

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

LEPU BIOPHARMA CO. LTD.,

Patent Owner.

Case No. IPR2025-00685

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

PATENT OWNER'S SUR-REPLY

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The epidermal growth factor receptor (EGFR) is frequently overexpressed on tumor cells, making it an attractive target for anti-tumor therapy. Despite numerous attempts to develop anti-EGFR antibody-drug conjugates (ADCs) since cetuximab's approval in 2004, none succeeded until Patent Owner's MRG003—the first anti-EGFR ADC approved for clinical use—in 2025. MRG003 embodies the claims of the '370 patent, employing the BA03 antibody linked to a cytotoxic payload via a cleavable linker. Although prevailing design strategies predicted that an antibody like BA03—with strong binding affinity but no tumor selectivity—would be undesirable for ADC development, Patent Owner discovered that combining BA03 with a cleavable linker unexpectedly achieved an effective balance of efficacy and toxicity.

Claim 1 is directed to an ADC comprising an anti-EGFR antibody with specific CDR sequences, a cleavable linker, and a cytotoxic agent. No prior art teaches the use of the claimed antibody in an ADC. Petitioner resorts to combining disparate references, proposing to substitute Liu's BA03 for Wei's and Leanna's respective antibodies. Petitioner's theories are driven by hindsight and fail to demonstrate motivation to combine with a reasonable expectation of success.

First, the purportedly desirable properties of BA03 that Petitioner identifies benefit only efficacy—while undisputedly harming the ADC's toxicity profile. No

POSA facing the paramount challenge of toxicity mitigation would have been motivated to use BA03 on that basis.

Second, Wei and Leanna each embodies a design strategy that mitigates toxicity through tumor selectivity. Replacing their tumor-selective antibodies with BA03 would undo those very strategies and their benefits, yet Petitioner identifies no superior property of BA03 over Wei's or Leanna's antibodies. With only downside and no upside, a POSA would have had no motivation to make the substitution.

Third, Petitioner makes no showing that the proposed BA03-vc-MMAE ADC would have been expected to have an acceptable therapeutic window—let alone one better than cetuximab-vc-MMAE's known unviable window. Without such a showing, there was no reasonable expectation of success.

Petitioner's only evidence that BA03 was suitable for use in an ADC is PO's own prospectus—published six years after the '370 patent's filing. This is textbook hindsight bias. And far from supporting Petitioner's obviousness theory, the success of PO's ADC is objective indicia of non-obviousness.

I. Petitioner’s Obviousness Theories Are Fundamentally Flawed For Failing to Address the Toxicity Side of the Therapeutic Window Equation

A. All known anti-EGFR ADC design strategies focused on a primary challenge: mitigating toxicity while maintaining efficacy.

EGFR’s expression by many tumors makes it an attractive target for anti-cancer therapies. POR, 7; Ex-2027, ¶12. But, because EGFR also has relatively high expression in other tissues such as the skin, the primary challenge in designing anti-EGFR ADCs was to control toxicity to normal tissues. POR, 8-11; Ex-2027, ¶13.

All three ADC references in the Petition—Wei, Leanna, and Tikhomirov—demonstrate this primary challenge. When cetuximab, a natural starting point for anti-EGFR ADC development, was combined with a cleavable linker, the ADC achieved efficacy only at the expense of unacceptable toxicity. *See, e.g.*, Ex-1009, 10-11; *infra* §III.A. Tikhomirov explains that “development of anti-EGFR immunoconjugates based on approved anti-EGFR antibodies ha[d] **not** been pursued because of concerns over enhanced skin toxicity” and “[a]nti-EGFR immunoconjugates [were] ... being designed **specifically to address these safety concerns.**” Ex-1009, 3 (emphasis added).

Wei and Leanna represent two strategies for mitigating toxicity. Wei uses antibodies preferentially activated in the acidic tumor microenvironment, reducing activity and toxicity in normal tissues. POR, 19-20; Ex-2027, ¶32. Leanna uses

antibodies targeting an EGFR epitope found only in tumors, limiting toxicity to normal tissues. POR, 20; Ex-2027, ¶¶33. Dr. Atanackovic confirmed that all known anti-EGFR ADC design strategies shared this common theme of mitigating activity on normal tissues. Ex-2027, ¶¶16-20.

Petitioner does not dispute that Wei, Leanna, and Tikhomirov all address the key challenge of mitigating toxicity and cannot identify a single anti-EGFR ADC design strategy known by 2015 that did NOT incorporate a mechanism for mitigating toxicity to normal tissues. Because the balance between efficacy and toxicity is captured by the concept of therapeutic window (Ex-2027, ¶9; Ex-1246, 235:12-236:4), a POSA would have regarded the therapeutic window as a primary consideration in designing an anti-EGFR ADC.

B. A POSA would not have been motivated to pursue ADC modifications expected to worsen or render unviable the therapeutic window.

Petitioner mischaracterizes PO as “fram[ing] the obviousness inquiry as if improving the therapeutic window ... were the only motivation to develop an anti-EGFR ADC.” Reply, 10. PO’s position is that because mitigating toxicity was the primary challenge in the field, a POSA would not have been motivated to modify an ADC in a manner known to worsen or render unviable the therapeutic window. POR, 24-35, 39-46, 47-50. Petitioner does not dispute this and indeed concedes that “an acceptable therapeutic index” is required. Reply, 10-11.

