



***CSPC Megalith Biopharmaceutical Co., Ltd.***

***v.***

***Lepu Biopharma Co. Ltd.***

**IPR2025-00685**

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

**Petitioners' Oral Argument Demonstratives  
July 15, 2026**

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

# **Summary**

- I. Overview of the '370 Patent and Claims**
- II. Ground 1: Obviousness Over Wei and Liu**
- III. Ground 2: Obviousness Over Leanna, Liu, and Wei**
- IV. Responding to Patent Owner's Defenses**
- V. Secondary Considerations Do Not Rebut Obviousness**

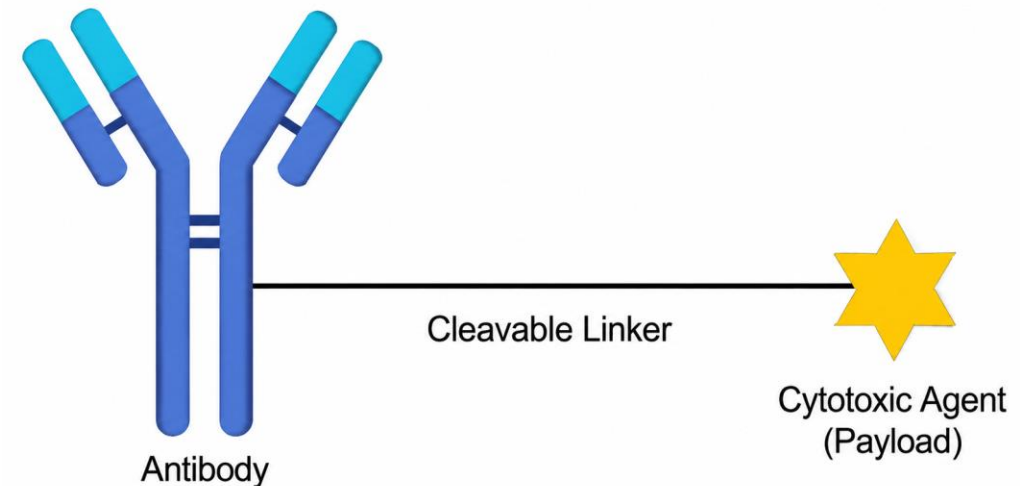
# The '370 Patent: ADC Composition Claims

**The patent claims a broad genus of antibody-drug conjugates (ADCs):**

- (1) Anti-EGFR antibody with BA03 CDR sequences
- (2) Cleavable linker (any – broad genus)
- (3) Cytotoxic agent (any – broad genus)

## Key Point:

- **The claims do NOT require:**
  - pH selectivity
  - Tumor-selective epitope binding
  - Therapeutic window improvement
  - Clinical success



Petition (Paper 1) at 1; Petitioner's Reply to Patent Owner's Response (Paper 23) at 1, 15, 26; EX1001 at 33:1-11 (claim 1).

# What did PO actually do to arrive at the challenged claims?

(12) **United States Patent**  
**Hu**

(10) **Patent No.:** **US 10,792,370 B2**  
(45) **Date of Patent:** **Oct. 6, 2020**

(54) **ANTIBODY-DRUG CONJUGATE** (56) **References Cited**

(71) Applicant: **SHANGHAI MIRACOGEN INC.,**  
Shanghai (CN)

(72) Inventor: **Chaohong Hu, Shanghai (CN)**

(73) Assignee: **SHANGHAI MIRACOGEN INC.,**  
CN

U.S. PATENT DOCUMENTS  
7,960,516 B2 \* 6/2011 Mathews ..... A61K 39/39591  
530/387.3

FOREIGN PATENT DOCUMENTS  
CN 103553264 A 6/2014

(\*) **19** **US 10,792,370 B2** **20**

transferred to a new Eppendorf centrifuge tube (weighed),  
and weighed; the protein concentration was measured and  
the total amount of protein was calculated. 2.5 times molar  
amount of DTT was added to the antibody and incubated at  
room temperature for 2 hours and continuously mixed. The  
mixture was buffer exchanged using a 15 ml 30 KD ultra-  
filtration device into a coupling buffer (50 mM Tris, pH 7.2,  
150 mM NaCl, 5 mM EDTA) for a total of three times. The  
concentrated solution was taken and weighed, measured by  
A280 to determine protein concentration, and the total  
amount of protein was calculated. 10 µl sample was taken  
and measured by Ellman's method to determine number of  
free thiol groups.

In addition, the molar concentration of its free thiol  
groups was calculated by the following formula:

$$C_{\text{free}} = \frac{A_{412} \times 112}{b \times 14150} (M)$$

b: optical path length of cuvette (usually 1 cm).

The mole number of free thiol groups was calculated from  
the molar concentration of free thiol groups and the volume  
of total protein solution.

