

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. IPR025-00685

Patent No. 10,792,370

**EXPERT DECLARATION OF
STYLIANOS BOURNAZOS, Ph.D.**

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I, Stylianos Bournazos, Ph.D., declare as follows:

1. I have been retained by counsel for CSPC Megalith Biopharmaceutical Co., Ltd. (“Petitioner”) in connection with the inter partes review (“IPR”) of U.S. Patent No. 10,792,370 (“the ’370 patent”) (EX1001), which is originally assigned to Shanghai Miracogen Inc. and recently assigned to Lepu Biopharma Co., Ltd. (“Patent Owner”). I previously submitted a declaration in support of Petitioner’s IPR petition for the ’370 patent (“Bournazos Decl.”) (EX1002). I now submit this reply declaration in response to the Patent Owner’s Response (“POR”) and the Declaration of Dr. Djordje Atanackovic (“Atanackovic Decl.”) (EX2027), submitted on behalf of Patent Owner.

I. INTRODUCTION

2. In preparing this reply declaration, I have reviewed the Patent Owner’s Response and Dr. Atanackovic’s declaration. I have also reviewed additional scientific literature and exhibits listed in the Table of Exhibits, as well as the materials listed in my original declaration (EX1001-EX1035). I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

3. I am being compensated for my time in connection with this IPR at my standard consulting rate of \$850 per hour. My compensation is not dependent in any way upon the outcome of this matter.

II. SUMMARY OF OPINIONS

4. After carefully reviewing Dr. Atanackovic's declaration and the Patent Owner's Response, it is my opinion that the arguments presented therein are scientifically unsound and fail to undermine the reasoning and conclusions set forth in my original declaration.

5. The Patent Owner's and Dr. Atanackovic's characterization of EGFR expression on normal tissues as a unique and prohibitive barrier to developing antibody drug conjugates ("ADCs") targeting EGFR is contradicted by the established history of ADC development, which demonstrates that target expression on normal tissues has never been a prohibitive barrier to the development of clinically efficacious ADCs. *See* POR at 7-11; EX2027, ¶¶12–13; *see infra* § III.

6. Dr. Atanackovic's heavy reliance on the Crombet model (EX2022) to predict the therapeutic window of anti-EGFR ADCs is scientifically inappropriate because the model was developed for naked antibodies, not ADCs, and relies on unvalidated assumptions, undisclosed parameters, and a comparison that is confounded by multiple variables. *See* EX2027, ¶¶22–26; EX2022 at 000003–000005, 000007; *see infra* § VII. Importantly, Crombet never categorically rejects pursuing anti-EGFR ADCs using high affinity anti-EGFR antibodies, such as cetuximab or BA03.

7. The assertion that higher antibody binding affinity is a disfavored property for ADC design contradicts established practices in ADC development, where higher affinity is generally viewed as beneficial for efficient target engagement and internalization, as recognized by Patent Owner's own document. *See* EX2027, ¶¶25-26, 60–61; *see infra* §§ VI, VIII; EX2032 at 000310 (“MRG003 has demonstrated the following competitive advantages: ... The mAb component of MRG003 is a humanized antibody, which has approximately six to sevenfold **increased binding affinity** to human EGFR, compared with cetuximab. It **facilitates rapid internalization** of MRG003 into tumor cells as demonstrated in our *in vitro* assays.”).

8. Dr. Atanackovic's opinion that the BA03 antibody lacks pH selectivity rests on improper and internally inconsistent grounds. He relies in part on post-filing data from WO 2023/088382, which he admits was not available to a person of ordinary skill in the art at the time of the '370 patent filing, and in part on an unsupported assumption that BA03, as a humanized cetuximab variant, would not be pH selective. At the same time, Dr. Atanackovic acknowledges that pH-selective antibodies are typically generated by introducing charged residues, such as aspartic acid, into complementarity-determining regions. Yet he cannot explain why BA03 would not exhibit pH-selective properties despite containing the same types of

charged CDR mutations that he asserts typically confer pH selectivity. *See infra* § XVI.

9. The dismissal of BA03's advantages over cetuximab in EGFR phosphorylation inhibition and ADCC activity overlooks well-established scientific principles demonstrating that receptor antagonism and Fc effector function are critical therapeutic mechanisms for anti-EGFR antibodies and ADCs. *See* EX2027, ¶¶62–64; *see infra* §§ IX–X.

10. BA03's advantages over Leanna's Antibody 1, including broader patient applicability, resistance to antigen-loss escape, and full-length EGFR targeting, would have motivated a POSA to replace Leanna's antibody with BA03. *See* EX1006, 24:19–24; *see infra* § XI.

11. Therefore, it is my opinion that Dr. Atanackovic's declaration and the Patent Owner's Response fail to establish that a POSA would have been deterred from developing an anti-EGFR ADC based on the BA03 antibody.

III. EXPRESSION OF ADC TARGETS IN NORMAL TISSUES HAS NEVER BEEN A BARRIER TO ADC DEVELOPMENT

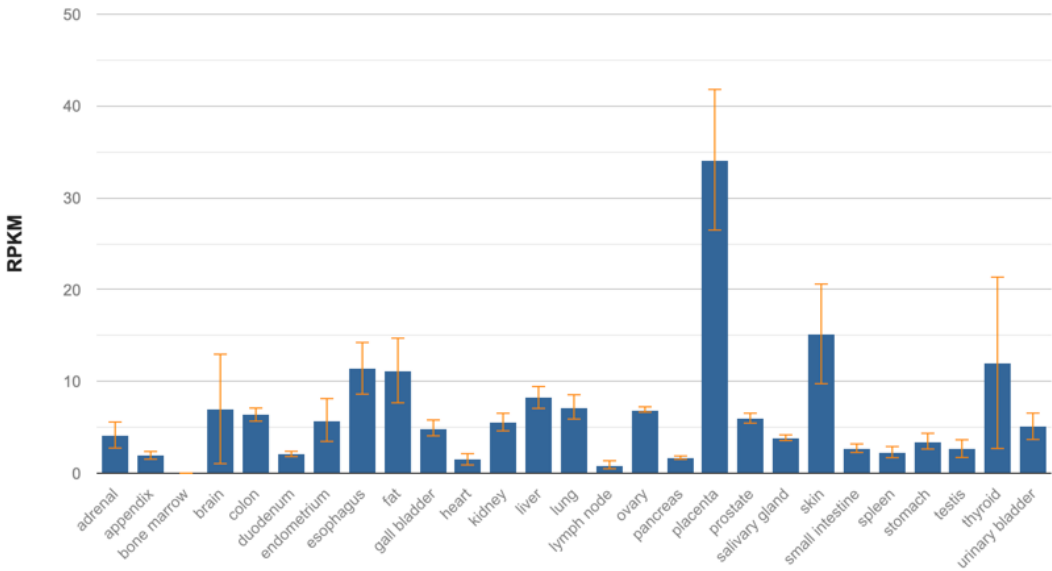
12. A central premise of both the Patent Owner's Response and Dr. Atanackovic's declaration is that EGFR's expression in normal tissues renders it uniquely challenging as an ADC target. *See* EX2027, ¶13; POR at 7–10. Dr. Atanackovic asserts that “EGFR's relatively high expression in normal tissues

differentiates it from other antigens” and concludes that “[a]n 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.” EX2027, ¶13. He further speculates that EGFR expression in normal tissues “is likely why, more than 20 years since cetuximab was approved as an anti-cancer drug, still no anti-EGFR ADC was approved anywhere in the world when the Petition was filed.” *Id.*

13. First, Patent Owner and Dr. Atanackovic ignore that the lack of an approved anti-EGFR ADC at the time the Petition was filed can be attributable to numerous factors unrelated to the therapeutic window, including the fact that cetuximab is not a humanized anti-EGFR antibody and business decisions, none of which were addressed or ruled out. Second, Patent Owner and Dr. Atanackovic’s speculation is based entirely on a single comparison of tissue expression levels between EGFR and CD30, and ignores well-established scientific evidence and extensive clinical experience from multiple ADC development programs in which targets with significant normal tissue expression were successfully advanced into clinical trials. EX2027, ¶13; POR at 7–10.

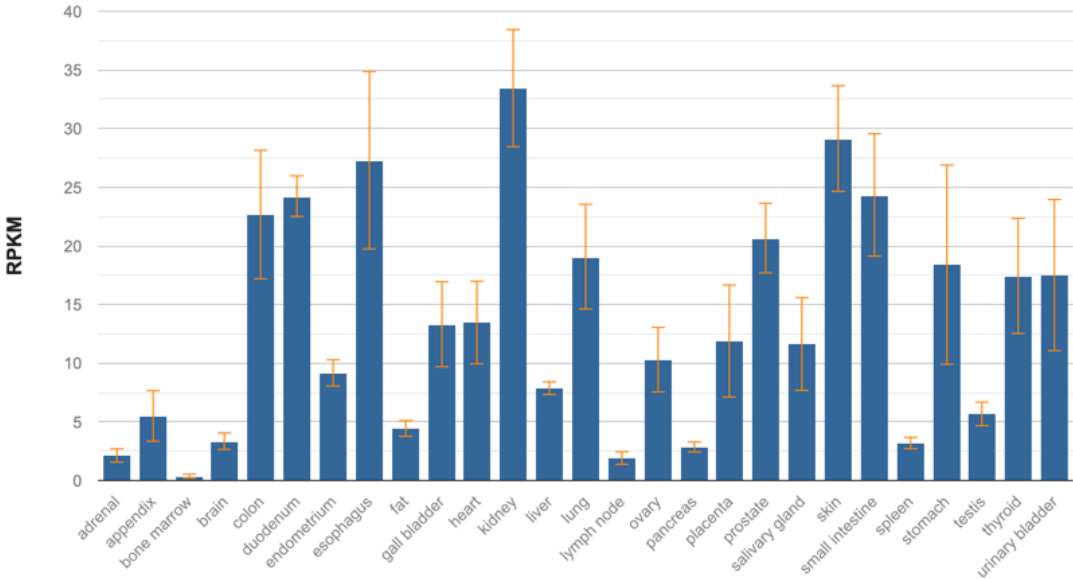
14. Using the same exact method and datasets that the Patent Owner used in their response, I analyzed the expression levels among 27 normal tissues for several targets of ADCs that were approved by FDA or in clinical trials by 2015, and the results are presented in Figure 1 below. *See* POR at 8-9; *see* EX1201–1209.

