

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 IPR2025-00685

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

Title: Antibody-Drug Conjugate

**PETITION FOR INTER PARTES REVIEW OF CLAIMS 1-23 OF U.S.
PATENT NO. 10,792,370**

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EX1001	U.S. Patent No. 10,792,370 to Hu (“the ’370 patent”)
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EX1005	U.S. Patent Application Publication No. US 2015/071923 (“Wei”)
EX1006	International Publication No. WO 2014/152199 (“Leanna”)
EX1007	Chinese Patent Application Publication No. CN103772504 (“Liu”)
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EX1009	International Publication No. WO 2015/000062 (“Tikhomirov”)
EX1010	Metrangolo & Engelholm, <i>Cancers</i> (Basel), 16(2):447 (2024)
EX1011	Tsurushita, et al., <i>Methods.</i> , 36(1):69-83 (2005)
EX1012	Jorissen, et al., <i>Exp Cell Res.</i> , 284(1):31-53 (2003)
EX1013	Olayioye, et al., <i>EMBO J.</i> , 19(13):3159-67 (2000)
EX1014	Bou-Assaly & Mukherji, <i>AJNR Am J Neuroradiol.</i> , 31(4):626-7 (2010)
EX1015	McCombs & Owen, <i>AAPS J.</i> , 17(2):339-51 (2015)
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EX1025	Atalay, et al., <i>Ann Oncol.</i> , 14(9):1346-63 (2003)
EX1026	Doronina, et al., <i>Nat Biotechnol.</i> , 21(7):778–784 (2003)
EX1027	Mao, et al., <i>Cancer Res.</i> , 64 (3): 781–788 (2004)
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EX1031	De Goeij, et al., <i>Mol Cancer Ther.</i> , 14(5):1130-40 (2015)
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EX1034	Foltz, et al., <i>Circulation.</i> , 127(22):2222-30 (2013)
EX1035	Certified English Translation of Chinese Patent Application No. 201510085038.8 (“the ’038.8 Provisional”)

I. INTRODUCTION

CSPC Megalith Biopharmaceutical Co., Ltd. (“Petitioner”) requests *inter partes* review of claims 1-23 (the “Challenged Claims”) of U.S. Patent No. 10,792,370 (“the ’370 patent”) (EX1001), assigned to Shanghai Miracogen Inc. (“Patent Owner”). For the reasons set forth below and in the accompanying Declaration of Dr. Stylianos Bournazos (EX1002), there is a reasonable likelihood that Petitioner will prevail in establishing that at least one of the Challenged Claims is unpatentable as obvious over the prior art.

The Challenged Claims are directed to a broad genus of antibody-drug conjugates (“ADCs”) comprising an anti-epidermal growth factor receptor (“EGFR”) antibody covalently linked to any cytotoxic agent by any cleavable linker where the antibody is defined by heavy chain and light chain sequences of a known anti-EGFR antibody.

However, everything about the Challenged Claims was known in the prior art. The exact same antibody used in the preferred embodiment of the ’370 patent and covered by the Challenged Claims – the BA03 antibody – with all of the claimed heavy chain and light sequences, was published in a prior art Chinese patent application (Liu) (EX1007, EX1008). The exact same cleavable linker (vc) attached to the same cytotoxic agent (MMAE) used in the preferred embodiment of the ’370 patent and covered by the claims – vc-MMAE - was also disclosed in prior art

published patent applications (Wei and Leanna) (EX1005, EX1006) that describe anti-EGFR ADCs. Moreover, the motivation to combine the prior-art BA03 antibody with vc-MMAE in an ADC was also known because, among other things, Liu discloses that the BA03 antibody has several advantages over the prior art. BA03 is a humanized version of the anti-EGFR cetuximab antibody, and Wei specifically teaches ADCs made with modified versions of cetuximab. If ADCs were being made in the prior art using modified cetuximab, a person of skill in the art (“POSA”) surely would have been motivated to create ADCs using the highly modified, humanized cetuximab antibody disclosed in Liu.

Patent Owner did not dispute during prosecution that a POSA would be motivated to make ADCs using the prior-art BA03 antibody. Instead, when confronted with prior art showing the obviousness of its then-pending claims, Patent Owner narrowed its claims to ADCs using “cleavable linkers” and then argued that a POSA would be dissuaded from using cleavable linkers in ADCs based on alleged toxicity concerns. However, Patent Owner’s arguments are wrong. As discussed above, the exact same cleavable linker of the preferred embodiment of the Challenged Claims was used in the prior art to make anti-EGFR ADCs despite Patent Owner’s purported toxicity concerns (Wei and Leanna). Moreover, the toxicity arguments did not even involve the claimed BA03 antibody, were limited to a small subset of linker-payloads incommensurate with the broad scope of the Challenged

Claims, were based on incomplete data riddled with errors, and were limited to pre-clinical tumor models that would not have discouraged the use of cleavable linkers for potential therapy. Finally, while Patent Owner argued during prosecution that the use of cleavable linkers in its invention was an unexpected result to rebut a *prima facie* case of obviousness, the vast majority of FDA-approved ADCs in both the prior art and post-filing art use cleavable linkers. Patent Owner's unexpected results arguments are therefore fatally flawed.