To the reduced antibody was added 1.1 times the mole  
number of free thiol groups of vc-MMAE (purchased from  
Haoyuan Chemical Technology Co., Ltd., No. HY-15575)  
(dissolved in DMSO), mixed at room temperature and  
reacted for 2 hours, intermittently mixed. To the reaction  
system was added with N-acetylcysteine in an amount of 20  
times the mole number of vc-MMAE in the reaction solu-  
tion, mixed, and the mixture was allowed to stand for 5  
minutes. The mixture was buffer exchanged using a 15 ml 30  
KD ultrafiltration device into a conjugate stock solution (20  
mM sodium citrate (Na-citrate), 0.3% NaCl, 5% Trehalose,  
16/2863 (2013.01); A61K 2039/505 (2013.01);  
C07K 2317/24 (2013.01); C07K 2317/73  
(2013.01); C07K 2317/76 (2013.01); G01N  
2030/027 (2013.01); G01N 2030/8809  
(2013.01)

(58) **Field of Classification Search**  
CPC ..... A61K 47/6889; A61K 47/6849; A61K  
38/1808; A61K 39/001104  
See application file for complete search history.

**23 Claims, 7 Drawing Sheets**  
Specification includes a Sequence Listing.

'370 Patent Example 1: "...To the reduced antibody was added 1.1 times the mole number of free thiol groups of vc-MMAE (purchased from Haoyuan Chemical Technology Co., Ltd., No. HY-15575)..."

As the Institution Decision recognized (which is not disputed), "Example 1 of the '370 patent discloses the preparation of a specific ADC (MYK-3), in which the previously-known BA03 anti-EGFR antibody, is connected to a commercially-obtained vc-MMAE linker-cytotoxic agent molecule."

Before JEFFREY N. FREDMAN, JOHN G. NEW, and RYAN H. FLAX,  
Administrative Patent Judges.

NEW, Administrative Patent Judge.

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

UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,  
Petitioner,  
v.  
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Patent Owner.

IPR2025-00685  
Patent 10,792,370 B2

Pages 10  
Date: October 14, 2025

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571-272-7822

EX1001 at 18:26-29; Institution Decision (Paper 10) at 4; Paper 1 at 10.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

# Representative Claims

- **Claim 1:**

An antibody-drug conjugate comprising an anti-EGFR antibody comprising [BA03 CDR sequences], a cleavable linker, and a cytotoxic agent.

- **The claim defines a BROAD genus covering *any* anti-EGFR antibody with BA03 CDR sequences, *any* cytotoxic agent, *any* cleavable linker.**
- PO's expert agreed that claim 1 covers antibodies with the same CDR sequences as those in BA03 but with "different sequences in the Fc region" and "account for *millions of different antibodies*".

Petition (Paper 1) at 1; EX1001 at 33:1-11, 34:23-36 (claims 1, 13); EX1246 (Dep. Tr. of Dr. Atanackovic) at 142:7-22.

# What the Claims Require vs. What PO Tries to Import

| Claimed Features                                                                                                                                              | Unclaimed Features PO Tries To Import                                                                                                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Any anti-EGFR antibody with BA03 CDR sequences</li><li>• Any cleavable linker</li><li>• Any Cytotoxic agent</li></ul> | <ul style="list-style-type: none"><li>• pH selectivity</li><li>• Tumor-selective epitope binding</li><li>• Therapeutic window improvement</li><li>• Clinical success</li></ul> |

**None of PO's asserted limitations appear in any challenged claim.**

Petition (Paper 1) at 1; EX1001 at 33:1-11 (claim 1); Patent Owner's Sur-Reply (Paper 35) at 2, 9-11, 18-19.

# Overview of Key Prior Art References

| Reference                | Key Teaching                                                                                                              |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------|
| <b>Wei (EX1005)</b>      | Humanized cetuximab variant (huY104D) ADCs with vc-MMAE; potent anti-tumor activity; also discloses cetuximab-vc-MMAE ADC |
| <b>Liu (EX1007/1008)</b> | BA03 antibody: higher affinity (~6-7x), stronger EGFR inhibition, higher ADCC, lower immunogenicity                       |
| <b>Leanna (EX1006)</b>   | Anti-EGFR ADC purification; Antibody 1-vc-MMAE; not limited to one antibody                                               |

Paper 1 at 15-31; EX1005 at ¶¶1116-1128; EX1006, Abstract, 8; EX1008 at ¶¶ 37, 60, 141-158; EX1009 at 10, 30.

# Liu Teaches BA03 – A Humanized Anti-EGFR Antibody Superior to Cetuximab

## BA03's advantages over cetuximab:

Higher binding affinity (~6-7x cetuximab)

Stronger EGFR phosphorylation inhibition

Higher ADCC activity

Lower immunogenicity (humanized)



Each of these properties is desirable in an ADC antibody as Dr. Bournazos explained and supported by literature in the field of ADC design.

Paper 1 at 27; Petitioner's Reply to Patent Owner's Response (Paper 23) at 5-7; EX1002 at ¶¶ 45-53, 87; EX1200 at ¶¶ 52-65.

