

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

LEPU BIOPHARMA CO., LTD.,

Patent Owner.

Case No. IPR2025-00685

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

PATENT OWNER'S ORAL HEARING DEMONSTRATIVES

**CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,
Petitioner,
v.
LEPU BIOPHARMA CO. LTD.,
Patent Owner.**

Case No. IPR2025-00685
U.S. Patent 10,792,370

Patent Owner's Demonstratives
July 15, 2026

Instituted Grounds

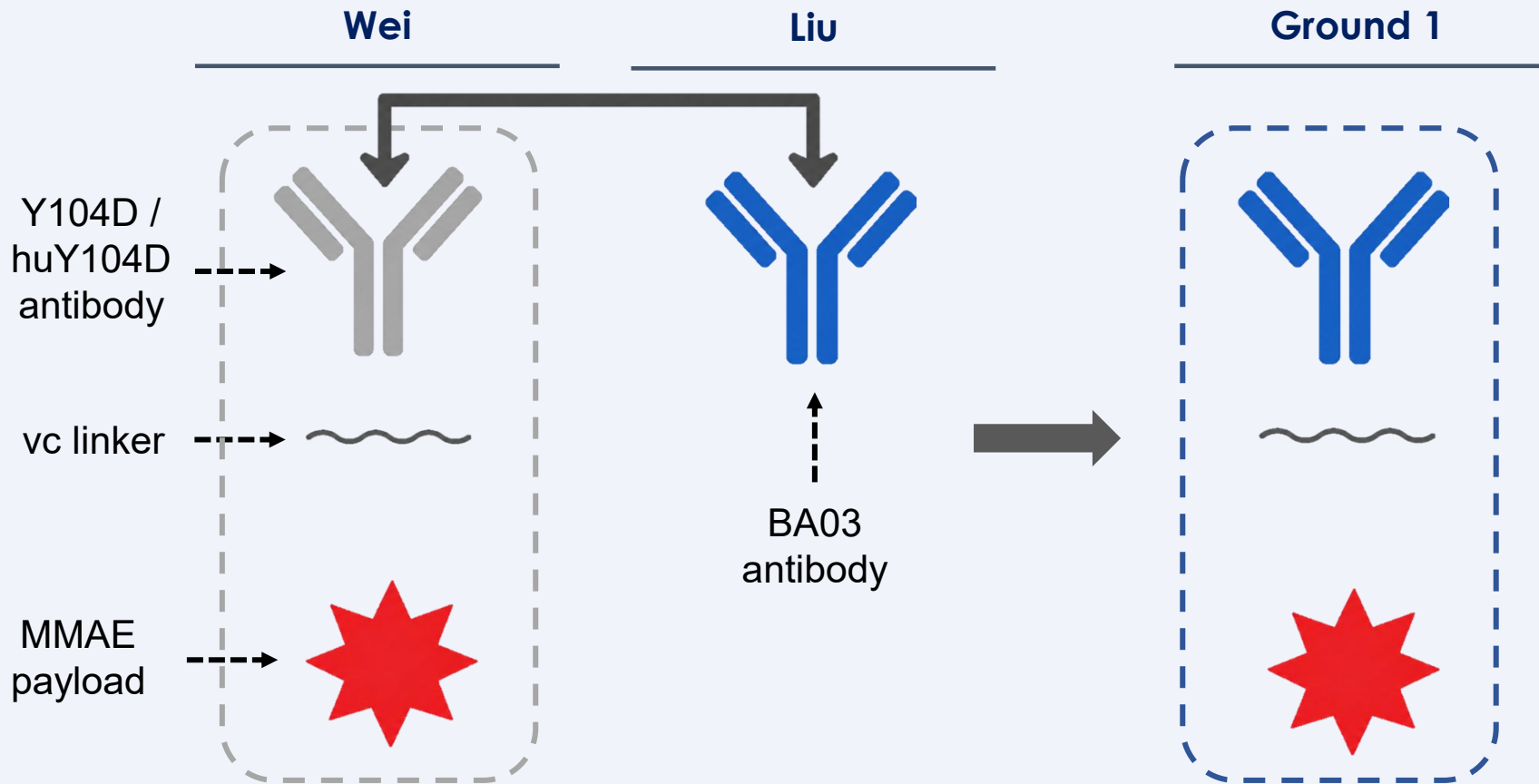
Grounds	Claims	Statutory Basis	Prior Art
1	1-23	§ 103	Wei and Liu
2	1-23	§ 103	Leanna, Liu, and Wei

'370 Patent – Claim 1

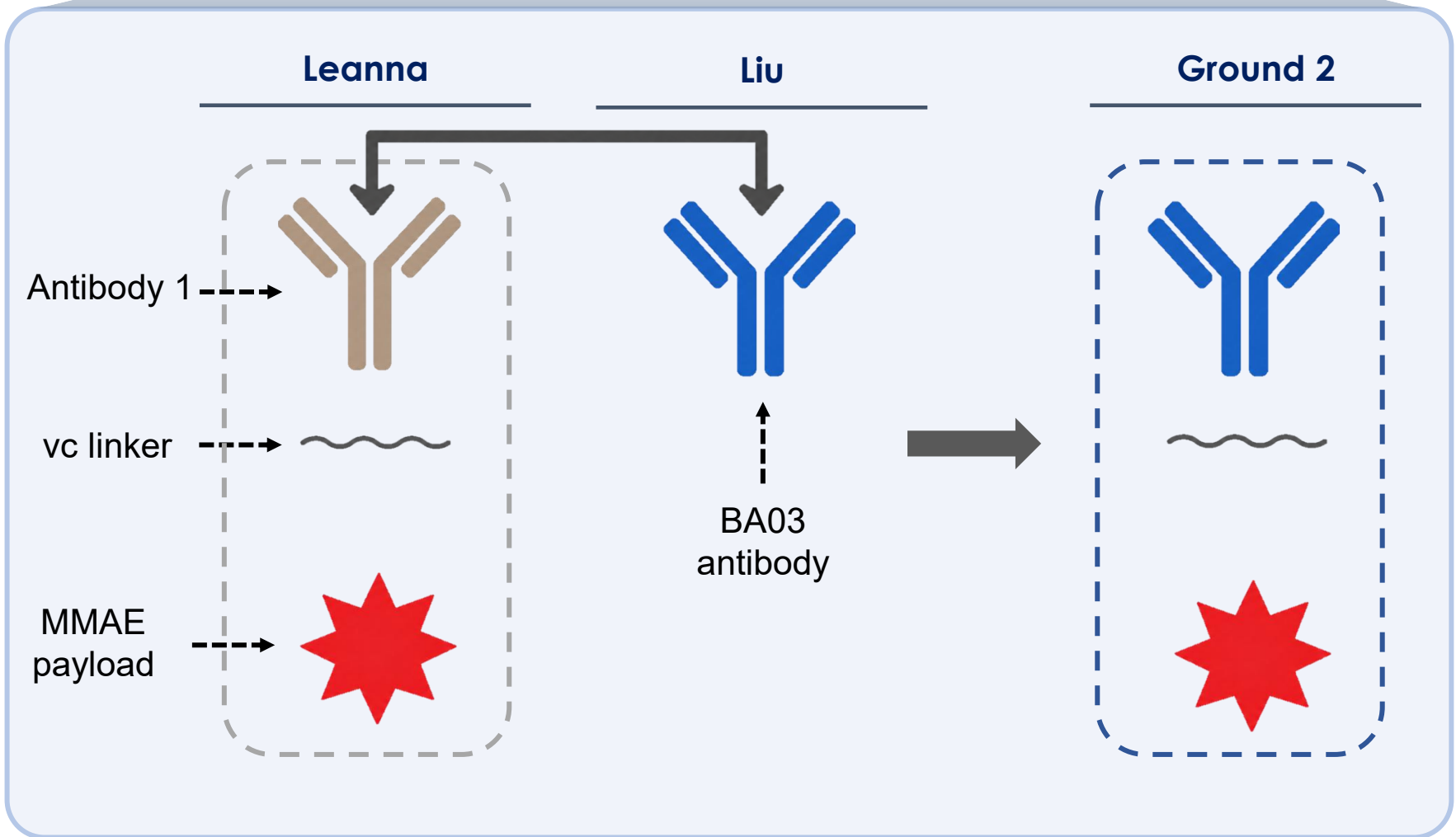
1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising
an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker,

wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.

Ground 1



Ground 2



Petitioner's Obviousness Theories Fail

Petitioner fails to address the primary challenge of toxicity mitigation in anti-EGFR ADC design.

A POSA would not have been motivated to modify Wei and Leanna as Petitioner proposes.

A POSA would have expected the proposed ADC to have an unviable therapeutic window.

Petition fails to overcome objective indicia of non-obviousness.