EGFR

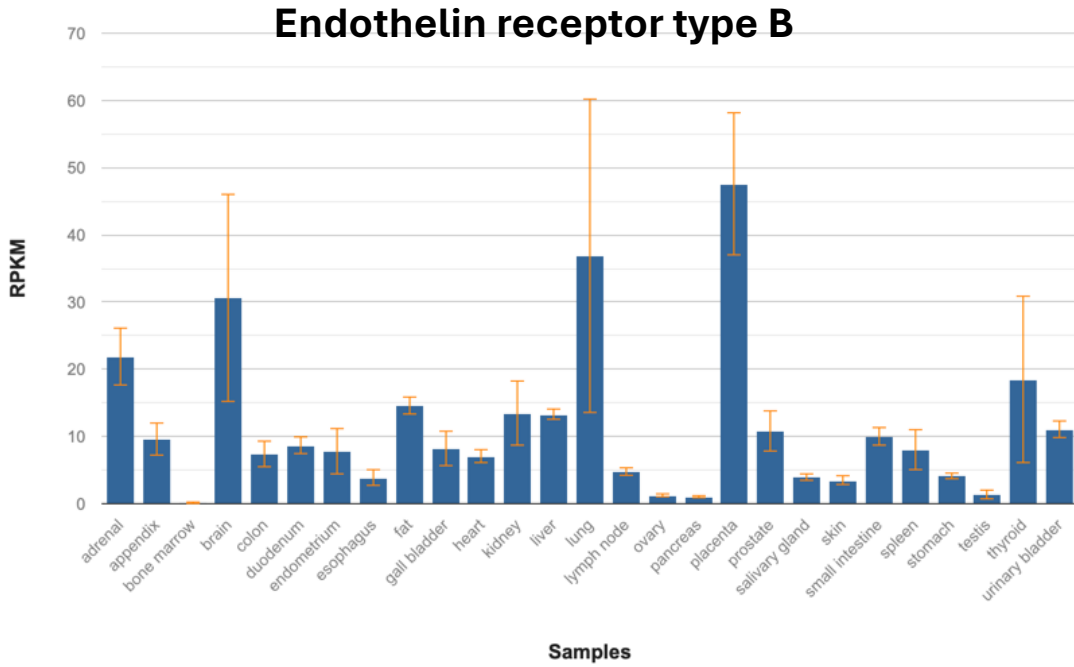
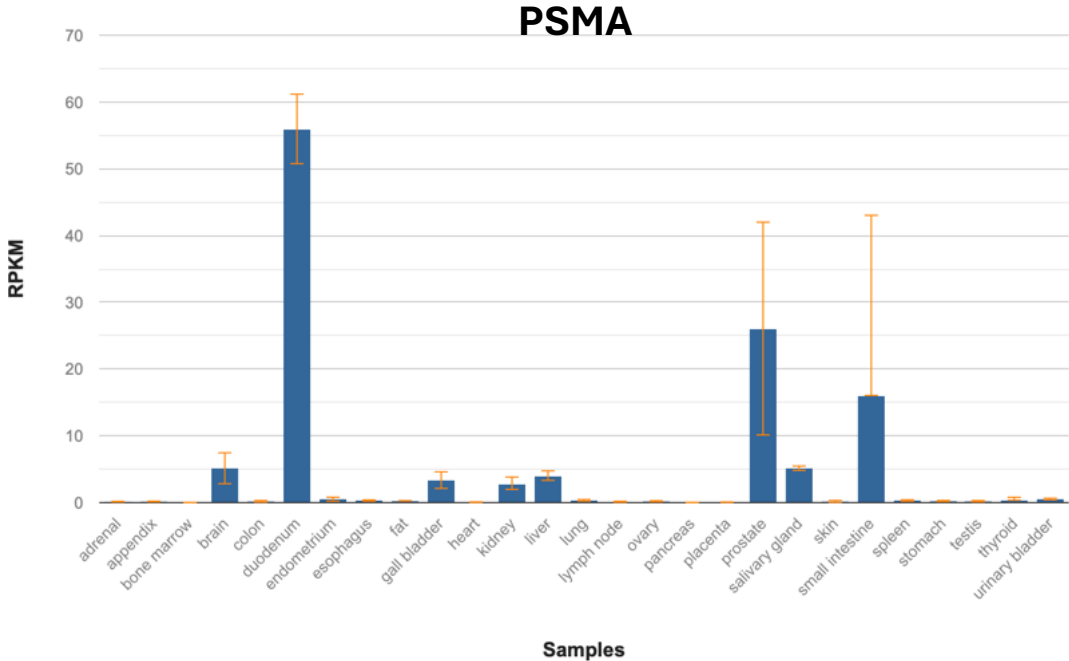


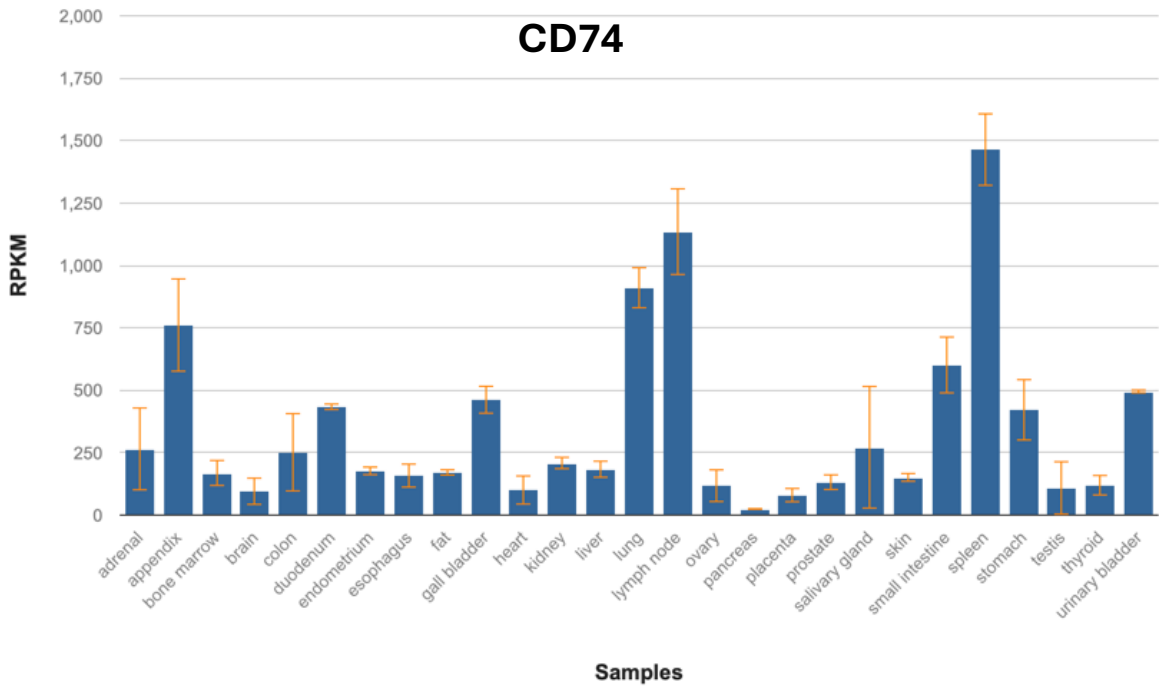
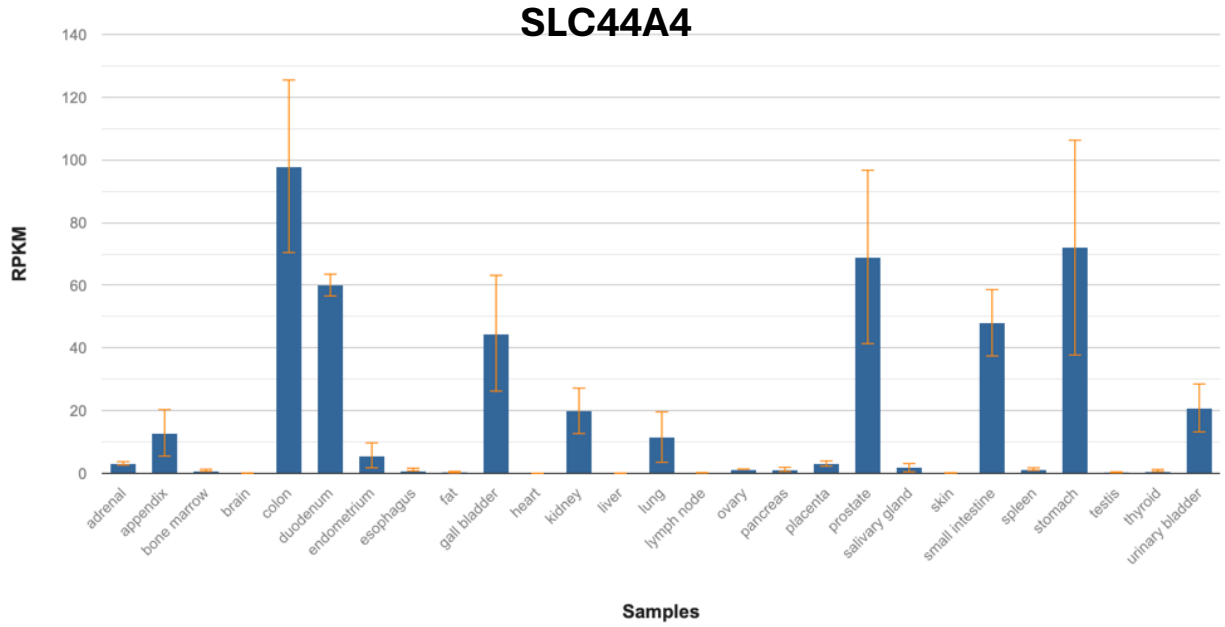
Samples

HER2



Samples





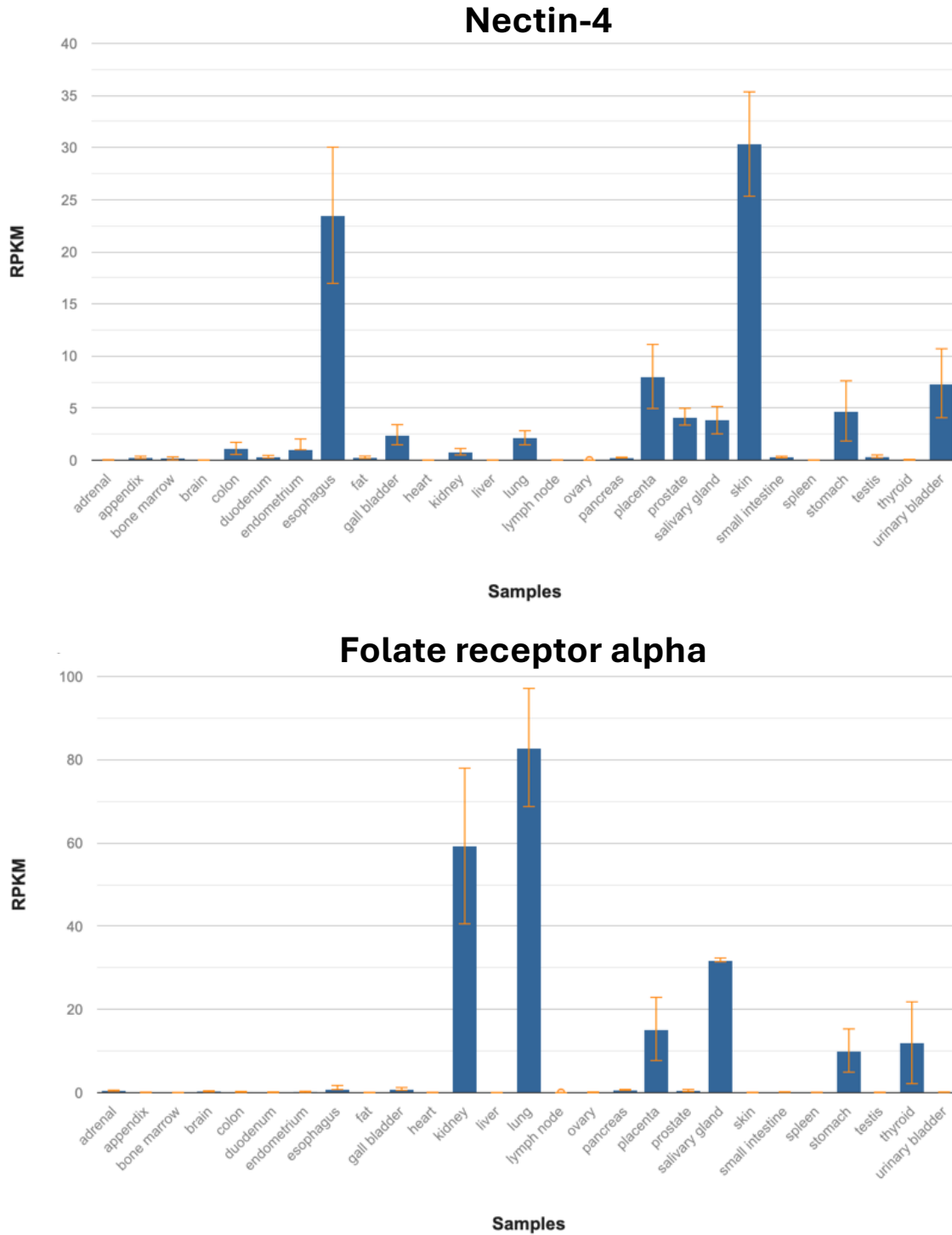


Figure 1

15. This analysis demonstrates that the expression of the target antigen on normal tissues has never been a prohibitive barrier to ADC development. Numerous

