited cleavable linker would be more toxic. Over this argument, the claims were allowed. Ex. 1004, 306, *et seq.* Moreover, as noted above, in a 2022 investor statement, Patent Owner identified “increased binding affinity” as a “carefully designed” advantage of its BA03-based ADC. Ex. 2032, 310.

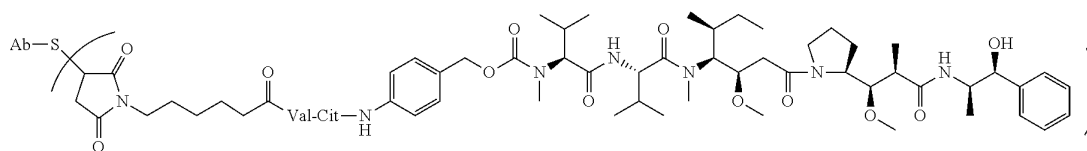
pages discuss using full antagonist antibodies and non-cleavable linkers, not mentioning lowering binding affinity)), Crombet (citing Ex. 2022, 5 (a “counterintuitive” model predicting high affinity antibodies lead to uptake by normal tissue, urging intermediate affinity for cancer therapy; says (at 7) that “higher affinity is not necessarily the best”)), and the foreign-approved nimotuzumab antibody with weaker binding affinity and no skin toxicity (Ex. 2023; Ex. 2024) for support that the ordinarily skilled artisan would not have made the invention. *Id.* (also citing Ex. 2027 ¶¶ 36, 60–61). Patent Owner’s argument is that the higher binding affinity of BA03 would lead to a narrower (i.e., increased risk of either inefficacy or dose toxicity) therapeutic window than a cetuximab-vc-MMAE ADC, making BA03’s adoption in an ADC undesirable.

Relatedly, Patent Owner argues that it would have been expected that using such an antibody (BA03) would negate Wei’s (and Leanna’s, relating to Ground 2) improvements to cetuximab. Resp. 50–52.

Patent Owner also argues (against Grounds 1 and 2) that Petitioner has failed to show a reasonable expectation of success in using BA03 in an ADC, arguing there’s no evidence of such a use in the record, and that the ordinarily skilled artisan would have not expected it because there must be development balances made between cancer-killing capabilities and toxicity (EGFR is present on cancer and normal cells and the therapy must distinguish between the two, which Patent Owner asserts BA03 does not do). Resp. 52–56 (citing, *inter alia*, Ex. 1002 ¶¶ 108, 178–189, 282; Ex. 1008; Ex. 2026, 59:13–60:4, 70:3–5, 72:11–73:8, 116:8–11; Ex. 2027 ¶¶ 81–82, 84).

Patent Owner also argues that evidence of objective indicia supports non-obviousness (against Grounds 1 and 2). We addressed this argument above as entitled to little if any weight. *See supra* Section II.E.

Patent Owner's arguments summarized above are directed to the invention of the '370 patent generally, for example, as defined by claim 1, without distinguishing any specific claims as patentable over the asserted prior art. Patent Owner does, however, separately argue that claim 13 is patentable over Petitioner's challenges, although the argument is quite brief. Resp. 66–67. As noted above, claim 13 depends from claim 9 (reciting the ADC is “Ab-(L-D)_p”) and further defines the ADC “is:



wherein Ab represents the anti-epidermal growth factor receptor antibody, p is 1-8.” Ex. 1001, 34:23–46. Patent Owner argues that this specific embodiment has much higher inhibitory activity than the naked BA03 antibody, and has an excellent efficacy-safety profile based on the MYK.3/MRG003/becotatug vedotin (interchangeable nomenclature) product, which “underscores the unexpected nature of the claimed ADC.” Resp. 66–67

In its Reply, Petitioner argues that there is no dispute that Wei discloses the claimed ADC architecture. Reply 3–4 (citing Resp 25–34; Ex. 1005 ¶¶ 1092–1127). This is not in dispute here; neither is the fact that Liu's BA03 antibody is the antibody of the claimed invention. *See generally* Resp.

Petitioner also responds that Liu's BA03's and Wei's huY104D are similar anti-EGFR antibodies, that the huY104D antibody may have some, but not meaningful pH selectivity compared to cetuximab, and that BA03's pH sensitivity is not known and is not established as absent. Reply 4–5 (citing Ex. 1005, 42, 44–45; Ex. 1008, 11; Ex. 1200 ¶¶ 90–91; Ex. 1246, 207:8–12, 217:20–219:13; Ex. 2008; Ex. 2026, 77:14–86:8, 104:1–105:15; Ex. 2027 ¶ 56). Petitioner's point, as we understand it, is that BA03 and huY104D are more alike than different and are substitutable as anti-EGFR antibodies for ADCs.

Petitioner further argues in reply that Liu identifies BA03 as superior to cetuximab in several ways, which is explicit motivation to select it as an antibody, and that it has advantages over cetuximab relevant to ADC design: rapid internalization into tumor cells; lower immunogenicity; phosphorylation inhibition; and higher ADCC. *Id.* at 5–7 (citing Ex. 1002 ¶¶ 45–53, 87, 185–187; Ex. 1008 ¶¶ 141–160, Figs. 2–6; Ex. 1200 ¶¶ 52–65; Ex. 1246, 306:9–307:20; Ex. 2027 ¶¶ 62–65). Petitioner notes that Patent Owner itself ultimately confirms in public statements that these are advantages in a BA03-ADC. *Id.* (citing Ex. 2032, 310).

