

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

SHANGHAI MIRACOGEN INC.,

Patent Owner.

Case No. IPR2025-00685

U.S. Patent No. 10,792,370

PATENT OWNER'S RESPONSE

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PATENT OWNER’S UPDATED EXHIBIT LIST

Exhibit No.	Description
2001	International Nonproprietary Names for Pharmaceutical Substances, WHO Drug Information, Vol. 38, No. 2, 2024
2002	Fei Han et al., Becotatug vedotin vs. chemotherapy in pre-heavily treated advanced nasopharyngeal carcinoma: A randomized, controlled, multicenter, open-label study
2003	Lepu Biopharma Co., Ltd., Voluntary Announcement, Breakthrough Therapy Designation Granted by the FDA to MRG003 for the Treatment of R/M NPC
2004	U.S. Food & Drug Administration, Fast Track
2005	U.S. Food & Drug Administration, Breakthrough Therapy
2006	EGFR expression in normal human tissues (HPA RNA-seq normal tissues) - https://www.ncbi.nlm.nih.gov/gene/1956
2007	CD30 expression in normal human tissues (HPA RNA-seq normal tissues) - https://www.ncbi.nlm.nih.gov/gene/943
2008	European Patent Application No. EP4434549A1
2009	CSPC Pharmaceutical Group Limited Voluntary Announcement, May 19, 2025
2010	Lu S. et al., “Abstract CT008: First-in-human study of SYS6010, a novel EGFR targeting antibody drug conjugate (ADC) for patients with advanced solid tumors,” <i>Cancer Res</i> (2025) 85 (8_Supplement_2): CT008
2011	International Publication No. WO2012/100346A1
2012	Huang L. et al., “Abstract 1217: Preclinical evaluation of a next-generation, EGFR targeting ADC that promotes regression in KRAS or BRAF mutant tumors,” <i>Cancer Res.</i> (2016) 76 (14_Supplement): 1217

2013	Phillips AC et al., “Characterization of ABBV-221, a Tumor-Selective EGFR-Targeting Antibody Drug Conjugate,” <i>Mol Cancer Ther</i> ; 17(4) April 2018 795-805
2014	Carneiro B. et al., “Phase I study of anti-epidermal growth factor receptor antibody-drug conjugate serclutamab talirine: Safety, pharmacokinetics, and antitumor activity in advanced glioblastoma,” <i>Neuro-Oncology Advances</i> 5(1), 1–12, 2022
2015	U.S. Patent Application Publication No. 2011/0076232 (“Old-232”)
2016	AbbVie, A Study Evaluating Safety and Pharmacokinetics of ABB-221 in Subjects with Advanced Solid Tumor Types Likely to Exhibit Elevated Levels of Epidermal Growth Factor Receptor. ClinicalTrials.gov Identifier NCT02365662 (March 30, 2018)
2017	Lepu Biopharma Co. Ltd. 2024 Annual Report
2018	Written Opinion of the International Searching Authority for WO2023/088382
2019	Conference Transcript for Proceedings on December 2, 2025
2020	Bournazos S et al., “Signaling by Antibodies: Recent Progress,” <i>Annu Rev Immunol</i> . 2017 Apr 26; 35:285-311. doi: 10.1146/annurev-immunol-051116-052433. PMID: 28446061; PMCID: PMC5613280
2021	Lepu Biopharma Co. Ltd. 2024 Inside Information Announcement
2022	Crombet T., et al., “Use of the Humanized Anti-Epidermal Growth Factor Receptor Monoclonal Antibody h-R3 in Combination with Radiotherapy in the Treatment of Locally Advanced Head and Neck Cancer Patients,” <i>Journal of Clinical Oncology</i> 22(9):1646-1654, 2004
2023	Garrido G. et al., “Bivalent binding by intermediate affinity of nimotuzumab, A contribution to explain antibody clinical profile,” <i>Cancer Biology & Therapy</i> 11:4, 373-382; 2011 (Garrido)
2024	Abdullah S. et al., “Dermatologic Toxicities from Monoclonal Antibodies and Tyrosine Kinase Inhibitors against EGFR: Pathophysiology and Management,” <i>Chemother Res Pract</i> . 2012 Sep 11; 2012:351210

2025	Burke P. et al., “Design, Synthesis, and Biological Evaluation of Antibody–Drug Conjugates Comprised of Potent Camptothecin Analogues,” <i>Bioconjug Chem</i> , 2009 Jun;20(6):1242-50
2026	Deposition Transcript of Dr. Stylianos Bournazos
2027	Declaration of Dr. Djordje Atanackovic
2028	ClinicalTrials.gov webpage for clinical trial NCT01741727 (downloaded from https://clinicaltrials.gov/study/NCT01741727 on January 19, 2026)
2029	Phillips A.C., et al., “ABT-414, an Antibody–Drug Conjugate Targeting a Tumor-Selective EGFR Epitope,” <i>Mol Cancer Ther</i> (2016) 15 (4): 661–669
2030	Yu J. et al., “Antibody-Drug Conjugates Targeting the Human Epidermal Growth Factor Receptor Family in Cancers,” <i>Front. Mol. Biosci.</i> , 27 February 2022;9:847835. doi: 10.3389/fmolb.2022.847835
2031	ClinicalTrials.gov webpage for clinical trial NCT06927986 (downloaded from https://clinicaltrials.gov/study/NCT06927986 on January 19, 2026)
2032	Lepu Biopharma Co., Ltd., Stock Code: 2157, “Global Offering” dated February 10, 2022
2033	CSPC Pharmaceutical Group Limited, 2020 Annual Report

I. INTRODUCTION

The '370 patent claims an antibody-drug conjugate (ADC) or a salt thereof that comprises an anti-epidermal growth factor receptor (anti-EGFR) antibody linked to a cytotoxic agent (payload) via a cleavable linker (claim 1). The antibody is defined with CDR (complementarity-determining region) sequences of an anti-EGFR antibody BA03. In claim 13, the structures of the cytotoxic payload and the cleavable linker are further specified. While the BA03 antibody was known in the art, the choice to use the BA03 antibody in an ADC was non-obvious. This is because BA03 lacks properties, such as tumor selectivity and low binding affinity, that were commonly believed to be required according to conventional ADC design strategies. Yet, Patent Owner's choice to use BA03 led to the success of its MRG003 ADC (also known generically as "becotatug vedotin"), the first ever regulatory approved anti-EGFR ADC worldwide after over 20 years since the first approval of an anti-EGFR antibody (i.e., cetuximab) and over 10 years of failed attempts by various companies in developing anti-EGFR ADCs.

Despite BA03 being known in the art, Petitioner could not find a single reference teaching the use of BA03 in an ADC. Instead, Petitioner argues that the claims should be found unpatentable based on two grounds of obviousness. For each ground, Petitioner argues that a POSA would have been motivated to replace the antibody used in the primary reference's ADC (i.e., Wei's Y104D/huY104D

antibody, Leanna's Antibody 1) with the BA03 antibody taught by the secondary reference Liu to arrive at the claimed invention.

Petitioner's obviousness arguments are entirely based on hindsight bias, which is reflected in Petitioner's inability to establish any reason that would have motivated a POSA to make the proposed replacements or a reasonable expectation of success in doing so. The Petition relies on Dr. Bournazos's testimony. Yet, Dr. Bournazos admitted that he had no idea how properties of the BA03 antibody differ from the original antibodies (e.g., Y104D/huY104D, Antibody 1) in the primary references' ADCs. Neither Petitioner nor Dr. Bournazos was able to identify any benefit of BA03 as compared to Wei's Y104D/huY104D or Leanna's Antibody 1 or any benefit that would have been achieved by performing the replacement. Nor does the Petition address whether a POSA would have had a reasonable expectation of success with respect to the BA03-vc-MMAE ADC proposed under both grounds.

Furthermore, the primary references Wei and Leanna both teach away from the claimed invention and discourage a POSA from replacing their antibodies with BA03. As noted by Dr. Atanackovic, who has extensive knowledge and experience in ADC development and the use of EGFR inhibitors in treatments, a primary challenge in ADC development was to have an acceptable therapeutic window. Ex-2027, ¶12. Dr. Atanackovic further explains that EGFR is uniquely challenging as

a target because it has relatively high expression in skin tissues, giving rise to safety concerns for EGFR-targeting agents and making it difficult to develop an anti-EGFR ADC that has an acceptable therapeutic window. Ex-2027, ¶13.

Noting safety issues associated with cetuximab, which binds to EGFR in both tumor and normal cells, Wei focuses on identifying tumor-targeting pH-selective derivatives of cetuximab. Wei's pH-selective antibodies are preferentially activated in the acidic pH of the tumor microenvironment and, therefore, have improved ability, compared to cetuximab, in distinguishing tumor cells from normal cells. When incorporated in ADCs, Wei's antibodies provide broader therapeutic windows.

Likewise, Leanna addresses the problem of toxicity arising from using anti-EGFR antibodies that bind to both tumor and normal cells. Leanna's antibody preferentially binds an EGFR epitope that is primarily expressed on tumor cells with minimum or no expression on normal cells. Leanna's antibody, therefore, also has improved ability, compared to cetuximab, in distinguishing tumor cells from normal cells and results in broader therapeutic windows when incorporated in an ADC.

Unlike the antibodies of Wei and Leanna, however, the BA03 antibody of Liu does not have pH selectivity or binding specificity to a tumor-specific EGFR epitope. A POSA would have expected an ADC incorporating the BA03 antibody

to have a narrower therapeutic window than those of Wei and Leanna. Because the BA03 antibody does not have the ability to distinguish tumor and normal cells, it is the exact type of antibody that Wei and Leanna both caution against using for safety concerns. Wei and Leanna would have discouraged a POSA from replacing their antibodies, which have improved ability to selectively target tumor cells, with the BA03 antibody that lacks such an ability.

Moreover, Liu teaches that the BA03 antibody has increased binding affinity to the EGFR antigen as compared to cetuximab. According to conventional knowledge, a POSA would have expected an anti-EGFR antibody having higher binding affinity than cetuximab to have a worse therapeutic window than cetuximab. Therefore, not only would the POSA have expected Petitioner's proposed ADC to be inferior to those in Wei and Leanna, but also that its therapeutic window would be unduly narrow because the cetuximab-based ADC was known to have an unduly narrow therapeutic window. A POSA would have expected the proposed ADC to fail and had no motivation to create it.

II. BACKGROUND

A. Antibody-Drug Conjugates

An antibody-drug conjugate (“ADC”) typically includes three main components: an antibody, one or more cytotoxic payloads, and a linker connecting each of the payloads to the antibody. Ex-2027, ¶3.

Each of the components of an ADC plays an important role. The antibody is responsible for targeting the ADC to a target cell, e.g., a tumor cell, that expresses the corresponding antigen. Once the antibody binds the antigen on the target cell, it is internalized by the target cell, thereby delivering the conjugated cytotoxic payload into the target cell. The cytotoxic payload is responsible for killing the target cell with its cytotoxic activity. Ex-2027, ¶4.

The linker is the means for attaching the cytotoxic payload to the targeting antibody. Moreover, the linker impacts how the payload is released to exert its cytotoxic activity in a target cell, and how the payload stays attached to the antibody prior to such release to prevent undesired toxicity prior to reaching the target cell, e.g., at normal tissues. Ex-2027, ¶5.

Linkers can be generally categorized as cleavable linkers and non-cleavable linkers. The former is designed to be cleaved at the target environment, e.g., tumor microenvironment, or within the target cell. A payload of an ADC with a non-cleavable linker, by contrast, only becomes activated when the ADC is destructed in the lysosomes within the target cell. Ex-1009, 6-7; Ex-2027, ¶6.

Cytotoxic payloads are typically anticancer agents on their own for ADCs intended for cancer treatments. There were multiple candidate cytotoxic payloads that can be used in ADCs, including monomethyl auristatin E (MMAE),

monomethyl auristatin F (MMAF), DM-1, DM-4 (Ex-1009, 14), and camptothecin analogues (Ex-2025, 1). Ex-2027, ¶7.

B. ADC Development Strategies

1. A primary challenge in ADC development is to have an acceptable therapeutic window.

A suitable payload needs to have acceptable safety and stability so that it stays inactive while attached to the antibody in systemic circulation. It also needs to have acceptable potency to kill the target cell once released in the target cell. There were multiple known payloads, such as MMAE, MMAF, DM-1, DM-4, and camptothecin analogues. Ex-2027, ¶8.

These payloads, belonging to the classes of tubulin inhibitors and topoisomerase inhibitors, were known to be highly potent. Accordingly, a primary challenge of designing a successful ADC was to identify one that has manageable toxicity without compromising on efficacy. In other words, a successful ADC needs to have an acceptable “**therapeutic window.**” The term “therapeutic window,” as well as the related terms “therapeutic index” and “safety window,” generally refer to dose ranges of a drug between boundaries of efficacy and toxicity. A drug candidate with a narrow therapeutic window is not as desirable as one with a wide therapeutic window, as the former is more likely to cause toxicities at close-to-efficacious doses. Ex-2027, ¶9.