ADCs that entered clinical testing well before 2015 were directed against antigens that are not only expressed in tumor cells but are also present on some subsets of normal cells and tissues, including HER2, Nectin-4, folate receptor alpha, TROP-2, CD74, Endothelin receptor type B, PSMA, and SLC44A4. *See* EX1201–1210. In this respect, these targets are not fundamentally different from EGFR, which is likewise expressed in normal tissues. *Id.* Table 1 below shows a list of ADCs that had been in clinical development before 2015 and their respective targets. *Id.*

Table 1

Target	Name	NCT Record	Trial start date
HER2	Trastuzumab emtansine (T-DM1)	NCT00829166	2009-02
Nectin-4	Enfortumab vedotin	NCT01409135	2011-07
Folate receptor alpha	Mirvetuximab soravtansine (IMGN853)	NCT01609556	2012-06
TROP-2	Sacituzumab govitecan	NCT01631552	2012-12
CD74	Milatumzumab doxorubicin (CD74-DOX)	NCT01101594	2010-07
Endothelin receptor type B	DEDN6526A	NCT01522664	2012-03
PSMA	Anti-PSMA ADC	NCT01695044	2012-09
PSMA	MLN2704	NCT00052000	2002-11
SLC44A4	ASG-5ME	NCT01166490	2010-07

16. Dr. Atanackovic admitted that “the inability of the antibody to discriminate between normal tissues and healthy tissues [] is one factor that would predict higher toxicity” and a POSA would “need more than just [] toxicity” to

compare therapeutic window of two ADCs. EX1246 (Atanackovic Deposition Transcript) at 278:2-20. It must be evaluated based on both efficacy and toxicity. EX2027, ¶9. He acknowledged that although cetuximab binds to EGFR expressed on normal cells, it is “efficacious” and has been approved for use for more than 20 years. EX1246 at 279:9-13.

17. The relevant issue for ADC development has not been the absolute absence of normal-tissue expression, but rather whether the target is sufficiently enriched in tumor cells to provide a usable therapeutic window. A recurring lesson from the field of ADC development prior to 2015 is that an ideal target does not have to be completely tumor-specific to be clinically actionable. EX1211 at 2-4. Instead, successful ADC development has generally relied on relative rather than absolute selectivity: (i) overexpression in tumor compared with normal tissue, and (ii) effective intracellular delivery of the payload. EX1211 at 1, 4-5.

18. Trastuzumab emtansine (T-DM1) is the clearest early example. *Id.* at 2–3. T-DM1 is a humanized monoclonal antibody that targets HER2, which is not a tumor-restricted antigen. EX1201 at 1. Yet T-DM1 was successfully developed and showed a favorable therapeutic index in the clinic. EX1211 at 2. Importantly, its development was not limited by a syndrome of severe on-target toxicity to normal HER2-expressing tissues, illustrating that normal-tissue expression alone did not preclude safe and effective clinical development. *Id.* at 2–3.

19. The same principle is evident across several other ADC programs initiated before 2015. EX1201–1210. Enfortumab vedotin entered first-in-human testing in 2011 against Nectin-4, a target well-known to be expressed at relatively high levels in normal epithelial tissues, namely skin. *See* EX1203 at 2-3. Despite this, the program advanced successfully, and the observed toxicities were recognizable and clinically manageable rather than prohibitive. *Id.* Likewise, TROP-2 is not completely tumor-specific and is expressed in some normal epithelial tissues, yet this did not prevent successful clinical development of an ADC targeting it. EX1205 at 1-2. Mirvetuximab soravtansine (IMGN853) entered clinical development in 2012 even though it targets folate receptor alpha, which is present in some normal tissues. EX1204 at 1-2. The same principle is also demonstrated by other historical examples, including DEDN6526A targeting Endothelin receptor type B, and PSMA-directed ADCs such as MLN2704 and PSMA ADC. EX1207-1209.

20. Thus, clinical experience demonstrates that the presence of target antigen on normal tissues has not prevented its use in ADC development. *See* EX1201–1210; EX1211 at 5–7. Rather, what has mattered is whether tumor-associated overexpression and biologic accessibility are sufficient to produce an acceptable therapeutic index. *See id.*; EX1212 at 8. Accordingly, the fact that EGFR is expressed in normal tissues should not be viewed as a reason to exclude it as an

ADC target, since many successful ADC programs have been pursued against antigens with comparable patterns of non-tumor expression. EX1201–1210.

21. A POSA with knowledge of established principles in ADC target selection would have chosen EGFR as a candidate target for ADC development, given EGFR's overexpression profile in multiple tumor types, established oncogenic role, and internalization activity. EX1211 at 8; EX1212 at 8.

IV. THE TOXICITY PROFILE OF ANTI-EGFR ANTIBODIES IS MANAGEABLE AND DOES NOT PRECLUDE ADC DEVELOPMENT

22. The Patent Owner's Response and Dr. Atanackovic's declaration extensively discuss the potential toxicity of anti-EGFR antibodies and identify several antibody properties as contributing factors, including binding affinity and the capacity to mediate ADCC activity. *See* EX2027, ¶¶24-36, 62–64; POR at 14–17, 34-35. However, one cannot dismiss EGFR as an unattractive target simply because anti-EGFR agents are associated with skin toxicity. *See* EX1009 at 2 (Tikhomirov acknowledging EGFR as “an attractive target”). The dermatologic effects of EGFR inhibition are real, common, and mechanistically expected, but they are also predictable, well characterized, and increasingly manageable in routine clinical practice. *See* EX2024 at 000001–000004. In fact, Dr. Atanackovic admitted that as early as clinical trials of cetuximab over 15 years ago, clinicians had already

been managing mild skin toxicity with “topical agents, like creams” and more extensive skin toxicity with antibiotics. EX1246 at 338:7-19.

23. Notably, International Publication No. WO2012/100346A1 (“Tikhomirov-346”), the very reference Dr. Atanackovic relies upon for the proposition that reduced binding affinity is the preferred ADC design strategy, itself concedes that “[c]onsidering the efficacy of anti-EGFR therapies in treating patients that overexpress EGFR the risk associated with severe skin reaction is currently considered acceptable when managed properly.” EX2011, 1:27–30. Tikhomirov-346 further identifies at least two practical management strategies available to clinicians, **antihistamine premedication and dose reduction**. *Id.* Dr. Atanackovic did not present either of these statements to the Board, despite their appearance in the very reference he cites as primary support for Strategy B4. *Compare* EX2011 at 1:27–30, *with* EX2027, ¶¶15–19 (omitting these concessions); EX1246 at 13:1-22 (expert not sure whether he presented these statements in his declaration). A POSA reading Tikhomirov-346 would have understood that the field viewed the toxicity caused by anti-EGFR ADCs as a manageable problem, not an insurmountable barrier. *See also* EX1009 at 25-27 (Tikhomirov itself providing a specific dosing regimen for its cetuximab-SMCC-DM1 primate study, confirming dosing optimization as another available engineering lever).

24. For example, the FDA label for cetuximab reports acneiform rash in 82% of treated patients, with 9.7% having grade 3-4 rash, while panitumumab labeling reports dermatologic toxicity in 90% of patients, with severe toxicity in 15%. EX1233 at 5; EX1236 at 1. Importantly, these toxicities are not a sign that EGFR is an unusable target; rather, they reflect that the on-target biology of EGFR in the skin is well known and are addressed through established monitoring, supportive care, and dose-modification algorithms.

25. The Patent Owner's Response ignores that the field already has extensive clinical experience in managing EGFR-related toxicities. *See* EX2024 at 000001–000003. Consensus guidelines specifically for EGFR inhibitor-associated dermatologic adverse events have been available for years, and prospective studies have demonstrated that proactive management materially reduces the burden of rash. *Id.* at 000004. In the randomized STEPP study with panitumumab, a pre-emptive regimen consisting of moisturizer, sunscreen, topical steroid, and doxycycline reduced protocol-specified grade ≥ 2 skin toxicities from 62% with reactive treatment to 29% with pre-emptive treatment, with better quality-of-life outcomes. EX1237 at 1.

26. The broader clinical experience with small-molecule EGFR inhibitors also undermines the claim that anti-EGFR antibodies are uniquely problematic due to their capacity to induce ADCC. *See* EX1234, EX1235. EGFR tyrosine kinase

inhibitors produce many of the same class-defining adverse events, especially rash and diarrhea, even though they engage EGFR through an entirely different binding mode that does not involve Fc effector function. *Id.* Erlotinib label reports rash in about 50-75% of patients and diarrhea in 20.3-54%, and gefitinib similarly showed diarrhea in 39% and rash in 47% at the recommended dose. EX1234 at 6-7; EX1235 at 5. This demonstrates that the main driver of these toxicities is pathway blockade itself, particularly in skin and gastrointestinal epithelium, rather than any property of the antibody format or its capacity to induce ADCC.

27. Anti-EGFR antibodies with different affinities for EGFR, and EGFR TKIs that do not rely on antibody-antigen affinity at all, still converge on a broadly similar safety phenotype dominated by rash and diarrhea. *See supra* ¶¶23-25. “Panitumumab is a high-affinity ($K_d = 5 \times 10^{-11}$ M), fully human IgG2 monoclonal antibody with specificity for the ligand-binding region of EGFR (Yang et al 2001). This represents an approximate 8-fold greater affinity compared with cetuximab ($K_d = 0.39$ nM).” EX1238 at 2; EX1244; EX1245; EX1247 at 1. Given their established safety profile and efficacy, a POSA would not have been discouraged from developing ADCs using anti-EGFR antibodies. *See supra* ¶¶22-25; EX1009 at 1–2.