Petitioner asserts that

The motivation to combine Wei and Liu flows naturally from their teachings. (EX1002, ¶¶ 185-195.) Wei shows that humanized cetuximab variant ADCs with cleavable vc-MMAE linkers exhibit potent anti-tumor activity. (EX1005, ¶¶ 1116-1127, Tables 44-45.) Liu shows that BA03 is an improved humanized cetuximab variant with enhanced properties relevant to therapeutic efficacy. (EX1008, ¶¶ 0141-0160, Tables 1-4.) A POSA seeking to develop an optimized anti-EGFR ADC would have been motivated to use BA03, with its documented advantages in binding affinity, EGFR inhibition, ADCC

activity, and internalization, to create a humanized cetuximab ADC which was disclosed in Wei's huY104D. (EX1002, ¶¶185-188.)

Reply 7 (citing Ex. 1002 ¶¶ 185–195). Petitioner argues that the similarity of BA03 (of Liu) and huY104D (of Wei) as humanized cetuximab variants supplies motivation to use one or the other in an ADC, and that Wei does not teach away from it merely because its antibody may have some pH selectivity. *Id.* at 8–9 (citing, *inter alia*, Ex. 1002 ¶¶ 187–188; Ex. 2026, 101:19–23, 103:23–106:19).

As for Patent Owner's "narrower therapeutic window" argument, Petitioner responds that the Tikhomirov reference cited by Patent Owner stated that some skin reaction is acceptable risk and that greater binding affinity was a goal in developing anti-EGFR antibodies, not a drawback, and that Liu's expressed advantages of BA03 would outweigh possible concerns about binding affinity. Reply 10–11 (citing, *inter alia*, Ex. 1002 ¶¶ 85–92; Ex. 1004, 177; Ex. 1008 ¶¶ 141–160, Figs. 2–6; Ex. 1200 ¶¶ 12–21, 29, 78–79; Ex. 1246, 12:11–14:18; Ex. 2011, 1:30–40). Petitioner also identifies Crombet as unreliable for Patent Owner's purposes because it does not address ADC design, but only naked antibodies, and only concludes that "higher affinity is not necessarily the best," rather than that it is some sort of disqualifying factor. *Id.* at 12–13 (citing, *inter alia*, Ex. 2022, 7).

As for the contested reasonable expectation of success, Petitioner argues that substantial evidence supports that it existed because, by the '370 patent's invention date, ADCs using cleavable linkers (vc) and cytotoxic payloads (MMAE) had already been FDA-approved, establishing that it was within the ordinary level of skill in the art to make and use such ADCs.

Reply 15–16 (citing, *inter alia*, Ex. 1010; Ex. 1019; Ex. 1020; Ex. 1021; Ex. 1026).

As for dependent claim 13, Petitioner responds that the clinical success of Patent Owner’s product does not equate to non-obviousness because the prior art teaches the BA03-vc-MMAE combination as well as the DAR range of this claim, where Wei’s Y104D-Mc-VCPAB-MMAE ADC (with the claimed linker and drug as claimed) with a DAR of 4, as well as Leanna’s Antibody 1-vc-MMAE ADR with a DAR of 3.85, applied to the Liu BA03 antibody. Reply 21 (citing Ex. Ex. 1002 ¶¶ 186–195, 275–283, 1005 ¶¶ 1092–1127; Ex. 1006, 32–52; Ex. 1200 ¶¶ 99–100). Petitioner asserts that there were known vc-MMAE ADCs in the prior art that used anti-EGFR antibodies, e.g., Tikhomirov’s cetuximab ADC, Wei’s Y104D ADC, and Leanna’s Antibody 1-vc-MMAE, so comparing Patent Owner’s product to a naked antibody or one co-administered with a drug was not a valid comparison for asserting efficacy-safety superiority. *Id.* at 21–22. And, asserts Petitioner, the facts that vc-MMAE was a well-known, validated, off-the-shelf platform, that anti-EGFR ADCs using the platform had already showed potent activity, and that BA03 had been shown to have key properties for a successful ADC antibody (e.g., binding activity, ADCC activity, lower immunogenicity, tumor inhibition), established a reasonable expectation of success in making and using the claimed ADC. *Id.* at 22 (citing Ex. 1005 ¶¶ 1116–1127; Ex. 1008 ¶¶ 141–160; Ex. 1020, 6; Ex. 1021, 1–2; Ex. 1200 ¶ 97; Ex. 2027 ¶¶ 91–92).

3. Analysis for Ground 1

Based on the parties’ positions and arguments, in view of the record, we are persuaded by Petitioner that each challenged claim would have been

obvious over the Wei-Liu prior art combination. In general, we agree with Petitioner's positions set forth in the Petition and adopt those positions as findings of fact herein. *See generally* Pet. 1–3, 6–32, 37–65; *see also supra* Sections I.C, II.D, and II.F.1 (reviewing the '370 patent, the asserted prior art, and Petitioner's positions thereon). We discuss further below.