# Wei and Leanna Teach Anti-EGFR ADCs with vc-MMAE

| Wei (EX1005)                                                                                                                                                                                                                       | Leanna (EX1006)                                                                                                                                                                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>huY104D-vc-MMAE ADC</b> <ul style="list-style-type: none"><li>• Potent anti-tumor activity</li><li>• Humanized cetuximab variant</li><li>• Also discloses cetuximab-MMAE</li><li>• vc linker + MMAE payload validated</li></ul> | <b>Antibody 1-vc-MMAE ADC</b> <ul style="list-style-type: none"><li>• Titled “Antibody Drug Conjugate (ADC) Purification” – not limited to any particular antibody</li><li>• Claims cover any antibody conjugated to a payload</li><li>• Antibody 1 is merely “an example”</li><li>• DAR of 3.85 disclosed</li></ul> |

***Both references validate the claimed linker-payload architecture (vc-MMAE).***

Paper 1 at 16-24, 71-72; Paper 23 at 3-4, 18, 21; EX1005 at ¶11116-1128; EX1006, Abstract, 8, 32-34, 51.

# Ground 1: Obviousness Over Wei and Liu

**Wei (EX1005)** – ADC platform: humanized cetuximab variant + vc-MMAE

+

**Liu (EX1007/1008)** – BA03 antibody with CDR sequences and superior properties(humanized cetuximab)

Paper 1 at 37-40; EX1005 at ¶¶1116-1128; EX1008 at ¶¶ 37, 60, 141-158.

# Motivation to Combine Wei and Liu

- A POSA could start with BA03 (Liu) and turn to Wei for the ADC platform and vc-MMAE linker payload
- BA03 and huY104D are both humanized cetuximab variants – “siblings” (EX1200, ¶¶ 73-76; EX1002, ¶¶ 187-188)
- Liu expressly teaches BA03’s multiple advantages over cetuximab (EX1008, Examples 1-8)
- The Examiner repeatedly found motivation to use BA03 in place of cetuximab in ADC references (EX1003 at 406; EX1004 at 156)
- **As the Board recognized in its *KSR* discussion, “it is in the nature of scientific research to continue to try new substitutions in drug therapy, even if a promising candidate has been discovered.”** (Paper 10 (Institution Decision) at 40)

# PO's lack of motivation to combine arguments are misleading

- PO tries to minimize the significance of BA03 by characterizing Liu as a “secondary” reference, even though Petitioner never characterized Liu as a secondary reference.
- In any event, characterizing references as primary and secondary has “no legal significance” to the obviousness analysis. See *Schwendimann v. Neenah, Inc.*, 82 F.4th 1371, 1384 (Fed. Cir. 2023).
- PO improperly limits the obviousness analysis by requiring the POSA to start with the ADCs disclosed in Wei or Leanna, and then requiring motivation to replace the antibody of these ADCs with Liu’s BA03 antibody.
- However, the POSA was not so constrained, and could also have started with recognizing the advantages of the BA03 antibody and determined whether there was prior art that disclosed modified cetuximab ADCs with the claimed linker payload.
- This is how the Patent Examiner found the motivation to combine BA03 with ADC prior art and was also recognized in the Board’s Institution Decision.

# The Board's Institution Decision

[Trials@uspto.gov  
571-272-7822

Paper 10  
Date: October 14, 2025

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.

IPR2025-00685  
Patent 10,792,370 B2

Before JEFFREY N. FREDMAN, JOHN G. NEW, and RYAN H. FLAX,  
*Administrative Patent Judges.*

NEW, *Administrative Patent Judge.*

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

We find, based upon the present record and for the purposes of this Decision, that Petitioner has sufficiently established that a person of ordinary skill in the art would have been **motivated to combine the teachings of Wei and Liu** to determine the activity and suitability of Liu's humanized anti-EGFR antibodies in an ADC...

...In the instance of Liu's humanized anti-EGFR antibody, a person of ordinary skill in the art would have recognized that its **advantages** (enhanced activity against tumor cells compared to chimeric cetuximab, thus requiring smaller dosages) **could balance or outweigh its possible disadvantages** (e.g., possible activity against non-tumor cells).

# BA03's Advantages Are Directly Relevant to ADC Design

| ADC Design Property | BA03 Advantage (Liu)           | Relevance to ADC                   |
|---------------------|--------------------------------|------------------------------------|
| Binding Affinity    | ~6-7x higher than cetuximab    | Desirable property                 |
| EGFR Inhibition     | Stronger phosphorylation block | Relevant to efficacy               |
| ADCC Activity       | Higher ADCC                    | Contributes to anti-tumor activity |
| Immunogenicity      | Lower (humanized)              | Reduces adverse events             |

Paper 1 at 27; Paper 23 at 7-8; EX1008, Examples 1-8, ¶¶[0141]- [0150], Tables 1-3; EX1200 at 20-22, 30-37.

# The Prosecution History Confirms Motivation

- **The Examiner found BA03 is:**  
*“the full-length antibody that is an antagonist of EGFR as demonstrated by Liu and has higher binding affinity and ligand blocking abilities than cetuximab.”*
- **Patent Owner never challenged motivation to use BA03 during prosecution.**  
PO focused solely on the cleavable linker limitation.

See Paper 1 at 2, 13, 42, 68-69; Paper 23 at 8-9; EX1003 at 406; EX1004 at 156.