28. Moreover, the same Tikhomirov-346 (EX2011) reference that Dr. Atanackovic cites for the reduced-affinity strategy simultaneously acknowledges that the broader field’s efforts are aimed at generating antibodies with *greater*, not

lesser, affinity. Tikhomirov-346 expressly states: “**Efforts to improve upon EGFR antibodies are aimed at generating antibodies having even greater affinity for the target antigen.**” EX2011, 1:36-37. This passage describes the field’s direction as being towards higher affinity and improved antagonist activity. Dr. Atanackovic did not present this passage from Tikhomirov-346 to the Board, despite it appearing in the same reference he cites as his primary support for the proposition that higher affinity is a disfavored property. *Compare* EX2011 at 1:36-37, *with* EX2027, ¶¶19, 26 (selectively quoting only the reduced-affinity portions of EX2011). The omission of this passage and the “acceptable when managed properly” language from the declaration’s analysis of Tikhomirov-346 represents a material gap in the presentation of the prior art.

29. Indeed, Patent Owner’s own Global Offering prospectus, cited by Patent Owner’s Response, that was presented to the public, indicates BA03-based ADC, MRG003, “was **well-tolerated** and among 61 patients enrolled in Phase Ia and Phase Ib clinical study, 14 patients (23%, four patients in Phase Ia and ten patients in Phase Ib) reported TRAE of Grade 3 or above.” *See* POR at vi; EX2032 at 000300-301, 000314.

V. ADCs EMERGE FROM CLINICALLY VALIDATED MONOCLONAL ANTIBODIES

30. A recurring theme in the ADC development field, well-established by the pre-2015 era, is that clinically relevant ADCs often emerged from targets that had already been clinically validated by naked-antibody programs. *See infra* Table 2 (examples of naked antibodies and antibody-drug conjugates in clinical development and use, targeting the same surface receptor). In many cases, the prior naked monoclonal antibody had already established that the antigen is accessible in patients, can be engaged with acceptable pharmacology, and is sufficiently tumor-associated to justify therapeutic development. In several instances, this was not merely target-level continuity but antibody-level continuity, which means the same antibody clone was often advanced in both naked and conjugated formats. Trastuzumab and trastuzumab emtansine (T-DM1) are the clearest example. EX1211 at 2–3.

Table 2

Target	Naked antibody	ADC
HER2	trastuzumab	trastuzumab emtansine (T-DM1)
CD74	milatuzumab	milatuzumab doxorubicin (hLL1-DOX)
CD30	SGN-30	brentuximab vedotin
CD70	cusatuzumab	vorsetuzumab mafodotin (SGN-75)
CD22	epratuzumab	pinatuzumab vedotin
Folate receptor alpha	farletuzumab	mirvetuximab soravtansine (IMGN853)
MUC16	oregovomab	DMUC5754A (sofituzumab vedotin)
CAIX/CA9	girentuximab	BAY 79-4620
Tissue factor	MORAb-066	tisotumab vedotin

31. On this basis, EGFR should not be viewed as an outlier. EX1214 at 1-2. Rather, it fits well within an established pattern in which clinically validated antibody targets are subsequently developed into ADCs. EX1211 at 8 (“multiple ADCs in early clinical development target EGFR, an oncogenic driver that is closely related to ERBB2”). Because EGFR is a clinically established antibody target, it is entirely consistent with historical field practice to expect anti-EGFR monoclonal antibodies, including cetuximab-class agents, to be further developed as ADCs. *Id.*; EX1009 at 1–2.

32. Relative to naked antibodies, ADCs offer several potential advantages. *See* EX1212 at 8–9. First, they add a direct cell-killing payload, so efficacy does not depend solely on receptor blockade, ligand inhibition, or Fc-mediated immune mechanisms. EX1211 at 8-9. Second, ADCs can achieve internalization-dependent selective killing of antigen-positive cells, and in some designs even a bystander effect, which may extend activity beyond the direct biologic effects of the unconjugated antibody. *Id.* at 8-9. Third, oncogenic-driver targets such as EGFR may offer an additional strategic advantage for ADCs because loss or downregulation of the target as a route of resistance may be more costly to the tumor. EX1211 at 8.

33. For cetuximab specifically, its commercial success, established clinical efficacy, and extensive trial and real-world experience make it a particularly attractive starting point for ADC development with high expectation of success and limited risk. *See* EX1014; EX1009 at 1–2. The target is clinically validated, the antibody scaffold is well characterized, manufacturing and translational behavior are well understood, and the medical community is already familiar with the biology of EGFR-directed therapy and any anticipated toxicities. *See* EX1014. That is exactly the basis from which many successful ADCs were successfully developed. EX1211 at 3–4.

VI. ADC DOSING CONSIDERATIONS AND THE IMPORTANCE OF HIGH-AFFINITY ANTIGEN RECOGNITION

34. A major distinction between ADCs and naked antibodies is dose. EX1211 at 6. Clinical dose levels of ADCs are substantially lower than those of most unconjugated antibodies. *Id.* The Patent Owner’s Response and Dr. Atanackovic’s declaration discuss Figure 3 of EX2022 (“Crombet”) and argue against using high-affinity anti-EGFR antibodies for ADC development, claiming these antibodies are expected to recognize EGFR in normal tissues. POR at 16-17; EX2027, ¶¶23–25; EX2022 at 5, 7 (Fig. 3). However, these arguments and the model on which they rely are inapplicable to ADCs because they fail to account for the fact that ADCs are administered at far lower clinical doses than naked antibodies. EX1211 at 7.

35. Representative clinical doses illustrate this point clearly. Trastuzumab is typically dosed at 4 mg/kg loading then 2 mg/kg weekly or 8 mg/kg loading then 6 mg/kg every 3 weeks, whereas T-DM1 is given at 3.6 mg/kg every 3 weeks; SGN-30 (brentuximab) was tested at 6-12 mg/kg weekly, whereas brentuximab vedotin is given at 1.8 mg/kg every 3 weeks; epratuzumab was studied at up to 1,000 mg/m² weekly, whereas pinatuzumab vedotin entered phase I at 0.1 mg/kg every 21 days. EX1239 at 1; EX1240 at 1; EX1241 at 1; EX1242 at 1; EX1243 at 3; EX1248 at 1.

36. Under those dose-limited conditions, the relevant question is not whether a somewhat lower-affinity antibody might theoretically spare normal tissue at a matched dose. Rather, the practical question is whether the antibody can still achieve sufficient tumor engagement when only a limited amount of antibody is administered. Contrary to the statements presented in the Crombet reference, the higher affinity of the antibody actually becomes advantageous under this condition, because the ADC must efficiently recognize and bind tumor cells despite the fact that substantially less antibody is being given overall. *See* EX2022 at 7.

37. An additional consideration is that binding affinity can influence not only target binding but also intracellular trafficking. Although no studies have been conducted in the specific context of EGFR, experimental evidence from antibodies against HER2, a receptor related to EGFR, provides useful insights into the impact of antibody affinity on internalization. EX1213 at 1–3. In this study, antibodies

recognizing the same HER2 epitope across a range of affinities showed that internalization and catabolism generally increased with affinity. *Id.* ADC specificity depends on internalization into target cells before drug release, and ADC potency correlates with internalization. Dr. Atanackovic also admitted that in principle, stronger binding affinity can result in a higher degree of internalization of ADC. EX1246 at 345:12-16, *see also* 66:22-67:7 (Q: So increased affinity, would that result in increased internalization of ADC? A: Yes, I think that's one possible outcome.). Thus, a higher-affinity antibody that promotes rapid or efficient internalization is a beneficial feature for ADC function, as it improves intracellular payload delivery. *Id.*; EX1213 at 1.

38. It is well established that ADCs operate as a pharmacologically distinct modality from naked antibodies, with clinical dose levels that are substantially lower. Accordingly, any assessment of antibody selectivity must be evaluated within this context. When antibody dose is limiting, the priority is to retain robust tumor recognition and internalization. In that setting, high affinity is not a liability but rather a significant advantage. A POSA with basic understanding of the pharmacodynamic properties of therapeutic antibodies and ADCs would have been motivated to select anti-EGFR antibodies with the highest binding affinity for the development of anti-EGFR ADCs with maximal therapeutic potential. *See supra* ¶¶34–37.

VII. THE CROMBET MODEL IS SCIENTIFICALLY UNRELIABLE AND INAPPLICABLE TO ADC DESIGN

39. Dr. Atanackovic relies heavily on a model from the Crombet reference to argue that anti-EGFR antibodies with higher affinity than cetuximab would have “poorer or even no ability” to distinguish tumor cells from normal cells. EX2022 at 7 (Fig. 3); EX2027, ¶25. However, a POSA would immediately recognize that the Crombet model has profound limitations and minimal biological relevance for ADC design. EX2022 at 3–5.

40. The Crombet model has several critical deficiencies: (i) several parameters used to derive the model are undisclosed, including tissue volumes, intercompartmental distribution clearance terms, the equation governing bound antibody concentration, and the conversion of EGFR receptor counts per cell into molar concentrations; (ii) the model relies on an assumption of standard tumor size, which does not reflect clinical reality; and (iii) the calculations were based on a fixed value of 240 hours for antibody half-life, which is substantially longer than that previously reported for the h-R3 antibody. EX2022 at 3–5. Importantly, as stated in Crombet, “h-R3 exhibits different pharmacokinetic properties when compared to other anti-EGFR antibodies. At the dose levels associated with systemic clearance saturation, h-R3 exhibits a more prolonged half-life and a higher area under the curve (AUC).” EX2022 at 2. Dr. Atanackovic admitted that he did not validate the Crombet model and that the reference does not disclose variables in equations used

to simulate antibody activity in different tissues, such as plasma tissue volume (V_p), tumor volume (V_t), liver volume (V_l), and skin volume (V_s). EX1246 at 109:14-110:4. He also admitted not knowing whether h-R3 and cetuximab have the same half-life of 240 hours assumed by the Crombet model. *Id.* at 129:3-22.

41. The Crombet model was developed to predict the biodistribution of naked anti-EGFR antibodies, specifically h-R3 (nimotuzumab), in the context of a Phase I/II clinical trial combining h-R3 with radiotherapy. EX2022 at 1–3. As Dr. Atanackovic confirmed, h-R3 is a naked antibody, not an ADC. EX1246 at 78:11-15. The model does not incorporate any ADC-specific pharmacokinetic parameters. Unlike naked antibodies, ADCs introduce additional biodistribution complexity, due to drug-to-antibody ratio-dependent hydrophobicity, linker instability, and payload release kinetics. *See* EX2022 at 3–5.

42. Furthermore, the Crombet model is limited in scope, comparing antibody distribution between tumor and only a narrow subset of healthy tissues, namely plasma, tumor, liver, and skin, and does not address distribution in other EGFR-expressing organs such as the kidneys, heart, gastrointestinal tract, lungs, thyroid, or esophagus. EX2022 at 3–4; EX1246 at 117:18-118:4 (Dr. Atanackovic confirmed that the Crombet model does not examine antibody binding with EGFR in thyroid, fat, or esophagus). Because the model was designed only to predict uptake in tumor versus a limited set of healthy tissues, it does not characterize antibody

biodistribution across the broader range of normal tissues relevant to assessing ADC behavior. *Id.*

43. Dr. Atanackovic also confirmed that Crombet reference compared toxicity profiles of h-R3 and cetuximab based on data from different clinical trials during which the two antibodies were administered at different dosages. EX1246 at 83:1-11; 86:19-87:16; EX2022 at 7 (Figure 3). H-R3 was administered at 100 mg and 200 mg, while cetuximab (IMC-C225) was administered “at the doses of 200/200 mg/m² (loading/maintenance) and 400/200 mg/m².” EX2022 at 7.