We find that combining Liu's BA03 antibody with Wei's ADC platform would have been desirable, predictable, and routine for the ordinarily skilled artisan based on the facts that: (1) cetuximab was a well-known and well-studied, U.S. regulatory approved, anti-EGFR antibody that would have served as a starting point for new cancer therapies; (2) humanization of therapeutic antibodies is generally desired (and "[e]very antibody can be humanized" and it is advantageous according to Patent Owner's counsel); (3) BA03 was a well-known humanized version of cetuximab that had several known advantages over cetuximab in addition to lower immunogenicity from humanization; and (4) Wei taught a similar cetuximab-derived antibody, and a humanized cetuximab-derived antibody, each provided in an ADC with a well-known and validated off-the-shelf linker-drug platform, i.e., vc-MMAE, that exhibited a strong anti-tumor response. *See, e.g.*, Ex. 1001, 1:57–2:32, 2:50–3:1, 5:6–53, 18:3–33, 19:26–29; Ex. 1002 ¶¶ 14, 38, 42–43, 45–53, 56–73, 84–92, 109–117, 178–189, 202–271; Ex. 1005 ¶¶ 9–10, 229–232, 434, 437, 476, 491–506, 664–675, 685, 688, 715, 732, 1103, 1092–1141; Ex. 1008 ¶¶ 3–6, 60, 74, 141–160; Ex. 2027 ¶¶ 7–8, 38, 50, 57 (confirming our understandings regarding the claimed antibody and linker-drug payload); Ex. 2023, 173, 300; *see also* Resp. 1, 5–6, 23 (Patent Owner made the "*choice*" to use the prior-art-known BA03 antibody, and known-candidate cytotoxic payload MMAE);

Hr'g Tr. 34:20–23, 36:6–38:20, 47:16–50:16 (Patent Owner's counsel's argument). When Liu's BA03 antibody is provided in an ADC with a vc-MMAE or a Mc-vcPAB-MMAE platform (and used as cancer therapy as the references instruct) the invention of the challenged claims is achieved.

Liu's BA03 is indisputably the '370 patent's claimed antibody. Ex. 1001, 18:3–5. Liu identified many reasons its BA03 antibody was a good replacement for cetuximab and a good candidate for cancer therapy. Ex. 1008 ¶¶ 3–6, 37, 60–61, 74, 139–160. For example, compared to cetuximab (the human-mouse chimeric successor to the original M225 murine antibody), humanized BA03 was less immunogenic, had higher activity for cell-surface EGFR, inhibited phosphorylation activity cell-surface EGFR, improved ADCC, was effective against several types of cancer, and was better in clinical applications. *Id.*; *see also* Ex. 1022 (humanization is generally desired for therapeutic antibodies).

Wei supports that cetuximab was a good starting point for cancer-therapy development and that a humanized cetuximab antibody was desirable (e.g., to reduce immunogenicity). *See, e.g.*, Ex. 1005 ¶¶ 9–10, 15, 36–42, 329, 391, 490, 501, claim 1. Wei, and others (e.g., Tikhomirov), had successfully conjugated cetuximab-based antibodies to MMAE via a valine-citrulline (cleavable) linker to produce a working ADC cancer therapy. *See, e.g.*, Ex. 1005; Ex. 1006; Ex. 1009. Wei provides several reasons, both general and specific, for producing anti-EGFR ADCs using cetuximab-based antibodies, for example, ADCs exhibit selective tumor targeting for delivery of cytotoxic agents and may be useful for diagnosis or treatment of cancer and other diseases or disorders, and ADCs using cetuximab variants (including humanized) with a vc-MMAE or Mc-vcPAB-MMAE platform

better inhibited tumor growth *in vivo* and exhibited reduced side effects. Ex. 1005 ¶¶ 666–675, 1086–1106, 1116–1132 (discussing the production and effectiveness of cetuximab variant anti-EGFR ADCs).

Based on these findings, the ordinarily skilled artisan would have had a reason with rational underpinning to combine Liu and Wei so as to develop an ADC with BA03 and a vc-MMAE or Mc-vcPAB-MMAE platform, and use it as a cancer therapy, and would have had a reasonable expectation of success in doing so, which would have taught or suggested the claimed invention. *See* Pet. 40–42; Ex. 1002 ¶¶ 187–188; *see also* Reply 5–7 (discussing the advantages of the combination).

We noted, above, Patent Owner’s foundational strawman argument. First, it is established that, when considering prior art combinations for obviousness analysis, asserted references are not considered *primary* and *secondary*, references are considered for what their combination teaches. *In re Bush*, 296 F.2d 491, 496 (CCPA 1961); *see also Schwendimann v. Neenah, Inc.*, 82 F.4h 1371, 1384 (Fed. Cir. 2023) (“[W]here the relevant factual inquiries underlying an obviousness determination are otherwise clear,” characterizing references “as ‘primary’ and ‘secondary’ is merely a matter of presentation with no legal significance.”). Here, contrary to Patent Owner’s framing of the case, we do not consider Wei a “primary” reference and Liu a “secondary” reference, where we must begin analysis with Wei and determine whether it would be modified per Liu. Rather, we look at the teachings of these references as they address the obviousness of the claimed invention. Second, Petitioner does not assert the references this way, but begins the “motivation to combine” argument by pointing to Liu’s improved BA03 antibody and then proposes its use in an ADC as taught by Wei.