Petitioner therefore requests that this Petition be granted and that claims 1-23 be cancelled as unpatentable.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real party-in-interest is CSPC Pharmaceutical Group Limited, CSPC NBP Pharmaceutical Co., Ltd, CSPC Innovation Pharmaceutical Co., Ltd, and CSPC Megalith Biopharmaceutical Co., Ltd.

B. Related Matters (37 C.F.R. § 42.8(b)(1))

Petitioner is unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this Petition.

C. Counsel and Service Information (37 C.F.R. §§ 42.8 (b)(3) and (4))

Petitioner identifies its lead and backup counsel as shown below:

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III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

The undersigned authorizes the Director to charge the fee set forth in 37 C.F.R. § 42.15(a), as required by 37 C.F.R. § 42.103, and any additional fees, to Deposit Account No. 50-1943.

IV. CERTIFICATION OF GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.104

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the '370 patent is available for *inter partes* review, and Petitioner is not barred or estopped from requesting this *inter partes* review.

V. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.104(b)

The Challenged Claims are unpatentable under 35 U.S.C. § 103.

The following is a list of prior art that renders obvious the Challenged Claims:

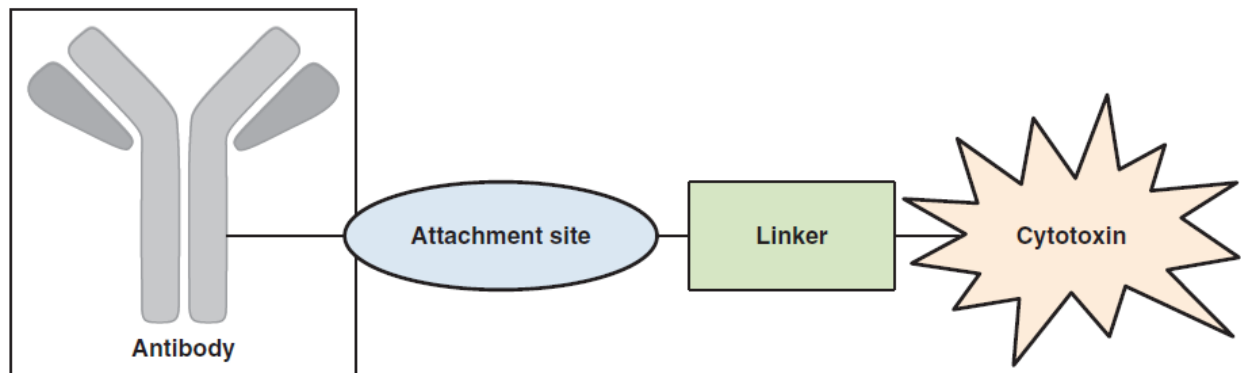
Exhibit	Description	Publication Date
EX1005	U.S. Patent Application Publication No. US 2015/071923 (“Wei”)	March 12, 2015, based on a filing date of September 12, 2014
EX1006	International Publication No. WO 2014/152199 (“Leanna”)	September 25, 2014
EX1007	Chinese Patent Application Publication No. CN103772504 (“Liu”)	May 7, 2014
EX1008	Certified English Translation of Chinese Patent Application Publication No. CN103772504 (“Liu”)	May 7, 2014

Petitioner requests cancellation of claims 1-23 on the following grounds:

Ground	Claims	Description
1	1-23	Obvious under 35 U.S.C. § 103 over Wei and Liu.
2	1-23	Obvious under 35 U.S.C. § 103 over Leanna, Liu, and Wei.

VI. BACKGROUND AND OVERVIEW OF THE '370 PATENT

ADCs are pro-drugs consisting of a tumor-selective monoclonal antibody covalently linked to a cytotoxic payload. As such, they can act as “magic bullets” that specifically target cancer cells overexpressing a desired surface antigen receptor, allowing for selective delivery of a cytotoxic payload for targeted tumor eradication.