In contrast to off-target toxicity exhibited by some drugs, where the toxicity is caused by a biological mechanism different from the mechanism by which the drugs are efficacious, the toxicity of ADCs is mainly on-target. That is, when the payload is released in a tumor cell expressing the antigen, it kills the tumor cell; if a non-tumor cell also expresses the antigen, it can be bound by the antibody and killed by the payload of the ADC as well, leading to toxicity in the normal tissue. Ex-2027, ¶10.

Therefore, the therapeutic window of an ADC, as readily recognized in conventional knowledge, primarily depends on whether the ADC can reduce binding to or payload release in normal tissues, while at the same time maintaining binding to and payload release in tumor tissues. Ex-2027, ¶11.

2. The EGFR target brings about unique challenges for therapeutic windows.

The epidermal growth factor receptor (EGFR) “is an attractive target” for anti-cancer therapies “because of the antigen’s expression by many tumors and its rapid internalization.” Ex-1009, 2.¹ Unlike many other tumor-associated antigens, however, EGFR also has relatively high expression in other tissues such as the skin, and thus EGFR-targeting agents are associated with “skin toxicities that

¹ The citations to Exhibit 1009 use stamped page numbers.

either demand dose reduction or in some cases are so severe as to warrant discontinuation of treatment.” *Id.*; Ex-2027, ¶12.

EGFR’s relatively high expression in normal tissues differentiates it from other antigens, including those that have been successfully targeted by ADCs. One such other antigen is CD30, which Petitioner mentions to be targeted by Brentuximab vedotin (Adcetris[®]), one of the first approved ADCs that included a cleavable linker. Pet., 50. While both EGFR and CD30 are highly expressed in tumor cells, CD30’s expression levels in normal tissues are minimal and considerably lower than that of EGFR. EGFR’s and CD30’s expression levels among 27 normal tissues, measured as RPKM (Reads Per Kilobase per Million reads) with RNA sequencing technology, are available from the NCBI (National Center for Biotechnology Information) database. As shown in the first (Ex-2006, 000002) and second (Ex-2007, 000002) figures below (FIG. 1), the median expression levels of EGFR and CD30 among these tissues are about 5.1 RPKM and 0.17 RPKM, respectively, a 30-fold difference. Ex-2027, ¶13, ¶76.

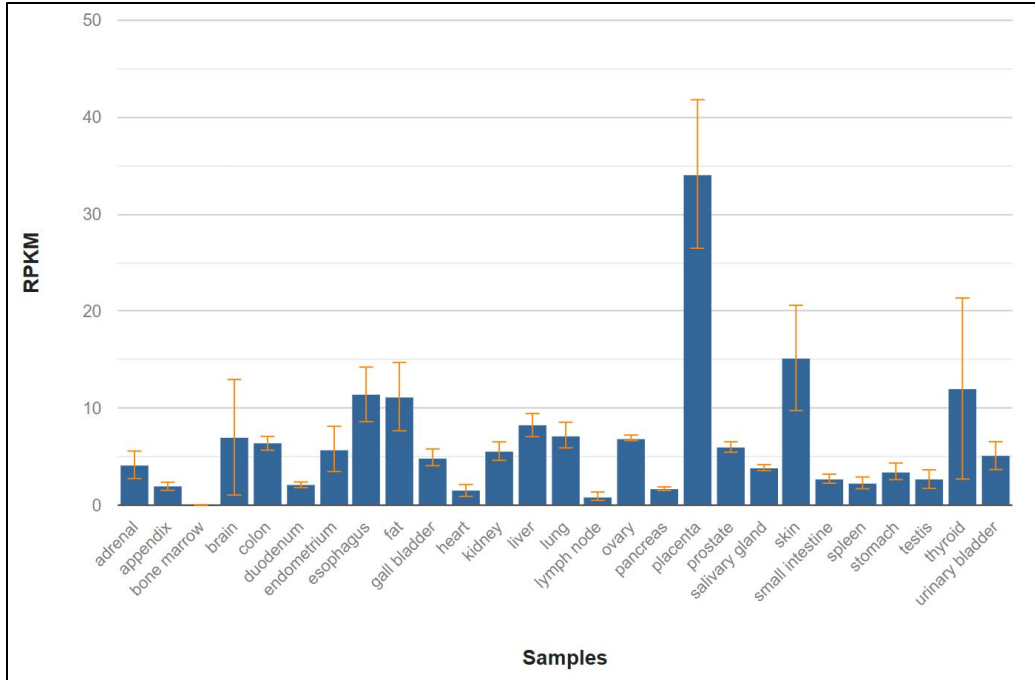


FIG. 1. EGFR expression levels in 27 normal tissues. Ex-2006, 000002.

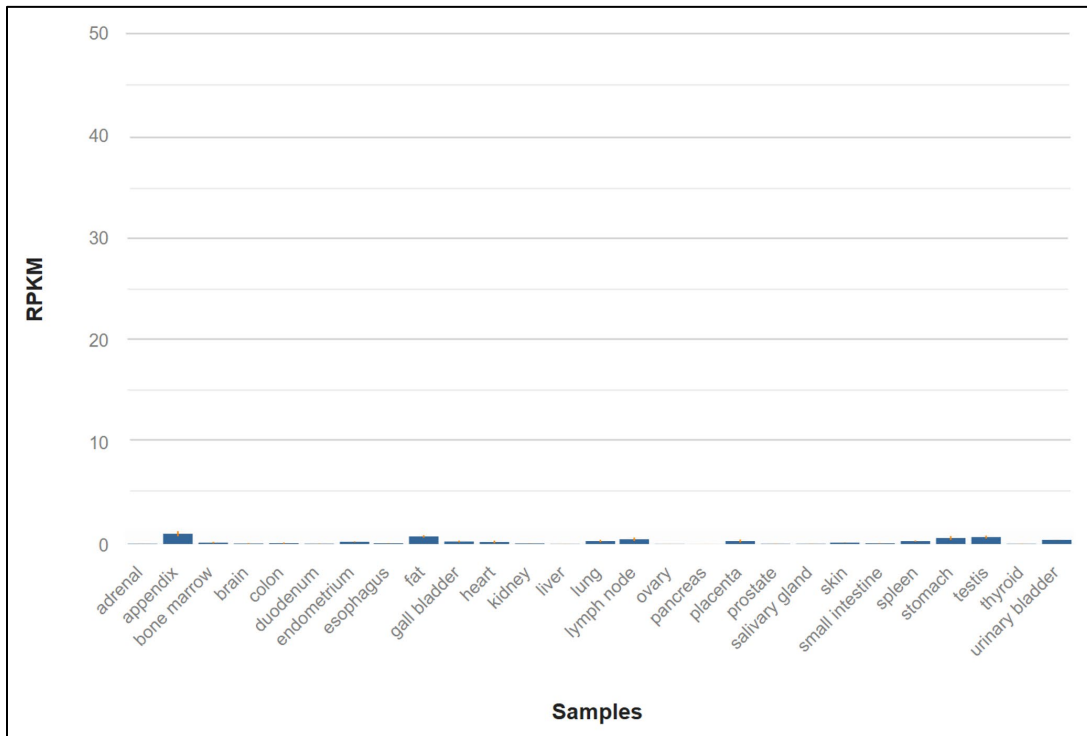


FIG. 2. CD30 expression levels in 27 normal tissues. Ex-2007, 000002 (modified to the same y-axis scale as Fig. 1).

EGFR's relatively high expression in normal tissues creates unique challenges faced by therapies targeting EGFR with respect to toxicity. Ex-2027, ¶13. Such challenges are emphatically acknowledged in Wei.

[A]nti-EGFR antibodies are associated with significant and characteristic adverse events including skin toxicities and digestive disturbances ..., that often lead to interruption of dosing and discontinuation of treatment. For example, EGFR, is highly expressed in pre-keratinocytes and basal cells of the skin. Blockade of EGFR signaling in the skin precursors by anti-EGFR antibodies leads to skin precursor growth inhibition, apoptosis and inflammation. This can result in skin toxicity, such as a rash and other skin lesions. In particular, existing anti-EGFR antibodies (e.g., cetuximab, panitumumab) exhibit high toxicity with up to 80% attributed to skin-related toxicity, including 25% that is Grade 3-4 (Cunningham et al. (2004) *NEJM*, 351:337). In particular, skin lesions can include rash with itchy erythematous follicular papules that can evolve into pustules. Ex-1005, ¶0477 (emphasis added).

An ADC that includes an anti-EGFR antibody, therefore, is significantly more likely to cause toxicity than an ADC that targets a different antigen, such as CD30. Ex-2027, ¶13.

This is exactly what Tikhomirov observed with the “Cetux 2C9-MMAE” ADC, which included a cytotoxic payload MMAE conjugated to cetuximab (Cetux 2C9) through a valine-citrulline (VC) linker. In Example 4, Tikhomirov showed

that Cetux 2C9-MMAE potentiated toxicity against normal cells along with its anti-tumor activities. Ex-1009, 10-11. More than 20 years since cetuximab was approved as an anti-cancer drug, no anti-EGFR ADC was approved anywhere in the world as of the filing date of the Petition. Ex-2027, ¶13.

3. Strategies for developing anti-EGFR ADCs of improved therapeutic window.

In view of the general challenges of ADC development and the unique properties of the EGFR target, Dr. Atanackovic summarizes the main strategies understood by the POSA and disclosed in various prior art references. Ex-2027, ¶¶14-29.

The strategies generally concern the selection of linkers and the selection of antibodies. Concerning linkers, Tikhomirov suggests that non-cleavable linkers should be used for “full antagonist” anti-EGFR antibodies such as cetuximab and panitumumab. According to Tikhomirov, a full antagonist antibody is one “that blocks completely or nearly so the transmission of a signal that is stimulated, in the normal course, by the EGF ligand through wtEGFR [(wild type human EGFR)] to the wtEGFR-coupled tyrosine kinase.” Ex-1009, 11. Moreover, “EGFR antibodies that are full antagonists are particularly EGFR antibodies that bind directly to EGFR domain III.” *Id.* Therefore, antibodies derived from a full antagonist antibody like cetuximab while retaining its binding specificity should also be full antagonist antibodies. By contrast, a “partial antagonist” is one “that allows

transmission of some EGF-mediated signal.” *Id.* at 12. Given the toxicity issue observed with Cetux 2C9-MMAE, an ADC with a full antagonist antibody and a cleavable linker, Tikhomirov suggests that an ADC that incorporates a full antagonist antibody should use a non-cleavable linker. *Id.* at 31; Ex-2027, ¶15.

With respect to the choice of antibodies, Dr. Atanackovic provides a summary of four conventional strategies outlined in Tikhomirov. Strategy one entails the use of anti-EGFR antibodies that “target a mutated but naturally occurring version of EGFR, known as EGFRvIII, or on conformational forms of the EGFR, both of which predominate on tumour cells and not on skin cells.” Ex-1009, 3. An example antibody of this nature is “MAb806.” *Id.* A humanized version of MAb806 was the antibody of focus in Leanna, “Antibody 1.” Ex-2027, ¶16.

Strategy two entails the use of anti-EGFR antibodies “that are preferentially activated in the tumor microenvironment.” Ex-1009, 3. This category of antibodies include those that are preferentially activated in the tumor microenvironment’s acidic pH conditions, i.e., pH-selective antibodies. Ex-2027, ¶17.

Strategy three entails the use of anti-EGFR antibodies “with partial antagonist activity against EGFR [which have] reduced activity against keratinocytes.” Ex-1009, 3; Ex-2027, ¶18.

Strategy four entails the use of anti-EGFR “antibodies with medium affinity that preferentially accumulate in the tumor and not normal tissues.” Ex-1009, 3-4; Ex-2027, ¶19. To this end, Tikhomirov referred to examples in PCT Application WO 2012/100346 (“Tikhomirov-346,” Ex-2011), which will be discussed in further details below. *See infra* §II.B.4.

These strategies are summarized in the table below:

Strategies for addressing anti-EGFR ADCs’ safety concerns

	Strategy
Linker	
	A. Use non-cleavable linker instead of cleavable linker for full-antagonist antibodies like cetuximab and derivatives
Antibody	
	B1. Use antibodies that target EGFR epitope found in tumors only
	B2. Use antibodies that are preferentially activated in tumor microenvironment
	B3. Use antibodies with reduced antagonist activity in normal cells
	B4. Use antibodies with reduced affinity

Ex-2027, ¶20.

Strategies B1 and B2 aim at preferentially increasing the binding or activity of the ADC in tumor tissues or preferentially decreasing the binding or activity of

the ADC in normal tissues. Such strategies, therefore, can increase the therapeutic window of the ADC. Strategy B3 aims to preferentially reducing the antibody's antagonist activity in normal cells to reduce toxicity to those cells. This strategy, therefore, can also increase the therapeutic window of the ADC. Ex-2027, ¶21.

4. Anti-EGFR antibodies having reduced affinity to EGFR relative to cetuximab have increased ability to distinguish tumor cells from normal cells.