Pet. 40–42. And, third, as we explained above, we agree with Petitioner that Liu and Wei, from the perspective of the ordinarily skilled artisan as of the time of the invention, invite their combination to use BA03 in an ADC with a vc-MMAE platform, for the reasons discussed above.

Wei does not teach away from either the invention or its own combination with Liu. Our reviewing court has stated

“[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” [*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).] Thus, the “mere disclosure of alternative designs does not teach away.” *In re Fulton*, 391 F.3d 1195, 1201 (Fed.Cir.2004).

In re Mouttet, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Wei’s focus on producing pH selectivity in its ADC’s antibodies is not discouragement of the use of an alternative and differently advantageous cetuximab variant, like Liu’s BA03, in an ADC for cancer treatment.

Moreover, even if it were true that using BA03 was somehow less effective for producing an ADC cancer therapy than using Wei’s humanized Y104D antibody, which is not established on this record, in addressing a known problem, the prior art combination need not be “the *best* option, only . . . a *suitable* option.” *Intel*, 61 F.4th at 1380 (quoting *Intel*, 21 F.4th at 800). On this record, we agree with Petitioner that there was a motivator, i.e., the need for new cancer therapies and the development of ADCs therefor. We also agree that the Liu-Wei BA03-ADC combination was suitable to address that motivator.

Patent Owner’s arguments that toxicity concerns and/or BA03’s increased affinity would have been seen as barriers to the prior art

combination are not persuasive. Cetuximab by itself was considered a success even though often toxic as a therapy. *See, e.g.*, Ex. 1001, 1:52–2:5 (U.S. FDA initially approved cetuximab for treatment of colorectal cancer initially, then again for head and neck cancers, and it is still being pursued for treating other cancers); Ex. 1005 ¶ 9; Ex. 1014 (cetuximab was successfully used to treat several types of cancer, identifying side effects); Ex. 1233 (Erbix FDA-approved prescribing information, identifying potential adverse reactions). The use of BA03, a humanized version of cetuximab, would have been expected to cause fewer side effects because its humanization decreases immunogenicity. Ex. 1008. Further, we are not persuaded that the affinity increase extolled by Liu to be an advantage of BA03 would have been considered anything other than a benefit (not a detriment). *Id.* Patent Owner’s arguments to the contrary lack credibility in view of, *inter alia*, Patent Owner’s own public statements (albeit made later than the invention date) that this very “increased binding affinity to human EGFR, compared with cetuximab,” was a *carefully designed* characteristic of the BA03-ADC that led to its success. Ex. 2032, 310.

We have above already addressed Patent Owner’s arguments concerning objective indicia of non-obviousness. As noted, “[a]lthough secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion,” and may “not overcome the strong showing of obviousness.” *Pfizer*, 480 F.3d at 1372. Even if we give Patent Owner’s evidence of objective indicia of non-obviousness the very little weight it might be argued to deserve, which is debatable, it is not persuasive enough to overcome the strong showing that the claims would have been obvious over Liu and Wei for the reasons set forth above.

As for the dependent claims, Patent Owner does not argue any but claim 13. As for claim 13, Patent Owner argues that the claimed species, i.e., BA03-Mc-vcPAB-MMAE (only parts of BA03 are required and 1–8 drug molecules may be attached), evidences the unexpected nature of the claimed ADC, which hints at, but does not actually make an unexpected results argument nor satisfy its burden to show such. Resp. 66–67. We find that there was good reason to have combined Liu’s and Wei’s teachings to produce BA03-Mc-vcPAB-MMAE and that claim 13 would have been obvious over this prior art combination. *See, e.g.*, Ex. 1005 ¶ 740.

In summary, having considered the parties’ positions and the record, we find that Petitioner has shown by a preponderance of the evidence that claims 1–23 would have been obvious over Wei and Liu and that the challenged claims are, therefore, unpatentable under 35 U.S.C. § 103. No arguments or evidence presented by Patent Owner persuades us otherwise.

G. GROUND 2—ASSERTED OBVIOUSNESS OVER LEANNA,
WEI, AND LIU

There is substantial overlap in the evidence and arguments concerning Grounds 1 and 2 and most of our analysis and conclusions set forth above regarding Ground 1 apply to Ground 2 as well.

1. Petitioner’s Positions

Ground 2, like Ground 1, challenges all claims of the ’370 patent and relies on the combination of Wei and Liu. Under Ground 2, Petitioner asserts that the combination of Leanna, Liu, and Wei teaches all elements of claims 1–23 and renders them obvious and unpatentable. Pet. 65–75 (citing, *inter alia*, Ex. 1001, 18:3–6; Ex. 1002 ¶ 188; Ex. 1003, 406–7; Ex. 1005

¶¶ 740, 742, 747, 1092–1141; Ex. 1006,²⁰ 1, 5–6, 8, 15, 26, 30–31, 34–38, 50–60, Fig. 1; Ex. 1008 ¶¶ 60, 85, 108, 123–124, 141–160; Ex. 1014).