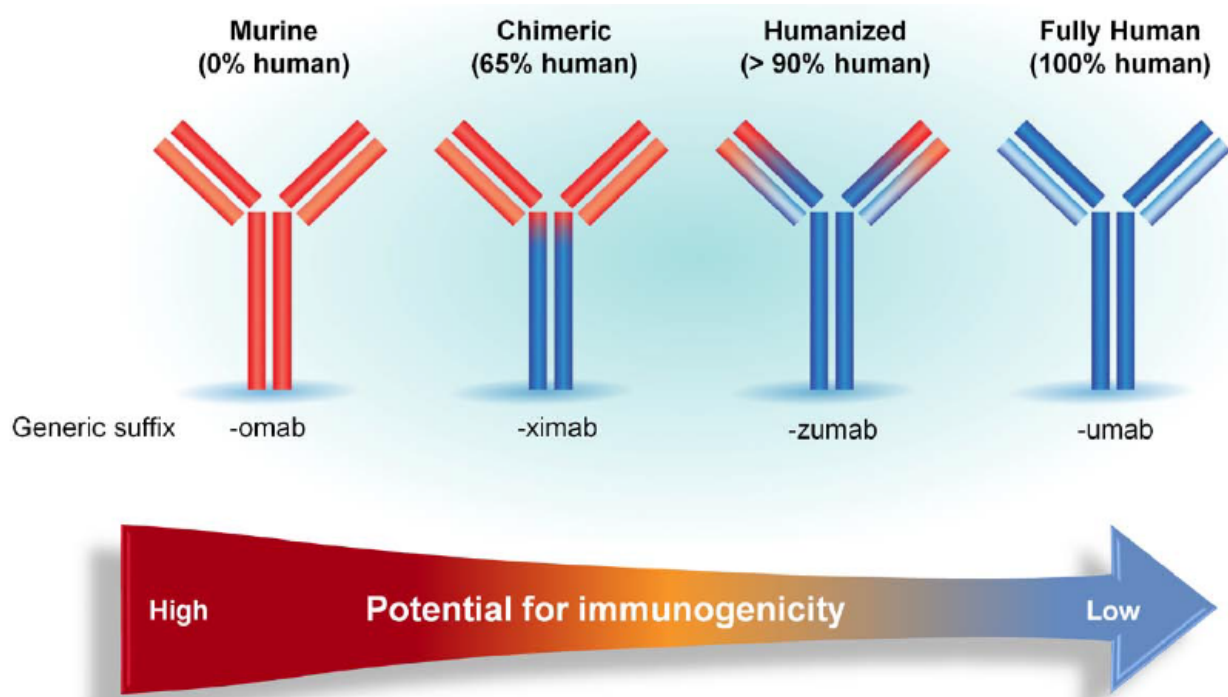
(EX1019, 4.)

This selective delivery of a desired payload to specific target sites enhances the therapeutic potential of the cytotoxic agent by minimizing drug exposure and resultant dose-limiting toxicities to non-target healthy cells when compared to standard non-selective chemo- and radiotherapies. Even compared with unconjugated antibodies efficacious against certain tumors, linking the antibody to a cytotoxic payload often provides increased efficacy and tumor eradication. As of the filing of the Challenged Claims, ADCs were extensively studied and reported. There were already two FDA-approved ADCs in the prior art—Mylotarg® (anti-

CD33) and Adcetris® (anti-CD30)— for use in cancer treatment which both used cleavable linkers. Currently, there are fourteen FDA-approved ADCs available on the market, twelve of which use cleavable linkers. (*See generally* EX1010.)

Antibodies make up a large part of the immune system. They are generally made by the immune system in response to substances foreign to the body, called antigens. The canonical representative Y-shaped antibody structure has two sets of heavy chain-light chain pairs, and variability in the antibody structure is well-documented. Antibody engineering often starts with creating antibodies in rodents, like mice, whose cell lines can be modified to induce an immune response resulting in the production of specific antibodies against a target antigen. However, antibodies formed in mice, when administered to humans, are often attacked by the human body's own immune system, negating their efficacy. Chimeric antibodies have been engineered with the murine (mouse) constant regions of the antibody replaced by human constant regions to render the antibody "more human," reducing the human immune response. Further antibody engineering includes humanization, where only the complementarity determining regions ("CDRs") of the variable regions are of mouse origin; the rest of the antibody is derived from human sequences. Fully human and humanized antibodies have an even lower risk of inducing an immune response in humans than murine or chimeric antibodies. (*See* EX1011.) A comparison progressing from fully mouse antibody to chimeric antibody to

humanized antibody to fully human antibody is represented below—the red domains constitute murine sequences; the blue portions are human.



(EX1034, 4.)

Epidermal growth factor receptor (“EGFR”), a cell surface receptor of the epidermal growth factor family, is a transmembrane glycoprotein consisting of 1186 amino acid residues with a molecular weight of 170 kD. (EX1012, 2.) EGFR is stably expressed in many epithelial tissues, including the skin and hair follicles. Overexpression of EGFR leads to many cancers, including colorectal cancer, head-neck cancer, lung cancer, ovarian cancer, cervical cancer, bladder cancer and esophageal cancer. (EX1013.) EGFR overexpression in tumors and roles in tumor

cell growth and differentiation make EGFR a promising target for antibody-based tumor therapy.

Prior to the filing of the Challenged Claims, there were two anti-EGFR antibodies on the market, including the human-mouse chimeric C225 antibody cetuximab. (EX1014.) The FDA approved cetuximab for the treatment of colorectal cancer in 2004 and the treatment of head and neck cancer in 2006. (*Id.*) At the filing of the Challenged Claims, cetuximab was being studied for use in many other cancers. (*Id.*) Because cetuximab is a human-mouse chimeric antibody, it induced an anti-therapeutic antibody response in 3.7% of patients in clinical trials. (EX1001, 2: 4-11.)