Petitioner's Obviousness Theories Fail



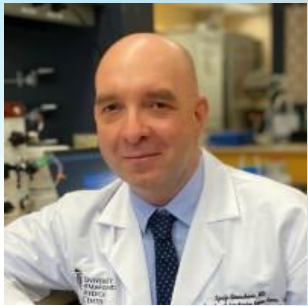
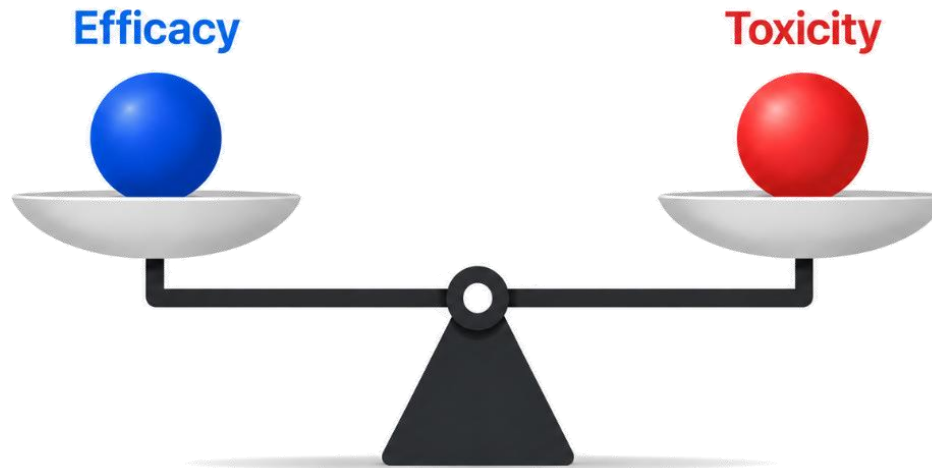
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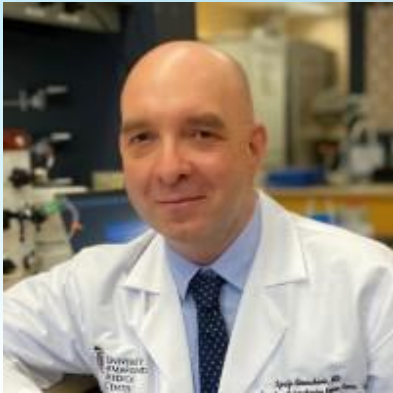
The concept of “therapeutic window” captures the balance between efficacy and toxicity



Dr. Atanackovic

“therapeutic window.” The term “therapeutic window,” as well as the related terms “therapeutic index” and “safety window,” generally refer to dose ranges of a drug between boundaries of efficacy and toxicity. A drug candidate with a narrow

Primary challenge in anti-EGFR ADC design: mitigating toxicity while maintaining efficacy



Dr. Atanackovic

Therefore, a primary challenge of designing a successful ADC was the identification of one that has manageable toxicity without compromising on the efficacy. In other words, a successful ADC needs to have an acceptable **“therapeutic window.”** The term “therapeutic window,” as well as the related

drug between boundaries of efficacy and toxicity. A drug candidate with a narrow therapeutic window (i.e., small difference between therapeutic and toxic doses) is not as desirable as one with a wide therapeutic window, as the former is more likely to cause toxicities at close-to-efficacious doses.

Primary challenge in anti-EGFR ADC design: mitigating toxicity while maintaining efficacy

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(71) Applicant: AVIDBIOMED, INC.
1800 Bayview Avenue, Suite 218
North York, Ontario M2N 6L1 (CA)

(72) Inventor: TIKHONOV, ALEXANDER
1800 Bayview Avenue, Suite 218
North York, Ontario M2N 6L1 (CA)

(74) Agent: PIASETZKY, ROBERT
1800 Bayview Avenue, Suite 218
North York, Ontario M2N 6L1 (CA)

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(54) Title: EGFR ANTIBODY-CONJUGATES

(57) Abstract: A maytansinoid is covalently linked through a non-cleavable linker to an EGFR antibody that is a full EGFR antagonist, such as cetuximab or panitumumab. The result is an anti-cancer agent having cytotoxicity that is potentiated in cancer cells but not normal cells. This benefit is not seen with EGFR antibodies that are partial antagonists, or with toxins that are not processed by lysosomes.

conc (nM)

Figure 6

CSPC Exhibit 1009
Page 1 of 46

caused severe toxicity against skin cells when delivered via a CD44v6 antibody. As a result, development of anti-EGFR immunoconjugates based on approved anti-EGFR antibodies has not been pursued because of concerns over enhanced skin toxicity of such immunoconjugates. Alternative strategies are being pursued for the development of anti-EGFR immunoconjugates.

Anti-EGFR immunoconjugates are now being designed specifically to address these safety concerns. These conjugates are based on antibodies that target a mutated but

Tikhomirov: combining cetuximab with cleavable linker achieved efficacy at the expense of unacceptable toxicity

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(71) Applicant: **AVIDBIOLOGICS INC.** [CA/CA]; 101 College Street, Suite 218, Toronto, Ontario, M5G 1L7 (CA)

(72) Inventor: **TIKHOMIROV, Ilya Alexandre**; 954 Queensway, Toronto, Ontario, M8Z 1P5 (CA)

(74) Agent: **PIASETZKI NENNIGER KVAS LLP**; 120 Elcude Street West, Suite 2308, Toronto, Ontario, M1T 1T1 (CA)

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(54) Title: **EGFR ANTIBODY CONJUGATES**

Transform of
 cell count (suftB) after 72h
 150
 100
 50
 0
 -4 -2 cond

(57) Abstract: A maytansinoid is covalently linked through a non-cleavable linker to an EGFR antibody that is a full EGFR antagonist, such as cetuximab or panitumumab. The result is an anti-cancer agent having cytotoxicity that is potentiated in cancer cells but not normal cells. This benefit is not seen with EGFR antibodies that are partial antagonists, or with toxins that are not processed by lysosomes.

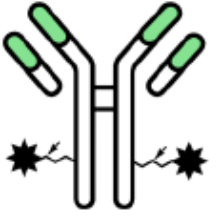
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CSPC Exhibit 1009
 Page 1 of 46

Figure 13 shows that conjugation of cetuximab to MMAE anti-microtubule payload by a cleavable linker (valine-citruline) potentiates its toxicity against both normal cells and MDA-MB-468 cancer cells (Cetux 2C9-MMAE), whereas conjugation via non-cleavable linker (SMCC) only (Cetux2C9-DM1) potentiates anti-cancer activity, thus demonstrating a favorable therapeutic window.

Nov 7, 2003, Vol 21: pp 778-784. Cleavable linker data demonstrate that when the fully antagonistic antibodies are conjugated to their payloads via cleavable linkers, their toxicity against normal cells is potentiated. Thus, a safe anti-EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker.

All known anti-EGFR ADC design strategies shared the common theme of mitigating activity on normal tissues

Benchmark ADC	Strategy	Resulting ADC	Example Antibodies/ADC
 (cetuximab-vc-MMAE)	A – non-cleavable linker for full antagonist antibody		- Cetux 2C9-DM1 (Tikhomirov)
	B2 – tumor-specific (pH-selective) antibody		- Y104 antibodies (Wei)
	B1 – tumor-specific (mutant-specific) antibody		- Antibody 1 (Leanna)
	B4 – antibody with >10-fold lower affinity than cetuximab		- h-R3 (Crombet) - Antibodies (Tikhomirov-346) - Nimotuzumab (Garrido)

Petitioner cannot deny toxicity concerns for anti-EGFR ADCs



Petitioner: according to Tikhomirov-346, (1) risk associated with skin reaction is considered acceptable and (2) efforts to improve EGFR antibodies are aimed at increasing affinity

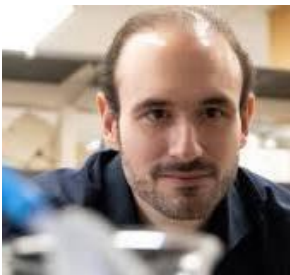
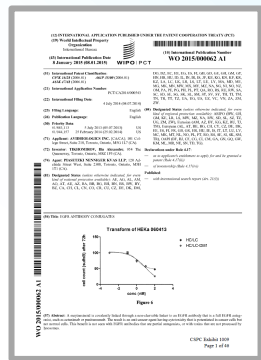
Tikhomirov-346's statements concern naked antibodies and do not show a lack of toxicity concern for anti-EGFR ADCs.

Tikhomirov

With immunoconjugates, the toxicity of these antibodies is amplified through conjugation to a potent cell toxin. This exacerbates the problem for antibodies that are already

Q. So if I understand your answer right, the fact that the naked antibody has an acceptable safety profile does not guarantee that an ADC made from that antibody will also have an acceptable safety profile?