Regarding motivation to combine Leanna, Liu, and Wei, Petitioner asserts that there was reason to use Liu’s humanized BA03 version of the FDA-approved anti-EGFR antibody cetuximab to produce Leanna’s (humanized) anti-EGFR ADC, which has a cleavable linker (vc) and payload (MMAE, like Wei), because of the known benefits of Liu’s humanized cetuximab-based antibody, e.g., lower immunogenicity. *Id.* at 67–69 (citing, *inter alia*, Ex. 1001, 183–6; Ex. 1002 ¶ 188; Ex. 1003, 406–7; Ex. 1006, 1, 5–6, 8, 50–60; Ex. 1008 ¶¶ 60 141–160; Ex. 1014). Moreover, Petitioner argues, Wei also suggests using a humanized version of cetuximab (huY104D) and the same cleavable vc linker and MMAE payload for an ADC. *Id.* at 68 (citing Ex. 1005 ¶¶ 740, 742, 1103, 1116–1127 (Example 20)).

This is basically the same rationale as set forth under Ground 1, which we conclude supports obviousness. Petitioner’s point is that, as all three references disclose using a humanized anti-EGFR antibody and producing such, and Leanna and Wei teach ADCs using such humanized anti-EGFR antibodies was well-established, the ordinarily skilled artisan would have reasonably expected to succeed in crafting an ADC using BA03, e.g., BA03-vc-MMAE, in accordance with the claims. *See* Reply 17 (citing Ex. 1002 ¶¶ 75–83; Ex. 1006, 26–32, 50–82).

Petitioner maps the teachings of Leanna, Liu, and Wei to each challenged claim. Pet. 65–67, 69–75.

²⁰ Petitioner’s cites to Leanna use the added page numbers at the lower right corner of each exhibit; for the sake of consistency we do the same here.

As for claim 1, Petitioner asserts that each of Leanna, Liu, and Wei discloses a humanized anti-EGFR antibody, with Leanna and Wei teaching ADCs having valine-citrulline (vc) cleavable linkers attaching MMAE (cytotoxic drug) thereto (*see* “Antibody 1-vc-MMAE ADC” of Leanna and “Y104D-MC-vcPAB-MMAE” of Wei), and that (as with Ground 1) Liu teaches antibody BA03, which includes the claimed amino sequences. *Id.* at 65–66.

Petitioner also addresses dependent claims 2–23. *Id.* at 69–75.

Claim 2, depending from claim 1 and adding “FR1, FR2, FR3, FR4 of the variable region of the heavy chain of the anti-epidermal growth factor receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 8 to 11,” is asserted to be obvious because Liu discloses these sequences are part of the BA03 antibody. Pet. 51, 69 (citing, *inter alia*, Ex. 1001, 18:1–36; Ex. 1008).

As for claim 3, which also depends from claim 1 and recites “FR1, FR2, FR3, FR4 of the variable region of the light chain of the anti-epidermal growth factor receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 15 to 18,” Petitioner asserts is disclosed by Liu because these sequences are part of the BA03 antibody. Pet. 52, 69–70 (citing, *inter alia*, Ex. 1001, 18:1–36; Ex. 1008).

Claim 4 also depends from claim 1 and adds “the heavy chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human IgG constant region, a human IgM constant region, a human IgA constant region, and a human IgD constant region,” which Petitioner asserts is disclosed by Liu and by Wei because the Liu BA03 antibody and Wei’s Y104D antibody have a human

IgG1 constant region. Pet. 52–53, 70 (citing Ex. 1005 ¶¶ 558–559; Ex. 1008 ¶ 37).

Claim 5 depends from claim 4 and recites “the IgG is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4,” which Petitioner asserts is taught by Wei’s and Liu’s antibodies that have a human IgG1 constant region. Pet. 53, 70 (citing Ex. 1005 ¶ 328; Ex. 1008 ¶ 37).

Claim 6 also depends from claim 4 and adds that “the constant region of the heavy chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 3,” which Petitioner asserts is taught by Liu because the BA03 antibody includes the sequence of amino acids. Pet. 53–54, 70 (citing, *inter alia*, Ex. 1001, 18:3–6; Ex. 1008).

Claim 7 depends from claim 1 and recites “the light chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human lambda constant region, and a human kappa constant region,” which Petitioner asserts is taught by Liu because the BA03 antibody has a human kappa light chain constant region, as does Wei’s antibody. Pet. 54, 70 (citing Ex. 1005 ¶¶ 558–559; Ex. 1008 ¶ 37).

Claim 8 depends from claim 7 and adds “the constant region of the light chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 4,” which Petitioner asserts is disclosed by Liu’s BA03 antibody, which includes the claimed amino acid sequence. Pet. 54–55, 70 (citing, *inter alia*, Ex. 1001, 18:3–6; Ex. 1008).