Petitioner's collateral arguments lack merit. First, Petitioner relies on Tikhomirov-346's statements regarding acceptable risks of anti-EGFR therapies and efforts to generate higher-affinity antibodies. Reply, 10. But these statements concern naked antibodies, not ADCs, for which toxicity is "amplified through conjugation to a potent cell toxin." Ex-1009, 3; Ex-2036 (Bournazos Dep.), 35:16-36:9 (admitting that a naked antibody's acceptable safety profile does not guarantee the same for a corresponding ADC).

Second, Petitioner cites ADCs against non-EGFR antigens to argue that "target-antigen expression on normal tissues has never been a prohibitive barrier to ADC development." Reply, 10-11. But PO never contended that EGFR expression on normal tissue is generally "prohibitive." POR, 7. Petitioner fails to address how those ADCs overcame toxicity on normal tissue and overlooks that some (e.g., ASG-5ME) failed due to an unacceptable therapeutic window. Ex-2036, 21:11-22:1 ("Q. Were you aware that the development of [the ASG-5ME ADC] was terminated due to its narrow therapeutic index...? A. No, because I never searched for that."); Ex-1200, ¶15.

C. Petitioner's obviousness theories are fundamentally flawed for relying on speculative efficacy benefits while disregarding toxicity implications.

Petitioner argues that Liu's advantages in factors "beyond therapeutic window" provide "ample motivation to select BA03 independent of any

therapeutic window considerations.” Reply, 11, 5-7. Relying on a review article titled “Antibody-drug conjugates: using monoclonal antibodies for delivery of cytotoxic payloads to cancer cells” (“Goldmacher”), Petitioner contends that “desirable ADC antibody properties include,” for example, “high binding affinity,” “long-circulation times,” and “ADCC.” Reply, 11 (citing Ex-1004, 177). Petitioner’s obviousness theory rests on BA03’s alleged possession of these properties. Reply, 11, 5-7. This argument has two fatal flaws.

First, Goldmacher itself undermines Petitioner’s argument, acknowledging that “it remains unknown how much any of these properties contribute to (**or interfere with**) the anti-tumor efficacy of ADCs” and that “there are no clinical data available that would compare the anti-tumor activities of ADCs differing in one or more of these antibody-dependent properties.” Ex-1004, 177 (emphasis added). Tellingly, Petitioner cannot identify any reference embodying an anti-EGFR ADC design strategy centered around the allegedly beneficial properties of BA03. Reply, 5-7.

Second, the identified properties are not “beyond” therapeutic window—they are alleged to benefit the efficacy side but undisputedly harm the toxicity side of the therapeutic window. Petitioner touts BA03’s “binding affinity, EGFR

inhibition, ADCC activity, and internalization¹” as “enhanced properties relevant to therapeutic efficacy,” but does not allege that any of them benefit toxicity mitigation. Reply, 7. Petitioner also fails to rebut PO’s showing that increased binding affinity harms the toxicity profile and therapeutic window (*infra* §III.B) and does not challenge Dr. Atanackovic’s explanation that increased EGFR inhibition and ADCC activity increase the killing of normal cells, merely quibbling with the magnitude of that effect. Reply, 27; Ex-2027, ¶¶63-64.

This reveals the fundamental flaw in Petitioner’s obviousness theories—a wholesale disregard of toxicity. Petitioner argues that purported efficacy advantages alone would have motivated a POSA to create an ADC, yet mitigating toxicity was the primary challenge in anti-EGFR ADC design and the focus of every ADC reference Petitioner relies on. *Supra* §I.A. A POSA would not have approached anti-EGFR ADC design with total disregard of toxicity or relied on Wei and Leanna without considering the very toxicity problem they set out to solve.

This flaw is particularly remarkable because the expected high toxicity of the proposed ADC was the very basis on which the claimed invention overcame

¹ Petitioner’s showing of BA03’s internalization properties is solely based on impermissible hindsight information. *Infra* §III.C.

the Examiner's rejections. Paper 6, 13; Ex-1004, 299–300, 306–13. Petitioner concedes that its obviousness theory aligns with those overcome rejections, further confirming its improper disregard of toxicity. Reply, 8-9.

Neither the Petition nor the Reply offers any affirmative showing that a POSA would have expected the proposed BA03-vc-MMAE ADC to have an acceptable toxicity profile or therapeutic window. This omission is dispositive. Petitioner cannot meet its burden to show obviousness while ignoring the primary challenge of the field and the very problem its primary references set out to solve.

II. Weighing Advantages and Disadvantages, a POSA Would Have Had No Reason to Modify Wei (Ground 1) and Leanna (Ground 2) as Proposed by Petitioner

Grounds 1 and 2 respectively replace Wei's Y104D/huY104D antibody and Leanna's Antibody 1 with Liu's BA03. Petitioner argues that "BA03's advantages outweigh any alleged toxicity concerns." Reply, 8. Not so. The proposed replacement would remove the tumor selectivity of Wei's and Leanna's antibodies, increasing toxicity to normal cells at the same level of efficacy. Meanwhile, all purported advantages are based on comparing BA03 with cetuximab—not with Wei's and Leanna's antibodies, which are NOT cetuximab. Petitioner thus establishes no advantage from the proposed substitution. Weighing the undeniable disadvantage against the total absence of advantage, a POSA would not have been motivated to make the proposed modification.