A. It does not guarantee...



Dr. Bournazos

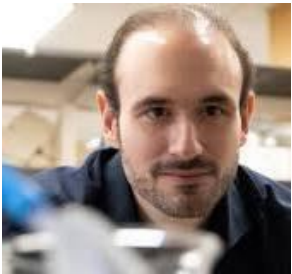
Petitioner cannot deny a POSA would have avoided modifications known to compromise an ADC's therapeutic window



Petitioner: “target-antigen expression on normal tissues has never been a prohibitive barrier to ADC development” considering example ADCs unrelated to EGFR

First, PO's arguments do not rely on a contention that EGFR expression on normal tissue is generally “prohibitive.”

Second, Petitioner fails to address how its example ADCs overcame toxicity on normal tissue and overlooks that some (e.g., ASG-5ME) failed due to an unacceptable therapeutic window.



Dr. Bournazos

Q. Were you aware that the development of [the ASG-5ME ADC] was terminated due to its narrow therapeutic index...?

A. No, because I never searched for that...

Petitioner's obviousness theories rely solely on speculative efficacy benefits

Goldmacher:

In general, desirable properties of antibodies for use in ADCs include: specificity; high binding affinity; long-circulation times; immune effector functions such as CDC, ADCC and antibody-dependent cellular phagocytosis; tumor-suppressing modulation of antigen's biological activity when possible; and minimal loss of the above-listed properties upon its conjugation to the drug of choice. To date, there are no clinical data available that would compare the anti-tumor activities of ADCs differing in one or more of these antibody-dependent properties (but made with the same drug, targeting the same antigen), and it remains unknown how much any of these properties contribute to (or interfere with) the anti-tumor efficacy of ADCs. Thus, the above-mentioned criteria are

Petitioner:

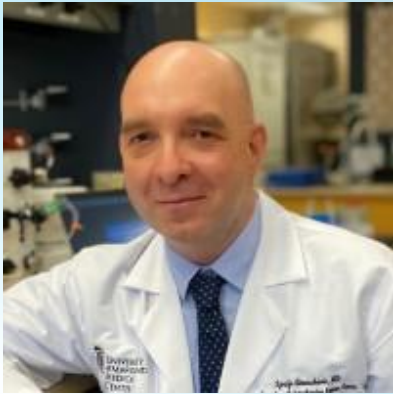
[Goldmacher] confirms that desirable ADC antibody properties include “specificity; high binding affinity; long-circulation times; immune effector functions such as CDC, ADCC and antibody-dependent cellular phagocytosis ...”

Petitioner ignores the sentence immediately following what it quotes for desirable properties.

Goldmacher:

[I]t remains unknown how much any of these properties contribute to (or interfere with) the anti-tumor efficacy of ADCs.

Petitioner's purported beneficial properties of BA03 harm the toxicity side of the therapeutic window



Dr. Atanackovic

tumor cells from normal cells. According to Crombet, an antibody having over 10-fold lower affinity than cetuximab would be expected to have the maximal ability in distinguishing tumor cells from normal cells; meanwhile, an antibody having a higher affinity than cetuximab would likely have no such distinguishing ability at all. *Supra* §I.

antibody could increase the ADC's killing of tumor cells, when the ADC binds to a normal cell, however, such increased EGFR phosphorylation inhibition activity would also translate into higher killing of the normal cells, leading to toxicity. The

tumor cells. Such increased ADCC would have been expected by the POSA to translate into increased killing of normal cells as well. Accordingly, this would not

Petitioner's Obviousness Theories Fail



Petitioner fails to address the primary challenge of toxicity mitigation in anti-EGFR ADC design.

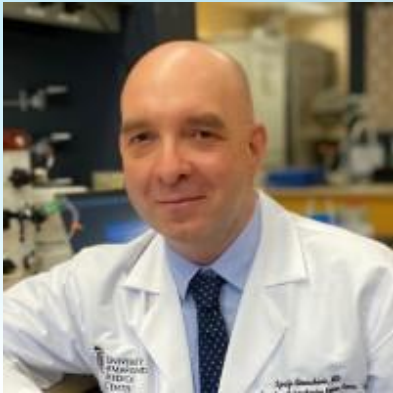


A POSA would not have been motivated to modify Wei and Leanna as Petitioner proposes.

A POSA would have expected the proposed ADC to have an unviable therapeutic window.

Petition fails to overcome objective indicia of non-obviousness.

Wei's Y104D/huY104D antibodies exhibit pH selectivity and improve ADC therapeutic window



Dr. Atanackovic

52. The Y104 mutants developed by Wei have greater activity at the acidic pH of the tumor microenvironment than at a neutral pH, which is common in normal tissues. As observed by Wei, “at pH 7.4, the wild-type cetuximab

of cell growth inhibition (CGI) against non-tumor keratinocytes. “Cetuximab-MMAE exhibited approximately 50% CGI at a concentration of approximately 0.1 ug/mL, whereas to achieve 50% CGI, 1 ug/mL Y104D-MMAE was required.” *Id.*, ¶1131 (emphasis added). This translates into a 10-fold difference in therapeutic index. The experimental data in Wei, therefore, demonstrates that the Y104D antibody it developed as a pH-selective derivative of cetuximab was able to increase the therapeutic index of ADCs with cetuximab by about 10-fold. Wei additionally observes that ADCs with huY104D “exhibit[s] greater pH-dependent activity” and further “reduced growth inhibition of non-tumor keratinocytes at pH 7.4.” Ex-1005, ¶1139.

Petitioner's position on Wei's pH selectivity contradicts the Petition



Petitioner's Reply: "Wei's data does not demonstrate biologically meaningful pH selectivity for Y104D as compared to cetuximab."

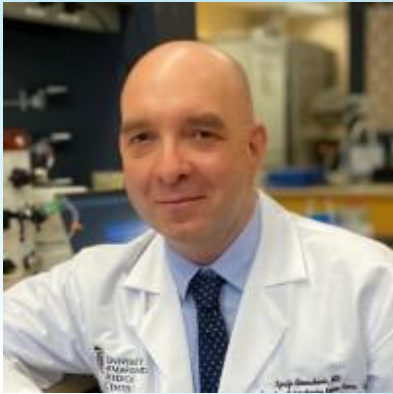
Petition:

Wei states that these cetuximab variants "exhibit greater activity (binding affinity) under conditions of acidic pH, such as is present in a tumor microenvironment, than under conditions of neutral pH, such as exists in non-tumor tissue." (*Id.*) Wei continues that "[b]y virtue of the pH-selective activity, the anti-EGFR antibodies provided produce fewer or lesser undesirable side-effects and/or exhibit improved efficacy in a treated subject by virtue of the ability to administer higher doses." (*Id.*,

Institution Decision:

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

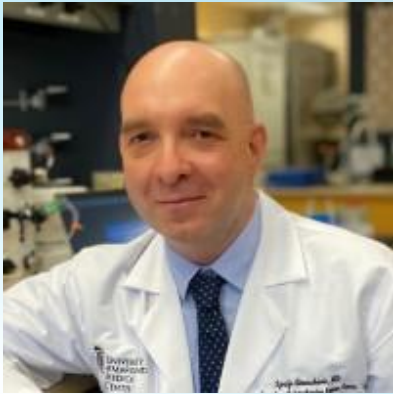
Leanna's Antibody 1 selectively binds tumor cells via a tumor-specific EGFR epitope



Dr. Atanackovic

have high endogenous levels of EGFR such as the liver and skin.”). A POSA would have found toxicity to liver and skin tissues undesirable and is elevated in the context of ADCs, which include highly toxic payloads. Antibody 1 solves this problem because it specifically targets an EGFR epitope that is expressed only on tumor cells and not on normal cells. Ex-2015, ¶15. The unique property of Antibody 1, therefore, is that it selectively recognizes an EGFR epitope on tumor cells and does not bind to normal cells. An ADC with such a tumor-specific antibody, therefore, would have been expected to provide an acceptable therapeutic window. A POSA would have been led by Leanna’s teachings to use antibodies

There was no basis to believe Liu's BA03 antibody possesses any tumor selectivity



Dr. Atanackovic

[U]nless specifically designed or screened for, a typical humanization process like that employed in Liu would not have conveyed tumor-targeting pH selectivity to a parental antibody. Accordingly, there is no basis to believe that the BA03 antibody has the pH-selectivity that Wei's antibodies have.

The BA03 antibody ... would have been expected to have the same binding activity to tumor and normal cells [as cetuximab]. In other words, the BA03 antibody lacks the ability of Antibody 1 of Leanna to recognize an EGFR epitope that is only present in tumor cells.

BA03 is not pH selective



Petitioner: “both BA03 and huY104D are humanized derivatives of cetuximab binding the same EGFR epitope; any difference in pH sensitivity is one of degree, not of kind.”

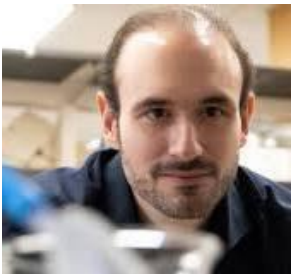
Petitioner’s patent application: BA03 does not have pH selectivity.