# Wei Does Not Teach Away

- As the Institution Decision acknowledged, “A teaching away requires a reference to actually ‘criticize, discredit, or otherwise discourage the [claimed] solution.’ *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004); see also *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (holding that ‘when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant’)...
- ...Nor does Patent Owner point to any express teaching or suggestion of Wei that expressly criticizes, discredits, or would have otherwise discouraged a person of ordinary skill in the art from combining its linker-cytotoxin constituent with other anti-EGFR antibodies. To be sure, Wei teaches that its modified cetuximab anti-EGFR has the advantage of being pH selective in its binding affinity, such that it binds preferentially to EGF receptors in the more acidic extracellular microenvironment of tumor tissue compared to receptors in non-tumor tissues at a physiological pH of 7.0–7.2. But, Patent Owner points to no teaching that would have discouraged a skilled artisan from combining its vc-MMAE moiety with another modified cetuximab anti-EGFR antibody whose pH binding affinity is unknown.”

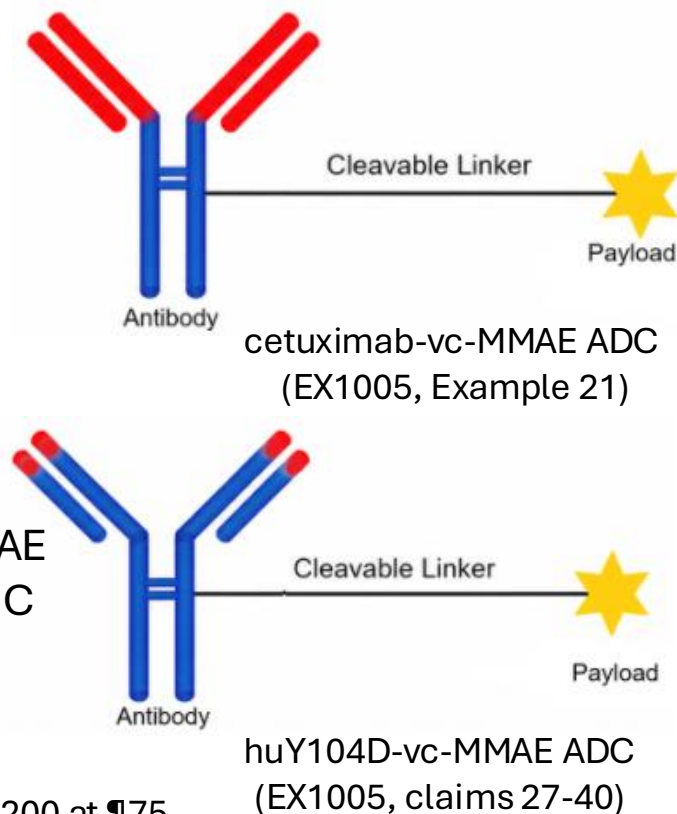
# Wei Does Not Teach Away

## Legal Standard (*Fulton*):

Teaching away requires “criticize, discredit, or otherwise discourage.”

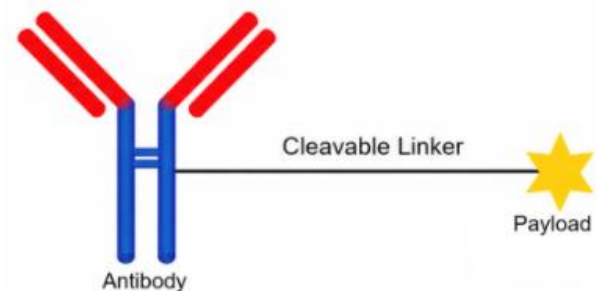
“Mere disclosure of more than one alternative does not constitute a teaching away.”

- Wei discloses Y104D as ONE approach – does not suggest others unsuitable
- Wei itself discloses cetuximab-MMAE with similar CGI on A431 cancer cells. Only 10% difference on keratinocytes (80% vs. 70% CGI at maximum doses)
- Wei’s disclosure of both a cetuximab+vc-MMAE ADC and a humanized cetuximab+vc-MMAE ADC clearly provides strong motivation to arrive at the BA03+vc-MMAE ADC invention.
- Based on Petitioner’s expert (Bournazos), Wei’s humanized cetuximab+vc-MMAE ADC and the claimed preferred embodiment humanized cetuximab+MMAE ADC are “substantially identical.”

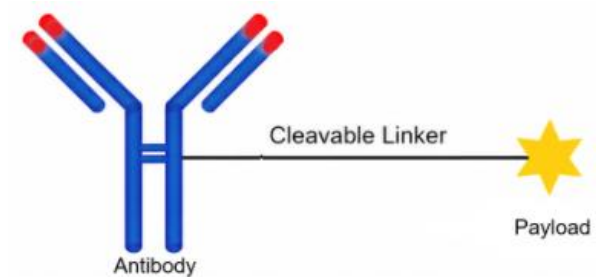


*In re Fulton*, 391 F.3d at 1195, 1201 (Fed. Cir. 2004); Paper 1 at 40; Paper 23 at 14-15; EX1002 at ¶188; EX1200 at ¶75.