44. The Crombet reference itself acknowledges that its model prediction “looks counterintuitive” and identifies three alternative explanations in addition to affinity for why h-R3 had less skin toxicity than cetuximab: (1) h-R3 has a higher degree of humanization; (2) h-R3 was obtained by humanizing an antibody raised against EGFR from human placenta, not cultured cells; and (3) h-R3 has different pharmacokinetic properties. EX2022 at 000006-7. The authors expressly state that “Other differences related to epitope specificity of the antibodies and to consequent changes in receptor signaling cannot be discarded to explain the lack of dermal reactions.” *Id.* at 7. Dr. Atanackovic also confirmed that these differences can contribute to the favorable toxicity profile of h-R3. EX1246 at 112:1-5.

45. Finally, the Crombet reference merely states “the mathematical model that we have built predicts that there is an affinity window that can be exploited for

EGFR antagonists, and that *higher affinity is not necessarily the best.*” EX2022 at

7. It never categorically rejects pursuing anti-EGFR ADCs using high affinity anti-EGFR antibodies, such as cetuximab or BA03.

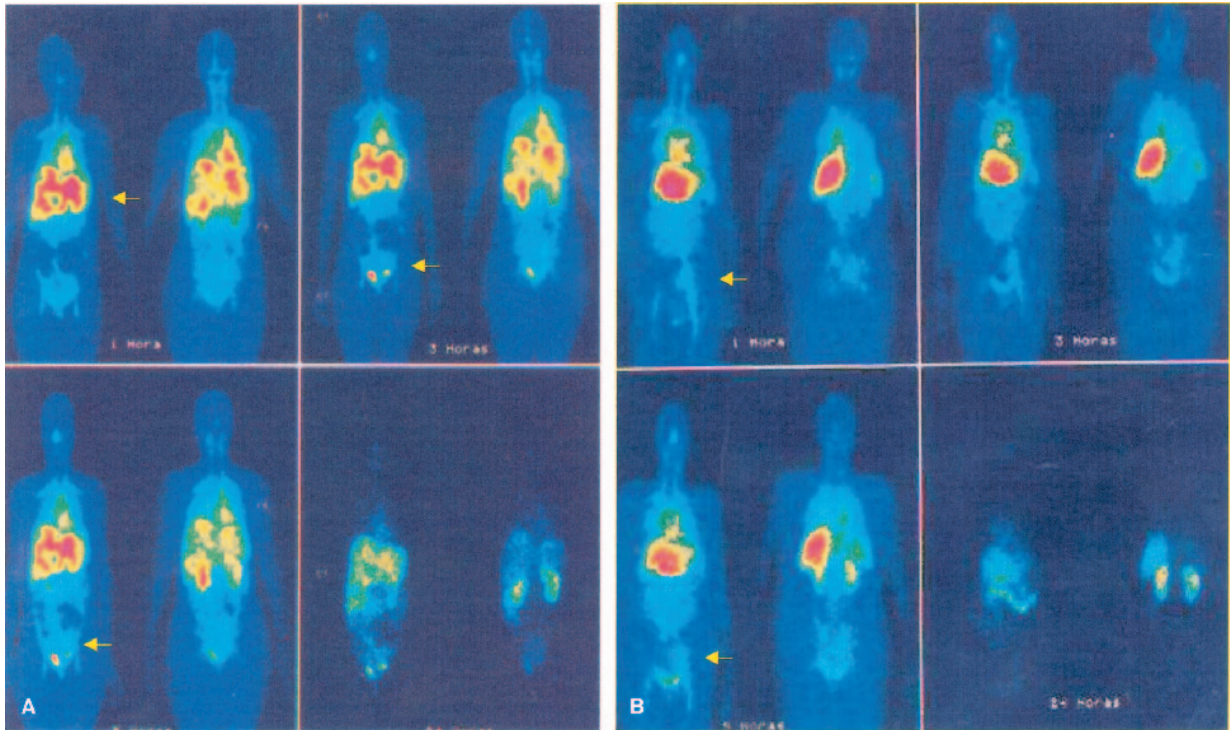
VIII. ANTI-EGFR ANTIBODIES WITH LOWER AFFINITY THAN CETUXIMAB STILL RECOGNIZE NORMAL TISSUES

46. Dr. Atanackovic asserts that reduced antibody affinity 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 antigen (*e.g.*, tumor cells).” EX2027, ¶22. However, this assumption contradicts established practices in the field of antitumor antibody therapeutics and ADCs. *See* EX2011, 1:36-37 (Tikhomirov-346 stating “[e]fforts to improve upon EGFR antibodies are aimed at generating antibodies having even greater affinity for the target antigen”). Affinity reduction has never been a general design principle for clinically established antitumor antibodies and ADCs targeting antigens that are also present on normal tissues. *Id.*

47. Panitumumab was developed several years after cetuximab and binds EGFR with substantially higher affinity (reported KD values are about 0.05 nM for panitumumab versus 0.39 nM for cetuximab), yet its development was not driven by the notion that affinity should be deliberately reduced because EGFR is also expressed on normal tissues. EX1238 at 2; EX1244 at 2; EX1245 at 1. If anything,

the historical trajectory went in the opposite direction. *See* EX2011, 2:14–15. Later anti-EGFR development accepted, and in practice favored, higher-affinity binding, since strong receptor engagement and efficient internalization have always been viewed as beneficial properties, not liabilities. EX1213 at 1–3.

48. Importantly, the biodistribution record does not support a categorical claim that nimotuzumab, the canonical affinity-reduced anti-EGFR antibody relied upon by Dr. Atanackovic, lacks meaningful normal-tissue binding. *See* EX2027, ¶¶27–29. In a clinical biodistribution study, the whole-body images showed antibody accumulation in the liver, heart, kidneys, urinary bladder, and spleen across all time intervals, with additional uptake in the large intestine in some patients. EX1218 at 1, 6 (Fig. 1). The authors explicitly state that h-R3 accumulation was seen in these organs and that, after humanization, the antibody “maintained the original in vivo recognition pattern of normal organs and tissues.” *Id.* at 5 (Table 2), 7 (Fig. 3), 8.



Id. at 6 (Fig. 1).

TABLE 2. *h-R3* biodistribution in patients expressed as percent of the injected dose at 1 and 24 hours after mAb administration

Source organ	Time, hrs.	% of injected dose			
		50 mg	100 mg	200 mg	400 mg
Heart	1	4.76 ± 0.7	5.84 ± 1.0	3.61 ± 0.6	4.07 ± 1.6
	24	1.12 ± 0.3	1.98 ± 0.78	1.71 ± 0.9	1.94 ± 1.1
Liver	1	24.76 ± 10.8	11.79 ± 2.5	9.88 ± 3.7	10.58 ± 0.9
	24	12.78 ± 4.9	10.35 ± 2.3	5.57 ± 3.8	5.98 ± 3.0
Spleen	1	0.96 ± 0.8	1.74 ± 0.1	1.58 ± 0.6	1.33 ± 0.1
	24	0.27 ± 0.03	1.03 ± 0.6	0.80 ± 0.4	0.69 ± 0.3
Kidneys	1	2.66 ± 0.6	2.46 ± 1.1	2.49 ± 0.2	3.04 ± 1.0
	24	11.02 ± 2.5	5.94 ± 4.8	8.82 ± 7.7	8.62 ± 1.6
Urinary bladder	1	1.37 ± 0.3	25.21 ± 4.1	4.21 ± 1.4	3.29 ± 1.4
	24	0.92 ± 0.8	4.34 ± 3.3	2.16 ± 1.3	3.04 ± 1.0

Id. at 5 (Table 2).

49. In the phase I/II dosimetry study, the source organs were again the liver, spleen, kidneys, and heart, with peak uptakes of $52.9 \pm 3.8\%$ ID in liver and $10.1 \pm 1.3\%$ ID in kidneys, and with significant urinary bladder and intestinal activity. EX1219 at 6 (Table 3). The observed biodistribution pattern of nimotuzumab (liver, kidney, spleen) matches the one reported for cetuximab, despite cetuximab having approximately 10-fold higher affinity. *Compare* EX1219, *with* EX1220.

50. There is also a profound lack of robust randomized head-to-head evidence showing that nimotuzumab is superior to cetuximab in terms of safety. The lower skin toxicity reported in some nimotuzumab studies should not be interpreted as proof of a fundamentally different biodistribution pattern or lack of binding to normal tissues. *See* EX1218–1220. Dose and exposure are obvious confounders. Nimotuzumab is often administered as a flat weekly dose of 200 mg, whereas cetuximab's approved regimen is 400 mg/m^2 followed by 250 mg/m^2 weekly, which for a typical adult generally results in substantially higher antibody exposure. EX1014 at 1. In that context, lower rash rates can be explained at least in part by lower administered dose and exposure, rather than by a unique absence of normal-tissue binding. *Id.*

51. Therefore, a POSA would have been motivated to select high-affinity anti-EGFR antibodies as scaffolds for ADC development. *See supra* ¶¶47–51; EX2011 at 000003; EX1213, EX1218–1220.

IX. THE IMPORTANCE OF THE ANTAGONISTIC ACTIVITY OF ANTI-EGFR ANTIBODIES

52. Dr. Atanackovic dismisses BA03's stronger EGFR phosphorylation inhibition as irrelevant to ADC design, arguing that "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." EX2027, ¶63. His argument overlooks a well-established principle of EGFR therapeutics and the key distinction between normal tissues and tumors. Despite a subset of normal cells expressing EGFR, normal tissues do not share the unique tumor-associated combination of (i) markedly increased EGFR surface expression and (ii) persistent or aberrant EGFR activation that makes the pathway therapeutically actionable in cancer. *See* EX1013 at 6; EX2006.

53. If strong EGFR antagonism were truly undesirable, one would expect the anti-EGFR antibodies that reached the clinic to have been designed as non-antagonists or partial agonists. Instead, the opposite is true. Cetuximab was developed to competitively inhibit ligand binding and block receptor phosphorylation, panitumumab prevents ligand-induced receptor autophosphorylation, and necitumumab blocks ligand binding and ligand-induced EGFR phosphorylation with consequent inhibition of downstream signaling. *See* EX1009 at 6; EX1014 at 1; EX1236 at 20. In other words, antagonism is not an

incidental property of this class but a key therapeutic principle on which the class was built.