A. Liu’s BA03 antibody lacks the desirable tumor-selective properties exhibited by Wei’s and Leanna’s antibodies.

First, Wei’s antibodies exhibit tumor selectivity by having greater activity at acidic pH (tumor microenvironment) than at more neutral pH (normal tissues).

POR, 26-27 (citing Ex-1005, ¶¶0994, ¶¶1139; Ex-2027, ¶¶52-54). Wei’s data demonstrates that this pH-selectivity yields at least a 10-fold reduction in toxicity while maintaining equivalent efficacy compared with a cetuximab-based ADC. Ex-2027, ¶¶52-54.

The Reply denies Wei’s pH selectivity (Reply, 4), but this position directly contradicts the Petition:

Wei states that these cetuximab variants [e.g., Y104D] “exhibit 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.”

Pet., 16-17, 20; *see also* Ex-1002, ¶¶62, ¶¶68, ¶¶188; Ex-2026, 84:6-85:2 (Petitioner’s expert admitting pH selectivity); D.I., 37 (finding Wei’s antibodies exhibit pH selectivity). Petitioner’s self-serving attempt to walk back its own representations and disparage Wei’s credibility (Reply, 4)—only after recognizing that pH selectivity undermines its obviousness theory—should be rejected.

Second, Leanna’s antibody selectively binds to tumor cells by targeting an EGFR epitope expressed only on tumor cells, not on normal cells. POR, 41 (citing

Ex-2015, ¶15; Ex-2027, ¶68). Petitioner does not dispute that Leanna's Antibody 1 exhibits tumor selectivity. *See* Reply, 18-20.

In both cases, the tumor selectivity of these antibodies is independent of the differential expression of wild-type EGFR between tumor and normal tissues—a differential that is an innate feature of the patient and cannot be altered by antibody design. Tumor selectivity achieved through antibody design is critical to improving an antibody's ability to distinguish tumor from normal tissue, particularly for antigens such as EGFR where the innate expression differential is limited.

Third, there is no basis to believe that Liu's BA03 antibody possesses any tumor selectivity. POR, 28, 42 (citing Ex-2027, ¶57, ¶70). Dr. Atanackovic explained that (1) tumor-selective properties were extremely rare, (2) BA03 is a humanized version of cetuximab and humanization typically does not convey tumor selectivity, and (3) no evidence indicates BA03 was designed to have tumor-selective properties. Ex-2027, ¶¶57-58, ¶70; Ex-1246, 197:10-15, 204:7-205:7, 206:3-8. Despite bearing the burden of proof, Petitioner presents no evidence that a POSA would have believed BA03 had tumor selectivity. Reply, 5, 19-20.

Petitioner argues that “therapeutic selectivity can be achieved through mechanisms beyond pH selectivity or tumor-exclusive epitope binding,” but identifies no such

mechanism applicable to BA03. Reply, 12, 19.² This is unsurprising because BA03 is simply not tumor selective and a POSA would have had no reason to believe otherwise.³

Petitioner faults Dr. Atanackovic for “not explain[ing] why BA03 would not exhibit pH selectivity given that BA03 contains the very types of charged CDR mutations he identified as conferring that property.” Reply, 5. But Dr. Atanackovic addressed this directly: Liu’s mutation “was to increase the affinity” and “it’s extremely unlikely that the same mutation ... led to pH selectivity at the same time.” Ex-1246, 218:13-219:7. He further explained that pH selectivity is “close to

² Petitioner argues that EGFR overexpression on tumor tissue “provides an alternative basis for selectivity.” Reply, 12. However, this is precisely the type of selectivity that Wei and Leanna found insufficient to improve the toxicity profiles of anti-EGFR ADCs—which is why both references instead resort to tumor selectivity that operates independently of EGFR overexpression.

³ Petitioner criticizes Dr. Atanackovic for relying on Petitioner’s own ’382 application to show that BA03 is not pH-selective. Reply, 5. But Petitioner offers no explanation for why a POSA would somehow have believed BA03 to be pH-selective when it objectively is not.

impossible” to achieve absent extensive screening efforts like Wei’s. Ex-1246, 219:8-220:3.

B. Petitioner’s proposed replacement of Wei’s and Leanna’s antibodies with Liu’s BA03 would have been expected to increase toxicity without any countervailing advantage.