# Wei Teaches Both Humanized Cetuximab ADC and Cetuximab (Chimeric) ADC



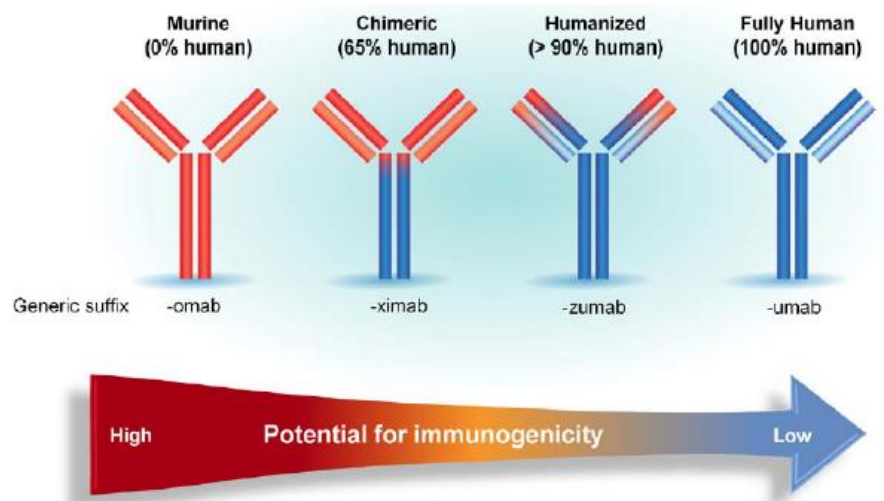
cetuximab-vc-MMAE ADC  
(EX1005, Example 21)



huY104D-vc-MMAE ADC  
(EX1005, claims 27-40)

| ADC                                     | Cetuximab-vc-MMAE                 | Y104D-vc-MMAE                     |
|-----------------------------------------|-----------------------------------|-----------------------------------|
| Inhibition of A431 cancer cells         | “Virtually identical”             | “Virtually Identical”             |
| Inhibition of keratinocyte (skin) cells | At maximum doses, “about 80%” CGI | At maximum doses, “about 70%” CGI |

Ex. 1005 (Wei) at ¶¶ 1130-1131.



Paper 1 at 8;EX1034 at 4; EX1005.

# Reasonable Expectation of Success

Legal standard: reasonable expectation of making/using, NOT guarantee of clinical success

PO expert Dr. Atanackovic conceded: claims do not require therapeutic or clinical success.

ADCs are modular – assembled from known, interchangeable components

vc-MMAE was clinically validated (Adcetris, 2011 FDA approval)

Wei's preclinical proof of concept with huY104D-vc-MMAE

BA03 has key ADC antibody properties (affinity, phosphorylation, ADCC)

Q Take a look -- can you take a look quickly, and then just let me know whether the claim 1 actually contains language that's specifically saying that the ADC has to be clinically or therapeutically successful.

If you don't see it, let me know.

A Well, yeah. No, I don't see it.

# Wei's Antibodies Achieved Pre-Clinical Success

[Trials@uspto.gov  
571-272-7822

Paper 10  
Date: October 14, 2025

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The Institution Decision acknowledged the pre-clinical success of Wei's anti-EGFR antibodies:

Moreover, although Patent Owner points to the alleged failure of three other ADCs incorporating anti-EGFR antibodies to advance beyond phase 1 clinical trials, Patent Owner is still faced with the evidence of Wei, which appears to have very successfully demonstrated pre-clinical success of such an antibody.

*See, e.g., id.* ¶¶ 10, 742, 1103. Wei also teaches a humanized version of this antibody (huY104D) that is similarly covalently linked to MMAE via the vc cleavable linker. *See, e.g., id.* ¶¶ 15, 36–42, 1116. Wei teaches that its ADCs are effective in inhibiting tumor cells, KRAS-mutated EGFR+ tumors both *in vitro* and *in vivo*. *Id.* at Examples 17–20.

Institution Decision (Paper 10) at 35, 43; EX1005, Examples 17-20.

## Ground 2: Obviousness Over Leanna, Liu, and Wei

**Claims 1-23 are obvious over the combination of:**

### **Leanna (EX1006) + Liu (EX1007/1008) + Wei (EX1005)**

- Leanna provides the ADC architecture (vc-MMAE, any anti-EGFR antibody)
- Liu provides BA03 with its superior properties
- Wei provides additional confirmation of humanized cetuximab ADC viability

# Leanna Is Not Limited to Antibody 1

- Leanna is titled “ADC Purification” – not limited to any single antibody
- Defines “anti-EGFR antibody” as any antibody that specifically binds EGFR
- Antibody 1 is merely “an example”
- Claims cover any “antibody conjugated to an auristatin”

**A POSA reading Leanna would understand its ADC architecture (anti-EGFR antibody with vc-MMAE payload) as applicable to any anti-EGFR antibody, including BA03.**

# PO's Tumor-Selective Epitope Argument Fails

- Leanna's specification and claims do not require tumor-selective epitope binding
- Leanna was cited for ADC architecture, not epitope specificity
- Motivation comes from Liu's teachings of BA03's advantages
- PO's tumor selectivity argument regarding Leanna's Antibody 1 is misleading.
  - Antibody 1's selectivity is compromised by the fact that it binds to an EGFR variant – EGFRvIII, which is only found in a subset of cases (from 24-67%).
  - Most patients (82%) lose expression of EGFRvIII upon recurrence (when cancer returns after treatment), which means Antibody 1 cannot remain effective across the disease course as its target disappears with disease progression.
  - Because BA03 more effectively targets a wider patient population, the POSA would recognize BA03 as also a suitable antibody candidate for Leanna's antibody-vc-MMAE ADC architecture.