54. This principle extends beyond naked antibodies and is particularly significant for ADC development. The ADC review literature specifically addresses this. An article by Chari *et al.* states that although the ADC approach does not require the antibody itself to possess functional activity, such activity “may confer additional therapeutic benefit,” and they specifically identify EGFR as a receptor “known to be well-internalized.” EX1212 at 8. Another article by Damelin *et al.* goes further, arguing that “tumorigenic functions of ADC targets may be beneficial,” and specifically cite ERBB2 and EGFR as oncogenic drivers. EX1211 at 8. In that setting, downregulation of the target to escape ADC binding “would also be deleterious to the tumor.” *Id.*

55. One example that demonstrates the importance of strong EGFR antagonism is trastuzumab emtansine (“T-DM1”), an ADC that targets HER2 antigen. EX1215 at 1. A preclinical study by Junttila *et al.* reported T-DM1 “retains the mechanisms of action of unconjugated trastuzumab,” specifically listing inhibition of the PI3K/AKT signaling pathway and inhibition of HER2 shedding among those retained functions. *Id.* at 1-2. The fact that one of the flagship ADCs in oncology was built not on a biologically inert carrier antibody, but on a clinically active HER2 antagonist whose signaling effects were preserved after conjugation,

undermines any argument that receptor antagonism or phosphorylation-pathway inhibition is undesirable for an ADC. *Id.*

56. The same principle is demonstrated by ADCs targeting the HER3 antigen. EX1216 at 1. Patritumab was developed as a *bona fide* blocking anti-HER3 antibody. *Id.* at 2. When patritumab was turned into an ADC named U3-1402, the preclinical study did not suggest that this antagonistic property had become a liability. EX1217 at 1. Rather, U3-1402 “was able to inhibit HER3-activated signaling similar to its naked antibody patritumab,” while the dominant cytotoxic effect was added by DXd payload delivery after efficient internalization. *Id.*

57. A particularly instructive example is c-MET, a target for which antibody agonism has historically been a major development concern. ABT-700 was developed as a bivalent anti-c-MET antibody with demonstrated antagonistic activity, and this same antibody was used as the scaffold for telisotuzumab vedotin (Teliso-V/ABBV-399), which was generated by conjugating ABT-700 to MMAE. EX1249 at 1; EX1250 at 2. The ADC was not built from a biologically inert carrier, but from an antibody specifically selected for its ability to disrupt c-MET signaling without agonizing the receptor. *See* EX1249 at 1-2.

58. Based on established paradigms from the clinical development of multiple successful ADCs (against targets that are also expressed in normal cells), a POSA would have viewed EGFR receptor antagonistic activity as a key antitumor

function that does not compromise, but rather complements, the ADC cytotoxic activity, thereby restricting potential routes of resistance to therapy. *See supra* ¶¶53–58.

X. ADCC AND Fc EFFECTOR FUNCTION ARE SIGNIFICANT COMPONENTS OF ANTI-EGFR ANTIBODY ACTIVITY

59. In the Patent Owner’s Response and Dr. Atanackovic’s declaration, the capacity of an anti-EGFR antibody to induce ADCC is portrayed as irrelevant or even unfavorable. EX2027, ¶64; POR at 34–35. Dr. Atanackovic states that “[s]uch increased ADCC would have been expected by the POSA to translate into increased killing of normal cells as well.” EX2027, ¶64. These statements lack scientific merit and ignore decades of experimental evidence demonstrating the importance of ADCC and Fc effector function in the antitumor activity of anti-EGFR antibodies, as well as the clinical development of Fc-engineered anti-EGFR antibodies specifically designed for enhanced ADCC activity. *See* EX1221–1227.

60. First, seminal studies published in 2000 provide the conceptual framework for the importance of Fc effector function in antitumor therapy, demonstrating that the *in vivo* activity of antitumor antibodies is not explained by receptor blockade alone. EX1221 (“Clynes”) at 1. After testing two therapeutic antibodies that are widely used in clinical practice, trastuzumab (anti-HER2) and rituximab (anti-CD20), Clynes concluded that “Fcγ receptor binding contributes

substantially to *in vivo* activity” and that this FcγR dependence was not restricted to a single antibody or target, but extended across multiple therapeutic antibodies. *Id.* at 3. Clynes further showed that an Fc-impaired HER2 antibody retained antigen binding and *in vitro* growth inhibition, yet lost ADCC activity and had markedly reduced antitumor efficacy *in vivo*. *Id.*

61. Second, the same framework was applied directly to cetuximab. EX1222 at 1. A 2013 study showed that “Cetuximab-induced tumor regression depends on both innate and adaptive immunity components, including CD8+ T cells, MyD88, and FcγR,” concluding that “Cetuximab can inhibit tumor growth by blocking oncogenic signals and initiating ADCC, which not only suppresses tumor growth but also triggers innate immunity to improve CTL cross-priming by DC,” ultimately generating “both innate and adaptive immunity against the tumor.” *Id.* at 1, 8. This is the main reason why Fc function remains therapeutically relevant even in tumors with EGFR downstream mutations. Even if signaling blockade is weakened by KRAS, BRAF, NRAS, or PI3K pathway alterations, Fc-dependent immune engagement can still provide clinical benefit through ADCC, dendritic cell cross-priming, and CD8 T-cell-mediated tumor control.

62. Third, human genetic association studies reinforce the importance of Fc effector function of cetuximab. EX1223 at 1. Studies focused specifically on EGFR downstream-mutated metastatic colorectal cancer reported that “those harbouring an

FcγRIIIa H/H genotype had a higher DCR than alternative genotypes.” *Id.* By multivariate analysis, FcγRIIIa-131H/H remained significantly correlated with disease control rate. *Id.* Similarly, Bibeau *et al.* reported that “Patients with FcγRIIIa-131H/H and/or FcγRIIIa-158V/V genotypes had longer PFS than 131R and 158F carriers,” with the difference remaining significant for mutated-KRAS patients. EX1224 at 2.

63. These mechanistic and clinical observations have directly motivated the development of Fc-optimized anti-EGFR antibodies designed to increase Fc effector function. EX1225 at 1. For example, GA201/RG7160 was developed with “glycoengineering of the Fc region of a therapeutic antibody to increase its binding affinity for FcγRIII,” resulting in “significantly enhanced induction of antibody-dependent cell-mediated cytotoxicity” and “superior *in vivo* efficacy” compared with cetuximab. *Id.* at 1-2. Additionally, independent glycoengineering studies provide further support. EX1226 at 1. In a separate engineered cetuximab-format molecule, the bisecting glycan-modified anti-EGFR antibody showed “3-fold higher cell lysis capability in the antibody-dependent cellular cytotoxicity assay,” together with increased Fcγ receptor binding. *Id.* The authors concluded that “the glycoengineering of anti-EGFR antibodies could optimize their function and minimize their side effects.” *Id.* at 6.

64. Consistent with these examples, the first-in-human phase I study of RG7160 reported that “No maximum-tolerated dose was reached,” and concluded that “RG7160 had an acceptable safety profile with manageable AEs and demonstrated promising efficacy,” despite being explicitly developed as a glycoengineered anti-EGFR antibody “with enhanced antibody-dependent cell-mediated cytotoxicity.” EX1227 at 1, 2. Additional support for this concept comes from a phase I study that sought not to redesign the antibody itself, but to pharmacologically augment cetuximab-induced ADCC with lenalidomide. *See* EX1228 at 1 (“This phase 1 trial evaluated the combination of cetuximab with lenalidomide to enhance ADCC activity in advanced colorectal (CRC) and head and neck squamous cell cancers (HNSCC).”). Importantly, the correlative data aligned with the mechanistic premise. *Id.* at 2 (“ADCC assay demonstrated increased cell lysis with increasing doses of lenalidomide, particularly with lenalidomide 25 mg.”). Even in this small, heavily pretreated cohort, the investigators also reported “evidence of anti-tumor activity and clinical efficacy,” with one partial response and seven patients with stable disease as best response. *Id.* at 2. Importantly, enhancing ADCC did not produce a signal of disproportionate added toxicity. In that study, “Grade 3 fatigue was the only DLT (dose-limiting toxicity),” and the authors concluded that “Cetuximab and lenalidomide are well-tolerated with minimal toxicity.” *Id.* at 2.

65. In fact, Dr. Atanackovic also admitted that ADCC activity “contribute[s] to antitumor effects” of an antibody. EX1246 at 307:5-14. Therefore, a POSA would not have been motivated to reduce ADCC activity and Fc effector function of anti-EGFR antibodies. All data presented supports that enhanced ADCC has always been viewed as a favorable, deliberately engineered property of anti-EGFR antibodies. The available preclinical and clinical evidence does not support the notion that stronger ADCC activity is associated with increased toxicity. *See supra* ¶¶60–65; EX1221–1228.

XI. BA03 HAS SIGNIFICANT ADVANTAGES OVER LEANNA’S ANTIBODY 1

66. Dr. Atanackovic argues that a POSA would have expected that an ADC made with BA03 would be “substantially inferior to Leanna’s ADC.” EX2027, ¶71. First of all, Leanna is titled “Antibody Drug Conjugate (ADC) Purification” and its primary focus is on methods for purifying ADCs. EX1006, 1 and 4. Anti-EGFR antibody, as defined in Leanna, “is meant to refer to an antibody that specifically binds to EGFR. An antibody ‘which binds’ an antigen of interest, *i.e.*, EGFR, is one capable of binding that antigen with sufficient affinity such that the antibody is useful in targeting a cell expressing the antigen. Antibody 1 is an example of an anti-EGFR antibody.” EX1006, 11:20–23. Indeed, Dr. Atanackovic acknowledges that Leanna’s disclosure is not limited to Antibody 1. *Id.*; EX1246 at 32:9-20; *see also*

EX1006, 7:18–19, 11:20–23, 16:10–14, 26:9–18, 83:1–89:11. According to Leanna’s definition, its anti-EGFR antibody would also encompass BA03 and cetuximab.

67. Additionally, well-established clinical and experimental evidence, as well as standard practices in drug development, demonstrate that a POSA would have been motivated to replace Antibody 1 in Leanna’s ADC with BA03 antibody disclosed by Liu. *See* EX1006; EX1008.

68. One major advantage of a full-length EGFR antibody such as cetuximab and BA03 is that it targets a broader and more pharmacologically versatile biology than an EGFRvIII-specific agent, such as Leanna’s Antibody 1. *See* EX1006 at 26. A fundamental limitation of EGFRvIII-specific antibodies is that they can only be used in a minority of patients, and even within those patients, they fail to address the full tumor cell population. EX1229 at 1; EX1246 at 283:13-21 (Dr. Atanackovic also confirmed that “not all the patients [] have this variant”). EGFRvIII is present in only a subset of EGFR-overexpressing tumors, which makes mandatory molecular screening a prerequisite before treatment can even be considered. EX1229 at 1 (“the most common EGFR mutant, EGFRvIII, is expressed in 24-67% of cases”).

69. Even within EGFRvIII-positive tumors, the variant is not uniformly distributed across all cancer cells, and this uneven expression is not biologically

inert. EX1230 at 1. Gan *et al.* demonstrated that “EGFRvIII actively contributes to the heterogeneity of GBM by acting indirectly on neighboring cells that are EGFRvIII negative” through paracrine cytokine signaling, meaning that a variant-specific agent would leave a substantial proportion of tumor cells completely unaffected. *Id.* at 8. An antibody such as cetuximab or BA03 that targets wild-type EGFR sidesteps this problem entirely, because EGFR overexpression is an early and widespread feature that affects the vast majority of tumor cells rather than being confined to a small subset. *Id.*

70. A second key advantage of full-length anti-EGFR antibodies such as BA03 is their reduced vulnerability to antigen restriction and antigen-loss escape. The clinical experience with EGFRvIII-targeting consistently revealed a serious problem: tumors frequently lose EGFRvIII expression over time, rendering the therapeutic target irrelevant at relapse. *See* EX1231, EX1232. Sampson *et al.* presented a phase II vaccine trial demonstrating that “at recurrence, 82% (95% CI, 48% to 97%) of patients had lost EGFRvIII expression ($P < .001$).” EX1231 at 2. Van den Bent *et al.* confirmed that “within the tumors expressing EGFRvIII at initial diagnosis, approximately one-half lose their EGFRvIII expression at tumor recurrence.” EX1232 at 1. By contrast, the same study found that overall EGFR amplification was retained in 84% of recurrent tumors, reinforcing that wild-type EGFR is a far more stable target across the disease course. *Id.*

71. The weight of this evidence leaves little doubt that EGFRvIII, however tumor-specific, is too heterogeneously expressed and too easily lost at recurrence to serve as a reliable therapeutic target. *See* EX1229–1232. By contrast, targeting full-length EGFR with antibodies like cetuximab and BA03 is a far more reliable and broadly applicable therapeutic strategy that a POSA would select to develop anti-EGFR ADCs.