A POSA would have expected Petitioner’s proposed modification—replacing Wei’s and Leanna’s tumor-selective antibodies with BA03, which lacks tumor selectivity—to increase toxicity and harm the therapeutic window of the resulting ADC. *See* POR, 31-32, 42; Ex-2027, ¶59, ¶71. Without tumor selectivity, the ADC would have been expected to exhibit increased activity on normal cells without corresponding gains on tumor cells. *Id.* Petitioner does not dispute this mechanism. *See* Reply, 14-15. Because BA03 lacks the tumor-selective properties of Wei’s and Leanna’s antibodies (*supra* §II.A), the proposed modifications would have been expected to yield increased toxicity at the same level of efficacy.⁴

Petitioner has not established any advantage that would have been expected from the proposed modification. Petitioner argues that a POSA would have been

⁴ Petitioner’s argument that the challenged claims do not require pH selectivity or tumor-selective epitope binding (Reply, 4, 19) is beside the point. Patent Owner’s showing is directed to motivation to combine—not to whether the prior art teaches a claimed limitation.

motivated to use BA03 because it is humanized and has benefits over cetuximab. Pet., 40-42, 67-69. The POR pointed out that these arguments are untethered from Grounds 1 and 2: Wei's and Leanna's antibodies are already humanized, and Petitioner fails to establish that BA03 possesses any superior property over Wei's and Leanna's antibodies. POR, 32-34, 44-45. The Reply offers no response, thereby acquiescing that a POSA would not have expected any advantage from the proposed modifications of Wei's and Leanna's ADCs. *See generally* Reply, 3-21.

Petitioner strategically chose Wei's and Leanna's ADCs over the Examiner's approach of using a cetuximab-based ADC—understandably so, given that the cetuximab-based theory was overcome during prosecution. The Board should not permit Petitioner to have it both ways: abandoning cetuximab-based references when their shortcomings prove fatal, yet recycling cetuximab-based motivations to combine.

The relevant inquiry is whether the proposed modifications to Wei's and Leanna's ADCs—replacing huY104D/Antibody 1 (not cetuximab) with BA03—are advantageous. They are not. Weighing the significant disadvantage of increased toxicity at the same level of efficacy against the total absence of any established countervailing advantage, a POSA would have had no motivation to make the proposed modifications.

C. Wei and Leanna teach away or at least discourage a POSA from undoing their respective ADC design strategies.

As the POR explains, Wei and Leanna each started with cetuximab—an anti-EGFR antibody with no tumor selectivity—and developed improved antibodies to widen the therapeutic window: Wei through pH-selective antibodies and Leanna through an antibody targeting a tumor-exclusive EGFR epitope. POR, 50. Petitioner’s proposed modification would negate these very improvements. POR, 52.

Petitioner does not dispute that its proposed modifications undo Wei’s and Leanna’s design strategies and their resulting improvements, contending only that Wei’s showing of the inferiority of cetuximab-based ADCs does not amount to a teach-away. Reply, 14-15.⁵ But the Federal Circuit has found teach-away

⁵ Petitioner’s reliance on the 70%/80% CGI figures to argue that Y104D-MMAE is similar to cetuximab-MMAE is misplaced. Reply, 14-15. Those figures reflect maximum cell growth inhibition at maximum doses—doses Wei does not disclose and that are unachievable in any clinical setting. The operative comparison is the concentration required to achieve 50% CGI against non-tumor keratinocytes: cetuximab-MMAE reached that threshold at approximately 0.1 µg/mL, while Y104D-MMAE required 1 µg/mL—a 10-fold difference in therapeutic index. Ex-1005, ¶1131; Ex-2027, ¶54. Wei itself confirms this, explicitly concluding that “the

established when a proposed modification “would necessarily involve altering the inventive concept” of the prior art. *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1376 (Fed. Cir. 2021). That is precisely the case here—Petitioner’s modification necessarily alters Wei’s and Leanna’s inventive strategies of using a pH-selective or tumor-epitope-specific antibody⁶, rendering their ADCs “inoperative for [their] intended purpose” of providing a viable therapeutic window through selective tumor targeting. *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009).

curve for the Y104D-MMAE treatment was shifted to indicate significantly reduced growth inhibition” of keratinocytes. Ex-1005, ¶1131.

⁶ Petitioner’s new argument that BA03 is advantageous over Antibody 1 because EGFRvIII-specific antibodies “can treat only a minority of patients” is both untimely—raised for the first time in the Reply—and meritless. Reply, 20. The purported broader patient coverage is simply the consequence of abandoning Leanna’s tumor-selective design strategy, a trait shared by any antibody targeting wild-type EGFR. By Petitioner’s own logic, there would be equal motivation to replace Antibody 1 with cetuximab—the very starting point Leanna sought to improve upon.

Even if Wei and Leanna do not teach away, both references would have discouraged a POSA from undoing their beneficial design strategies. *See 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...”). Petitioner does not propose replacing Wei’s or Leanna’s design strategy with an alternative strategy known to be effective—it simply proposes reverting to an antibody with no tumor selectivity. This is precisely what the Federal Circuit found impermissible in *Eisai Co. v. Dr. Reddy’s Laboratories, Ltd.*, 533 F.3d 1353, 1358 (Fed. Cir. 2008), which held there was “no discernible reason for a skilled artisan to begin with [the prior art compound] only to drop the very feature ... that gave [its] advantageous property.” So too here: Petitioner chooses Wei’s and Leanna’s ADCs as the bases of its theories yet provides no reason to drop the very features that confer their advantageous tumor selectivity.