Under strategy B4, when the affinity of an antibody is reduced, the reduction can impact how the antibody acts on both the tumor and normal tissues. But it was well established that such reduction has a significantly more pronounced effect on cells having lower expression of the antigen (e.g., normal cells) than on cells having higher expression of the antibody (e.g., tumor cells). In other words, relative to a high-affinity anti-EGFR antibody such as cetuximab, an anti-EGFR antibody having lower affinity would have been expected to have a wider therapeutic window. Ex-2027, ¶22.

Dr. Atanackovic references Crombet to explain the impact of the affinity of an anti-EGFR antibody on its ability to distinguish normal cells from tumor cells. Crombet observed that an anti-EGFR antibody, h-R3, “elicited similar response in advanced SCCHN compared with what is published for other anti-EGFR antibodies, but at lower doses and without skin toxicity.” Ex-2022, 000005.

Crombet notes that h-R3 “has less affinity ($K_D = 10^{-9}$ M) than IMC-C225 ($K_D = 10^{-$

¹⁰ M) for the EGFR.” *Id.* IMC-C225 is cetuximab. Based on such experimental data and mathematical modeling, Crombet concluded that “intermediate affinity mAbs (10^{-8} and 10^{-9} M) will have the maximum effect (high tumor uptake and low uptake in normal tissues), while lower affinity antibodies would have little tumor uptake and higher affinity antibodies would induce a rapid uptake by normal tissues reducing again the therapeutic index (Fig 3).” *Id.*; Ex-2027, ¶23.

According to Crombet, therefore, anti-EGFR antibodies having an affinity that is at least 10-fold (between 10-fold and 100-fold) lower than cetuximab would have the maximal capability in distinguishing normal cells from tumor cells. This is illustrated in Fig. 3, which is partially reproduced below, with annotations added. Ex-2027, ¶24.

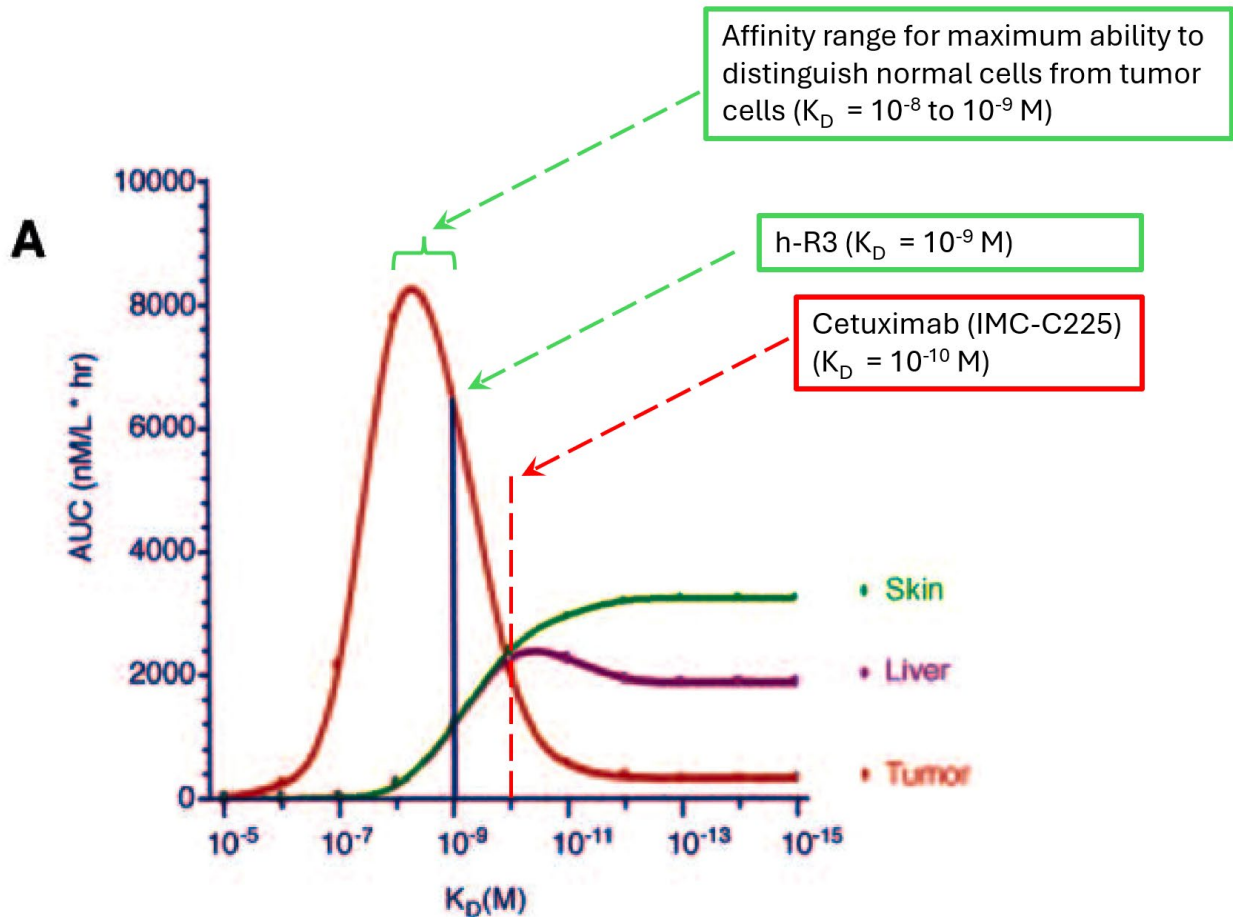


FIG. 3. Figure 3A of Crombet, with annotations added (dotted lines and texts in rectangular boxes). Ex-2022, 000007.

As can be easily seen from the figure above, cetuximab's binding affinity to EGFR is too high, and has poor ability in distinguishing normal cells from tumor cells. An ideal antibody should have a binding affinity that is about 10 times lower than cetuximab (with a K_D in the range of 10^{-8} to 10^{-9} M). It can also be readily predicted that anti-EGFR antibodies with a higher binding affinity than cetuximab

(i.e., with a $K_D < 10^{-10}$ M) would have poorer or even no ability in selectively binding to tumor cells without binding to normal cells. Ex-2027, ¶25.

Crombet's model had been validated by multiple examples since its publication in 2004. For example, in International Publication No. WO2012/100346A1 ("Tikhomirov-346," Ex-2011), example antibodies had "a binding affinity for EGFR that is about 10-fold or more weaker than the EGFR binding affinity of cetuximab." Ex-2011, 5:22-30. Such reduction of the affinity "substantially eliminates binding to [normal] cells presenting EGFR at a normal EGFR density, and retains effective binding at targeted disease cells that present EGFR at a greater density relative to normal cell EGFR density." *Id.*, 3:12-16; Ex-2027, ¶26.

Another anti-EGFR antibody that has a binding affinity that is 10-fold or more weaker than cetuximab is nimotuzumab. Nimotuzumab has been approved in multiple countries for cancer treatment and it "has a ten-fold lower affinity for the extracellular domain of EGFR than the Fab of cetuximab." Ex-2023, 000002 ("Garrido"). It was not surprising, therefore, nimotuzumab was "reported to have lesser or no skin toxicity" (Ex-2024, 000003) and "has demonstrated a unique safety clinical profile, where antitumor activity was observed with a very low toxicity profile" (Ex-2023, 000002); Ex-2027, ¶27.

Nimotuzumab provided an explanation on why the reduced affinity of nimotuzumab improved its ability to distinguish normal cells from tumor cells. With such low affinity, its stable binding to EGFR requires bivalent (i.e., both arms of the antibody are bound to EGFR) interaction. Such low-affinity bivalent binding, Garrido suggested, “is transient” on cells on which “EGFR density is low, such as on normal tissues.” *Id.*, 000007. By contrast, “cetuximab continues to interact strongly with [EGFR]” on such normal tissues. *Id.* This explanation is illustrated in Figure 6 of Garrido, which is reproduced below. Ex-2027, ¶28.

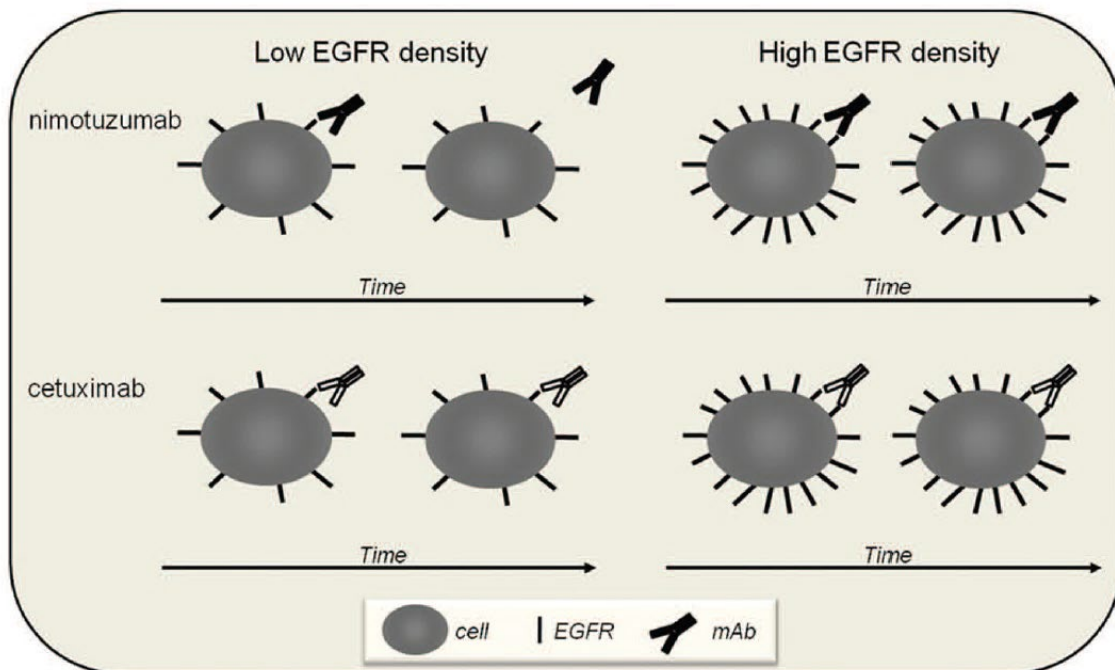


FIG. 4. Figure 6 of Garrido. Ex-2023, 000008.

In other words, Garrido reasoned that anti-EGFR antibodies having at least 10-fold lower affinity than cetuximab require a minimum EGFR density on normal cells to keep stable binding. As normal cells do not have such a minimum density,

they are spared from binding by these low-affinity antibodies and thus are free from toxicity. Ex-2027, ¶29.

5. Each of Wei, Leanna, Tikhomirov-346, and Tikhomirov exemplifies a well-established ADC development strategy.

The aforementioned ADC development strategies were not only well recognized in conventional knowledge; they have also been implemented and substantiated in various prior art references, including those cited by the USPTO during prosecution and Petitioner.

a. Strategy B2 as implemented in Wei

Strategy B2 entails the use of antibodies that are preferentially activated in tumor microenvironment. The tumor microenvironment is generally more acidic than non-tumor tissues. Therefore, if an antibody's activity depends on an acidic pH, the antibody is more likely inactive/safe in normal tissues (neutral pH) at a dose that is efficacious in tumors.

Wei is directed to such an approach. In the Background section, Wei points to the toxicity concerns associated with existing anti-EGFR antibodies (such as cetuximab) and states that its objective was to identify anti-EGFR antibodies, for use in ADCs, with tumor-specificity. Ex-1005, ¶9. Ex-2027, ¶32.

Pursuing that objective, Wei found that mutations at Y104 of cetuximab rendered the antibody activity dependent upon pH. These Y104 mutants, Wei describes, “exhibit[ed] greater binding activity under acidic pH conditions and/or

elevated lactate levels (e.g., present in a tumor microenvironment) than under neutral pH conditions/normal lactate levels” (Ex-1005, ¶476) and thus are tumor-specific. Humanized versions of these mutants (Y104D and Y104E) were also prepared and tested, including huY104D and huY104E. Ex-1005, ¶1116. Ex-2027, ¶32.

The Y104D and Y104E mutants of cetuximab disclosed in Wei, as well as their humanized counterparts, “exhibit[ed] greater activity (binding affinity) under conditions of acidic pH, such as is present in a tumor microenvironment, than under conditions of neutral pH, such as exists in non-tumor tissue, such as that which exists in the basal layer of the skin.” Ex-1005, ¶10. With such tumor specificity, Wei’s ADC incorporating the Y104D mutant exhibited a therapeutic index that was about 10-fold wider than cetuximab. Ex-2027, ¶32.

b. Strategy B1 as implemented in Leanna

Strategy B1 entails the use of antibodies that target EGFR epitope found in tumors only. The antibody of Leanna, “Antibody 1,” is such an antibody. Antibody 1 “recognizes de2-7 EGFR and amplified EGFR, but does not recognize normal, wild-type EGFR.” Ex-1006, 24:19-24. Since only “the tumor expresses the truncated version of the EGFR de2-7” (*id.*, 12:25-13:12), Antibody 1 does not bind normal cells, and thus avoids the safety concerns associated with cetuximab. The antibody of Leanna, therefore, is consistent with Strategy B1. Ex-2027, ¶33.