72. Notably, every anti-EGFR ADC clinical candidate that used an EGFRvIII-specific antibody, such as ABT-414, ABBV-221, and ABBV-321, has been terminated. EX2027, ¶¶85–88; EX2030 at 4. Meanwhile, the Patent Owner’s anti-EGFR ADC (MRG003) uses BA03, which targets wild-type EGFR. EX2021 at 1; EX2027, ¶92. This clinical record suggests that there are significant disadvantages to the EGFRvIII-specific approach that outweigh the theoretical advantage of tumor specificity.

XII. ANTIBODIES BA03, Y104D, huY104D, AND CETUXIMAB ARE SUBSTANTIALLY IDENTICAL

73. Liu’s BA03, Wei’s Y104D and huY104D, and cetuximab are indeed substantially identical on both the structural and molecular levels. EX1002, ¶¶80–90. Most critically, their complementarity-determining regions (CDRs), the six hypervariable loops that constitute the antigen-binding site and define antibody identity, are virtually indistinguishable across these antibodies. *Id.* Across all 73

CDR residues spanning the six loops, even the most divergent pair among these antibodies shares 68 positions identically, and three CDR loops (VH-CDR2, VL-CDR1, and VL-CDR2), collectively encoding 38 residues, are residue-for-residue identical across all four antibodies. *Id.* This is not a peripheral observation, as these three loops form the conserved core of the paratope and are the primary determinants of antigen recognition. *Id.*

74. The observed differences in binding affinity and pH selectivity among these antibodies do not undermine this conclusion. *See* EX1008, ¶¶140–142; EX1005, ¶¶476, 1116. Instead, they are entirely consistent with the well-established principle that single amino acid substitutions at or near antigen contact positions can modulate binding thermodynamics without altering fundamental antibody identity. The fact that Liu’s BA03 and Wei’s huY104D were both engineered through humanization of the same parental clone, cetuximab, while retaining the defining CDR architecture is compelling evidence that all three antibodies are recognized, by their own designers, as variants of cetuximab. EX1008, ¶140; EX1005, ¶¶476, 1116.

75. In fact, Wei demonstrated that an ADC constructed with its cetuximab variant antibody exhibits comparable functional performance to a cetuximab ADC. Specifically, Wei disclosed not only a Y104D-MMAE conjugate but also a cetuximab-MMAE conjugate. *See* EX1005, ¶ [1128]. Both ADCs demonstrated virtually identical cell growth inhibition (“CGI”) against cancerous A431 cells. *Id.*

¶ [1130]. Although Wei stated that Y104D-MMAE exhibited less inhibition of non-cancerous keratinocytes than the cetuximab-MMAE ADC, the actual data showed only a modest 10% difference: “[a]t the maximum doses, Cetuximab achieved about 80% CGI and Y104D-MMAE exhibited a CGI of about 70%.” *Id.*, ¶ [1131]. Notably, the dose required to achieve growth inhibition in normal keratinocytes is 100-fold higher than that required for tumor cells (cancerous A431 cells). This evidence establishes that ADCs made with cetuximab and a humanized cetuximab variant (Y104D-MMAE) display substantially similar properties and comparable tumor selectivity over normal tissues. Accordingly, a POSA would not have been discouraged from using another humanized cetuximab antibody, namely, Liu’s BA03 to make ADCs with the claimed vc-MMAE linker-payload. If anything, the prior art would have *motivated* a POSA to create a BA03-vc-MMAE ADC.

76. By any reasonable molecular definition, namely CDR sequence conservation, clonal lineage, paratope architecture, and antigen specificity, cetuximab, Y104D, huY104D, and BA03 are variants of a single antibody. Their functional differences represent refinements of the same molecule rather than evidence of structurally distinct antibodies. *See* EX1002, ¶¶80–90; EX1008, ¶140; EX1005, ¶¶476, 1116; EX1009, SEQ ID Nos. 1–6.

XIII. TIKHOMIROV-346's REDUCED-AFFINITY STRATEGY WAS NOT VALIDATED AND WAS REJECTED BY TIKHOMIROV ITSELF

77. Dr. Atanackovic relies extensively on Tikhomirov-346 (EX2011) as support for Strategy B4, the use of antibodies with reduced binding affinity. EX2027, ¶¶19, 26, 34. However, Dr. Atanackovic's reliance on this reference is materially undermined by Tikhomirov (EX1009) itself. Tikhomirov expressly states that one of the antibodies of Tikhomirov-346, the 6-LC cetuximab variant, are "not suitable" for use in its immunoconjugates: "at least the following known antibodies are not suitable for use in the present immunoconjugates: J2898A, intellimab 6-LC (a cetuximab variant taught in WO 2012/100346), nimotuzumab, and matuzumab." EX1009 at 11.

78. Further, Tikhomirov-346 contains statements that directly contradict Dr. Atanackovic's declaration's central narrative. Tikhomirov-346 states that "Considering the efficacy of anti-EGFR therapies in treating patients that overexpress EGFR the risk associated with severe skin reaction is currently considered acceptable when managed properly." EX2011, 1:27–30. Dr. Atanackovic did not present this statement to the Board, despite it reflecting the field's own contemporaneous assessment that anti-EGFR therapy-associated skin toxicity was acceptable and manageable. *Compare* EX2011, 1:27–30, *with* EX2027, ¶¶15–19.

79. Most significantly, Tikhomirov-346 also states: "Efforts to improve upon EGFR antibodies are aimed at generating antibodies having even greater

affinity for the target antigen.” EX2011, 2:14–15. This passage describes the field’s direction as being towards higher affinity and improved antagonist activity, which is precisely what Liu’s BA03 achieves. *See* EX1008, ¶140. Dr. Atanackovic did not present this passage in his declaration either, despite it appearing in the very reference he cites as his primary support for the proposition that higher affinity is a disfavored property. *Compare* EX2011, 2:14–15, *with* EX2027, ¶¶19, 26.

XIV. TIKHOMIROV TEACHES TOWARDS, NOT AWAY FROM, CETUXIMAB-CLASS ADCs

80. Tikhomirov (EX1009) is centrally relied upon by Dr. Atanackovic and the Patent Owner to argue that anti-EGFR ADCs with cleavable linkers are inherently too toxic. *See* EX2027, ¶¶15, 48–49; POR at 11–14. However, a fair reading of Tikhomirov as a whole tells a very different story. Tikhomirov explicitly identifies EGFR’s rapid internalization as a key reason it is an attractive target. EX1009 at 2 (“Another cell surface protein, epidermal growth factor receptor, or EGFR, is an attractive target for the development of anti-cancer immunoconjugates because of the antigen’s expression by many tumors and its rapid internalization.”).

81. Tikhomirov’s Summary of the Invention expressly states that “the activity of maytansinoid-conjugated cetuximab is potentiated only against cancer cells and not against keratinocytes.” EX1009 at 3-4. Tikhomirov further demonstrates that another full antagonist anti-EGFR antibody, panitumumab, “also

demonstrates selective potentiation at EGFR+ cells when conjugated to an anti-microtubule payload such as a maytansinoid, in showing toxicity to EGFR+ cancer cells while sparing EGFR+ normal cells such as keratinocytes.” *Id.* at 4. The demonstrated ability of cetuximab-class and panitumumab-class ADCs to achieve selective cytotoxicity against cancer cells without comparable harm to normal keratinocytes weighs directly in favor of using cetuximab-class antibodies, including BA03, as ADC targeting moieties. *Id.*

82. Tikhomirov states that full antagonist EGFR antibodies “having an EGFR binding affinity of 5 nanomolar (nM) or less are particularly preferred” for inclusion in its anti-EGFR ADCs. EX1009 at 11. BA03 has comparable binding affinity to cetuximab, which is 0.39 nM, well within the preferred affinity range taught by Tikhomirov, and ten times tighter than this preferred threshold. EX1244 at 2 (Table 1). By Tikhomirov’s own affinity criterion, BA03 would be among the most preferred antibodies for inclusion in an anti-EGFR ADC. *See* EX1009 at 11.

83. Tikhomirov expressly contemplates using humanized cetuximab variants in its anti-EGFR ADC design, stating: “chimeric cetuximab can be further humanized using standard methods to create a more human-like version of the antibody” and that such humanized variants are “useful herein.” EX1009 at 6, 11. BA03 is precisely such a humanized variant of cetuximab. EX1008, ¶140. By Tikhomirov’s own selection criteria, including (i) full EGFR antagonist, (ii)

competes with cetuximab for EGFR binding, and (iii) has affinity of 5 nM or less, BA03 would be a suitable antibody for inclusion in a Tikhomirov-type anti-EGFR ADC. *See* EX1009 at 2 (Claims 1–2), 3-4, 11.

84. Tikhomirov’s non-human primate safety study tested its preferred ADC at 10 mg/kg and found that “no severe dermatologic toxicities or other severe and qualitatively new dermatologic side-effects other than those that are expected as a result of naked cetuximab treatment” were observed. EX1009 at 26-27. This demonstrates that a cetuximab-class ADC can achieve an acceptable safety profile indistinguishable from naked cetuximab alone, directly refuting the suggestion that cetuximab-class ADCs are inherently too toxic. *Id.*

XV. DR. ATANACKOVIC’S “PARALLEL CHANGES” ASSUMPTION IS UNSUPPORTED

85. A critical foundation of Dr. Atanackovic’s analysis is the assertion that BA03’s increased EGFR phosphorylation inhibition and increased ADCC activity would translate into “parallel changes” of killing activity against both tumor and normal cells, resulting in “no change to the ADC’s therapeutic window.” EX2027, ¶63. Notably, this assertion is presented without any supporting experimental data or cited reference. *See* EX2027, ¶¶63–64.