It was against this backdrop that Patent Owner filed the application that matured into the '370 patent. As background, the '370 patent highlights that although cetuximab is one of two FDA-approved anti-EGFR antibodies on the market, cetuximab is generally recognized as treating tumors without a particular genetic mutation—the KRAS mutation. (EX1001, 1:57-2:37.) The inventors described a “need in the art to have humanized anti-epidermal growth factor receptor antibody drugs with biological activity, especially antibody drugs, such as antibody-drug conjugates, with curative effects to KRAS mutants, so as to further improve therapeutic efficacy and reduce side effects.” (*Id.*, 2:50-55.)

In purporting to describe different embodiments of the invention, the patent describes various anti-EGFR antibodies comprising different CDR1, CDR2, and CDR3 regions with specific sequences and homology to these sequences based on percentages ranging from greater than 70% to 99%. (*Id.*, 3:50-4:63.) The '370 patent then lists potential cytotoxic agents well-known in the art, including Monomethyl auristatin E (MMAE). (*Id.*, 5:6-22.) The patent then lists cleavable and non-cleavable linkers also well-known in the art, including the cleavable linker valine-citrulline (vc). (*Id.*, 5:23-38.) The patent then states that a particular embodiment for the linker and cytotoxic portion of the ADC is vc-MMAE and provides the chemical structure of this prior art embodiment. (*Id.*)

The '370 patent then generically lists different pharmaceutical compositions of the ADC (*id.*, 6: 3-11), known chemotherapeutic agents that can be included with the pharmaceutical composition (*id.*, 6:11-22), and different diseases associated with EGFR tumors (*id.*, 6:23-8:56).

The '370 patent has 6 working examples. (*Id.*, Examples 1-6.) Example 1 shows the preparation of a specific ADC (MYK-3) where the prior art BA03 anti-EGFR antibody, which the patent describes with a specific reference to Liu (*id.*, 18:3-5), is attached to the vc-MMAE linker-cytotoxic agent molecule, reportedly purchased off-the-shelf commercially. (*id.*, 19:26-29). As discussed below, Liu discloses that the BA03 antibody is a humanized version of cetuximab. (EX1008,

[0058-0060].) Example 2 compares the inhibitory activity of the MYK-3 ADC to the BA03 antibody in commercially available *in vitro* cancer cell lines. Example 3 purports to describe an *in vivo* tumor xenograft test of the MYK-3 ADC in mice. Applicant reported that the tumor volume was lower and tumor growth inhibition rate was higher in the MYK-3 treatment group. Example 4 compared the inhibitory activity of the MYK-3 ADC and the BA03 antibody in *in vitro* colorectal cancer cells, with MYK-3 showing greater inhibitory activity. Example 5 compared effects of MYK-3 with the chimeric C-225 Erbitux® (cetuximab) antibody against transplanted tumor cells of KRAS-mutant colon cancer cells (LoVo) in nude mice; MYK-3 was reportedly more potent. Finally, Example 6 compared the inhibitory activity of MYK-3 against other BA03 ADCs with the MC-MMAE linker-payload and an MCC-MMAE linker-payload, with MYK-3 cell proliferation inhibitory activity reportedly greater than the other BA03 ADCs.

The '370 patent issued with 23 claims. Claim 1 recites:

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.

(EX1001, 33:1-33:11.)

VII. PROSECUTION OF THE '370 PATENT

The application that issued as the '370 patent, Application Serial Number 15/550,995, was filed on August 14, 2017 as a U.S. national phase application of International Patent Application Number PCT/CN2016/073844 (“the '844 appl.”), filed on February 16, 2016. (EX1003, 51-87.) The '844 appl. claims the benefit of Chinese Patent Application Number 201510085038.8, filed on February 17, 2015. (*Id.*, 260-98.)

Applicant filed a preliminary amendment concurrently with the national phase application that canceled certain claims and amended certain others, leaving claims 2-16, 23-28, 35, and 36 pending from the originally filed claims. (*Id.*, 94-101.)

On April 4, 2019, the Office issued a first Non-Final Office Action (“NFOA”) acknowledging the preliminary amendment and rejecting all claims. (*Id.*, 394-410.) The Office issued numerous rejections under §112 for formal matters. (*Id.*, 396-402.) The Office also rejected numerous claims under §103 as obvious over Tikhomirov

(EX1009) in view of Liu (EX1007), Brand (EX1004, 105-21), and Chung (*id.*, 1-9). The Office rejected additional claims as obvious over Tikhomirov, Liu, and Chung in view of, alternatively, Chari (*id.*, 18-49), Lievre (*id.*, 50-53), or DiNicolantonio (*id.*, 10-17).

In response, Applicant amended the claims to delete certain recitations to overcome the §112 rejections and to introduce “a cleavable linker” that links the anti-EGFR antibody to the cytotoxic agent. (*Id.*, 129.) Applicant only argued the patentability of the claims in view of the newly recited “cleavable linker” and did not challenge the Office’s rejections regarding the remaining elements present in the previously pending claims. (*Id.*, 137-41.) Applicant first argued that a POSA would not have been motivated, and would have been discouraged, to use a cleavable linker because Tikhomirov “almost exclusively focuses on non-cleavable linkers” and only discloses cleavable linkers “as optional, less desirable embodiments.” (*Id.*, 137-38.) In support, Applicant highlighted a portion of Tikhomirov that disclosed the potential of “toxicity against normal cells” when “fully antagonistic antibodies are conjugated to their payloads via cleavable linkers.” (*Id.*, 138-39 (quoting EX1009, 31).) Applicant also argued that a POSA would not have expected an anti-EGFR ADC having a cleavable linker to be superior to those having non-cleavable linkers because such “superiority is not taught or suggested by any of the cited references.” (*Id.*, 139-40.)