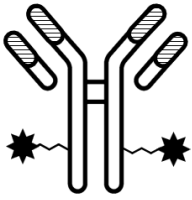
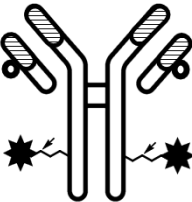

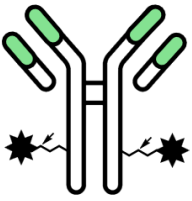
c. Strategy B4 as implemented in Tikhomirov-346

Strategy B4 entails the use of antibodies with reduced affinity, e.g., as compared to cetuximab. To this end, the antibodies of Tikhomirov-346 has “a binding affinity for EGFR that is about 10-fold or more weaker than the EGFR binding affinity of cetuximab.” Ex-2011, 5:22-30. Such reduction of the affinity “substantially eliminates binding to [normal] cells presenting EGFR at a normal EGFR density, and retains effective binding at targeted disease cells that present EGFR at a greater density relative to normal cell EGFR density.” *Id.*, 3:12-16; Ex-2027, ¶34.

d. Strategy A as implemented in Tikhomirov

Strategy A was proposed by Tikhomirov based on its comparison of anti-EGFR ADCs using cetuximab as the antibody, with cleavable and non-cleavable linkers. As noted in Tikhomirov, “[w]ith non-cleavable linkers, release of the cytotoxic payload occurs by intracellular destruction of the drug conjugate by lysosomes.” Ex-1009, 6-7. By contrast, a cleavable linker can release the cytotoxic payload outside tumor cells. For a strongly antagonistic anti-EGFR antibody like cetuximab, Tikhomirov states that “a safe anti-EGFR ADC should incorporate ... a non-cleavable linker.” Ex-1009, 31; Ex-2027, ¶31.

The aforementioned implementations of known ADC design strategies in the prior art references are summarized in the table below. Ex-2027, ¶35.

Benchmark ADC	Strategy	Resulting ADC	Example Antibodies/ADC
 (cetuximab-vc-MMAE)	A – non-cleavable linker for full antagonist antibody		- Cetux 2C9-DM1 (Tikhomirov)
	B2 – tumor-specific (pH-selective) antibody		- Y104 antibodies (Wei)
	B1 – tumor-specific (mutant-specific) antibody		- Antibody 1 (Leanna)
	B4 – antibody with >10-fold lower affinity than cetuximab		- h-R3 (Crombet) - Antibodies (Tikhomirov-346) - Nimotuzumab (Garrido)
Legend: Arrow (↗) – linker is cleavable Circle (●) – pH-dependency of antigen-binding fragment Asteroid (*) – mutant EGFR recognized by antibody Shaded antigen-binding fragment (⊗) – EGFR-binding affinity similar to cetuximab Green antigen-binding fragment (⊗) – EGFR-binding affinity lower than cetuximab			

C. The '370 Patent

The '370 patent was issued from U.S. Patent Application No. 15/550,995, which was filed August 14, 2017 as a U.S. national phase application of International Patent Application No. PCT/CN2016/073844 (filed February 16,

2016) and claims priority to Chinese Patent Application No. 201510085038.8 (filed February 17, 2015).

The '370 patent has a single independent claim:

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.

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).

Also, as compared to cetuximab, BA03 had “stronger activity in blocking the ligand from binding to the epidermal growth factor receptor on the cell surface” (Ex-1008, ¶144) and “stronger activity in inhibiting the phosphorylation of the epidermal growth factor receptor on the surface of A431 cells” (*id.*, ¶148). As noted in Tikhomirov, cetuximab is a “full antagonist” (Ex-1009, 11-12).

Tikhomirov distinguishes full antagonist anti-EGFR antibodies from partial ones based on their epitope. Given that BA03 is derived from cetuximab and binds to the same epitope as cetuximab, it is also a full antagonist.

Petitioner argues that “the Challenged Claims are not entitled to priority from the filing of [the 038.8 application].” Pet., 37. For purposes of this proceeding, resolution of the priority date issue is immaterial. Accordingly, Patent Owner does not address the priority date issue at this time but expressly reserves all rights regarding entitlement to priority in this and any related proceedings.

III. FOR GROUND 1, A POSA WOULD NOT HAVE BEEN MOTIVATED TO MODIFY WEI BASED ON LIU’S TEACHINGS.

As the Supreme Court recognized in *KSR*, “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art” and “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). The Petition fails to meet the requirement of *KSR* because it establishes no reason that would have prompted a POSA to modify Wei in the proposed manner and overlooks clear reasons against doing so.

Petitioner’s Ground 1 relies on modifying the primary reference Wei’s ADC by replacing its antibody with Liu’s antibody. The problem with this proposed modification is that Wei addresses well-known safety concerns associated with

anti-EGFR ADCs by using the Y104D/huY104D antibody, which is pH-selective and more active in a tumor microenvironment than non-tumor environment. *Supra* §II.B.5.a. Liu’s BA03 antibody, however, lacks pH selectivity and the ability to distinguish tumor and normal cells. A POSA would have expected replacing Wei’s pH-selective antibody with BA03 to harm the ADC’s therapeutic window and been dissuaded from pursuing the replacement. Furthermore, Petitioner has completely failed to identify any benefit that would have resulted from the replacement, as Dr. Bournazos admitted that he did not analyze how the properties of Wei’s and Liu’s antibodies differ from each other, providing no reason for a POSA to modify Wei based on Liu.

A. A POSA would have been discouraged from replacing Wei’s antibody with Liu’s antibody because the replacement would have harmed the ADC’s performance by eliminating pH selectivity.

1. Wei aims at developing pH-selective antibodies and demonstrates that the Y104D mutant is pH-selective.

The safety concerns associated with cetuximab were well-documented prior to filing of the ’370 patent. Ex-2027, ¶48. For instance, Wei remarked that as anti-EGFR antibodies like cetuximab “can bind to EGFR in healthy cells and tissue [, they] exhibit limitations when administered to patients.” Ex-1005, ¶9. The primary objective of Wei’s invention was to “provide improved anti-EGFR antibodies that exhibit increased EGFR binding activity in a tumor microenvironment compared to in a non-tumor environment.” Ex-1005, ¶0009 (emphasis added).

Consistent with its objective, Wei developed the Y104 mutants aiming at addressing the safety concerns. *See supra* §II.B.5.a. The Y104 mutants have greater activity at the acidic pH of the tumor microenvironment than at a neutral pH, which is common in normal tissues. As observed by Wei, “at pH 7.4, the wild-type cetuximab antibody exhibited a slightly higher EC₅₀ than at pH 6.5 or pH 6.0. In contrast, for the Y104 mutants and the FDP-h3 control, binding was substantially weaker at pH 7.4 than at pH 6.5 or pH 6.0, as evidenced by a higher EC₅₀ under the neutral pH tested conditions than the acidic pH tested conditions. Thus, each of the mutants exhibit a greater ratio of binding at acidic pH 6.0 or 6.5 than at pH 7.4.” Ex-1005, ¶0994; Ex-2027, ¶52.

The therapeutic index of an ADC incorporating the Y104D mutant (Y104D-MMAE), relative to that with the parental cetuximab antibody (Cetuximab-MMAE), was also measured in Example 21 of Wei. The tumor cell inhibition efficacy “was virtually identical between” the two ADCs. *Id.*, ¶1130. Their toxicities against normal cells of these ADCs, however, were drastically different. The toxicities were measured in terms of rates of cell growth inhibition (CGI) against non-tumor keratinocytes. “Cetuximab-MMAE exhibited approximately 50% CGI at a concentration of approximately **0.1 µg/mL**, whereas to achieve 50% CGI, **1 µg/mL** Y104D-MMAE was required.” *Id.*, ¶1131 (emphasis added). This translates into a 10-fold difference in therapeutic index. The experimental data in

Wei, therefore, demonstrate that the Y104D antibody it developed as a pH-selective derivative of cetuximab was able to increase the therapeutic index of ADCs with cetuximab by about **10-fold**. Ex-2027, ¶54. Wei additionally observes that ADCs with huY104D “exhibit[s] greater pH-dependent activity” and further “reduced growth inhibition of non-tumor keratinocytes at pH 7.4.” Ex-1005, ¶1139; Ex-2027, ¶54.

As the Board found in the Institution Decision, “Wei teaches that its modified cetuximab anti-EGFR has the advantage of being pH selective in its binding affinity, such that it binds preferentially to EGF receptors in the more acidic extracellular microenvironment of tumor tissue compared to receptors in non-tumor tissues at a physiological pH of 7.0–7.2.” D.I., 37. A POSA would have recognized the Y104D/huY104D antibody as having improved ability to distinguish tumor cells from normal cells, as compared to the parental antibody, cetuximab. Ex-2027, ¶55.

2. Liu’s BA03 antibody lacks pH selectivity and the ability to distinguish between tumor and normal cells.

The tumor-targeting pH-selectivity of Wei’s antibodies, as Dr. Atanackovic explains, is not a property that is possessed by a typical antibody. Ex-2027, ¶55. An antibody that is generated through animal immunization is typically active at physiological pH conditions (e.g., 7.0-7.5) and can be the same or less active at acidic pH. *Id.*

pH-selective antibodies are typically obtained by substituting an amino acid residue at an antigen-binding site, i.e., in the CDRs, with a histidine residue or one of the negatively-charged residues, aspartic acid or glutamic acid. The Y104D mutation is such an example, where the tyrosine (Y) residue within heavy chain CDR3 is replaced with aspartic acid (D). Ex-2027, ¶56.

Liu's BA03 antibody is a humanized version of cetuximab. In a humanization process, many of the residues in the framework regions of animal origin are replaced with human counterparts. Typically, few changes are made to the CDR regions to avoid interfering with the parental antibody's binding activity. Therefore, unless specifically designed or screened for, a typical humanization process like that employed in Liu would not have conveyed tumor-targeting pH-selectivity to a parental antibody. Accordingly, there is no basis to believe that the BA03 antibody has the pH-selectivity that Wei's antibodies have. Ex-2027, ¶57.

Petitioner's own experiments also confirmed that BA03 does not have pH selectivity. BA03 and BA03-containing ADCs were tested in an international patent application filed by Petitioner, WO2023/088382 ("the '382 application," filed on November 17, 2022), whose counterpart Europe Application No. EP4434549A1 (Ex-2008) is in English. The '382 application describes ADC molecules that incorporated each of four anti-EGFR antibodies, SWY2110, SWY2111, SWY2112, and SWY2113. The light chain and heavy chain sequences

of SWY2110 (see Ex-2008, 000019) are identical to those of the BA03 antibody and thus they are the same antibody. SWY2110 (BA03) was used as the parental antibody to produce three pH-selective (also referred to as “pH-dependent” in Ex-2008) derivatives. *Id.*, 000034. The pH-selectivity of all four antibodies was measured. As shown in Table 1 (reproduced below), SWY2110 (BA03) exhibited almost identical binding affinity to EGFR at neutral (pH 7.4) and acidic (pH 6.0) conditions, and thus does not have pH-selectivity. For comparison, all three derivatives of SWY2110 (BA03) had considerably lower binding at the neutral pH and thus had pH-selectivity. *Id.*, 000035; Ex-2027, ¶58.

Table 1 (of Ex-2008): Result of Antibody Affinity Determination

FACS(EC ₅₀)	SWY2110	SWY2111	SWY2112	SWY2113
pH7.4 (nM)	0.49	1.45	2.35	4.76
pH6.0 (nM)	0.51	0.60	0.67	3.39

Moreover, consistent with Wei’s teaching, Petitioner further observed that ADCs incorporating their pH-selective antibodies “had reduced toxicity to normal tissues” as compared to one with the BA03 antibody (SWY2110-JSSW-001). *Id.*, 000065. This suggests that, compared to its pH-selective derivatives, SWY2110 (BA03) has poorer ability to distinguish tumor cells from normal cells. Therefore, more than five years after the ’370 Patent was filed, Petitioner’s own data still showed that the BA03 antibody was an inferior choice as compared to its pH-selective counterparts. Ex-2027, ¶58.

Petitioner makes an overboard argument that “humanized cetuximab variant ADCs were more selective in targeting tumor cells than chimeric ADCs” based solely on Wei’s teaching that the humanized huY104D has stronger pH selectivity than the chimeric Y104D. Pet. 41. However, this argument is rebutted by Petitioner’s own expert, who admitted that humanization does not increase the pH selectivity of an antibody as a general matter. Ex-2026, 88:23-89:10.

In sum, Liu’s BA03 antibody lacks the pH selectivity exhibited by Wei’s Y104D/huY104D antibodies as well as the accompanying ability to distinguish tumor cells from normal cells.