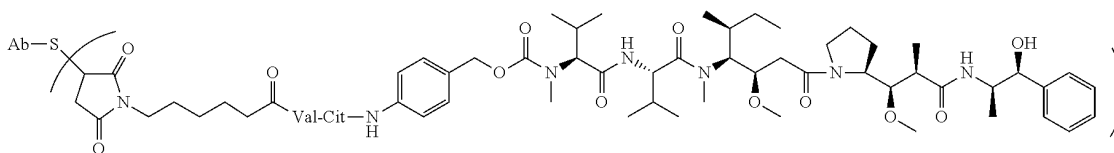
Claim 9 depends from claim 1 and recites that the ADC “has a structure as shown in Formula I, Ab-(L-D)_p Formula I wherein: Ab

represents the anti-epidermal growth factor receptor antibody; L represents a cleavable linker; D represents the cytotoxic agent; p represents 1-9,” which Petitioner asserts is taught by Leanna’s Antibody 1-vc-MMAE ADC having a DAR of 3.85. Pet. 71 (citing Ex. 1006, 34, 51, Fig. 1); *see also id.* at 55–56 (citing Wei (Ex. 1005) ¶ 1103 as teaching the same subject matter).

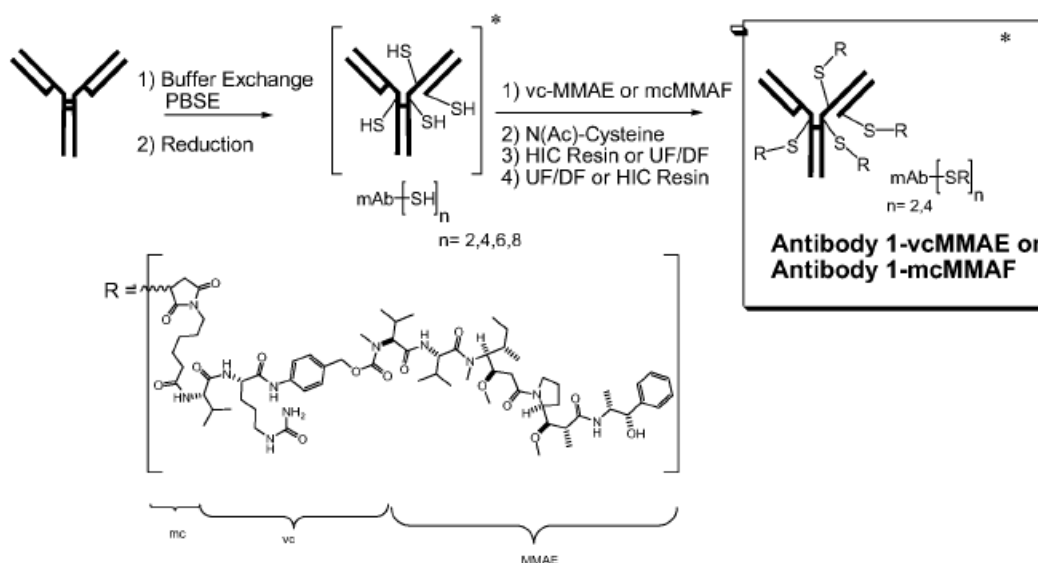
Claim 10 depends from claim 9 and adds that “the cytotoxic agent is selected from the group consisting of chemotherapeutic agents, . . . ,” and, claim 11 depends from claim 10 and further adds that “the cytotoxic agent is selected from the group consisting of Monomethyl auristatin E (MMAE), . . . ,” which Petitioner asserts is taught by Leanna’s ADC because the MMAE payload is a cytotoxic chemotherapeutic agent. Pet. 71 (citing Ex. 1006, 30–31); *see also id.* at 56–57 (citing Ex. 1005 ¶ 434).

Claim 12 depends from claim 9 and adds that “the linker is selected from the group consisting of valine-citrulline (val-cit), . . . and 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB),” which Petitioner asserts is taught by Leanna’s ADC because it contains a val-cit cleavable linker. Pet. 71 (citing Ex. 1006, 34, 51, Fig. 1); *see also id.* at 57 (citing Ex. 1005 ¶ 1103).

Claim 13 also depends from claim 9 and it recites that the ADC “is:



wherein Ab represents the anti-epidermal growth factor receptor antibody, p is 1-8,” which Petitioner asserts is taught by Leanna in disclosing an ADC including a linker and payload according to the following figure (portion):



and in disclosing an MC-vc-PAB-MMAE ADC with a DAR of 3.85, which teaches the recited p value. Pet. 71–72 (citing Ex. 1005, 51, Fig. 1 (shown in part above)); *see also id.* at 58–59 (citing Ex. 1005 ¶¶ 740, 742, 1102–1103, claim 40).

Claim 14 also depends from claim 9 and recites “the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB),” which Petitioner asserts is taught by Leanna teaching Antibody 1-MC-vc-PAB-MMAE. Pet. 73 (citing Ex. 1006, Fig. 1); *see also id.* at 59 (citing Ex. 1005 ¶ 1103).

Claim 15 depends from claim 1 and adds that the ADC composition, “optionally, further comprises at least one pharmaceutically acceptable carrier, diluent or excipient,” which, although only optional and therefore not limiting, Petitioner asserts is taught by Leanna’s disclosing ADCs in pharmaceutical formulations with a carrier or excipient. Pet. 73 (citing Ex. 1006, 37–38); *see also id.* at 59–60 (citing Ex. 1005 ¶¶ 238, 861–875).