The Office issued a Final Office Action (“FOA”) on October 18, 2019 maintaining all rejections notwithstanding Applicant’s amendments and arguments. (*Id.*, 148-62.) Specifically, the Office noted that controlling case law held “[t]he prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of” the disclosed alternatives absent explicit criticism or discrediting of such disclosures. (*Id.*, 160 (quoting MPEP §2123(II) and *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004)). The Office also noted “that expression of an antigen of interest on normal tissue does not necessarily preclude the development of an ADC targeting the antigen.” (*Id.*, 160.)

Applicant responded on December 16, 2019, again amending the claims to delete certain recitations and submitting arguments to overcome various rejections under §112. (*Id.*, 197-99.) Applicant reiterated its previous arguments against the obviousness rejections and responded in detail to the Office’s responses thereto, focusing again on the potentiated toxicity associated with the use of anti-EGFR ADCs linked to a cytotoxic agent via a cleavable linker. (*Id.*, 199-207.)

On January 17, 2020, the Office issued an NFOA and rejected a majority of the claims as obvious over Tikhomirov, Liu, Brand, Chung, and Doronina. (*Id.*, 242-43.) The Office added a citation to Doronina to further support the disclosure of Tikhomirov and Liu and a POSA’s motivation to use a cleavable linker to conjugate an antibody. (*Id.*, 247.) The Office again rejected Applicant’s arguments that

toxicity associated with the use of cleavable linkers in conjunction with EGFR targeting demonstrates a POSA's lack of motivation to use a cleavable linker in the claimed ADC. (*Id.*, 248-49.) However, the Office indicated that claims 27, 28, 35, and 36, limiting the treated tumor to those with KRAS and BRAF gene mutations, respectively, contained allowable subject matter. (*Id.*, 251.)

In its response dated March 26, 2020, Applicant again maintained its arguments regarding toxicities associated with anti-EGFR ADCs with cleavable linkers. (*Id.*, 298-302.) On June 18, 2020, the Office issued a Notice of Allowance without providing any reasons for doing so. (*Id.*, 308-11.) 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, notwithstanding the abundant disclosure and use of cleavable linkers in anti-EGFR ADCs in the prior art. No other arguments regarding the content and scope of the prior art were presented. Applicant paid the issue fee on August 27, 2020, and the '370 patent issued on October 6, 2020.

VIII. SUMMARY OF THE PRIOR ART REFERENCES

A. Wei

Wei is a U.S. patent application No. 14/485,620 which was filed on September 12, 2014 and published as US 2015/0071923 on March 12, 2015. (EX1005, 1.) It is

prior art under 35 U.S.C. § 102(a) because it was filed before the earliest possible filing date of the '370 patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Wei discloses anti-EGFR antibodies and ADCs of these antibodies, where the anti-EGFR antibodies are modified cetuximab antibodies. As background, Wei states that cetuximab is an exemplary anti-EGFR antibody used clinically to treat and diagnose diseases and that it “is approved for the treatment of recurrent or metastatic head and neck cancer, colorectal cancer, and other diseases and conditions.” (*Id.*, [0009].) However, Wei also states that anti-EGFR antibodies can bind to EGFR in healthy cells and tissues, limiting the dosages of cetuximab. (*Id.*)

Wei describes modified cetuximab antibodies where the antibodies contain an amino acid replacement in the variable heavy chain “corresponding to position 104 with reference to amino acid positions set forth in SEQ ID NO: 2 or 7.” (*Id.*, [0010].) 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.*, [0011].) One of these modified cetuximab antibodies is Y104D, “where the tyrosine

(Y) at a position corresponding to position 104 is replaced with D [aspartic acid].” (*Id.*, [0660], Examples 1-2.)

Wei also discusses ADCs with the Y104D cetuximab variant. Example 18 discloses generation of a Y104D-Mc-VcPAB-MMAE ADC (also referred to as Y104D-MMAE ADC), where Y104D “was conjugated to MMAE via the cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyl linker (maleimidocaproyl-vcPAB-MMAE) as described in Francisco *et al.* Blood 102:1458-1465 (2003).” (*Id.*, [1103].) Wei states that “[t]he final conjugated product had a drug:antibody (DAR) ratio of approximately 4 as assessed by hydrophobic interaction chromatography.” (*Id.*)

When tested in murine tumor models, the Y104D-MMAE ADC exhibited “substantially reduced tumor growth” compared to the vehicle control, especially at higher doses where the tumor growth regressed back to baseline volume, as shown in Table 39. (*Id.*, [1106].)