Table 1: Result of Antibody Affinity Determination

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

BA03

Petitioner’s expert: humanization does not increase the pH selectivity of an antibody as a general matter.



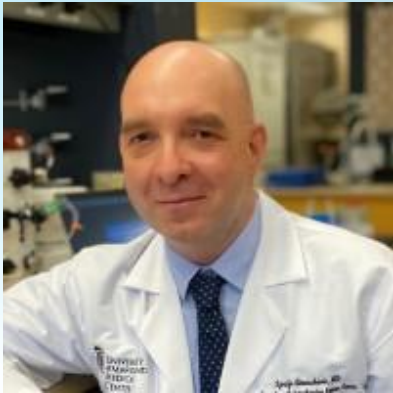
Dr. Bournazos

Q. So it is your opinion that humanization always increases the pH selectivity of an antibody?

. . .

A. No, I didn't say that...

Removing tumor selectivity would have been expected to increase toxicity at the same level of efficacy



Dr. Atanackovic

[T]he therapeutic window of an ADC ... primarily depends on whether the ADC can reduce binding to or payload release in normal tissues, while at the same time maintaining binding to and payload release in tumor tissues.

[A] POSA would have expected the replacement [of Wei's antibodies with BA03] to increase the toxicity and harm the therapeutic window of the resulting ADC.

[A] POSA would have expected the proposed modification of Leanna's ADC based on Liu to significantly increase the ADC's toxicity toward normal cells at the same level of efficacy [and] harm the therapeutic window.

Petitioner shows no meaningful advantage of BA03 as compared with Wei's and Leanna's antibodies

BA03 vs. Wei's antibodies

Q. Have you analyzed how the properties of Liu's BA03 antibody differ from those of Wei's chimeric Y104D antibody?

A. ...it's not possible for us to lead to any conclusions in differences in any of the properties of these antibodies.

Q. Have you analyzed whether Liu's BA03 antibody has a higher or lower binding affinity than Wei's Y104D antibody, either chimeric or humanized?

A. I cannot comment on that...

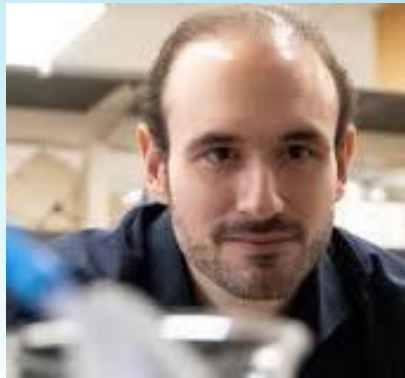
Q. So you do not know whether Liu's BA03 antibody has a higher or lower immunogenicity than Wei's Y104D antibody, either humanized or chimeric; correct?

A. Correct...

BA03 vs. Leanna's antibodies

Q. Have you analyzed how the properties of Liu's BA03 antibody differ from those of Leanna's Antibody 1?

A. I haven't done any comparison between Leanna's Antibody 1 and BA03. All I know is that both are anti-EGFR antibodies.



Dr. Bournazos

Petitioner's obviousness theories are based on BA03's purported benefits over cetuximab

Patent Owner's Response:

- Because Wei and Leanna both teach humanized antibodies, any general preference of humanized antibodies would not have motivated a POSA to modify Wei and Leanna.
- Petitioner and its expert did not analyze how Liu's BA03 antibody differs from Wei's and Leanna's antibodies and could not identify any benefits of the former over the latter.

Petitioner's Reply:

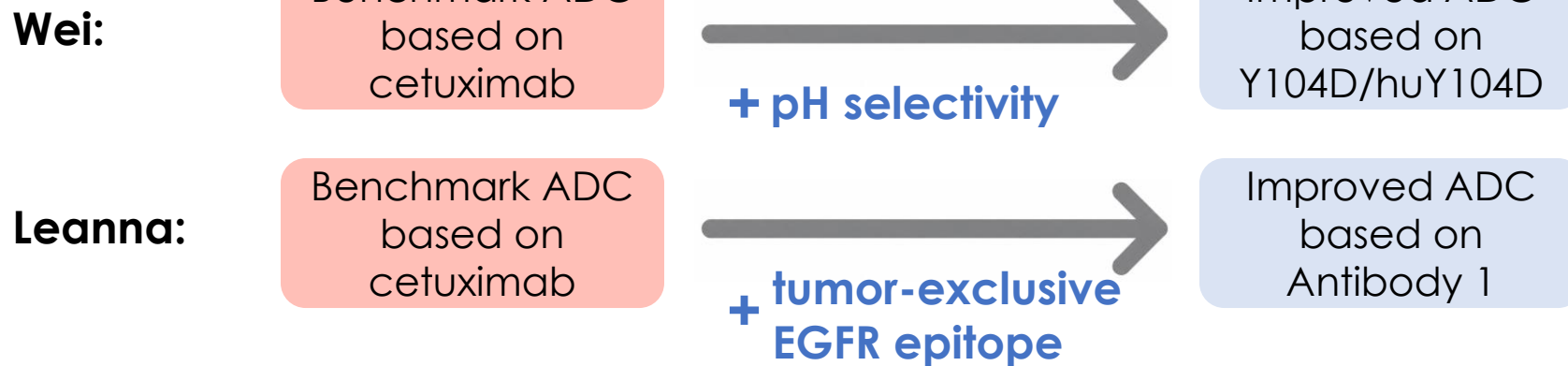
Liu's express teaching of BA03's advantages over cetuximab (the parent of both BA03 and Y104D) supplies ample motivation to incorporate BA03 into Wei's ADC platform. (EX1002, ¶¶185-188.) A POSA could have started with BA03,

Weighing significant disadvantage against total absence of advantage, no motivation to modify Wei and Leanna

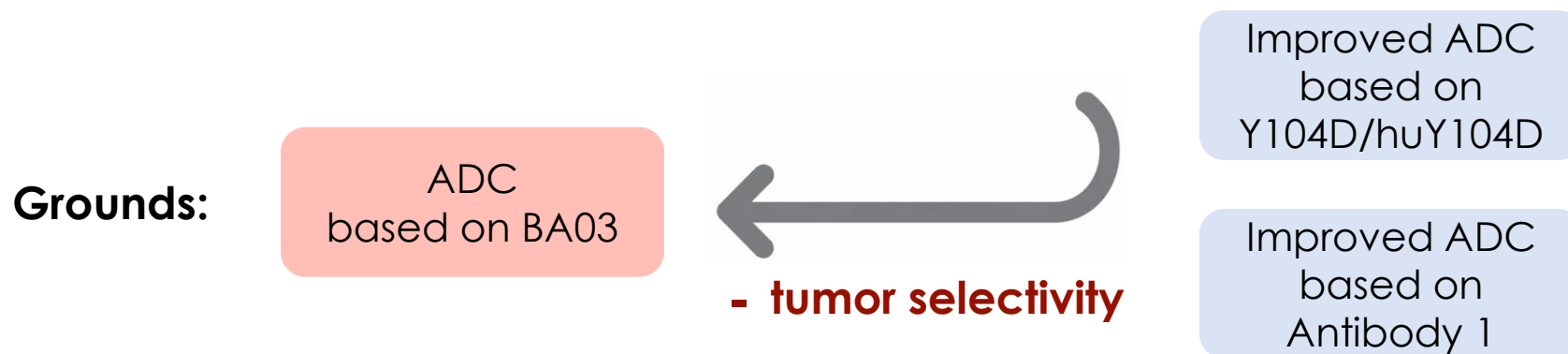
- **Significant Disadvantage:** replacing Wei's and Leanna's antibodies with BA03 removes tumor selectivity, which would have been expected to **increase toxicity at the same level of efficacy**.
- **No Advantage:** Petitioner only compares BA03 with cetuximab (not used in Wei and Leanna) and demonstrates **no benefit of BA03 as compared with Wei's and Leanna's antibodies**.

Petitioner's proposed combinations undo Wei's and Leanna's design strategies

Wei and Leanna use tumor-selective antibodies to widen the therapeutic window:



Grounds 1 and 2 do not employ any known anti-EGFR ADC design strategy:



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



“[Prior art] teaches away from the claimed invention” when proposed modification “necessarily involve altering the [prior art’s] inventive concept.”

Chemours Co. FC, LLC v. Daikin Indus., Ltd., 4 F.4th 1370, 1376 (Fed. Cir. 2021)



Obviousness is not shown when there is “no discernible reason for a skilled artisan to begin with [prior art compound] only to drop the very feature ... that gave [its] advantageous property.”

Eisai Co. v. Dr. Reddy's Laboratories, Ltd., 533 F.3d 1353, 1358 (Fed. Cir. 2008)

Petitioner's Obviousness Theories Fail



Petitioner fails to address the primary challenge of toxicity mitigation in anti-EGFR ADC design.