3. Wei teaches away from using BA03 in an ADC and discourages a POSA from replacing Y104D/huY104D with BA03.

Wei discourages the use of antibodies that have equal binding activities in tumor and non-tumor environments, explaining that these antibodies “limit[] the dosages that can be administered.” Ex-1005, ¶9. A POSA would have been led to use antibodies that “exhibit increased EGFR binding activity in a tumor microenvironment” in ADCs by Wei’s disclosure of such antibodies as a solution to the dosage limitation problem. Ex-1005, ¶9. This is a direction of ADC design that is “divergent from the path that was taken in the claim[s],” where the BA03 antibody, which has no preferentially increased EGFR binding activity for tumor cells, is used in an ADC. *Meiresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed.

Cir. 2017). Therefore, Wei teaches away from the claimed use of the BA03 antibody in an ADC. Ex-2027, ¶59. *See, e.g., Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (upholding the district court’s finding that the prior art teaches away from using 200 ppm benzalkonium chloride (“BAK”), even when 200 ppm falls within ranges disclosed by the prior art, because “the prior art taught that BAK should be minimized in ophthalmic formulations to avoid safety problems”); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1355 (Fed. Cir. 2012) (holding that, when prior art teaches four medicine dosage options and “ruled out” the dosage forms according to one of the options, the prior art “teaches away from such formulations” and the district court erred by finding the dosage forms obvious); *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1372 (Fed. Cir. 2013), *vacated on other grounds*, 574 U.S. 318 (2015) (upholding the district court finding that the prior art teaches away from using lower molecular weight copolymer-1 when it “stated that copolymer-1 with a molecular weight lower than 17 kDa was ineffective for treating multiple sclerosis”).

At the very least, Wei’s teachings would have dissuaded a POSA from replacing its Y104D/huY104D antibody, shown to have the desirable ability to cause an ADC to exhibit less activity on normal cells than on tumor cells, by Liu’s BA03 antibody that equally targets tumor and normal cells. A POSA would have expected the replacement to increase the toxicity and harm the therapeutic window

of the resulting ADC and would not have been motivated to modify Wei's ADC using Liu's antibody. Ex-2027, ¶59; *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1051 n.15 (Fed. Cir. 2016) (holding that "even if [a reference] does not teach away, its statements regarding [preferences of solutions] are relevant to a finding regarding whether a skilled artisan would be motivated to combine...").

B. Petitioner fails to establish any reason that would have motivated a POSA to replace Wei's antibody with Liu's antibody.

1. Petitioner does not establish any benefit of Liu's BA03 as compared to Wei's Y104D/huY104D.

The crux of Petitioner's motivation-to-combine argument is that a POSA would have been motivated to use BA03 because it is a humanized antibody and has multiple benefits over cetuximab, a chimeric antibody. Pet., 40-42. However, because Wei itself teaches humanizing its Y104D antibody to obtain the huY104D antibody, any general preference of humanized antibodies to chimeric antibodies is irrelevant to the proposed modification of Wei and would not have motivated a POSA to replace Wei's antibody with Liu's antibody. Simply put, a POSA would have had no reason to use BA03 where a humanized antibody, huY104D, is already present in Wei.

In fact, Petitioner's expert Dr. Bournazos admitted that he did not know any benefit of Liu's BA03 over Wei's Y104D/huY104D. Dr. Bournazos never compared Liu's BA03 antibody and Wei's Y104D antibody or analyzed how their

properties differ from each other. Ex-2026, 110:4-20. He did not know how BA03's binding affinity compares with Wei's Y104D/huY104D antibody. Ex-2026, 110:21-111:1 (Q. Have you analyzed whether Liu's BA03 antibody has a higher or lower binding affinity than Wei's Y104D antibody, either chimeric or humanized? A. I cannot comment on that...). He also did not know whether BA03 has higher or lower immunogenicity than Wei's Y104D/huY104D antibody. Ex-2026, 111:11-17 ("Q. So you do not know whether Liu's BA03 antibody has a higher or lower immunogenicity than Wei's Y104D antibody, either humanized or chimeric; correct? A. Correct ..."), *see also* 25:11-19 (testifying that a humanized version of an antibody does not necessarily have lower immunogenicity than the chimeric version of a different antibody). Dr. Bournazos also did not know how BA03 differs from Y104D/huY104D in terms of EGFR phosphorylation inhibition and ADCC activity. Ex-2026, 112:1-113:6.

In sum, Petitioner and its expert never analyzed how Liu's BA03 antibody differs from Wei's Y104D/huY104D antibody and cannot possibly identify any benefits of the former over the latter. Nor does Petitioner identify any benefit that can be achieved by replacing the Y104D/huY104D antibody in Wei's ADC with BA03. Therefore, Petitioner fails to establish any motivation for a POSA to modify Wei's ADC as proposed by Ground 1, let alone any benefit that would have offset

the significant harm of losing pH selectivity caused by replacing Y104D/huY104D with BA03. *Supra* §III.A.

2. BA03’s purported benefits over cetuximab are unrelated to the proposed modification of Wei and, in any event, would not have motivated a POSA to use BA03 in an ADC.

Petitioner argues that “BA03 has numerous benefits *over cetuximab*, including stronger EGFR phosphorylation inhibition, higher ADCC activity, and significantly lower immunogenicity.” Pet., 40 (emphasis added). These benefits are irrelevant to the proposed modification of Wei because the relied-upon ADC of Wei uses Y104D/huY104D rather than cetuximab and Petitioner has failed to establish that BA03 has the same benefits over Wei’s antibody. Ex-2027, ¶62.

Even assuming BA03’s purported benefits in EGFR phosphorylation inhibition and ADCC activity are somehow relevant (they are not), they would not have motivated a POSA to use the BA03 antibody. EGFR phosphorylation inhibition is part of the antagonist activity of an anti-EGFR antibody arising from its binding to the EGFR and blocking the interaction between EGFR and its ligand EGF. To the extent the increased EGFR phosphorylation inhibition activity of the BA03 antibody could increase the ADC’s killing of tumor cells, it would also result in higher killing of the normal cells, leading to increased toxicity. The parallel changes of the ADC’s killing activity against tumor and normal cells, therefore, would mean no change to the ADC’s therapeutic window. Accordingly,

such an alleged benefit of the BA03 antibody would not have been considered a benefit in the context of ADC design, as it cannot at all address the fundamental concern associated with anti-EGFR ADCs, i.e., narrow therapeutic window. *See supra* §II.B.1; Ex-2027, ¶63.

Likewise, to the extent the increased ADCC activity could lead to increased killing of tumor cells, it would have been expected by a POSA to also increase killing of normal cells. Accordingly, this would not have changed the ADC's therapeutic window either. A POSA would not have considered the alleged increase of ADCC activity as a benefit that motivates one to use BA03 in an ADC.

Finally, Petitioner attributes BA03's lower immunogenicity to the humanization process. *Pet.*, 40. As explained above, because Wei teaches humanizing its antibodies and using humanized antibodies in ADCs, the purported benefit of lower immunogenicity would not have motivated a POSA to modify Wei. *Supra* §III.B.1; Ex-2027, ¶65.

C. Petitioner fails to establish any motivation to replace Wei's antibody with Liu's antibody based on their alleged similarity or an obviousness-to-try theory.

Petitioner's expert Dr. Bournazos admitted on deposition that "[t]here are millions of ways [to] modify cetuximab" to create cetuximab variants. Ex-2026, 78:19-22. Petitioner asserts that Liu's BA03 antibody is "substantially identical" to Wei's huY104D antibody solely because both of them are among the millions of

possible cetuximab variants. Because BA03's properties are significantly different from those of huY104D, the mere fact that they are both cetuximab variants would not have motivated a POSA to replace the latter with the former. Furthermore, Petitioner has not established any reason that a POSA would have viewed the BA03 antibody as an obvious option to try in forming an ADC.

1. Petitioner's alleged similarity between Wei's antibody and Liu's antibody lacks basis and does not provide a motivation to modify Wei.

Petitioner asserts that Wei's and Liu's antibodies are "substantially identical," relying solely on a sentence in Dr. Bournazos's declaration that mirrors the Petition. Pet. 40; Ex-1002, ¶187. The only basis for Dr. Bournazos's testimony is that both antibodies are derived from cetuximab. Ex-2026, 105:4-13. This testimony lacks support because Dr. Bournazos failed to analyze how the antibodies differ in terms of their properties. For example, he was "not sure what degree of similarity [the antibodies] would have." Ex-2026, 101:19-102:1. He also did not know "differences in the properties of these two antibodies" other than that they "target the same epitope," and had never tried to determine the differences in properties. Ex-2026, 102:19-103:16, *see also* 102:2-12, 108:2-15, 109:6-111:17, 112:1-113:21.

Petitioner overlooks the significant difference in pH selectivity between Wei and Liu. *Supra* §III.A. Wei describes a cetuximab derivative, Y104D, that has a

single mutation on cetuximab and yet has improved tumor selectivity than (hence different from) cetuximab. Wei's teaching directly belies Dr. Bournazos's allegation that just because two antibodies are both derived from a common parental antibody, cetuximab, they must be substantially identical. Ex-2027, ¶46. The mere fact that BA03 is a cetuximab variant would not have motivated a POSA to use it to replace Wei's carefully selected antibody. Ex-2027, ¶¶45-46.

2. Petitioner fails to establish obviousness to try using Liu's BA03 antibody in an ADC.

In the Institution Decision, the Board noted that "it is in the nature of scientific research to continue to try new substitutions in drug therapy, even if a promising candidate has been discovered." D.I., 39-40. However, a showing of obviousness to try requires "a finite number of identified, predictable solutions." *KSR*, 550 U.S. at 421. Scientists' general interest in trying new therapy options is insufficient to establish obviousness:

[A]n invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art. When "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful" an invention would not have been obvious.

Bayer Schering Pharma AG v. Barr Lab'ys, Inc., 575 F.3d 1341, 1347 (Fed. Cir. 2009) (*In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).

Here, both parties' experts agree that hundreds of anti-EGFR antibodies were known and millions of ways to modify cetuximab were available. Ex-2027, ¶¶78-79; Ex-2026, 27:7-14 ("I would say hundreds" of "anti-EGFR antibodies have been developed or described in the scientific literature."), 78:19-22 ("There are millions of ways that you can modify cetuximab."). Petitioner's cited art provides no direction suggesting that the BA03 antibody is likely to be successful when used in an ADC. Liu, the only reference that teaches the BA03 antibody, does not contemplate incorporating it in an ADC. *See generally* Ex-1008; Ex-2026, 116:8-11 (admitting that Liu does not teach using BA03 in ADC). The purported benefits of BA03 over cetuximab taught by Liu are directed to BA03 as a naked antibody and would not have suggested to a POSA that BA03 was suitable for use in an ADC. Given its inability to distinguish tumor and normal cells and expected unduly narrow therapeutic window (*supra* §III.A, *infra* §V.A), there is no reason why BA03 would have stood out from the hundreds of known anti-EGFR antibodies or the millions of potential cetuximab variants. Ex-2027, ¶80. Nor does Petitioner establish that a POSA would have had a reasonable expectation of success using BA03 in an ADC, as explained below. *Infra* §VI. Therefore, a POSA would not have found it obvious to try using the BA03 antibody in an ADC when

there were a near infinite number of possible antibodies in the field unreduced by direction of the prior art.

IV. FOR GROUND 2, A POSA WOULD NOT HAVE BEEN MOTIVATED TO MODIFY LEANNA BASED ON LIU'S TEACHINGS.

Under Ground 2, Petitioner proposes to replace Antibody 1 in Leanna's ADC with Liu's BA03 antibody. Similar to Ground 1, such a proposed replacement contradicts Leanna's own teaching.

Leanna's Antibody 1 selectively binds to tumor cells by targeting an EGFR epitope that is expressed only on tumor cells and not on normal cell, which allows its Antibody 1-vc-MMAE ADC to achieve efficacy without unacceptable toxicity against normal cells. *See supra* §II.B.5.b. Liu's BA03 antibody is less suitable for use in an ADC than Leanna's Antibody 1 because it recognizes the wild-type EGFR, which is expressed both on tumor cells and normal cells. A POSA would have expected the proposed modification of Ground 2 to result in a worse ADC and refrained from making the modification.

A. A POSA would have been discouraged from replacing Leanna's Antibody 1 with Liu's BA03 because the replacement would have harmed the ADC's performance by eliminating tumor selectivity.

Ground 2 proposes to replace the "Antibody 1" in Leanna's ADC with Liu's BA03 antibody. Pet., 65-69; Ex-1002, ¶282. Leanna's Antibody 1 selectively binds to tumor cells by targeting an EGFR epitope that is expressed only on tumor cells

and not on normal cells. This property allows Leanna's Antibody 1-vc-MMAE ADC to achieve efficacy without unacceptable toxicity against normal cells. In contrast, Liu's BA03 antibody targets the wild-type EGFR protein, which is expressed both on tumor and normal cells, thereby lacking the ability to distinguish between tumor and normal cells. This makes the BA03 less suitable than Antibody 1 for use in an ADC that has a highly toxic payload (e.g., MMAE). A POSA would have expected BA03 to be inferior to Antibody 1 for use in an ADC and be unwilling to replace Antibody 1 with BA03.