TABLE 39

Y104D-MMAE Effect on Tumor Growth									
Time (Days)	Vehicle		Y104D-MMAE						
	—		1.5 mg/kg		5 mg/kg		15 mg/kg		
	AVG	StDev	AVG	StDev	AVG	StDev	AVG	StDev	
-1	364.54	66.04	356.82	59.04	358.84	65.57	357.65	69.35	
2	626.74	147.98	520.37	165.34	568.76	143.75	586.35	145.36	
6	977.94	163.14	704.14	292.50	543.00	120.95	484.38	98.17	
10	1190.49	164.37	922.94	488.02	499.82	102.25	386.04	101.80	
14	1539.80	269.41	1106.85	635.47	438.17	81.56	374.90	93.21	
17	1888.41	471.35	1360.03	906.79	415.13	53.15	344.23	109.79	

In Example 20, the Y104D-MMAE ADC and an ADC with humanized versions of the cetuximab variant, huY104D-MMAE and huY104E-MMAE, were administered in breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors, which were shown to be resistant to cetuximab (Table 41). (*See id.*, [1122-1127].) Wei discloses that administration of the Y104D-MMAE ADC compared to the vehicle control resulted in tumor regression below the baseline tumor volume and that mice administered the humanized version of the ADC also exhibited a strong anti-tumor response and tumor regression. (*Id.*, Tables 44 and 45).

TABLE 44

Breast Tumor Growth Following huY104D-MMAE Treatment						
Time (Days)	Vehicle —	Y104D- MMAE 10 mg/kg	huY104D-MMAE			
			3 mg/kg	6 mg/kg	10 mg/kg	30 mg/kg
-1	397.8 ± 35.9	400.7 ± 28.3	404.0 ± 31.5	403.6 ± 33.4	398.3 ± 39.9	396.1 ± 42.9
3	565.3 ± 121.0	513.9 ± 118.1	675.3 ± 159.1	614.9 ± 153.7	535.4 ± 99.5	465.2 ± 127.5

TABLE 44-continued

Breast Tumor Growth Following huY104D-MMAE Treatment						
Time (Days)	Vehicle —	Y104D- MMAE 10 mg/kg	huY104D-MMAE			
			3 mg/kg	6 mg/kg	10 mg/kg	30 mg/kg
6	783.0 ± 148.7	478.4 ± 112.3	668.6 ± 137.1	602.6 ± 130.8	480.6 ± 114.7	418.6 ± 95.4
9	1026.9 ± 208.8	354.3 ± 84.2	725.2 ± 135.2	543.5 ± 185.6	308.7 ± 52.8	255.5 ± 79.6
13	1398.3 ± 442.9	223.5 ± 91.7	901.4 ± 146.4	561.3 ± 221.1	122.4 ± 43.5	154.2 ± 26.6
16		202.3 ± 145.3	1301.3 ± 456.5	617.1 ± 246.8	77.3 ± 69.1	90.7 ± 56.7
20		262.7 ± 252.8		811.1 ± 349.8	67.3 ± 69.5	47.6 ± 44.2
23		332.9 ± 329.7		958.5 ± 378.5	57.5 ± 38.2	28.8 ± 22.9

TABLE 45

Breast Tumor Growth Following huY104E-MMAE Treatment						
Time (Days)	Vehicle —	Y104D- MMAE 10 mg/kg	huY104E-MMAE			
			3 mg/kg	6 mg/kg	10 mg/kg	30 mg/kg
-1	397.8 ± 35.9	400.7 ± 28.3	398.4 ± 39.7	398.4 ± 37.8	403.6 ± 36.2	401.0 ± 30.4
3	565.3 ± 121.0	513.9 ± 118.1	488.7 ± 77.6	523.7 ± 150.6	516.5 ± 81.6	458.2 ± 66.6
6	783.0 ± 148.7	478.4 ± 112.3	532.6 ± 95.7	525.9 ± 73.3	461.1 ± 89.9	496.5 ± 94.8
9	1026.9 ± 208.8	354.3 ± 84.2	543.8 ± 129.6	571.2 ± 187.6	323.5 ± 39.8	343.8 ± 57.8
13	1398.3 ± 442.9	223.5 ± 91.7	771.0 ± 322.7	581.2 ± 249.6	232.8 ± 133.6	172.5 ± 73.7
16		202.3 ± 145.3	871.5 ± 462.2	664.8 ± 480.3	193.2 ± 176.7	116.1 ± 62.0
20		262.7 ± 252.8	1167.1 ± 446.5	865.0 ± 577.1	173.5 ± 189.2	84.3 ± 53.2
23		332.9 ± 329.7	1416.7 ± 465.4	1134.6 ± 741.1	201.7 ± 233.3	50.5 ± 34.2

Wei concludes that “[t]hese results confirm that the Y104D-MMAE conjugate, and the humanized forms huY104D-MMAE and huY104E-MMAE,

exhibit a strong anti-tumor response in KRAS mutated, EGFR+ tumor model” and that “[t]he anti-tumor response of each of the tested antibodies achieves tumor growth regression.” (*Id.*, [1127].) Notably, Wei also states that at pH levels of the human body, the humanized ADCs exhibited reduced growth inhibition of non-tumor cells compared to the chimeric ADC.