A POSA would not have been motivated to modify Wei and Leanna as Petitioner proposes.



A POSA would have expected the proposed ADC to have an unviable therapeutic window.

Petition fails to overcome objective indicia of non-obviousness.

The cetuximab-vc-MMAE ADC was known to have an unviable therapeutic window

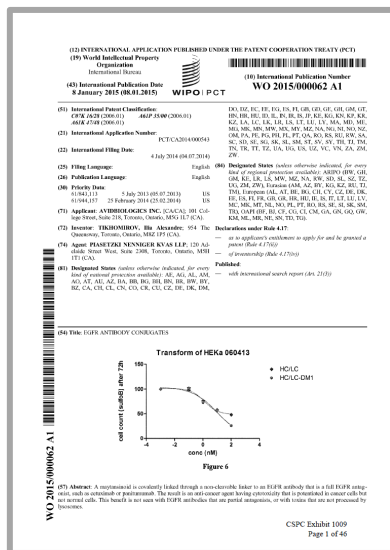


Figure 13 shows that conjugation of cetuximab to MMAE anti-microtubule payload by a cleavable linker (valine-citruline) potentiates its toxicity against both normal cells and MDA-MB-468 cancer cells (Cetux 2C9-MMAE), whereas conjugation via non-cleavable linker (SMCC) only (Cetux2C9-DM1) potentiates anti-cancer activity, thus demonstrating a favorable therapeutic window.

Nov 7, 2003, Vol 21: pp 778-784. Cleavable linker data demonstrate that when the fully antagonistic antibodies are conjugated to their payloads via cleavable linkers, their toxicity against normal cells is potentiated. Thus, a safe anti-EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker.



Dr. Atanackovic

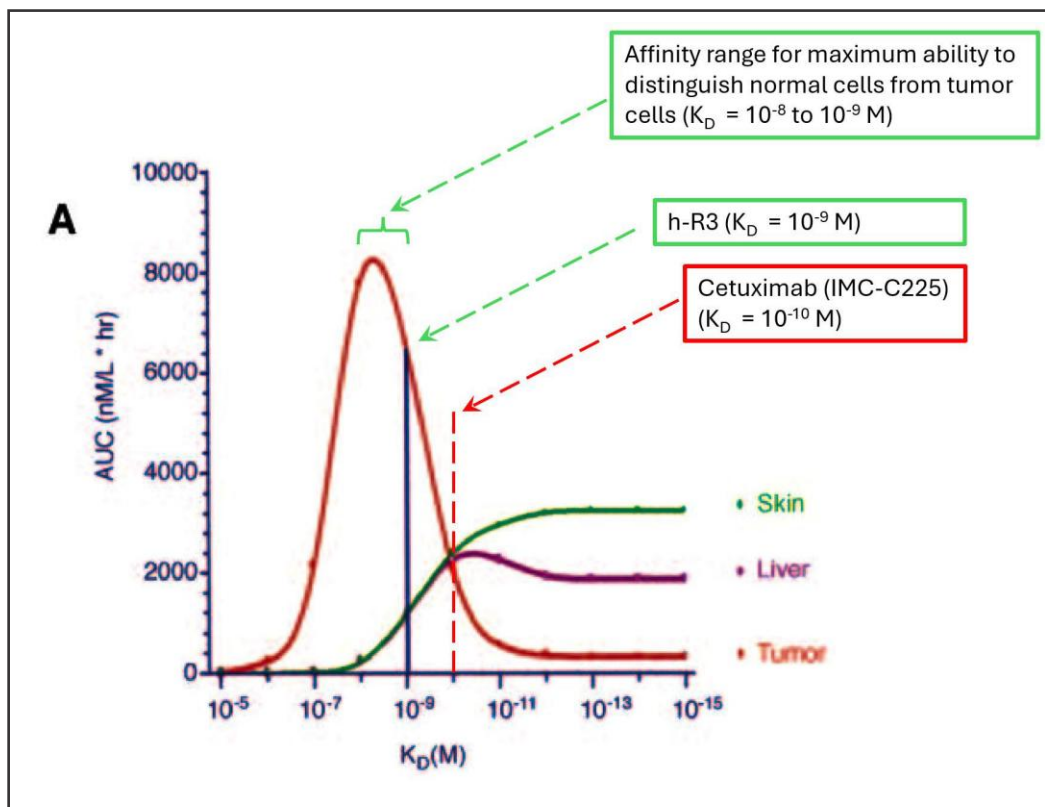
therapeutic window than and be inferior to the cetuximab-vc-MMAE ADC. The cetuximab-vc-MMAE ADC was known to have an unduly narrow therapeutic window for having potentiated toxicity against normal cells, as Tikhomirov teaches. Ex-1009, 31 (“[A] safe anti-EGFR ADC should incorporate a strongly

Higher binding affinity was known to lead to weaker tumor selectivity



Dr. Atanackovic

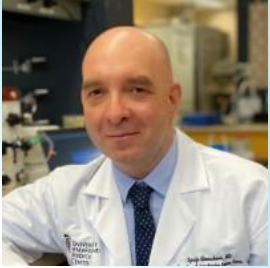
Crombet has demonstrated a negative correlation between an anti-EGFR antibody's affinity and its ability to distinguish tumor cells from normal cells. According to Crombet, ... an antibody having a higher affinity than cetuximab would likely have no [ability to distinguish tumor cells from normal cells] at all.



Crombet
Fig. 3A

A POSA reading Crombet would have learned the negative correlation between binding affinity and tumor selectivity

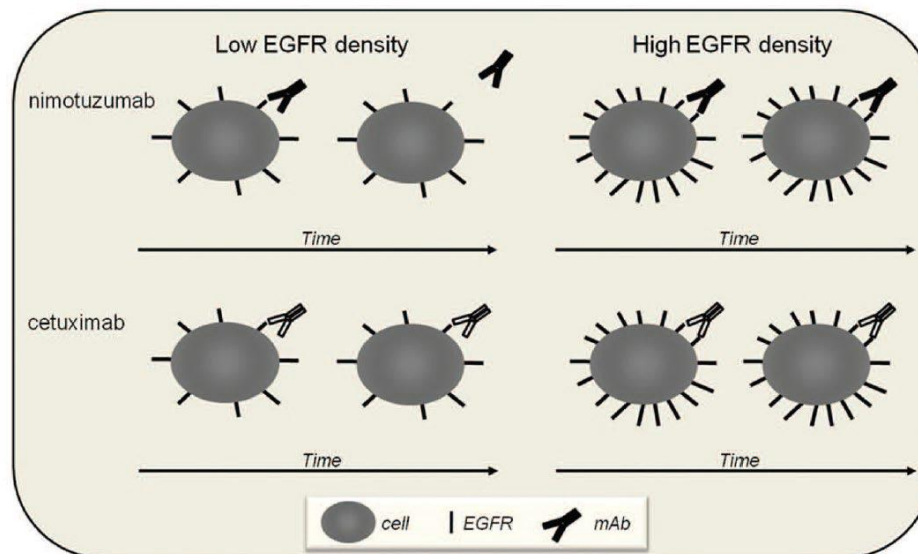
Crombet is a reliable source:



Dr. Atanackovic

[Crombet] is a paper that was published in the [Journal of Clinical Oncology], which is a leading paper in the field, has an impact factor I think of close to 30. ... it will undergo peer view, and for a paper like this, this means like leading expert in this particular field. They would question everything ... publications like this come with ... extensive validation.

Garrido independently confirms Crombet's negative correlation:



Garrido
Fig. 6

The known negative affinity-selectivity correlation had been applied in ADC design

Tikhomirov-346 teaches the strategy of achieving broad ADC therapeutic window by reducing antibody binding affinity.

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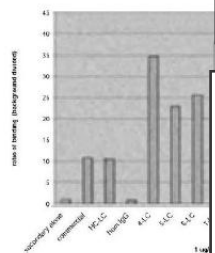
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(71) Applicants (for all designated States except US): YMA BIOSCIENCES INC. [CA/CA]; 5045 Orbitor Drive, Suite 400, Building 11, Mississauga, Ontario L4W 4Y5 (CA); NATIONAL RESEARCH COUNCIL OF CANADA [CA/CA]; 1200 Montreal Road, Bldg. M-58, Ottawa, Ontario K1A 0R6 (CA).