Claim 16 also depends from claim 1 and recites “[a] method for treatment of a disease associated with epidermal growth factor receptor (EGFR), comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1,” and claim 17 depends from claim 16 and adds that “the disease associated with epidermal growth factor receptor (EGFR) is a tumor associated with overexpression of EGFR,” which Petitioner asserts is taught by Leanna’s anti-EGFR ADC, disclosed as used to treat tumors, cancer, pre-cancer, or other conditions relating to hyperproliferative cell growth. Pet. 73–74 (citing Ex. 1006, 15, 35–36); *see also id.* at 60–61 (citing Ex. 1005 ¶¶ 239, 442, 666).

Claim 18 depends from claim 1 and recites “[a] method for inhibiting tumor angiogenesis, delaying tumor progression, inhibiting tumor growth, or inhibiting tumor cell proliferation, comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1,” and claim 19 depends from claim 18 and adds that “the tumor is selected from . . . head and neck cancer, . . . breast cancer . . .,” which Petitioner asserts is taught by Leanna’s ADC used to treat hyperproliferative cell growth and tumor progression and also a variety of cancer types, e.g., neck and breast. Pet. 74 (citing Ex. 1006, 15, 34–36); *see also id.* at 61–63 (citing Ex. 1005 ¶¶ 441–458, 903, 1086–1127, claims 48, 58).

Claim 20 depends from claim 17 and adds “the tumor is a tumor with KRAS gene mutation,” and claim 22 depends from claim 19 and adds “the tumor is a tumor with KRAS gene mutation,” which Petitioner asserts is taught by Wei’s ADC, which was tested and shown to effectively treat breast

cancer with KRAS-mutated tumors. Pet. 63, 64–65, 74–75 (citing Ex. 1005 ¶¶ 1116–1127).

Claim 21 also depends from claim 17 and it recites “the tumor is a tumor with BRAF gene mutation,” and claim 23 depends from claim 19 and adds that “the tumor is a tumor with BRAF gene mutation,” which Petitioner asserts is taught by Wei’s ADC, which was tested and shown to effectively treat breast cancer with BRAF-mutated tumors. Pet. 63–65, 74–75 (citing Ex. 1005 ¶¶ 939, 942).

Reviewing Petitioner’s assertions and the evidence of record, we find that Petitioner has accounted for the teaching of each element of each challenged claim as taught by the Leanna-Wei-Liu combination. Petitioner has shown each of Leanna, Wei, and Liu to be prior art and has established a reason with rational underpinning why the person of ordinary skill in the art would have combined these references with a reasonable expectation of success.

We turn to Patent Owner’s arguments and Petitioner’s responses.

2. Patent Owner’s Positions (and Petitioner’s Responses Thereto)

Those of Patent Owner’s arguments that apply collectively to Grounds 1 and 2, which we have noted and address above (e.g., objective indicia of non-obviousness, avoiding BA03-vc-MMAE because of higher binding affinity causing worse therapeutic window, no expectation of success) will not be reviewed again. We analyzed these positions and are not persuaded thereby. *See supra* Sections II.E and II.F.

Regarding Ground 2, specifically, Patent Owner argues the ordinarily skilled artisan would not have been motivated to replace Leanna’s Antibody 1 with Liu’s BA03 antibody, as with Ground 1 and the Wei

antibody. Resp. 39–46 (citing, *inter alia*, Ex. 1006, 24; Ex. 1009, 3; Ex. 2015 ¶¶ 5, 15, 177, 244–245, Figs. 55A, 55B; Ex. 2026, 93:20–24, 115:23–25; Ex. 2027 ¶¶ 68, 70–75). Patent Owner argues that Antibody 1 of Leanna is selective to EGFR on tumor cells respective of normal cells and BA03 targets wild-type EGFR, which is expressed on both tumor and normal cells, making BA03 less attractive to treat cancer and carry a toxic payload. *Id.* Patent Owner also argues that the disadvantages of using BA03 (increased toxicity, worse therapeutic window—see discussion of Ground 1 above) are not addressed in the Petition and that, because Leanna’s ADC design diverged away from using the BA03 antibody, it teaches away therefrom. *Id.*

Petitioner responds that Leanna is not limited to only the Antibody 1 example, but is a broad disclosure of ADCs with an auristatin (e.g., MMAE); therefore, Patent Owner’s arguments that Antibody 1 is not substitutable or its specific attributes are required are mischaracterizations of the reference. Reply 18 (citing Ex. 1002 ¶¶ 74–83; Ex. 1006, 4, 9, 11, 18, 26, 83–89, claims 1–50; Ex. 1200 ¶ 66). Petitioner argues that the challenged claims do not require tumor-selectivity of the antibody, arguing such is essentially immaterial to the patentability challenges. *Id.* at 18–19. Petitioner argues that the advantages of BA03 are set out in Liu and Leanna is cited to show an ADC architecture, i.e., anti-EGFR antibody with the known vc-MMAE platform. *Id.* (citing Ex. 1002 ¶¶ 275–282). Petitioner argues that tumor selectivity could be achieved by means other than epitope selectivity, for example, cancer cells’ overexpression of EGFR was a well-recognized factor in ADC cancer therapy development, and understood to provide preferential therapy respective of normal cells. *Id.* at 19 (citing

Ex. 2026, 67:14–24, 129:11–131:8, 149:18–151:3). Petitioner also argues that Dr. Bournazos explained that BA03, as compared to Antibody 1, has certain advantages: Antibody 1’s EGFRvIII-specificity only applies to a minority of patients and patients lose this protein over time; the full-length anti-EGFR BA03 antibody avoids such problems. *Id.* at 20 (citing Ex. 1200 ¶¶ 66–72).