D. Petitioner’s new obviousness theories are untimely and unavailing.

Confronted with the aforementioned deficiencies, Petitioner now contends that its theory is not limited to “start[ing] with the ADCs disclosed in Wei and Leanna” and that a POSA “could have also started with the BA03 antibody.” Reply, 2-3. Petitioner further claims Wei discloses “a cetuximab-MMAE

conjugate” and Leanna is “not limited to Antibody 1 or to any particular anti-EGFR antibody.” Reply, 14, 18.

To the extent Petitioner now advances a theory not involving substitution of Wei’s or Leanna’s antibodies with BA03, it is untimely. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1367 (Fed. Cir. 2015) (holding that a petitioner who asserted in its reply previously unidentified prior-art disclosures “to make a meaningfully distinct contention” was impermissibly raising a new theory of unpatentability). The Petition’s theories are plainly substitution-based. For Ground 1, the Petition relied on Wei’s “Y104DMc-vcPAB-MMAE ADC” and the Examiner’s theory of “**replac[ing]** cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu.” Pet., 37, 40-42. For Ground 2, the Petition relied on Leanna’s “Antibody 1-vc-MMAE ADC” and the Examiner’s theory of “**replac[ing]** the BA03 antibody in place of cetuximab ADCs.” Pet., 65, 69. The Reply confirms this framework, relying on “substantial identity” between BA03 and huY104D and similarity between BA03 and Antibody 1⁷ (Reply, 9, 19-20), and stating that “substituting one humanized anti-EGFR antibody (BA03) for

⁷ The alleged similarity lacks merit as these antibodies fundamentally differ in terms of tumor selectivity. *Supra* §II.A.

another (huY104D) in a proven platform would yield a functional product with predictable properties” (Reply, 16-17).

Regardless of which reference is primary, a POSA would not have been motivated to combine the references to use BA03 in place of Wei’s or Leanna’s antibodies, given the expected disadvantages and contradiction of established design strategies. *Supra* §II.B; *see* Reply, 8-9 (analogizing the new theory that “started with BA03” with the Examiner’s theory of “us[ing] BA03 in place of cetuximab in ADCs”). Nor does the Petition provide support for any theory involving antibodies other than Wei’s Y104D/huY104D and Leanna’s Antibody 1, or directly combining BA03 with a linker and payload outside an existing ADC. To the extent Petitioner asserts such theories, it cannot meet its burden of proof.

III. A POSA Would Have Expected the Proposed ADC to Have an Unviable Therapeutic Window

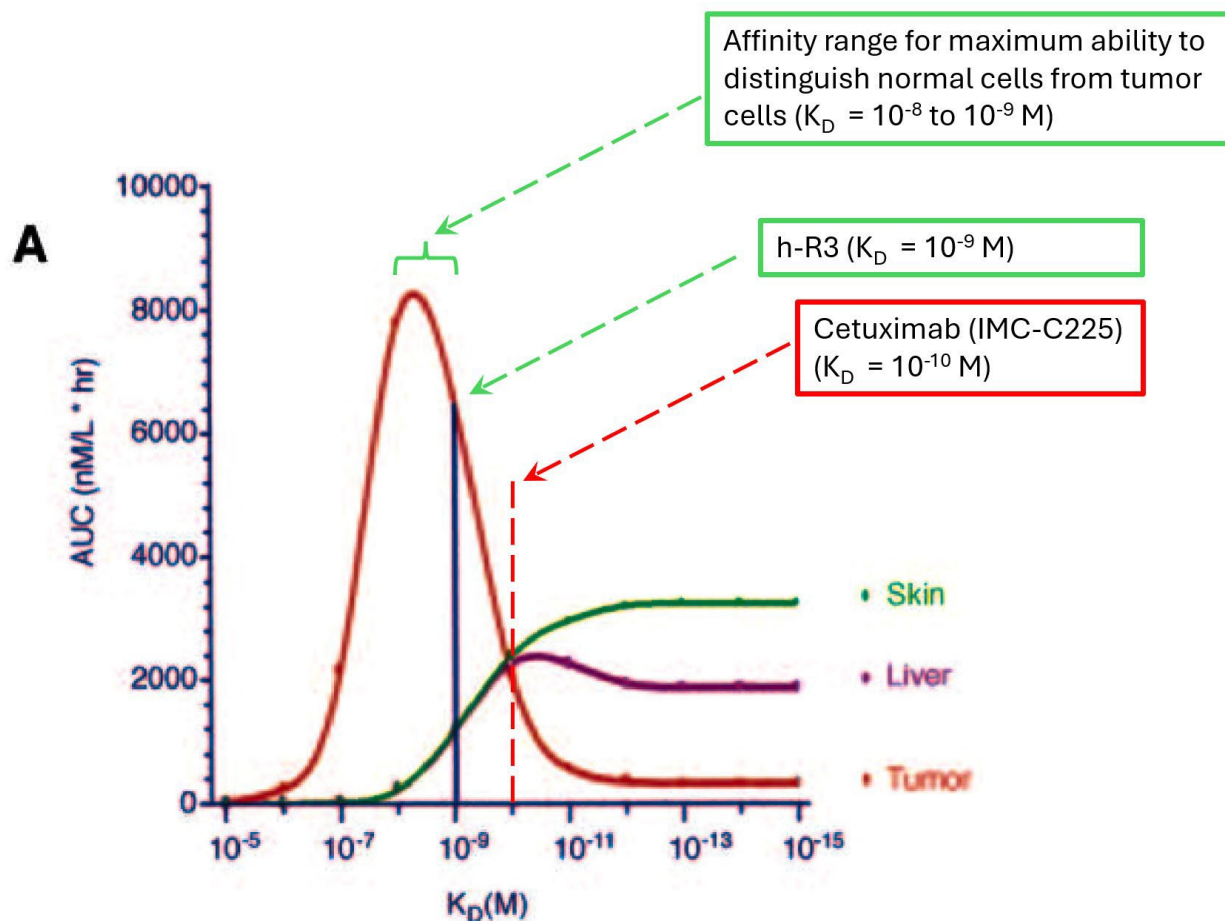
A. Undisputed facts confirm a POSA would have expected BA03-vc-MMAE’s therapeutic window to be no better than that of cetuximab-vc-MMAE, which was known to be unviable.