(72) Inventors; and
(73) Inventors/Applicants (for US only): TIKHOMIROV, Ilya Alexandre [CA/CA]; 954 The Queensway, Toronto, Ontario M8Z 1P5 (CA); JARAMILLO, Maria L. [CA/CA]; 183 Westcroft, Beaconsfield, Quebec H9W 2M2 (CA); O'CONNOR-MCCOURT, Maureen D. [CA/CA]; 186 Sherbrooke, Beaconsfield, Quebec H9W 1P2 (CA); SULEA, Traian [CA/CA]; 61 Old Forest, Kirkland, Quebec H9J 3A2 (CA); GILBERT, Renald [CA/CA];

(54) Title: ANTIBODIES SELECTIVE FOR CELLS PRESENTING



(57) Abstract: Herein described are antibodies to epidermal growth factor receptor (EGFR) that are sufficient to kill disease cells presenting EGFR at high density, but this achieved while avoiding adverse events that result from immunogenicity.

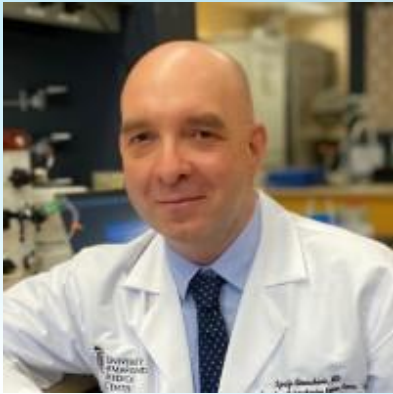
In embodiments, the present EGFR antibodies having a binding affinity for EGFR that is about 10 fold or more weaker than the EGFR binding affinity of cetuximab. Desirably,

In other embodiments, the substituting amino acid is selected to reduce EGFR binding affinity of the antibody or bivalent fragment to a level that substantially eliminates binding to cells presenting EGFR at a normal EGFR density, and retains effective binding at targeted disease cells that present EGFR at a greater density relative to normal cell EGFR density.

In summary, this data indicates that mutant antibodies can be generated that bind highly selectively to cells that present EGFR at abnormally high density, and that these antibodies may be useful in oncology and other diseases as antibody-drug conjugates with broad therapeutic windows, and/or as diagnostic agents for the detection of EGFR overexpressing cells.

Shanghai Miracogen Inc. - Ex. 2011, Page 000001
IPR2025-00685 (CSPC Megalith Biopharmaceutical Co., LTD. v. Shanghai Miracogen Inc.)

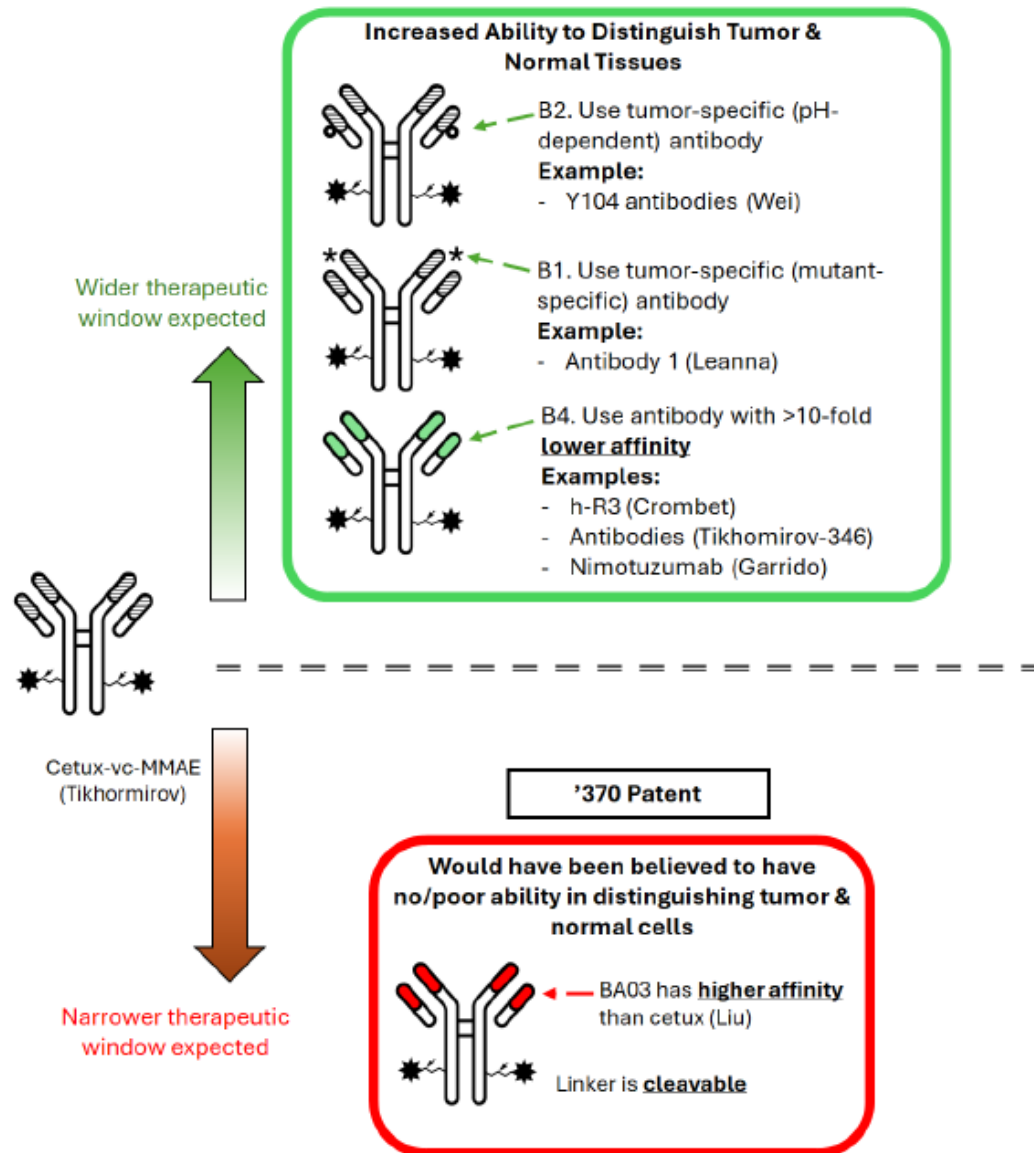
BA03-vc-MMAE's therapeutic window was expected to be worse than that of cetuximab-vc-MMAE



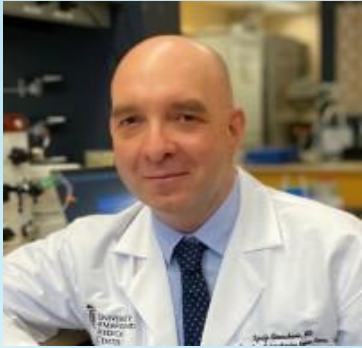
Dr. Atanackovic

¶87. According to the conventional knowledge and Crombet, therefore, a POSA would have expected the BA03 antibody to have poor or even no ability in distinguishing tumor cells from normal cells. *Supra* §I. Such an antibody, as well as its ADCs, therefore, would be expected to have no or a very narrow therapeutic window. In other words, such ADCs would be expected to be unable to avoid safety issues and be unsuccessful. A POSA would have expected that the higher binding affinity of BA03 causes the BA03-vc-MMAE ADC to have a worse therapeutic window than and be inferior to the cetuximab-vc-MMAE ADC. The

BA03-vc-MMAE's therapeutic window was expected to be worse than that of cetuximab-vc-MMAE

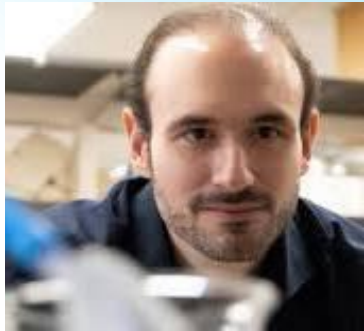


Therapeutic window and toxicity were key considerations in assessing whether an ADC would have been successful



Dr. Atanackovic

In determining whether an ADC is expected to be successful, a POSA would have analyzed a series of factors[, including] “differentials of expression level of target antigen between cancer cells and normal cells” and “the balance between cancer killing activity of ADC and its toxicity.”

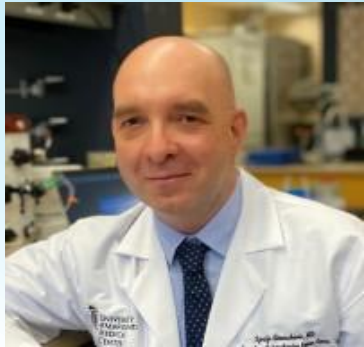


Dr. Bournazos

Q. What are some issues or obstacles that can make the effort of creating an ADC unsuccessful?

A. It can be toxicity...

A POSA would have expected the BA03-vc-MMAE ADC to be unsuccessful



Dr. Atanackovic

A POSA would have expected [the balance between cancer killing activity and toxicity] to be impossible for the proposed BA03-vc-MMAE ADC because (1) the BA03 antibody has no ability to distinguish tumor and normal cells and (2) BA03's higher-than-cetuximab binding affinity would have caused the BA03-vc-MMAE ADC to have an even narrower therapeutic window than the cetuximab-vc-MMAE ADC, which was known to be unviable.