As the Board found, "Leanna teaches that its humanized cetuximab anti-EGFR antibody, when incorporated into an ADC (an 'immunoconjugate' in Leanna) displays enhanced cytotoxicity against cancer cells without a corresponding increase in cytotoxicity against skin cells." D.I., 51 (citing Ex-1006, 3, 24). Leanna incorporates U.S. Patent Application Publication No. 2011/0076232 by Old et al. ("Old-232") for its teachings regarding Antibody 1. Ex-1006, 24:14-17 ("The sequences and characteristics of antibody 1 are described below (see also WO 2011/041319 and US20110076232 (see, e.g., antibody sequence of Figure 55), incorporated by reference in its entirety herein)."). Old-232 refers to Antibody 1 (shown in its Figures 55A and 55B) as the "hu806" antibody, which is a humanized version of the mouse antibody "mAb806." Ex-2015 (Old-232), ¶177 ("FIGS. 55A and 55B show the hu806 translated amino acid

sequences ...”), ¶¶244-245 (explaining mouse, chimeric, and humanized versions of the 806 antibody—mAb806, ch806, and hu806); Ex-2027, ¶67.

Similar to Wei’s Y104D/huY104D antibody, Leanna’s Antibody 1 (i.e., hu806) was developed to address the problem that the use of anti-EGFR antibodies was constrained by their toxicity to normal cells. *See* Ex-2015, ¶5 (“The use of [anti-EGFR] antibodies, however, may be limited by uptake in organs that have high endogenous levels of EGFR such as the liver and skin.”); Ex-2027, ¶68.

Antibody 1 solves this problem because it specifically targets an EGFR epitope that is expressed only on tumor cells and not on normal cells:

[T]he antibodies of the present invention [i.e., mAb806, ch806, hu806, etc.] recognize an EGFR epitope which is found in tumorigenic, hyperproliferative or abnormal cells and is not generally detectable in normal or wild type cells, wherein the epitope is enhanced or evident upon aberrant post-translational modification. ... Importantly, these antibodies did not bind significantly to normal tissues such as liver and skin, which express levels of endogenous, wild type (wt) EGFR that are higher than in most other normal tissues, but wherein EGFR is not aberrantly expressed or amplified.

Ex-2015, ¶15; Ex-2027, ¶68.

The mAb806 antibody is also discussed in Tikhomirov as a known solution to the problem that “current EGFR antibodies” “all display significant binding to normal organs such as skin in humans.” Ex-1009, 3. Tikhomirov explains that

mAb806 is superior to cetuximab because it has the ability to distinguish cancer cells from normal cells, as it “targets an EGFR epitope found only on cancer cells.” Ex-1009, 3. This ability makes it feasible for mAb806 to be directly conjugated with cytotoxic agents, whereas doing the same for other anti-EGFR antibodies would have induced severe toxicity:

[I]t is recognized that “the most important advantage of MAb 806 compared to current EGFR antibodies, is that MAb 806 can be directly conjugated to cytotoxic agents”, an approach not feasible with other EGFR antibodies since the “cytotoxic conjugation would almost certainly induce severe toxicity” (US 7589180).

Ex-1009, 3.

Liu’s BA03 antibody does not have tumor selectivity or the ability to distinguish tumor cells from normal cells. Ex-2027, ¶70; *see supra* §III.A.2. Ground 2’s replacement of Antibody 1 in Leanna’s ADC with BA03 would have eliminated the ability of Leanna’s ADC to selectively target tumor cells and significantly increase its activity on normal cells. Similar to Ground 1, the proposed change of antibody under Ground 2 would have essentially reinstated the problem that the use of anti-EGFR antibodies was constrained by their toxicity to normal cells, which Antibody 1 was designed to solve. Ex-2027, ¶68.

Leanna discourages the use of antibodies that do not have the ability to distinguish tumor and normal cells because the use of such antibodies “may be

limited by uptake in organs that have high endogenous levels of EGFR such as the liver and skin.” Ex-2015, ¶5. A POSA would have found toxicity to liver and skin tissues undesirable and is elevated in the context of ADCs, which include highly toxic payloads. Ex-2027, ¶68. A POSA would have been led to use antibodies that can distinguish tumor and normal cells, such as by targeting an EGFR epitope that is only expressed on tumors, in ADCs. Ex-2027, ¶68. This is a direction of ADC design that is “divergent from the path that was taken in the claim[s],” where the BA03 antibody, which has equal binding activity for tumor and normal cells, is used in an ADC. *Meiresonne*, 849 F.3d at 1382. Leanna thus teaches away from the claimed use of the BA03 antibody in an ADC. *See, e.g., Allergan*, 796 F.3d at 1305; *Santarus*, 694 F.3d at 1355; *Teva*, 723 F.3d at 137.

A POSA at least would have expected the proposed modification of Leanna’s ADC under Ground 2 to significantly increase the ADC’s toxicity toward normal cells at the same level of efficacy, harm the therapeutic window, and make the modified ADC substantially inferior to Leanna’s ADC. Ex-2027, ¶71. A POSA would have been discouraged from replacing Antibody 1 with BA03, or at least had no motivation to carry out the replacement. *Id.*

B. Petitioner fails to establish any reason that would have motivated a POSA to replace Leanna’s antibody with Liu’s antibody.

Petitioner’s motivation-to-combine arguments for Ground 2 rely on Wei and largely resemble those for Ground 1,² centered on the fact that BA03 is a humanized antibody and has multiple purported benefits over cetuximab. Pet., 67-69. However, as Petitioner admits, “both Leanna and Liu disclose humanized anti-EGFR antibodies.” Pet., 68. BA03 being a humanized antibody would not have motivated a POSA to use it to replace Antibody 1, which is already humanized. Ex-2027, ¶74. Also, as explained in the discussion of Ground 1, the allegedly improved EGFR phosphorylation inhibition and ADCC of the BA03 antibody, as compared to cetuximab, are irrelevant to Leanna and would have been expected by a POSA to have no impact on its therapeutic window. *Supra* §III.B.2; Ex-2027, ¶¶72-73.

² Seemingly to address the fact that Leanna’s antibody, unlike that of Wei, is not a cetuximab variant, Petitioner additionally alleges that cetuximab was one out of two FDA-approved anti-EGFR antibodies. Pet., 67. However, this generic allegation does not provide any particular reason for a POSA to modify Leanna’s ADC, especially given that the FDA approved cetuximab as a naked antibody rather than as part of an ADC and Liu’s BA03 antibody is not covered by the FDA’s approval of cetuximab.

Petitioner also fails to establish any benefit of BA03 over Antibody 1. *See* Pet., 65-67. Petitioner’s expert Dr. Bournazos admitted that no comparison between BA03 and Antibody 1 had been performed. Ex-2026, 115:23-25 (“I haven’t done any comparison between Leanna’s Antibody 1 and BA03. All I know is that both are anti-EGFR antibodies.”). Without performing any comparison between BA03 and Antibody 1, Petitioner does not and cannot establish any advantage that would have been achieved by replacing Leanna’s Antibody 1 with Liu’s BA03. As a result, Petitioner completely fails to show any motivation for a POSA to carry out the modification of Leanna’s ADC as proposed under Ground 2.

Petitioner overlooks the significant disadvantages of eliminating tumor selectivity, thereby increasing toxicity and harming therapeutic window, that would have resulted from the proposed modification of Leanna’s ADC (*supra* §IV.A). The failure to recognize the important tumor-selective property of Leanna’s Antibody 1 is unsurprising given Petitioner and its experts lack a basic understanding of Antibody 1. This is shown by Dr. Bournazos’s admission that he “[had not] reviewed what is Antibody 1” and was “not familiar with Antibody 1.” Ex-2026, 93:20-24. A POSA, considering the significant disadvantages and the total absence of benefit, would have expected replacing Leanna’s antibody with

Liu's antibody to only result in a worse ADC and would have had no motivation to carry out the replacement. Ex-2027, ¶¶71-75.

V. A POSA WOULD HAVE AVOIDED THE BA03-VC-MMAE ADC AS PROPOSED UNDER BOTH GROUNDS, IN LIGHT OF WELL-ACCEPTED ADC DESIGN STRATEGIES.

Petitioner relies on Wei's teaching of the Y104D/huY104D-vc-MMAE ADC and Leanna's teaching of the Antibody 1-vc-MMAE. Pet., 37-38, 65-66. Each ADC uses the vc linker and MMAE payload along with an antibody (e.g., Y104D/huY104D, Antibody 1) that improves upon cetuximab in terms of its ability to distinguish between tumor and normal cells. Under both Grounds 1 and 2, Petitioner proposes to use the same linker and payload, while replacing Wei's/Leanna's antibody with Liu's BA03 antibody to arrive at the BA03-vc-MMAE ADC. The use of the BA03 antibody, which has a higher binding affinity than cetuximab, contradicts the conventional ADC design strategy of improving tumor selectivity by decreasing the antibody's binding affinity. A POSA would have expected the use of BA03 to negate the improvements provided by Wei's and Leanna's antibodies. Furthermore, a POSA would have expected the BA03-vc-MMAE ADC to have an even worse therapeutic window than the cetuximab-vc-MMAE ADC, the baseline on which Wei and Leanna made improvements. Because cetuximab-vc-MMAE was known to have an unduly narrow therapeutic

window, a POSA would have expected BA03-vc-MMAE, whose therapeutic window is even narrower, to be unsuccessful and would have avoided it.

A. In light of conventional ADC design strategies, a POSA would have expected the BA03-vc-MMAE ADC to have a therapeutic window even worse than the unviable cetuximab-vc-MMAE ADC.

Both Grounds 1 and 2 propose to form a BA03-vc-MMAE ADC, based on Wei's/Leanna's vc linker and MMAE payload and Liu's BA03 antibody. Pet., 37-40, 65-67; Ex-2026, 122:25-123:1. The proposed ADC, however, would have been expected to have a worse therapeutic window than the cetuximab-vc-MMAE (referred to as Cetux 2C9-MMAE in Tikhomirov) ADC tested and found unviable in Tikhomirov. This is because BA03 has a higher binding affinity than cetuximab.

As explained above, an important design strategy for anti-EGFR ADCs, strategy B4, involves the use of antibodies with a lower binding affinity, more specifically ones having at least 10-fold lower binding affinity than cetuximab. *Supra* §II.B.4. In particular, Crombet has demonstrated a negative correlation between an anti-EGFR antibody's affinity and its ability to distinguish tumor cells from normal cells. According to Crombet, an antibody having over 10-fold lower binding affinity than cetuximab would be expected to have substantially increased ability in distinguishing tumor cells from normal cells; meanwhile, an antibody having a higher affinity than cetuximab would be expected to have no such distinguishing ability at all. *Supra* §II.B.4; Ex-2027, ¶60.

The BA03 antibody has a higher binding affinity than cetuximab. Ex-1008, ¶140; Pet, 39. According to conventional knowledge and Crombet, a POSA would have expected the BA03 antibody to have poor or even no ability to distinguish tumor cells from normal cells. *Supra* §II.B.4. Such an antibody, as well as its ADCs, therefore, would have been expected to have no or a very narrow therapeutic window. A POSA would have expected that the higher binding affinity of BA03 causes the BA03-vc-MMAE ADC to have a narrower therapeutic window than and be inferior to the cetuximab-vc-MMAE ADC. Ex-2027, ¶36, ¶61.

The cetuximab-vc-MMAE ADC was known to have an unduly narrow therapeutic window for having potentiated toxicity against normal cells, as Tikhomirov teaches. Ex-1009, 31 (“[A] safe anti-EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker.”). Figure 13 of Tikhomirov shows that Cetux 2C9-MMAE had significantly higher toxicity against skin cells than all other molecules tested. Ex-1009, Fig. 13, 10-11.³ Because a POSA would have expected the proposed

³ Petitioner attacks Tikhomirov, arguing that its results cannot be generalized to all cleavable linkers based on “a single observation” and no control of the payload. Pet., 45-47. However, Petitioner does not dispute that Tikhomirov’s observation at least applies to the specifically tested cetuximab-vc-MMAE ADC and would have

BA03-vc-MMAE ADC to have a therapeutic window that is even narrower than the cetuximab-vc-MMAE ADC, the POSA would have had significant safety concerns about BA03-vc-MMAE and expected it to be unsuccessful. This would have discouraged a POSA from creating the BA03-vc-MMAE ADC. Ex-2027, ¶61.