Tikhomirov teaches that cetuximab-vc-MMAE was unviable due to an unduly narrow therapeutic window. POR, 48; Ex-2027, ¶¶61; Ex-1009, 31, 10-11, Fig. 13. The Reply does not address, let alone dispute, this teaching. Dr. Bournazos likewise evades it by broadly discussing “cetuximab-class and panitumumab-class ADCs”—concepts nowhere mentioned in Tikhomirov and unrelated to PO’s argument. *See* Ex-1200, ¶¶80-84.

Petitioner does not—and cannot—contend that BA03-vc-MMAE would have been expected to have a better therapeutic window than cetuximab-vc-MMAE. Petitioner’s own expert calls BA03 and cetuximab “substantially identical” (Ex-1200, ¶73), and BA03 lacks the tumor selectivity of huY104D and Antibody 1 (*supra* §II.A). A POSA would thus have had no reason to expect BA03-vc-MMAE’s therapeutic window to exceed cetuximab-vc-MMAE’s known unviable window. This alone warrants finding that a POSA would have been discouraged from creating BA03-vc-MMAE.

B. Petitioner fails to rebut Patent Owner’s showing that BA03-vc-MMAE’s therapeutic window was expected to be worse than cetuximab-vc-MMAE.

A POSA would have expected BA03-vc-MMAE to have an even worse therapeutic window than cetuximab-vc-MMAE because BA03’s binding affinity is higher than cetuximab. POR, 47-48; Ex-2027, ¶36, ¶61. Dr. Atanackovic explained the known negative correlation between binding affinity and tumor selectivity: relying on Crombet’s Figure 3A, he showed that antibodies with K_D between 10^{-8} and 10^{-9} M best distinguish tumor from normal cells, and that selectivity decreases as binding affinity increases beyond that range. Ex-2027, ¶¶60-61. This figure is reproduced below:



Ex-2022, Fig. 3A (annotations added); POR, 15-16; Ex-2027, ¶¶24-25. Garrido and Tikhomirov-346 further validated Crombet's model. Ex-2027, ¶¶26-29 (citing Ex-2011, Ex-2023).

Petitioner does not deny the negative correlation between binding affinity and tumor selectivity, nor that poorer tumor selectivity would worsen the therapeutic window. *See* Reply, 12-13. Absent any contradicting evidence, PO's showing that BA03-vc-MMAE's therapeutic window was expected to be worse than cetuximab-vc-MMAE's stands unrebutted.

Petitioner's criticism of Crombet (Reply, 12-13) lacks merit. Petitioner attacks Crombet as being "scientifically unreliable." Reply, 12-13 (citing Ex-1200, ¶44, ¶46). This perpetuates Petitioner's tactic of disparaging any evidence that it does not have a response to. *See, e.g.*, Reply, 4 (attacking Wei's credibility); Pet., 30 (attacking Tikhomirov's methods); Ex-2036, 29:10-14 (Dr. Bournazos stating "no need" to verify data when "they support my own analysis"). But Crombet is "a leading paper in the field," published in the Journal of Clinical Oncology, peer-reviewed by "leading expert[s]," and extensively validated. Ex-1246, 106:17-108:20. Regardless of Dr. Bournazos' doubts, a POSA reading Crombet would have learned its teaching on the negative correlation between binding affinity and tumor selectivity.

Petitioner's criticism also falls short of undermining Crombet's results. Petitioner complains that Crombet "us[es] data from different clinical trials at different dosages" (Reply, 13), but does not explain how this is somehow prohibited in scientific research or invalidates the correlation shown in Figure 3A. Dr. Atanackovic confirmed on cross-examination that the specific trial configurations and dosages would not "change anything" about Crombet's teaching on the negative correlation between affinity and tissue selectivity. Ex-1246, 88:19-89:14, 98:4-99:11. Petitioner's reliance on Crombet's statement that "higher affinity is not necessarily the best" (Reply, 13) is self-defeating—this

statement further supports the negative correlation between binding affinity and tumor selectivity.