Paper 23 at 18-20; EX1200, ¶¶66-72; EX1229 at 1; EX1231 at 2.

## Ground 2 – Conclusion

### **Same motivation to combine as Ground 1:**

Liu's teachings of BA03's advantages motivate combining BA03 with Leanna's vc-MMAE ADC architecture

### **Same reasonable expectation of success:**

ADC modularity + clinically validated vc-MMAE + BA03's desirable properties

### **Wei provides additional confirmation:**

Preclinical success of closely related humanized cetuximab variant ADC

# Responding to Patent Owner's Defenses

**Addressing each argument in the Patent Owner's Sur-Reply**

# PO: “Petitioner Ignores Toxicity”

## PO’s Argument:

Petitioner’s case ignores the primary challenge of anti-EGFR ADC toxicity.

## Petitioner’s Response: This is a mischaracterization

- PO improperly narrows the POSA to a single design objective
- Petitioner acknowledges therapeutic window – but the POSA considers MULTIPLE factors
- The legal question is what a POSA would find **obvious** – not what would be **optimal**

# The POSA Considers Multiple ADC Design Factors

- Binding affinity
- Internalization rate
- ADCC activity
- Immunogenicity
- Pharmacokinetics
- Manufacturability
- Overall anti-tumor efficacy
- Patient coverage

***In re Fulton***: The proper question is whether the prior art as a whole suggests the desirability of the combination. See *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004).

# Normal-Tissue Expression Has Never Been Prohibitive

| Approved ADC              | Target      | Normal Tissue Expression? |
|---------------------------|-------------|---------------------------|
| Trastuzumab emtansine     | HER2        | Yes                       |
| Enfortumab vedotin        | Nectin-4    | Yes                       |
| Sacituzumab govitecan     | TROP-2      | Yes                       |
| Mirvetuximab soravtansine | FR $\alpha$ | Yes                       |



Tikhomirov (EX1009) indicates EGFR is "**an attractive target**"

**Tikhomirov-346 (EX2011) concedes:**

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. The risk of anti-EGFR therapy-associated toxicity can be reduced by prior administration of anti-histamine, or by administering anti-EGFR antibody at a reduced and less effective dose.

**PO expert FAILED to present this passage to the Board.**

# PO: “No Advantage from Replacing Wei’s/Leanna’s Antibodies”

**PO’s Argument:** BA03’s benefits are only relative to cetuximab, not to huY104D/Antibody 1.

## Our Response:

- Obviousness analysis is not limited to “start with Wei/Leanna and substitute” – POSA could start with BA03
- BA03 and huY104D are “siblings” – substantially identical
- Liu’s express teachings motivate use of BA03 in any anti-EGFR ADC

# PO: “Reply Contradicts Petition on pH Selectivity”

**PO’s Argument:** Petitioner’s Reply “denies Wei’s pH selectivity”, contradicting the Petition.

## Our Response:

- No contradiction
  - Petition described what Wei claims.
  - Petitioner’s Reply showed that Wei’s data does not demonstrate biologically meaningful pH selectivity.
- Dr. Bournazos’s analysis shows the data is inconsistent and variable (EX1005, Tables 42, 44, 45)
- **Regardless, claims do NOT require pH selectivity**

# PO's pH Selectivity Theory Collapses

Claims don't require pH selectivity

PO expert Dr. Atanackovic's opinion relies on POST-FILING evidence (EX2008) he conceded was unavailable to POSA

BA03 contains the very types of charged CDR mutations Atanackovic says confer pH selectivity – he cannot explain the inconsistency

# PO's Crombet Model Is Unreliable

- Developed for NAKED antibodies, not ADCs
- Omits ADC-specific parameters (DAR, linker stability, payload kinetics)
- Compared data from DIFFERENT clinical trials at DIFFERENT dosages
- Crombet says “higher affinity is not necessarily the best” – NOT that it is disqualifying
- **ADC doses are substantially lower than naked antibody doses – at lower doses, high affinity becomes an advantage.**

# PO: “Hindsight Bias”

**PO’s Argument:** Petitioner’s reliance on the 2022 prospectus is “textbook hindsight.”

## Our Response:

- We cite the prospectus to impeach PO’s expert – PO promotes BA03’s high affinity as a “**competitive advantage**” while PO's expert calls it “**disqualifying**”
- The prospectus CONFIRMS what the prior art already taught – Liu disclosed BA03’s advantages before the priority date
- The motivation comes from Liu and Wei, both published BEFORE the priority date

# PO: “New Theories Are Untimely”

**PO’s Argument:** Starting with BA03 is a new theory raised in Petitioner’s Reply.

## Our Response:

- Petitioner's grounds are based on prior art *combinations*; does not restrict Liu as a secondary reference
- The Petition already presented this: the Examiner’s theory of “replacing cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu”

Paper 1 at 40-42; Paper 23 at 2-3, 8-9; Paper 35 at 7-8, 16.