Petitioner fails to establish a reasonable expectation of success

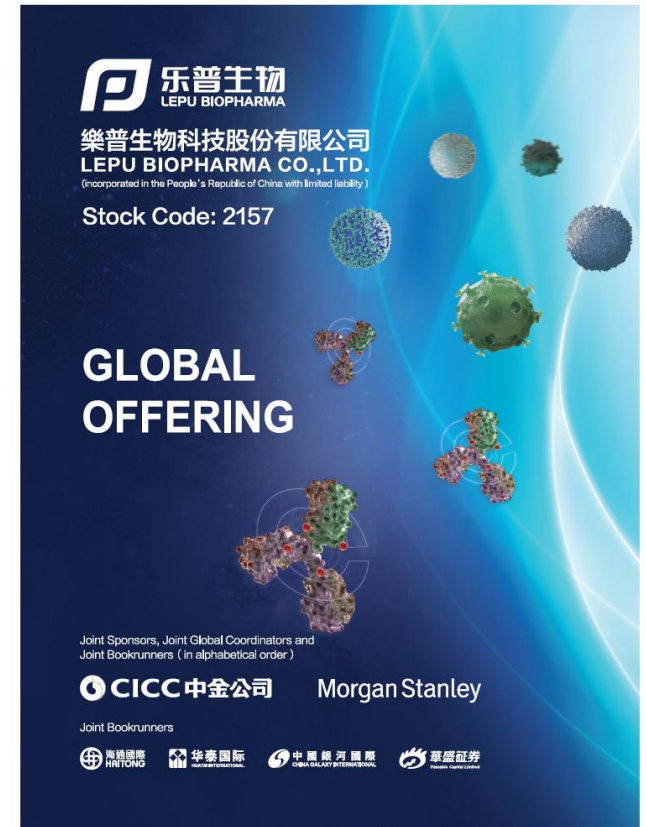
- **FAILS** to affirmatively show that BA03-vc-MMAE would have been expected to have **a viable therapeutic window or toxicity profile.**
- **FAILS** to provide evidence that BA03-vc-MMAE would have been expected to have **a therapeutic window better than that of cetuximab-vc-MMAE**, which was known to be unviable.
- **FAILS** to rebut PO's showing that **higher binding affinity leads to weaker tumor selectivity and worse therapeutic window.**

Petitioner's case for high binding affinity rests entirely on impermissible hindsight

Petitioner argues that high binding affinity is desirable because PO's 2022 Global Offering prospectus identifies it as an advantage.

internalization of ADC.” (EX1246, 50:19-51:4, 345:11-16.) PO's own Global Offering prospectus likewise identifies BA03's roughly six-to-sevenfold higher EGFR binding affinity over cetuximab, and its facilitation of “rapid internalization of MRG003 into tumor cells,” as “competitive advantages.” (EX2032, 000310.) The very property Dr. Atanackovic calls disqualifying is what PO promotes as a competitive advantage. (EX1200, ¶96.)

Petitioner's Reply



PO's 2022 Global Offering prospectus, **six years after the '370 patent was filed**

Petitioner's Obviousness Theories Fail



Petitioner fails to address the primary challenge of toxicity mitigation in anti-EGFR ADC design.



A POSA would not have been motivated to modify Wei and Leanna as Petitioner proposes.



A POSA would have expected the proposed ADC to have an unviable therapeutic window.



Petition fails to overcome objective indicia of non-obviousness.

Post-Institution: Patent Owner's Embodying ADC Achieved First Worldwide Anti-EGFR ADC Approval

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LEPU BIOPHARMA CO., LTD.

樂普生物科技股份有限公司

(A joint stock company incorporated in the People's Republic of China with limited liability)

(Stock Code: 2157)

INSIDE INFORMATION ANNOUNCEMENT

MARKETING APPROVAL OBTAINED IN CHINA FOR MEIYOUHENG (BECOTATUG VEDOTIN INJECTION)

This announcement is made by Lepu Biopharma Co., Ltd. (the “Company”) pursuant to Rule 13.09 of the Rules Governing the Listing of Securities on The Stock Exchange of Hong Kong Limited (the “Listing Rules”) and the Inside Information Provisions (as defined in the Listing Rules) under Part XIVA of the Securities and Futures Ordinance (Chapter 571, Laws of Hong Kong).

The board of directors of Medical Products Administration for our drug candidate MEIYOUHENG (Becotatug Vedotin Injection) (“ADC”) is (“EGFR”) for the treatment of recurrent or metastatic nasopharyngeal cancer (“R/M NPC”).

A. IMPACT ON THE

MEIYOUHENG (Becotatug Vedotin Injection) for marketing in China. MEIYOUHENG (Becotatug Vedotin Injection) treatment outcomes.

Building on this achievement, the Company will continue to explore potential marketing for MEIYOUHENG (Becotatug Vedotin Injection) to accelerate the realization of its potential commercial value.

B. ABOUT MEIYOUHENG (BECOTATUG VEDOTIN INJECTION)

MEIYOUHENG (Becotatug Vedotin Injection) is an ADC comprised of an EGFR-targeted monoclonal antibody conjugated with the potent microtubulin inhibiting payload monomethyl auristatin E via a valine-citrulline linker. It binds specifically with high affinity to EGFR on the surface of tumor cells, releases the potent payload upon internalization and lysosomal protease cleavage of the linker and results in tumor cell death. EGFR is highly expressed in colorectal cancer, lung cancer, head and neck cancer and other malignant solid tumors, and is expressed in 89% advanced NPC. Therefore, EGFR is an important target for cancer treatment.

The board of directors of the Company (the “Board”) is pleased to announce that, the National Medical Products Administration (the “NMPA”) has recently granted marketing approval in China for our drug candidate MEIYOUHENG (Becotatug Vedotin Injection), an innovative antibody drug conjugate (“ADC”) independently developed by us targeting epidermal growth factor receptor (“EGFR”) for the treatment of recurrent or metastatic nasopharyngeal cancer (“R/M NPC”).

PO's MRG003 addressed a long-felt and unresolved need for a clinically viable anti-EGFR ADC

UNDISPUTED



Despite strong industry interest, multiple clinical trials employing conventional ADC design strategies before MRG003 were all terminated.



PO's MRG003, which embodies claims of the '370 patent, became the first regulatory approved anti-EGFR ADC worldwide.



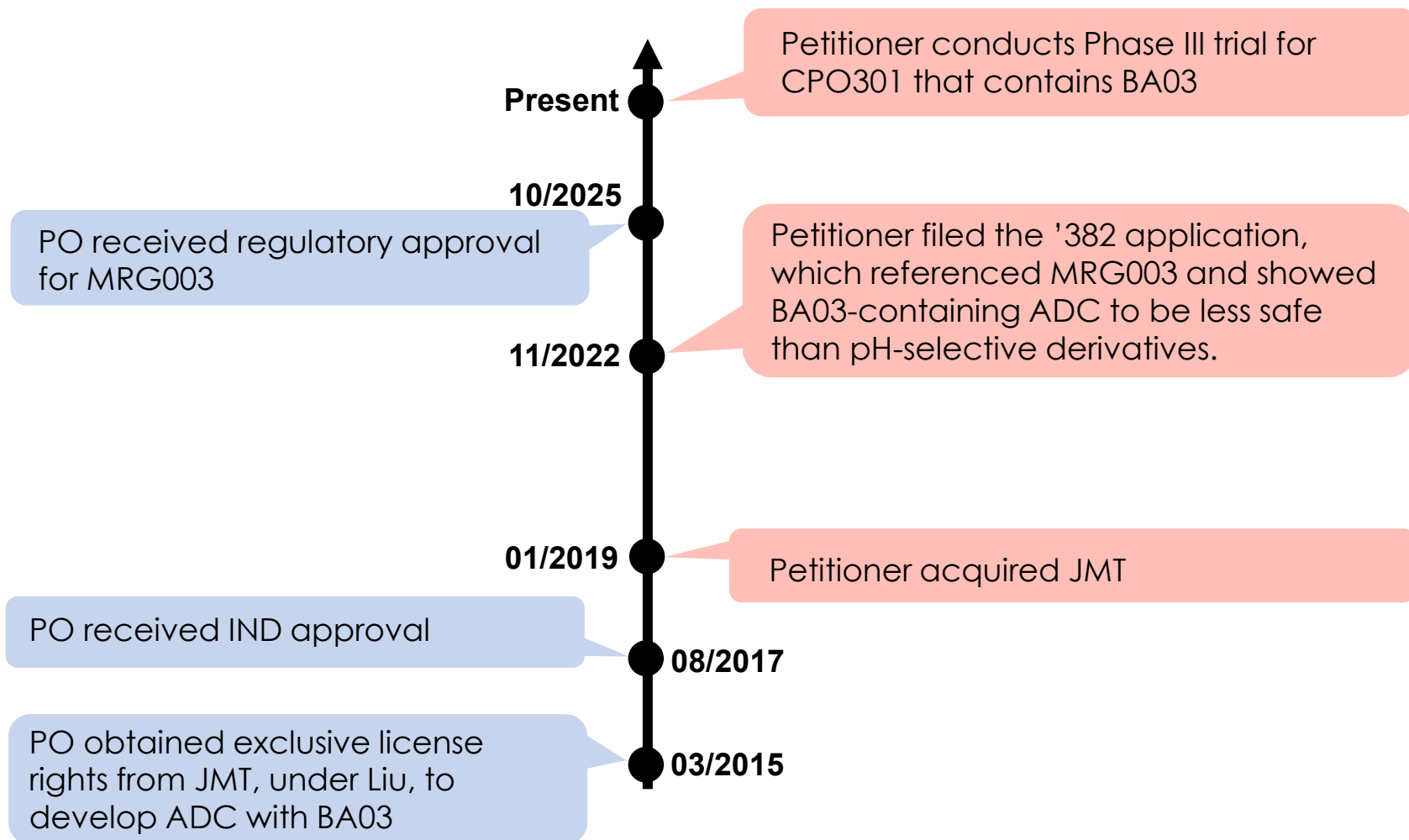
Petitioner's CPO301, the second most advanced anti-EGFR ADC, also embodies claims of the '370 patent.