Furthermore, Garrido independently confirms Crombet's negative correlation. Ex-2027, ¶27; POR, 17-18. Garrido further explains a mechanism for the negative correlation: anti-EGFR antibodies with at least 10-fold lower affinity than cetuximab require a threshold EGFR density for stable binding that normal cells do not meet. Ex-2027, ¶¶28-29 (citing Ex-2023, Fig. 6, 000008). Because the Reply does not address Garrido, and this evidence stands undisputed.

Second, Petitioner argues that Crombet “was developed for naked antibodies” and is “inapplicable to ADC design.” Reply, 12-13. But Tikhomirov-346 directly demonstrates how characteristics of an antibody's binding affinity and tumor selectivity are applicable to ADC design. Tikhomirov-346 reduces antibody binding affinity to 10-fold or more weaker than cetuximab, which “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.” Ex-2027, ¶26 (citing Ex-2011, 3:12-16, 5:22-30); POR, 17. Tikhomirov-346's antibody was used to form ADCs with broad therapeutic windows: “mutant antibodies can be generated that bind highly selectively to cells that present EGFR at abnormally high density, and [] these antibodies may be

useful in oncology and other diseases as *antibody-drug conjugates with broad therapeutic windows*.” Ex-2011, 27:15-19 (emphasis added).

Because a POSA would have known the negative correlation between binding affinity and tissue selectivity, the POSA would have expected BA03-vc-MMAE to have a worse therapeutic window than cetuximab-vc-MMAE due to its weaker ability to selectively target tumor tissue, and thus would have been dissuaded from creating BA03-vc-MMAE.

C. Petitioner’s only answer to Patent Owner’s showing that a POSA would have expected BA03-vc-MMAE to fail due to an unviable therapeutic window is impermissible hindsight.

Faced with PO’s showing that BA03’s high binding affinity would have been expected to produce an unviable therapeutic window, Petitioner asserts that high affinity is desirable because “[c]linical ADC doses are substantially lower.” Reply, 13. But lower dosing relative to unconjugated antibodies is a feature common to all ADCs, and Petitioner cannot identify a single anti-EGFR ADC design strategy⁸ known by 2015 that pursued higher binding affinity. Reply, 13. Instead, Petitioner resorts to PO’s 2022 Global Offering prospectus—a document published **six years after the ’370 patent was filed**—to argue that higher EGFR

⁸ The “HER2 data” that Petitioner relies on (Reply, 13) is not related to the EGFR antigen or tissue selectivity. Reply, 13.

binding affinity is desirable. Reply, 13 (citing Ex-2032, 000310). This is textbook impermissible hindsight reasoning.

Petitioner's hindsight extends further. Recognizing that BA03's higher binding affinity would have been considered detrimental, Petitioner now asserts BA03's "rapid[] internaliz[ation]" as its leading advantage over cetuximab despite the Petition's complete silence on internalization. *Compare* Reply, 5-6 with Pet. 37-42, 65-69. But Liu includes no teachings about BA03's internalization properties, as Petitioner's expert admits. *Compare* Reply, 5 (relying on ¶¶0154-0160 of Liu as teaching rapid internalization) with Ex-2036 (Bournazos Dep.), 37:6-38:14 (admitting those paragraphs are "[n]ot [about] internalization"). Petitioner's attempt to tie internalization to Liu's binding affinity teachings (Reply, 13) is likewise refuted by its own expert. Ex-2026 (Bournazos Dep.), 49:13-16 ("Q. Is antibody binding in any way related to internalization? A. No."). Petitioner also mischaracterizes Dr. Atanackovic's testimony on this point: the proposition that "stronger binding affinity can result in a higher degree of internalization of ADC" (Reply, 13) was Petitioner's question, to which Dr. Atanackovic merely responded "[t]hat's possible." Ex-1246, 345:11-16, 50:19-51:4. The earliest evidence of BA03's internalization properties is again PO's 2022 prospectus. Reply, 5-6.

That Petitioner's sole evidence for its arguments regarding binding affinity and internalization, PO's 2022 prospectus, postdates the '370 patent by at least six years is itself a concession that no contemporaneous basis existed for a POSA to view these properties as desirable.

Other than hindsight, Petitioner has no meaningful answer to PO's showing that a POSA would have expected the proposed ADC to fail. Both experts agree that a POSA would have considered "the balance between cancer killing activity of ADC and its toxicity" in assessing whether an ADC would succeed, and Dr. Bournazos admitted that "toxicity" is among "obstacles that can make the effort of creating an ADC unsuccessful." POR, 54 (citing Ex-2027, ¶82; Ex-1002, ¶108; Ex-2026, 72:11-73:8, 59:13-60:4). The Reply does not dispute these showings. As the POR explains, a POSA would have expected BA03's higher-than-cetuximab binding affinity to yield an even worse therapeutic window than cetuximab-vc-MMAE's known unviable window. POR, 55.

The Reply confirms Petitioner has no answer. Reply, 15-17. Petitioner first argues that cleavable linkers and the vc-MMAE configuration were validated. Reply, 15-16. This is beside the point—PO's argument is that BA03's high binding affinity would have been expected to render the proposed ADC unviable, not that the linker-payload technology was unproven. Second, Petitioner claims Wei's ADC would have given a POSA confidence in similar ADCs (Reply, 16), but

BA03 is not similar as it lacks the pH selectivity that distinguishes Wei's antibody.