In the Institution Decision, the Board found that “a person of ordinary skill in the art would have recognized that [Liu’s BA03 antibody’s] advantages (enhanced activity against tumor cells compared to chimeric cetuximab, thus requiring smaller dosages) could balance or outweigh its possible disadvantages (e.g., possible activity against non-tumor cells).” D.I., 40. Dr. Atanackovic’s testimony, which was not presented before the Board in the institution stage, explains that a POSA would have been aware of the negative correlation between an anti-EGFR antibody’s affinity and its ability to distinguish tumor cells from normal cells (Ex-2027, ¶¶60-61). Given this knowledge, a POSA would have

informed a POSA that this ADC had a narrow therapeutic window. Ex-2027, ¶61. In particular, Figure 13 of Tikhomirov shows that the cetuximab-vc-MMAE ADC has similar toxic concentrations for both skin and tumor cells (compare the panel on the left to that on the right in Figure 13). Ex-1009, Fig. 13.

expected the disadvantages of activity against non-tumor cells to outweigh any advantages of enhanced activity against tumor cells in the case of BA03.

B. A POSA would have expected the BA03-vc-MMAE ADC to negate the improvements provided by Wei's and Leanna's ADCs.

Each of Wei and Leanna took cetuximab as a starting point and used improved antibodies to develop anti-EGFR ADCs with wider therapeutic windows than cetuximab-vc-MMAE. In Wei, the cetuximab-derived antibodies are pH-selective and thus are better than cetuximab in distinguishing tumor cells from normal cells. *Supra* §III.A.1. In Leanna, the antibody recognizes an EGFR mutant that is only expressed on tumor cells and thus is also better than cetuximab in distinguishing tumor cells from normal cells. *Supra* §IV.A.

Their relationship is illustrated in the figure below:

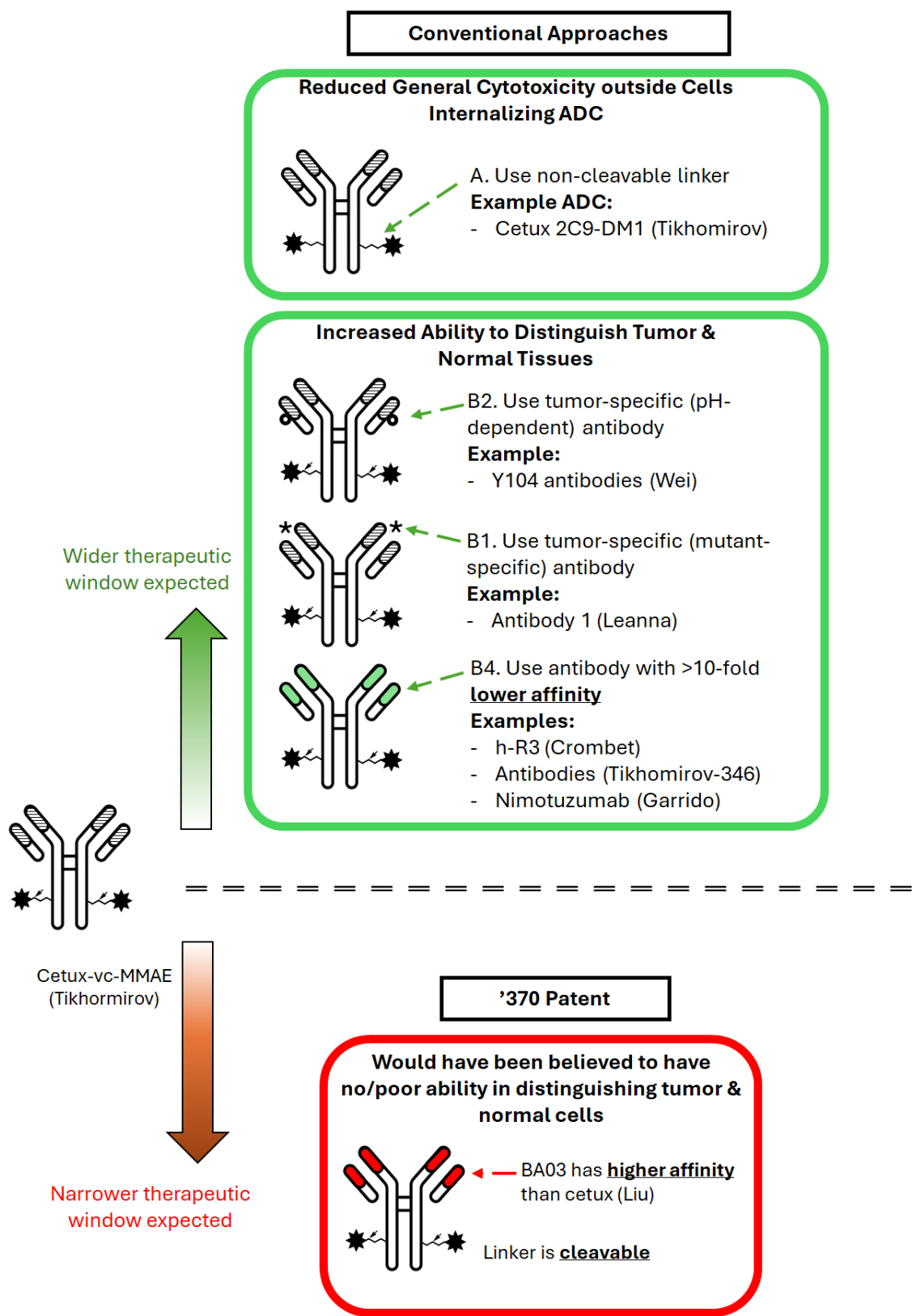


FIG. 5

Both Wei and Leanna improve cetuximab-vc-MMAE's safety profile by employing antibodies with better abilities to distinguish tumor and normal cells than cetuximab. Petitioner's proposed modification of Wei's and Leanna's ADCs using the BA03 antibody not only would have negated the improvements made by Wei and Leanna, but also would have resulted in an ADC that is even worse than the starting point, cetuximab-vc-MMAE. Therefore, a POSA would not have been motivated to replace the antibodies in Wei and Leanna with BA03, as doing so was expected to bring back safety problems that Wei and Leanna set out to solve.

VI. PETITIONER FAILS TO ESTABLISH A REASONABLE EXPECTATION OF SUCCESS.

To show obviousness, Petitioner bears “the burden to prove that [1] a skilled artisan would have been motivated to combine prior art references and ... [2] the skilled artisan would have had a reasonable expectation of successfully achieving the claimed invention from the combination.” *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021). The requirement of reasonable expectation of success is separate and distinct from a showing of a motivation to combine. *Id.* (“A finding by the Board that a patent challenger has demonstrated a motivation to combine references does not necessarily imply that the challenger has also met its burden of showing a reasonable expectation of success.”).

Petitioner fails to satisfy its burden of proof because the Petition is completely silent as to whether a POSA would have had a reasonable expectation

of success in achieving the claimed invention from the combination. Furthermore, a POSA would not have expected the combination of Ground 1 or Ground 2 to result in a viable ADC with an acceptable toxicity level or therapeutic window.

A. Petitioner fails to satisfy its burden to establish a reasonable expectation of success for Grounds 1 and 2.

The Petition's complete silence on the reasonable-expectation-of-success issue precludes a finding of obviousness. To begin with, the Petition does not present any prior art that teaches the BA03 antibody had been or would be used to create an ADC. The only reference that mentions the BA03 antibody, Liu, does not discuss the concept of ADCs or contemplate using the BA03 antibody in an ADC. *See generally* Ex-1008; Ex-2026, 116:8-11.

The Petition does not present any evidence or argument regarding whether a POSA would have had a reasonable expectation of success in creating the proposed BA03-vc-MMAE ADC, and cannot present such evidence for the first time in its Reply. *See* Pet., 37-42, 65-69. The declaration of Dr. Bournazos is also deficient. For Ground 1, the declaration does not at all discuss the issue of reasonable expectation of success. *See* Ex-1002, ¶¶178-189. For Ground 2, Dr. Bournazos argues that a POSA would have had a reasonable expectation of success for the sole reason that "Leanna teaches detailed processes for preparing the Antibody 1-vc-MMAE ADC..." Ex-1002, ¶282. This reasoning is misplaced because Leanna's teaching is directed to its unmodified ADC and does not by itself

inform a POSA as to whether the proposed modification would have had a reasonable expectation of success. Ex-2027, ¶81.

Petitioner's complete failure to show a reasonable expectation of success in combining Wei and Liu (Ground 1) and Leanna, Liu, and Wei (Ground 2) to achieve the claimed invention is dispositive and precludes a finding of obviousness.

B. A POSA would not have had a reasonable expectation of success in incorporating the BA03 antibody in an ADC.

A POSA would have expected the BA03-vc-MMAE ADC proposed by both grounds to be unsuccessful. According to the experts for both parties, a POSA would have considered various factors in forming an expectation as to whether an ADC would have been successful, including characteristics of the target, the antibody, the cytotoxic drug, the linker, and the ADC overall. Ex-2027, ¶82; Ex-1002, ¶108; Ex-2026, 72:11-73:8. Among the factors to consider are “differentials of expression level of target antigen between cancer cells and normal cells” and “the balance between cancer killing activity of ADC and its toxicity.” *Id.* Dr. Bournazos further admitted that “toxicity” is among “obstacles that can make the effort of creating an ADC unsuccessful.” Ex-2026, 59:13-60:4.

Considering these factors, a POSA would have realized that the targeted EGFR antigen has relatively high expression on both cancer and normal cells. *Supra* §II.B.2. The difference in expression level of EGFR between cancer and

normal cells is much lower than many other antigens, such as the CD30 antigen, for which Petitioner contends that there have been FDA-approved ADCs (Pet., 6-7). *Supra* §II.B.2; Ex-2026, 70:3-5 (admitting that “CD30 has higher expression difference between tumor and normal cells than EGFR”).

EGFR’s low differential of expression level between cancer and normal cells would have made it particularly challenging to balance cancer killing activity and toxicity of a potential ADC incorporating an anti-EGFR antibody. *Supra* §II.B.2; Ex-2027, ¶84. A POSA would have expected such a balance to be impossible for Petitioner’s proposed BA03-vc-MMAE ADC because (1) the BA03 antibody has no ability to distinguish tumor and normal cells and (2) BA03’s higher-than-cetuximab binding affinity would have caused the BA03-vc-MMAE ADC to have an even worse therapeutic window than the cetuximab-vc-MMAE ADC, which was known to be unviable. *Supra* §V.A; Ex-2027, ¶84.

Before the filing of the ’370 patent and the success of Miracogen’s ADC, a POSA would not have expected that the BA03 antibody could successfully be used in an ADC with a cleavable linker. Petitioner’s conclusory argument that, just because an antibody was known in the art, it would have been obvious to create an ADC based on the antibody is a textbook example of hindsight bias and the type of pitfall addressed by the reasonable-expectation-of-success requirement. The Board should reject Petitioner’s obviousness arguments because a POSA would not have

had a reasonable expectation of success in combining the prior art references to achieve the invention of the '370 patent.

VII. OBJECTIVE EVIDENCE PRECLUDES FINDING THAT THE '370 PATENT IS OBVIOUS.

The Federal Circuit has consistently held that objective indicia ““may often be the most probative and cogent evidence’ of nonobviousness.” *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000) (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983)).

Objective indicia are essential safeguards that protect against hindsight bias. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). A Petitioner bears the burden of persuasion on all matters of unpatentability, including demonstrating that objective evidence does not negate obviousness. *Id.* at 1078 (citing *Microsoft Corp. v. I4I Ltd. P'ship*, 564 U.S. 91, 100 (2011)).

As demonstrated above, nothing other than hindsight supports Petitioner’s argument that just because the BA03 antibody was known, it would have been obvious to use in an ADC. *See supra* §§III-VI. Such hindsight bias is rebutted by objective indicia that (1) the claimed invention addressed a long-felt and unresolved need for a clinically viable anti-EGFR ADC by leading to the first ever regulatorily approved anti-EGFR ADC and (2) Petitioner deliberately decided to

copy the inventive idea of using the specific BA03 antibody in an ADC after considering multiple options.

A. The claimed invention addresses a long-felt and unresolved need for a clinically viable anti-EGFR ADC by leading to the first ever regulatory approved anti-EGFR ADC.

1. There had been a long-felt need for developing a clinically viable anti-EGFR ADC.

Dr. Atanackovic observes that, more than 20 years since cetuximab was approved as an anti-cancer drug, no anti-EGFR ADC was approved anywhere in the world when the Petition was filed. Ex-2027, ¶13.

EGFR is frequently overexpressed on tumor cells and thus is an attractive target for anti-tumor therapy. There are currently at least five EGFR-targeting antibodies approved worldwide, including cetuximab (Erbix[®]), panitumumab (Vectibix[®]), nimotuzumab (BIOMAB-EGFR[®]), necitumumab (Portrazza[®]), and amivantamab (Rybrevant[®]). Cetuximab was first approved for medical use in the United States in 2004. Ex-2027, ¶85.

The lack of approved anti-EGFR ADCs is not due to a lack of interest, however. At least as early as in 2012, clinical trials with anti-EGFR ADC were submitted. For example, clinical trial NCT01741727 was first submitted on September 19, 2012 (*see* “First Submitted” date on Ex-2028, 00008). This clinical trial proposes to study ABT-414, an anti-EGFR ADC, in patients with solid tumors. “ABT-806 is a humanized form for the monoclonal antibody mAb 806.”