3. Analysis for Ground 2

We are persuaded by Petitioner that each challenged claim would have been obvious over the Leanna-Wei-Liu prior art combination. We again agree with Petitioner’s positions set forth in the Petition and adopt those positions as findings of fact herein. *See generally* Pet. 1–3, 6–32, 40–42, 65–75; *see also supra* Sections I.C, II.D, II.F, and II.G.1 (reviewing the ’370 patent, the asserted prior art, and Petitioner’s positions thereon). In summary, we agree that it would have been obvious to produce and use a cancer therapy by pairing the BA03 antibody with a vc-MMAE or Mc-vcPAB-MMAE platform because Liu identifies several advantages of BA03 and Leanna and Wei identify advantages of the platform and ADCs generally, which renders the claimed subject matter obvious. We discuss further below.

As with Ground 1, Patent Owner’s main argument over Ground 2 is that the person of ordinary skill in the art would not have replaced Leanna’s Antibody 1 with Liu’s BA03, for several reasons. As we noted above, we do not agree with Patent Owner that Petitioner’s case depends on such a substitution. *See supra* Section II.F.

We find that combining Liu’s BA03 antibody with Leanna’s and/or Wei’s ADC would have been desirable, predictable, and routine for the

ordinarily skilled artisan. As Petitioner initially pointed out in the Petition and confirmed in the Reply, the person of ordinary skill in the art would have been motivated to improve the FDA-approved cancer therapy cetuximab antibody, which would have led to Liu's humanized BA03 with lower immunogenicity, better binding affinity, and ligand blocking abilities (*see* Ex. 1008), and the ordinarily skilled artisan would have been motivated to improve on that naked antibody by developing an ADC with a cleavable linker (e.g., val-cit) and a cytotoxic payload (e.g., MMAE) to provide effective cancer therapy (*see* Ex. 1005; Ex. 1006). Pet. 40–42, 67–69; Reply 2–3, 7–9, 20. For similar reasons as set forth above concerning Ground 1, we agree with Petitioner that Liu, Leanna, and Wei would have been combined by the ordinarily skilled artisan with a reasonable expectation of success. Once combined, there is no real dispute here that the references teach or suggest the claim limitations.

As is the case with Wei, Leanna does not teach away from the invention or its combination with Liu. *See Mouttet*, 686 F.3d at 1334. Leanna's focus on Antibody 1 as preferred in its ADCs is not a discouragement of the use of an alternative, also advantageous, humanized cetuximab variant (Liu's BA03) in an ADC for cancer treatment. *Id.* And, again, even if, in some ways, the BA03-vc-MMAE ADC of the prior art combination could be considered to be less advantageous than Leanna's or Wei's ADCs, it would still be a *suitable* option, and no more is needed for an obviousness determination. *Intel*, 61 F.4th at 1380.

For these reasons we are not persuaded by any of Patent Owner's arguments that Petitioner's case under Ground 2 is deficient. In summary, having considered the parties' positions and the record, we find that

Petitioner has shown by a preponderance of the evidence that claims 1–23 would have been obvious over Leanna, Wei, and Liu and that the challenged claims are, therefore, unpatentable under 35 U.S.C. § 103.

III. CONCLUSION²¹

On the record before us, Petitioner demonstrates by a preponderance of the evidence that claims 1–23 of the '370 patent would have been obvious over the asserted prior art, under each asserted ground. Accordingly, all challenged claims of the '370 patent are unpatentable under 35 U.S.C. § 103.

Our final decision is summarized as follows:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–23	103	Wei, Liu	1–23	
1–23	103	Leanna, Wei, Liu	1–23	
Overall Outcome			1–23	

²¹ Should Patent Owner wish to pursue amendment of the Challenged Claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding, 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

ORDER

Accordingly, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, per *inter partes* review of claims 1–23 of U.S. Patent 10,792,370 B2, the challenged claims are unpatentable; and

FURTHER ORDERED that, as this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

FOR PETITIONER:

Joe Chen
Ryan Miller
Howard Suh (admitted *pro hac vice*)
FOX ROTHSCHILD LLP
joechen@foxrothschild.com
rmiller@foxrothschild.com
hsuh@foxrothschild.com

FOR PATENT OWNER:

Christopher Ponder
Alex Nie
Fangzhou Qiu
SHEPPARD, MULLIN, RICHTER & HAMPTON LLP
cponder@sheppardmullin.com
anie@sheppardmullin.com
fqiu@sheppardmullin.com