## PO: “Wei and Leanna Teach Away”

- Teaching away requires “criticize, discredit, or otherwise discourage”, “mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives.” *In re Fulton*, 391 F.3d at 1201.
- **Wei does not teach away:**
  - Wei does not state other humanized cetuximab variants would be unsuitable
  - A preference for Y104D does not teach away from alternatives
  - Showing one preference is not discouragement when it does not disparage alternatives
- **Leanna does not teach away:**
  - Leanna is not limited to Antibody 1
  - Antibody 1 of Leanna has drawbacks: (1) only targets sub-population of patients having EGFRvIII; and (2) most patients lose expression of EGFRvIII upon recurrence
  - A POSA could consider Liu's BA03 due to its broad-targeting ability (targeting wild type EGFR) and known superior properties

# PO's Federal Circuit Cases Are Distinguishable

| Case Cited                                                                                 | PO's Theory                        | Why Inapplicable                                               |
|--------------------------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------|
| <i>Chemours Co. FC, LLC v. Daikin Indus., Ltd.</i> , 4 F.4th 1370 (Fed. Cir. 2021)         | Altering “inventive concept”       | ADC platform’s “inventive concept” is not pH selectivity alone |
| <i>DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.</i> , 567 F.3d 1314 (Fed. Cir. 2009) | “Inoperative for intended purpose” | Wei/Leanna platforms function with different antibodies        |
| <i>Eisai Co. v. Dr. Reddy's Laboratories, Ltd.</i> , 533 F.3d 1353 (Fed. Cir. 2008)        | “No reason to drop the feature”    | Liu provides an affirmative reason to select BA03              |

**Substituting BA03 does not render Wei/Leanna “inoperative.”**  
**The “inventive concept” is the ADC platform, not pH selectivity alone.**

Paper 23 at 16, 19-20; Paper 35 at 15-16.

# PO: “BA03-vc-MMAE Would Have Unviable Therapeutic Window”

**PO’s Argument:** BA03-vc-MMAE would be no better than cetuximab-vc-MMAE.

## **Our Response:**

- PO's argument has no scientific basis – no citation provided to support this conclusory statement
- **The legal standard does NOT require expected therapeutic or clinical success**
- Dr. Atanackovic conceded: claims contain no language requiring the ADC to be therapeutically or clinically successful (EX1246, 145:3-148:9)
- The POSA would have had a reasonable expectation of making and using the claimed ADC

## BA03's Higher Binding Affinity is an Advantage

- ADC doses are substantially lower than naked antibody doses
- At lower ADC doses, high affinity allows efficient target binding
- High affinity Influences internalization rate and catabolism

**Contradiction:** PO markets BA03's high affinity as a “**competitive advantage**” for investors – but tells the Board it is “**disqualifying.**”

Paper 23 at 13; EX1200 at ¶¶ 34-38; Paper 35 at 27.

# PO's Attempt to Recharacterize Its Expert's Testimony

**PO's claim:** The proposition about binding/internalization was merely “Petitioner’s question.”

## The Record:

**Dr. Atanackovic answered and conceded the scientific plausibility. This is PO's own expert's admission.**

Q That's what it says, right?

Correct me if I'm wrong. Earlier you testified that stronger binding, in principle, can result in higher degree of internalization of ADC, correct?

A That's possible, yeah.

# Claim 13: No basis for non-obviousness

Known elements and predictable combination (known ADC architecture)

| Element      | Wei (EX1005)    | Leanna (EX1006)   |
|--------------|-----------------|-------------------|
| vc linker    | ✓ Disclosed     | ✓ Disclosed       |
| MMAE payload | ✓ Disclosed     | ✓ Disclosed       |
| DAR          | ~4 (within 1-8) | 3.85 (within 1-8) |

## No unexpected results:

- Relies on prior-art BA03 and its previously recognized advantages.
- Utilizes clinically validated vc-MMAE linker-payload platform (Adcetris approved 2011). MMAE is a highly potent cytotoxic agent, and the cleavable vc linker enables a known bystander effect.
- Employs conventional and widely used conjugation chemistry.
- The alleged superior result involves comparison only to the naked antibody.
- No head-to-head data are provided comparing MRG003 with any prior-art ADC, making it impossible to attribute any purported advantages to the claimed construct.

Paper 23 at 21-22; EX1005 at ¶ [1103]; EX1006 at 51; EX1241 at 14.