Therefore, these results show that ADC conjugates of **the humanized forms** of the Y104D- and Y104E-anti-EGFR variants **exhibit greater** pH-dependent activity than the **chimeric** Y104D-MMAE conjugate. For example, while each are as effective as the chimeric Y104D-MMAE for inhibiting tumor cell growth at pH 6.8, each exhibit reduced growth inhibition of non-tumor keratinocytes at pH 7.4 compared to the chimeric Y104D-MMAE.

(*Id.*, [1139] (emphasis added).)

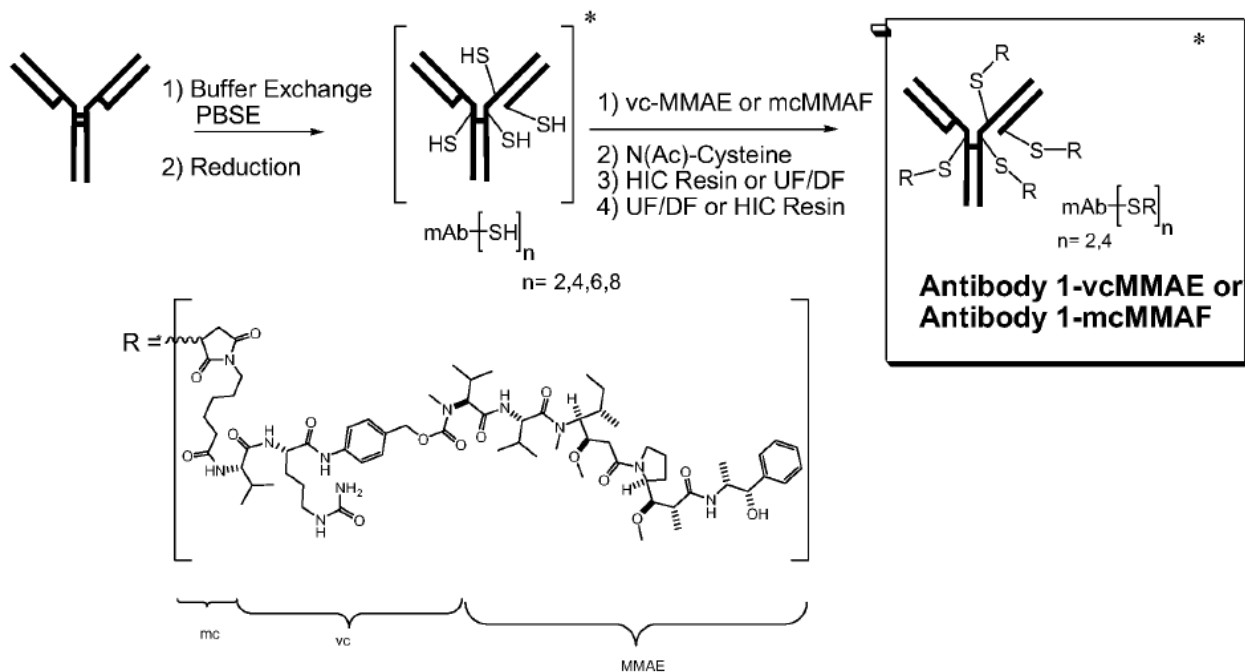
In addition to disclosing these ADCs, Wei also discloses pharmaceutical compositions that include any of the disclosed antibodies and ADCs with acceptable carriers or excipients, and describes numerous well known drug formulations for various types of administration. (*Id.*, [0238].)

Wei also discloses methods of treating conditions responsive to the disclosed antibodies and ADCs, including cancers, such as head and neck cancer, non-small cell lung cancer, or colorectal cancer. (*Id.*, [0442].)

B. Leanna

Leanna is a PCT application with the publication number WO2014/152199 and a publication date of September 25, 2014. (EX1006, 1.) It is prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the '370 patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Leanna, entitled “Antibody Drug Conjugate (ADC) Purification,” provides methods for obtaining compositions having ADCs with specified drug to antibody ratios as well as methods ADC mixtures. Among the ADCs disclosed in the invention are an anti-EGFR antibody attached to a vc-MMAE linker-payload molecule. (*See id.*, 1.) Figure 1 depicts the reduction of Antibody 1, the conjugation of Antibody 1 to vc-MMAE, and purification of the ADC using batch purification.