Ex-2029, 000001. ABT-806, therefore, corresponds to Antibody 1 of Leanna.

However, “enrollment in [a phase II/III study] has been halted since 2019 due to lack of survival benefit for patients receiving ABT-414.” Ex-2030, 000004; Ex-2027, ¶85.

Subsequently, more anti-EGFR ADCs entered into clinical trials and were terminated. The following table summarizes a few important clinical candidates and their statuses. Ex-2027, ¶86.

Sponsor	ADC Name	EGFR antibody	Status
AbbVie	ABT-414	EGFRvIII-specific	Terminated
AbbVie	ABBV-221 (losatuxizumab vedotin)	EGFRvIII-specific	Terminated
AbbVie	ABBV-321 (serclutamab talirine)	EGFRvIII-specific	Terminated
Halozyme	HTI-1511	Tumor microenvironment (TME)-specific	Terminated

AbbVie’s drug candidate ABBV-221 (losatuxizumab vedotin) is also an anti-EGFR ADC. The antibody in ABBV-221, AM1, is “an affinity-matured [anti-EGFR antibody] ABT-806” and binds EGFRvIII. Ex-2013, 000004. After the report in Ex-2013 that “ABBV-221 has advanced to a phase I clinical trial” as of 2018 (id., 000001), there has been no report of phase I results or phase 2 or 3 testing. In fact, the Phase I study of ABB-221 has reportedly been terminated. Ex-2016, 000001; Ex-2027, ¶87.

Another ADC drug candidate by AbbVie is ABBV-321 (serclutamab talirine). This ADC includes the same AM-1 antibody as ABBV-221. Ex-2014, 000002. AbbVie reported phase 1 results in Ex-2014 in 2022. Nevertheless, no further phase 2 or 3 testing has been reported, suggesting that its development has been terminated. Ex-2027, ¶88.

Halozyme reported the preclinical testing of HTI-1511 in 2016. *See* Ex-2012. HTI-1511 is an anti-EGFR ADC that includes an antibody which “was engineered with increased tumor microenvironment (TME) specificity for EGFR” (Ex-2012, 000001), suggesting that it is a pH-selective antibody. Like the pH-selective antibodies of Wei, the antibody in HTI-1511 “demonstrated undetectable *in vivo* binding to human donor foreskins grafted onto nude mice, while binding to human A431 tumor xenografts with similar intensity to cetuximab.” *Id.* Since 2016, however, there has been no report of clinical testing for HTI-1511, suggesting that its development has been terminated. Ex-2027, ¶89.

The fact that EGFR is an attractive target for anti-tumor therapy and the industry has had a strong interest in developing anti-EGFR ADCs shows that there has been a long-felt and unresolved need for a clinically viable anti-EGFR ADC. Ex-2027, ¶87. The failures by others in moving candidate anti-EGFR ADCs through preclinical or clinical development demonstrate that the claimed ADC was non-obvious. Ex-2027, ¶90; *Advanced Display Sys. v. Kent State Univ.*, 212 F.3d

1272, 1285 (Fed. Cir. 2000) (“[E]vidence of failed attempts by others could be determinative on the issue of obviousness.”); *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (holding that “failure of two pharmaceutical companies to obtain FDA approval” constitutes objective indicia of non-obviousness that “must always be considered”).

2. Patent owner addressed the long-felt and unresolved need by creating the first ever approved anti-EGFR ADC globally.

On October 30, 2025, Patent Owner received approval for its anti-EGFR ADC drug, MRG003 (becotatug vedotin), in China for the treatment of certain nasopharyngeal carcinoma. Ex-2021, 000001. MRG003 embodies claims of the ’370 patent by using the BA03 antibody linked to a cytotoxic payload with a cleavable linker, and has since become the first approved anti-EGFR ADC worldwide.

In the U.S., MRG003 has been granted Fast Track designation and Breakthrough Therapy designation by the FDA for the treatment of certain nasopharyngeal cancer. Ex-2003, 000001.

The eventual regulatory approval of MRG003 (becotatug vedotin), after over 20 years since the approval of cetuximab and over 10 years of clinical trials for anti-EGFR ADCs that tested various antibodies, demonstrates that the selection of the specific BA03 antibody for use in an ADC was not obvious. *Apple Inc. v.*

Samsung Elecs. Co., 839 F.3d 1034, 1056 (Fed. Cir. 2016) (“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.”).

3. Petitioner’s ADC Candidate CPO301 has been successful so far as well.

Petitioner’s ’382 application describes four anti-EGFR ADC molecules. Three of them included pH-dependent antibodies, SWY2111, SWY2112, and SWY2113, and one of them used BA03 (SWY2110). *See* Ex-2008, ¶¶80-87 (showing sequences).

Petitioner is conducting clinical trials for its anti-EGFR ADC drug candidate, CPO301 (or SYS6010). Petitioner stated in a voluntary announcement that “CPO301 is a humanized monoclonal antibody, optimized from cetuximab, and conjugated with a topoisomerase I inhibitor.” Ex-2009, 000001-2. Further, the topoisomerase I inhibitor is connected to the antibody “via a cleavable glycine-glycine-phenylalanine-glycine tetrapeptide linker.” Ex-2010, 000001. Such description of CPO301 matches that of the SWY2110-ADC described in Petitioner’s patent application. Moreover, in Petitioners’ Response to Patent Owner’s Request for Discretionary Denial of Institution filed July 7, Petitioner acknowledges that the instant claims would “block Petitioner’s cancer treatments from the market.” Resp. to Discretionary Denial Request, 47. Accordingly, Patent

Owner believes that CPO301, which includes the non-tumor-specific antibody of the '382 application, also embodies claim 1 of the '370 patent.

CPO301 has been granted three Fast Track designations by the FDA. Ex-2009, 000001. More recently, it entered Phase III clinical trials in China, Ex-2031, 000001. CPO301, therefore, is likely the second most advanced anti-EGFR ADC candidate worldwide, just after MRG003.

The success of Petitioner's CPO301 candidate supports a finding of nexus between the claimed invention and the secondary consideration evidence. In particular, MRG003 and CPO301 both use the BA03 antibody and a cleavable linker, but differ in terms of the specific linker and payload used. CPO301's differences from MRG003 did not prevent it from being successful. This demonstrates that the success of the two most advanced anti-EGFR ADC candidates worldwide is attributable to their commonality—the claimed BA03 antibody and cleavable linker.

B. Petitioner considered different approaches in creating an anti-EGFR ADC and chose to copy the ADC claimed by the '370 patent.

Patent Owner's anti-EGFR ADC drug, MRG003 (becotatug vedotin), has recently received regulatory approval for the treatment of cancer and has become the first ever approved one worldwide after over 20 years since the first approval of an anti-EGFR antibody (i.e., cetuximab). Petitioner's anti-EGFR ADC

candidate, SYS6010 (CPO301), is believed to be the second most advanced worldwide. Both ADC molecules are encompassed by claim 1 of the '370 patent. Public records detailed below suggest that Petitioner copied core features of Patent Owner's MRG003 because of its clinical success.

In March 2015, Patent Owner entered into a patent licensing agreement with the owner of Liu, Shanghai JMT-Bio, Inc. ("JMT"). Ex-2032, 000035. Through the agreement, Patent Owner obtained exclusive license rights, under the Licensed Patent (Liu), to develop, manufacture, and commercialize ADCs. This and a few relevant events are listed in the table below, chronologically.

Time	Events (Patent Owner)	Events (Petitioner)
03/2015	Patent Owner obtained exclusive license rights from JMT, under Liu, to develop <u>ADC</u> with BA03	
08/2017	Patent Owner received IND approval	
01/2019		Petitioner acquired JMT
11/2022		Petitioner filed the '382 application, which referenced MRG003 and showed BA03-containing ADC to be <u>less safe than</u> pH-selective derivatives
10/2025	Patent Owner received regulatory approval for MRG003	
Present		Petitioner conducts Phase III trial for SYS6010 that contains BA03

Shortly following the license agreement, Patent Owner's effort in developing MRG003 was visible publicly. In August 2017, Patent Owner received regulatory approval for the investigational new drug (IND) application of MRG003.

While the Phase I trial of MRG003 was underway, Petitioner acquired JMT in January 2019. Ex-2033, 000129. It is important to note that JMT still retained the patent right to develop products that are not an ADC, and had the know-how and likely supplies of the BA03 antibody. Through such an acquisition, Petitioner acquired such know-how and supplies as well, after Patent Owner's publicly visible progress with MRG003.

The fact that Petitioner was aware of Patent Owner's effort and progress was reflected in Petitioner's own '382 application. The '382 application explicitly mentioned Patent Owner's MRG003 ADC in its discussion of background art. Ex-2008, 000003 ("Currently, MRG003 from Meiyake Pharmaceutical Co., Ltd.⁴, a subsidiary of Lepu Biopharma, is the first EGFR ADC drug in China to enter the clinical stage.").

In the '382 application, Petitioner followed the strategy of Wei to identify derivatives of the BA03 antibody (referred to as "SWY2110") with pH-selectivity.

⁴ "Meiyake" is a phonetic translation of Patent Owner's Chinese name.

Id., 000034. Three candidate pH-selective derivatives were obtained, including SWY2111, SWY2112 and SWY2113. As shown in the '382 application, not only did these BA03 derivatives have pH-selectivity, but their ADCs also “had reduced toxicity to normal tissues” as compared to one with the BA03 antibody. *Id.*, 000065.

Petitioner’s pre-clinical finding concerning the toxicity of these ADCs was consistent with the teaching of Wei, *i.e.*, pH-selective antibodies have a wider therapeutic index than their non-pH-selective counterparts. In other words, Petitioner has confirmed what a POSA would have expected of a BA03-containing ADC as having a narrower therapeutic window than those of Wei, Leanna, and the '382 application. Nonetheless, Petitioner ultimately chose to develop SYS6010 into a clinical drug candidate, an ADC molecule that contains the BA03 antibody, which they themselves had demonstrated to be less safe than the other candidates they had made and tested for pre-clinical studies.

Given that Petitioner determined multiple alternative options to be superior to the BA03 option but still decided to copy the BA03 feature of Patent Owner’s ADC, the only logical motivation behind such copying was Patent Owner’s clinical success with MRG003. Petitioner’s decision to copy the features of Patent Owner’s ADC, including the specific sequence of the BA03 antibody, after considering multiple superior options indicates that the claimed invention was non-obvious.

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1336 (Fed. Cir. 2016) (“The fact that a competitor copied technology suggests it would not have been obvious.”) (citing *Windsurfing Int’l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1000 (Fed. Cir. 1986) (“[C]opying the claimed invention, rather than one within the public domain, is indicative of non-obviousness.”)).

VIII. PETITIONER FAILED TO SHOW THAT CLAIM 13 IS OBVIOUS.

Claim 13 further specifies the cleavable linker as the vc linker and the cytotoxic payload as MMAE, and defines the drug-to-antibody ratio (p) as 1-8. Such a specific ADC was tested in the experimental examples of the ’370 patent, referred to as MYK-3. Against colorectal cancer cells, MYK-3 exhibited an inhibitory activity “much higher than those of monoclonal antibody BA03 itself and BA03 plus free vcMMAE.” Ex-1001, 19; Ex-2027, ¶91.

More importantly, in an in vivo safety testing of Example 3, “MYK-3 showed no significant change [of body weight] as compared with the control group (*see* FIG. 8), indicating that MYK-3 had no[] toxic effect of reducing body weight of mice.” *Id.*

Such an excellent efficacy-safety profile of MYK-3 (now known as “MRG003” and “becotatug vedotin”) has been further confirmed with clinical data both in the U.S. and in China. Also, more than 20 years since cetuximab was first approved in the U.S., the regulatory approval of MRG003 as the first anti-EGFR

ADC drug in the world underscores the unexpected nature of the claimed ADC. Ex-2027, ¶92. This further demonstrates that claim 13 is non-obvious.

IX. CONCLUSION

Petitioner relies on hindsight to argue that just because the BA03 antibody was known in the art, it would have been obvious to use it to replace antibodies in existing ADCs. The Petition fails to establish any motivation to make the proposed modification and fails to address compelling considerations that would have advised a POSA against doing so. As a result, the challenged claims are not unpatentable.

Date: January 21, 2026

Respectfully,
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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on this date, copies of the foregoing Patent Owner's Response and Exhibits 2020-2033 were served via email to all parties to this proceeding at the addresses indicated:

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**CERTIFICATE OF COMPLIANCE WITH
TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS,
AND TYPE STYLE REQUIREMENTS**

1. This Patent Owner's Response complies with the type-volume limitation of 14,000 words, comprising 13,618 words, as counted using the Microsoft Word software that was used to prepare this paper, excluding the parts exempted by 37 C.F.R. § 42.24(b).

2. This Patent Owner's Response complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word in 14-point Times New Roman.

Respectfully submitted,

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