Supra §II.A. Third, Petitioner repeats its assertions about BA03's "high-affinity target binding, efficient internalization, and anti-tumor activity." Reply, 16.

However, as explained above, BA03's internalization properties were not known in the relevant timeframe. High-affinity target binding has been shown to harm the therapeutic window (*supra* §III.B), and Petitioner provides no evidence that any of these properties would have been expected to cure cetuximab-vc-MMAE's fatal toxicity problem. Finally, Petitioner's assertion that ADC construction was predictable (Reply, 16-17) is irrelevant to whether BA03-vc-MMAE would have been expected to fail due to its unviable toxicity profile. Petitioner's failure to rebut this showing warrants a finding that a POSA would not have had a reasonable expectation of success.

IV. Petitioner Fails to Overcome Objective Evidence of Non-Obviousness

The POR recounts objective evidence demonstrating non-obviousness. POR, 56-66. Petitioner does not dispute the vast majority of key facts supporting PO's showing.

First, Petitioner does not dispute that despite strong industry interest in anti-EGFR ADCs, multiple clinical trials before MRG003 were all terminated. POR, 57-60. Petitioner admits these failures "involve[ed] ADCs with different antibodies, linkers, or payloads than those claimed" and used the conventional

design strategies Dr. Atanackovic identified. Reply, 24. This confirms a long-felt and unresolved need for a clinically viable anti-EGFR ADC.

Second, Petitioner does not dispute that PO's MRG003 and Petitioner's CPO301 are the two most advanced anti-EGFR ADCs worldwide, nor does Petitioner dispute that MRG003 addressed the long-felt need for a clinically viable anti-EGFR ADC. Tellingly, Petitioner attributes MRG003's success to "BA03's roughly six-to-sevenfold higher EGFR binding affinity over cetuximab," characterizing it as "competitive advantages" in light of post-filing information. Reply, 13 (citing PO's 2022 prospectus). Yet the very high binding affinity Petitioner now credits for MRG003's success was precisely the feature a POSA would have regarded as "disqualifying" (to use Petitioner's own word, Reply, 13) prior to PO's invention. *Supra* §III.B. That the attribute once expected to doom an anti-EGFR ADC turned out to be the key to its clinical success underscores the non-obvious nature of PO's invention.

Third, Petitioner contends that "PO has not shown that MRG003's alleged success stems from features unique to the claims" (Reply, 23), yet fails to dispute PO's showing on this point. MRG003 and CPO301 both use BA03 and a cleavable linker but differ in terms of the specific linker and payload used. POR, 62; Reply, 25. As different companies, PO and Petitioner also differ in "clinical development expertise, manufacturing capability, regulatory strategy, or the dose and schedule

used in trials.” Reply, 23. The success of the two most advanced anti-EGFR ADCs worldwide is thus attributable to their commonality—the claimed BA03 antibody and cleavable linker—establishing nexus. POR, 62. Indeed, Petitioner itself attributes MRG003’s efficacy to BA03’s rapid internalization and high binding affinity (Reply, 5, 13), while identifying nothing distinctive about MRG003’s particular linker or payload. Petitioner’s failure to come forward with rebuttal evidence is fatal to its nexus challenge. *Crocs, Inc. v. Int’l Trade Comm’n*, 598 F.3d 1294, 1311 (Fed. Cir. 2010) (“Once the patentee demonstrates a prima facie nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger.”).

Finally, Petitioner argues that differences in linker and payload “defeats any inference of copying.” Reply, 25. Not so. Petitioner does not dispute that it evaluated different approaches to creating an anti-EGFR ADC and chose to use the BA03 antibody—to which PO held an exclusive ADC-development license—considering the success of PO’s ADC candidate. POR, 62-66. This is not merely a “competing product that arguably falls within the scope of a patent,” but an affirmative decision to copy PO’s patented product features—precisely the evidence required to establish copying. *Liqwd, Inc. v. L’Oreal USA, Inc.*, 941 F.3d 1133, 1139 (Fed. Cir. 2019); *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004).

Date: June 13, 2026

Respectfully,

SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

/Christopher Ponder/

Christopher Ponder (Reg. No. 77,167)
Attorneys for Patent Owner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Patent Owner's Sur-Reply contains 5,545 words and therefore complies with the 5,600 word type-volume limit specified by 37 C.F.R. §42.24(c)(4). The word count does not include those portions excepted by 37 C.F.R. §42.24(c) and was calculated by Microsoft Word 365.

Date: June 13, 2026

/Christopher Ponder/
Christopher Ponder (Reg. No. 77,167)

CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on this date, copies of the foregoing Patent Owner's Sur-Reply and Exhibits 2035-2036 were served via email to all parties to this proceeding at the addresses indicated:

Joe G. Chen, Ph.D. (joechen@foxrothschild.com)

Howard S. Suh (hsuh@foxrothschild.com)

Ryan N. Miller (rmiller@foxrothschild.com)

ipdocket@foxrothschild.com

Date: June 13, 2026

Respectfully,
SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

/Christopher Ponder/
Christopher Ponder (Reg. No. 77,167)
Attorneys for Patent Owner