86. The “parallel changes” assumption is scientifically unsound for several reasons. First, tumor cells typically overexpress EGFR by 10-fold to 100-fold

relative to normal cells. EX1013 at 1; EX2006. A stronger EGFR antagonist acting on a cell with significantly more EGFR would be expected to produce a substantially greater signaling blockade in that cell than in a normal cell with lower EGFR density. *Id.* The 100-fold difference in EGFR expression means that the therapeutic effect of stronger antagonism would be disproportionately greater in tumor cells, not proportional. *Id.*

87. Second, EGFR signaling inhibition produces its cytostatic and pro-apoptotic effects through downstream pathways that are driven by EGFR activation. EX1013 at 1. In normal tissues, EGFR is not constitutively overactivated, so blockade of a signaling pathway that is already at baseline would be expected to have a less dramatic effect than blockade of the hyper-activated pathway in EGFR-overexpressing tumor cells. *Id.*

88. Moreover, clinical data directly contradicts the assertion that enhanced ADCC causes increased toxicity to normal cells. *See* EX1225, EX1227. Glycoengineered anti-EGFR antibodies such as GA201/RG7160, which were specifically designed to have enhanced ADCC compared to cetuximab, showed acceptable safety profiles in Phase I clinical trials with no maximum-tolerated dose reached. EX1227 at 1. The clinical evidence for anti-EGFR antibodies shows that stronger Fc effector function correlates with better clinical outcomes, not worse safety profiles. *See* EX1223, EX1224, EX1225.

89. Indeed, Dr. Atanackovic admitted that by “parallel changes” caused by BA03’s stronger phosphorylation inhibition, he meant the increase in killing of tumor cells and normal cells “happens in parallel” and “the type of effect is the same” but “that doesn’t mean it’s the same extent”. EX1246 at 293:10-294:8. He also admitted that “it is not realistic” to compare the therapeutic windows of BA03 and Wei’s Y104D, because change in toxicity and change in efficacy are two different measures and cannot be compared directly. *Id.* at 297:15-298:7, 299:8-300:13.

XVI. DR. ATANACKOVIC’S ASSUMPTION OF LACK OF PH SELECTIVITY OF BA03

90. Dr. Atanackovic assumes that the BA03 antibody lacks pH selectivity based primarily on: (1) post-filing data submitted by Petitioner in WO 2023/088382 (“the ’382 application,” filed November 17, 2022) (EX2008), which was filed approximately seven years after the priority date of the ’370 patent; and (2) his view that BA03, as a humanized variant of cetuximab, would be similar to cetuximab and thus does not have pH selectivity. EX2027, ¶¶ 51–59. Dr. Atanackovic acknowledged that the post-filing data in the ’382 application (EX2008) was not available to a POSA at the time the ’370 patent was filed. EX1246 at 207:8–12.

91. Dr. Atanackovic further states that pH-selective antibodies are typically generated by substituting an amino acid residue at an antigen-binding site, namely within a complementarity-determining region (CDR), with a histidine residue or a

negatively charged residue such as aspartic acid or glutamic acid. EX2027, ¶ 56. He identifies the Y104D mutation as one such example, in which a tyrosine (Y) residue in heavy-chain CDR3 is replaced with an aspartic acid (D). *Id.* However, Dr. Atanackovic was unable to explain why BA03 would not also exhibit pH-selective properties, given that BA03 contains mutations that introduce charged residues, including aspartic acid, into CDR regions. EX1008 at 11. These are the same types of mutations that Dr. Atanackovic himself asserts typically confer pH selectivity. EX2027, ¶ 56; EX1246 at 217:2-219:13.

XVII. THE LONG-FELT NEED ARGUMENT IS UNSUPPORTED

92. Dr. Atanackovic argues that the failures of ABT-414, ABBV-221, ABBV-321, and HTI-1511 demonstrate a “long-felt and unresolved need” for a clinically viable anti-EGFR ADC. EX2027, ¶¶85–90. I have carefully examined these programs, and Dr. Atanackovic’s inference that their failures were attributable to the therapeutic window challenge is unsupported by the record. *Id.*, ¶¶86–89.

93. All four of these candidates used antibodies designed with tumor-selective or TME-selective properties, which is consistent with the very strategies Dr. Atanackovic advocates. *See id.*, ¶¶86–89 (describing EGFRvIII-specific or TME-specific antibodies). None of them used a cetuximab-class antibody targeting wild-type EGFR. *Id.* ABT-414 was terminated for “lack of survival benefit for patients receiving ABT-414,” which Dr. Atanackovic confirmed is an efficacy

failure, not a toxicity failure. EX2030 at 4; EX2027, ¶85; EX1246 at 265:1-12, 267:167-168:6. For ABBV-221, ABBV-321, and HTI-1511, the declaration does not identify any specific reason why those programs were terminated. *See* EX2027, ¶¶87–89. The only characterization offered is that “development has been terminated” or that “no further phase 2 or 3 testing has been reported.” *Id.* In fact, Dr. Atanackovic admitted that “there could be a number of reasons” these trials were terminated, not just safety. EX1246 at 270:13-14. It is particularly notable that the failed anti-EGFR ADC candidates all used the very tumor-selective strategies that Dr. Atanackovic advocates (EGFRvIII-specific or TME-specific antibodies). Their failure undermines, rather than supports, his position that these strategies are superior. *See* EX2027, ¶¶86–89. Meanwhile, the Patent Owner’s anti-EGFR ADC (MRG003) uses BA03, which targets wild-type EGFR, demonstrating that a different approach was what ultimately succeeded. EX2021 at 1.

XVIII. DR. ATANACKOVIC’S PREDICTION THAT SUCCESS WAS “IMPOSSIBLE” HAS BEEN PROVEN WRONG

94. In paragraph 84 of his declaration, Dr. Atanackovic states that “[a] POSA would have expected such a balance to be impossible for the proposed BA03-vc-MMAE ADC.” EX2027, ¶84. The use of the word “impossible” is an extraordinarily strong and scientifically unjustified assertion. *Id.* Yet Dr. Atanackovic bases this prediction on (1) the Crombet model, a theoretical model for

naked antibodies with undisclosed parameters (*see supra* § VII; EX2022 at 3-5), and (2) Tikhomirov's data, which compared ADCs with different payloads and linkers (*see* EX1009 at 42 (Fig. 13)). Neither provides direct evidence about BA03-vc-MMAE. In fact, the Crombet reference merely states "the mathematical model that we have built predicts that there is an affinity window that can be exploited for EGFR antagonists, and that *higher affinity is not necessarily the best.*" EX2022 at 7. It never categorically rejects pursuing anti-EGFR ADCs using high affinity anti-EGFR antibodies, such as cetuximab or BA03, as impossible.

95. The clinical record has now definitively refuted Dr. Atanackovic's prediction. MRG003 (BA03-vc-MMAE) has received regulatory approval in China for the treatment of certain nasopharyngeal carcinoma. EX2021 at 1. Patent Owner's own Global Offering prospectus reports that among 61 patients enrolled in Phase Ia and Phase Ib clinical trials, "14 patients (23.0%) reported TRAE of Grade 3 or higher" and "[a]ll Grade 3 and higher related AEs occurred in the 2.5 mg/kg dose group." EX2032 at 000314-315. The most common treatment-related adverse events were Grade 1 and Grade 2. *Id.* This clinical safety profile demonstrates that MRG003 was "well-tolerated" in human patients at therapeutically effective doses and directly contradicts Dr. Atanackovic's prediction that a BA03-based ADC would have "no or a very narrow therapeutic window." EX2032 at 000314; *see also* EX2027, ¶64.

96. Patent Owner itself links BA03's higher binding affinity directly to rapid internalization. EX2032 at 000310. The prospectus states that BA03 "has approximately six to sevenfold increased binding affinity to human EGFR, compared with cetuximab" and that "[i]t facilitates rapid internalization of MRG003 into tumor cells as demonstrated in our *in vitro* assays." *Id.* The very property Dr. Atanackovic identifies as disqualifying, higher binding affinity, is what Patent Owner itself promotes as a competitive advantage of MRG003. *See* EX2027, ¶¶22–25; EX2032 at 316; *see also* EX2033 (CSPC 2020 Annual Report) at 85–86 (describing MRG003 clinical development).

97. Dr. Atanackovic criticizes my original declaration for not sufficiently addressing the reasonable expectation of success. *See* EX2027, ¶¶81–84. I understand that the legal standard for reasonable expectation of success requires only that a POSA would have had a reasonable expectation of successfully making and using the claimed invention, not a guarantee of clinical or therapeutic success. *See id.*, ¶¶81–84. From a scientific standpoint, I believe that standard is readily met.

98. In my assessment, by the filing date of the '370 patent, each component of the claimed ADC was individually known and well characterized: (1) the BA03 antibody was known in the art (*see* EX1008, ¶140); (2) MMAE was known as an effective cytotoxic payload for ADCs (*see* EX1009 at 13–14 (identifying MMAE as an anti-microtubule toxin); EX1015 (McCombs 2015); EX1016 (Kovtun 2007)); (3)

the vc cleavable linker was known and widely used in ADC design (*see* EX1015; EX1016); and (4) the technique of conjugating antibodies to payloads via cleavable linkers was well established (*see* EX1015; EX1016). Patent Owner's own Response acknowledges that "the BA03 antibody was known in the art." POR at 1.

99. Leanna (EX1006) provides complete, validated, step-by-step protocols for making and purifying anti-EGFR antibody-vcMMAE ADCs with controlled DARs, and these protocols are not limited to Antibody 1. EX1006, 14:1–14. Leanna expressly states that the methods and compositions described "may be used to purify anti-EGFR antibody-auristatin ADCs, particularly, in a certain embodiment, anti-EGFR ADCs comprising Antibody 1." *Id.* at 14:10-14, 24:14–24 (Antibody 1 description). The word "particularly" introduces a preferred embodiment; it does not limit the disclosure to Antibody 1. *See id.* at 14:1–14 ("may be used to purify anti-EGFR antibody-auristatin ADCs, *particularly*, in a certain embodiment") (emphasis added).

100. As I understand the field, the conjugation chemistry described in Leanna, namely a partial reduction of interchain disulfide bonds using TCEP followed by coupling to vcMMAE, is a standard antibody conjugation methodology applicable to any IgG1 antibody with accessible interchain cysteine residues. *See* EX1006, 48:1–49:15. A POSA would understand this chemistry to be equally

applicable to BA03, which is also an IgG1 antibody derived from cetuximab. *See id.*; EX1008, ¶140.

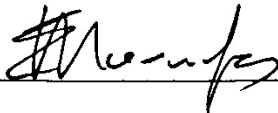
101. Furthermore, the factors Dr. Atanackovic himself lists as relevant to ADC success evaluation, including target internalization, antibody binding affinity, and payload potency (*see* EX2027, ¶¶81–84), all favor BA03-vc-MMAE. EGFR is a rapidly internalizing receptor (*see* EX1009 at 1); BA03 has high binding affinity that satisfies Tikhomirov’s own 5 nM threshold with tenfold margin (*see* EX1009 at 11; EX1244 at 2 (Table 1).); MMAE is an FDA-validated cytotoxic agent used in multiple approved ADCs (*see* EX1015; EX1016); and the vc linker has proven efficiency in multiple approved products (*see* EX1015; EX1016). A POSA would have had a reasonable expectation of success in combining these elements to produce a functional ADC. *See* EX1009 at 1, 11 (identifying EGFR as “attractive target” and preferring antibodies with ≤ 5 nM affinity); EX1015; EX1016.

XIX. CONCLUSION

102. For the reasons set forth above, and based on my scientific expertise and review of all relevant prior art, I maintain my opinion that claims 1-23 of the ’370 patent would have been obvious over the combinations of prior art references identified in Grounds 1 and 2 of the Petition.

103. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Signature:  _____

Stylianos Bournazos, Ph.D.

Date: 05/01/2020