# **Secondary Considerations Do Not Rebut Obviousness**

**PO fails to establish nexus, long-felt need, or copying**

## PO Fails to Establish Nexus

- Nexus presumption rebutted for broad claims. *ClassCo, Inc. v. Apple, Inc.*, 838 F.3d1214,1221-22 (Fed. Cir. 2016); *Palo Alto Networks, Inc. v. BT Americas Inc.*, IPR2023-00889, Paper 32, at 69–71 (PTAB Nov. 7, 2024)
- **Claims cover a BROAD genus:** any cytotoxic agent + any cleavable linker + any anti-EGFR antibody with BA03 CDRs
- PO's expert conceded that claims encompass “millions of different antibodies”
- **MRG003 is a narrow species** within this broad genus
- PO has not shown success stems from features unique to the claims vs. other factors (clinical expertise, manufacturing, dose/schedule)

## No Long-Felt Need or Failure of Others

| Failed ADC | Strategy                   | Outcome                      |
|------------|----------------------------|------------------------------|
| ABT-414    | Tumor-selective (EGFRvIII) | Failed for EFFICACY          |
| ABBV-221   | Tumor-selective            | Terminated (reasons unknown) |
| ABBV-321   | Tumor-selective            | Terminated (reasons unknown) |
| HTI-1511   | Tumor-selective            | Terminated (reasons unknown) |

**All four failed candidates cited by PO used TUMOR-SELECTIVE antibodies: These failures UNDERMINE PO's theory that tumor selectivity is the path to success.**

PO's expert does not know reasons for 3 out of 4 terminations.

# No Copying

## CPO301 (Petitioner's product) vs. Challenged Claims:

| Feature  | MRG003 (PO)            | CPO301 (Petitioner)                                  |
|----------|------------------------|------------------------------------------------------|
| Antibody | BA03                   | BA03                                                 |
| Linker   | vc (valine-citrulline) | <b>DIFFERENT linker</b>                              |
| Payload  | MMAE                   | <b>DIFFERENT payload (Topoisomerase I inhibitor)</b> |

**Fundamental differences in linker and payload defeat copying inference.**

PO merely purchased vc-MMAE from a commercial catalog and attached it to the known BA03 antibody.

# Petitioner Owns the Rights to BA03 Antibody which is Used by PO

As admitted by PO in its POR:

“In March 2015, Patent Owner entered into a patent licensing agreement with the owner of Liu, Shanghai JMT-Bio, Inc. (“JMT”). Ex-2032, 000035....

...While the Phase I trial of MRG003 was underway, **Petitioner acquired JMT in January 2019**. Ex-2033, 000129.”

Patent Owner’s Response (Paper 19) at 63-64 (emphasis added).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

SHANGHAI MIRACOGEN INC.,

Patent Owner.

Case No. IPR2025-00685

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

PATENT OWNER’S RESPONSE

# PO's Contradiction on MRG003's Success

**PO argues:** MRG003 is the “first anti-EGFR ADC approved for clinical use”

- PO does not dispute failed candidates used tumor-selective strategies PO advocates
- PO attributes MRG003's success to BA03's high binding affinity – the very property PO simultaneously claims a POSA would have considered disqualifying

## **Fatal Contradiction:**

- PO tells investors: BA03's high affinity is a “competitive advantage”
- PO tells the Board: BA03's high affinity is “disqualifying”
- **Both cannot be true.**

# PO's Expert Dr. Atanackovic's Declaration Is Unreliable

## Key omissions – selective presentation of prior art

### (1) Tikhomirov-346:

“The risk associated with severe skin reaction is currently considered acceptable when managed properly.” EX2011 at 1:30-32.

### (2) Tikhomirov-346:

“[E]fforts to improve upon EGFR antibodies are aimed at generating antibodies having even greater affinity for the target antigen.” EX2011 at 2:14-15.

**PO's Expert Dr. Atanackovic conceded at deposition that he did not present either passage to the Board. (EX1246, 12:11-14:18).**

Paper 23 at 10; EX1200 at ¶¶29, 78-79; EX1246 at 12:11-14:18; EX2011 at 1:30-32, 2:14-15.

# Key Admissions

pH selectivity opinion relied on post-filing evidence (EX1246, 207:5-14)

Does not know reasons for termination of 3 out of 4 failed ADC candidates (EX1246, 265:19-270:14)

"Parallel changes" retreated to "it's possible" (EX1246, 293:10-301:6)

Conceded ADCC “contributes to antitumor effects” (EX1246, 306:9-307:20)

Failed to analyze the very ADC design factors he identified as relevant (EX1246, 164:11-167:22)

# Summary

## Ground 1 (Wei + Liu)

- All elements taught
- Ample motivation to combine
- Reasonable expectation of success

## Ground 2 (Leanna + Liu + Wei)

- All elements taught
- Same motivation analysis
- Same expectation of success

### **PO's defenses fail:**

Claims do not require unclaimed features

No teaching away

pH selectivity theory collapsed

Secondary considerations: lack nexus and no unexpected results

Expert testimony unreliable

# The Board Should Find Claims 1-23 Unpatentable

**Petitioner respectfully requests that the Board find all challenged claims unpatentable.**

- The prior art teaches every element of Claims 1-23
- Motivation to combine flows from the references themselves
- PO's defenses rely on unclaimed features, an unreliable expert, and hindsight-informed reasoning
- Secondary considerations lack nexus to the broad genus claims