The success of MRG003 was at least partially attributable to BA03's high binding affinity.

PO's MRG003 addressed a long-felt and unresolved need for a clinically viable anti-EGFR ADC.

Undisputed timeline of events demonstrates affirmative act of copying



Petitioner determined multiple alternative options to be superior to the BA03 option but still decided to copy the BA03 feature of Patent Owner's ADC.

Petitioner fails to rebut PO's showing of nexus

The success of the two most advanced anti-EGFR ADCs is attributable to their commonality—the claimed BA03 antibody and cleavable linker.

Commonalities between MRG003 and CPO301	Differences between MRG003 and CPO301
• BA03 antibody • Linker being cleavable	• Linker used • Payload used

Petitioner attributes MRG003's success to antibody properties, while identifying nothing distinctive about linker and payload.

internalization of ADC.” (EX1246, 50:19-51:4, 345:11-16.) PO’s own Global Offering prospectus likewise identifies BA03’s roughly six-to-sevenfold higher EGFR binding affinity over cetuximab, and its facilitation of “rapid internalization of MRG003 into tumor cells,” as “competitive advantages.” (EX2032, 000310.) The

Petitioner's Reply

Other issues

EGFR overexpression is insufficient to provide an acceptable toxicity profile



Petitioner: “EGFR is overexpressed on many tumors relative to normal tissues, and that differential expression provides an alternative basis for selectivity.”

Wei: selectivity based on EGFR overexpression on tumor tissue is insufficient

Cetuximab. Cetuximab is approved for the treatment of recurrent or metastatic head and neck cancer, colorectal cancer and other diseases and conditions. It can also be used in the treatment of other diseases or conditions involving overexpression of EGFR or aberrant signaling or activation of EGFR. Administered anti-EGFR antibodies can bind to EGFR in healthy cells and tissue. This limits the dosages that can be administered. Hence, Cetuximab and other anti-EGFR antibodies exhibit limitations when administered to patients. Accordingly, it is among the objects herein to provide improved anti-EGFR antibodies that exhibit increased EGFR binding activity in a tumor microenvironment compared to in a non-tumor environment.

Petitioner recycles the Examiner's obviousness theories while disregarding the reason that they were overcome

Petitioner: the Petition's cetuximab-based MTC theory is the same as the Examiner's

Liu's express teaching of BA03's advantages over cetuximab ... supplies ample motivation to incorporate BA03 into Wei's ADC platform. ... **The prosecution history confirms this.** ... The Examiner repeatedly found that a POSA would be motivated to use BA03 in place of cetuximab in ADCs because 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."

Petitioner: the Examiner's rejection was overcome based on toxicity considerations

In its response dated March 26, 2020, Applicant again maintained its arguments regarding toxicities associated with anti-EGFR ADCs with cleavable linkers. ... On June 18, 2020, the Office issued a Notice of Allowance without providing any reasons for doing so. ... Thus, throughout the prosecution of the '370 patent, Applicant exclusively argued that **potentiated toxicity to normal cells obviated any motivation to combine** anti-EGFR ADCs linked to a cytotoxic payload using cleavable linkers...

Petitioner disparages evidence that it does not have a response to

Petitioner attacks the credibility of its own prior art reference Wei:

Second, Wei's purported pH selectivity data does not establish a meaningful distinction. Petitioner's expert, Dr. Bournazos, testified that Wei's data does not demonstrate biologically meaningful pH selectivity for Y104D as compared to cetuximab. (EX2026, 77:14-86:8.) Wei's Tables 42, 44, and 45 show variable,

Petitioner disparages Crombet, a peer-reviewed article, as scientifically unreliable:

Dr. Bournazos explains that the Crombet model (EX2022) on which Dr. Atanackovic relies is scientifically unreliable and inapplicable to ADC design. (EX1200, ¶¶39-45.) Crombet was developed for naked antibodies and omits ADC-

Petitioner expert admitted that he did not verify favorable data:

Q. Did you independently verify the data in the database?

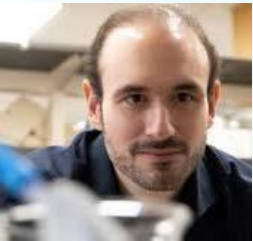
A. There was no need to do that because they support my own analysis...

Petitioner's internalization arguments rely solely on hindsight



Petitioner: “Liu shows that BA03 rapidly internalizes upon EGFR engagement. (EX1008, ¶¶0154-0160.) ... A POSA would therefore have recognized BA03 as a particularly attractive ADC candidate.”

Liu includes no teachings about BA03's internalization properties



Dr. Bournazos

Q. Can you please review Paragraphs 154 until Paragraph 160. ... Do these paragraphs discuss the BA03 antibodies internalization properties?

A. Not internalization.

Petitioner's earliest evidence about BA03's internalization is PO's 2022 Global Offering prospectus, published 6 years after the '370 patent was filed

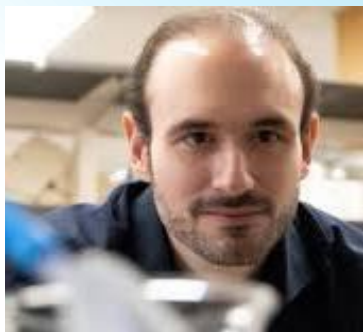
Reply:

attractive ADC candidate. (*Id.*) Indeed, PO's own Global Offering prospectus identifies BA03's facilitation of “rapid internalization of MRG003 into tumor cells” as a “competitive advantage[.]” (EX2032, 000310.)

A POSA would have had no reason to try using BA03 in an ADC



Dr. Atanackovic



Dr. Bournazos

80. From such a large number of anti-EGFR antibodies that were known or could have been readily produced, it was not obvious to select the BA03 antibody for inclusion in an ADC, in particular given its properties (e.g., lack of tumor selectivity, high binding affinity) that would have been viewed unfavorably by the POSA.

Q. To your knowledge, approximately how many anti-EGFR antibodies have been developed or described in the scientific literature?

...

A. I would say hundreds....

...

Q. Does Y104D represent the only way to modify cetuximab?

A. No. There are millions of ways that you can modify cetuximab.

The '370 patent was the first to demonstrate desirable efficacy-safety profile of a BA03-based ADC

Efficacy:

loading mole number of MYK-3 and BA03 alone. However, MYK-3 as an ADC molecule that was formed by conjugating BA03 with vcMMAE showed an inhibitory activity on growth of DiFi colorectal cancer cells much higher than those of monoclonal antibody BA03 itself and BA03 plus free vcMMAE in an amount equivalent to the loading mole number of MYK-3, and EC50 values were elevated by about 8 times.

Toxicity:

Body weight of mice: the body weight of mice administered with MYK-3 showed no significant change as compared with the control group (see FIG. 8), indicating that MYK-3 had not toxic effect of reducing body weight of mice.

Date: July 10, 2026

Respectfully,

SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

/Christopher Ponder/

Christopher Ponder (Reg. No. 77,167)
Attorneys for Patent Owner Lepu
Biopharma Co., Ltd.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on July 10, 2026, a complete copy of the foregoing document was served via email to all parties to this proceeding at the addresses indicated:

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

Howard S. Suh (hsuh@foxrothschild.com)

Ryan N. Miller (rmiller@foxrothschild.com)

ipdocket@foxrothschild.com

Date: July 10, 2026

Respectfully,
SHEPPARD, MULLIN,
RICHTER & HAMPTON LLP

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