(*Id.*)

Antibody 1 is a humanized anti-EGFR antibody previously described in WO2011/041319 and US20110076232 (*see, e.g.*, antibody sequence of FIG. 55). (*Id.*, 26.) Leanna defines a “humanized antibody” as antibodies that comprise heavy and light chain variable region sequences from a non-human species (*e.g.*, a mouse) but in which at least a portion of the V_H and/or V_L sequence has been altered to be more “human-like,” *i.e.*, more similar to human germline variable sequences. (*Id.*, 13.) In a particular embodiment, the term “humanized antibody” refers to an antibody or antibody variant, derivative, or fragment that specifically binds to an antigen of interest, comprises a framework (“FR”) region having substantially the amino acid sequence of a human antibody, and comprises CDRs having substantially the amino acid sequence of a non-human antibody. (*See id.*)

Leanna discloses that the methods described are based on ADCs comprising anti-EGFR antibodies that specifically bind to EGFR conjugated to auristatin. (*Id.*, 25.) Leanna also states that in one embodiment, the anti-EGFR ADC comprises Antibody 1-vc-MMAE. (*Id.*, 34.) Leanna also discloses that in one embodiment, “the linker linking MMAE to the anti-EGFR antibody is stable in extracellular fluid (*i.e.*, the medium or environment that is external to cells), but is cleaved by cathepsin once the ADC has bound to the specific cancer cell antigen and entered the cancer cell, thus releasing the toxic MMAE and activating the potent anti-mitotic mechanism.” (*Id.*, 31.)

Leanna also discloses that anti-EGFR ADCs can be used to prepare pharmaceutical compositions for use in methods of treating cancer in a subject comprising administering a composition comprising the described anti-EGFR ADCs, such as Antibody 1-vc-MMAE. (*Id.*, 10, 34-49.) The pharmaceutical compositions may comprise, in addition to the active ingredient (ADC), a pharmaceutically acceptable excipient, carrier, buffer, stabilizer, or other materials well-known to those skilled in the art. (*Id.*, 37-38.)

Leanna discloses a method for treating a subject comprising administering a therapeutically effective amount of an anti-EGFR ADC, wherein the subject has a disorder, such as a tumor, a cancerous condition, a precancerous condition, and any condition related to or resulting from hyperproliferative cell growth to alleviate the

symptoms and/or progression. (*Id.*, 34-36.) The cancer is selected from the group consisting of squamous tumors (including squamous tumors of the lung, head and neck, cervical, etc.), glioblastoma, glioma, non-small cell lung cancer, lung cancer, colon cancer, head and neck cancer, breast cancer, squamous cell tumors, anal cancer, skin cancer, and vulvar cancer. (*Id.*, 15, 35-36.) Leanna specifically discloses that ADCs are used to treat a solid tumor having overexpression of EGFR and to treat a subject having an advanced solid tumor likely to overexpress EGFR. (*See id.*)

C. Liu

Liu is a Chinese patent application designated with application number CN103772504 with a publication date of May 7, 2014. (EX1008, 1.) It is prior art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the '370 patent, and none of the exceptions of 35 U.S.C. § 102(b) apply.

Liu, entitled “Humanized antibody against epidermal growth factor receptor and application thereof,” describes humanizing anti-EGFR antibodies that originated from mouse sources with reduced immunogenicity. Among Liu’s working embodiments is the humanized antibody BA03, which is described as the humanized version of the chimeric cetuximab antibody. (*Id.*, [0060].) The BA03 heavy chain and light chain variable regions are disclosed, which correspond to SEQ ID NOs: 5 to 7, SEQ ID NOs: 12 to 14, SEQ ID NOs: 8 to 11, and SEQ ID NOs: 15 to 18

claimed in the '370 patent. (EX1008, [0085]; *see also* EX1002, 90-92.) Dr. Bournazos demonstrates that the sequences of the heavy chain variable regions of BA03 in MYK-3 of the '370 patent (upper sequence) are identical to those of BA03 disclosed by Liu (lower sequence).

```
US370_SID1      QVQLQESGPGLVKPSSETLSLTCTVSGFSLSNYDVHWVRQAPGKGLEWLGVIWSGGNTDYN 60
LIU_BA03_SID5  QVQLQESGPGLVKPSSETLSLTCTVSGFSLSNYDVHWVRQAPGKGLEWLGVIWSGGNTDYN 60
*****

US370_SID1      TPFTSRLTISVDTSKNQFSLKLSVTAADTAVYYCARALDYDYEFAYWGQGLTVTVSS 119
LIU_BA03_SID5  TPFTSRLTISVDTSKNQFSLKLSVTAADTAVYYCARALDYDYEFAYWGQGLTVTVSS 119
*****
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(EX1002, 90.)

Dr. Bournazos also shows that the sequences of the light chain variable regions of BA03 in MYK-3 of the '370 patent (upper sequence) are identical to those of BA03 disclosed by Liu (lower sequence).

```
US370_SID2      EIVLTQSPDFQSVTPKEKVTITCRASQSIGTNIHWYQQKPDQSPKLLIKYASESISGIPS 60
LIU_BA03_SID13  EIVLTQSPDFQSVTPKEKVTITCRASQSIGTNIHWYQQKPDQSPKLLIKYASESISGIPS 60
*****

US370_SID2      RFSGSGSGTDFTLTINSLEAEDAATYYCQQNNEWPTSFGQGTKLEIK 107
LIU_BA03_SID13  RFSGSGSGTDFTLTINSLEAEDAATYYCQQNNEWPTSFGQGTKLEIK 107
*****
```

(*Id.*)

Liu also discloses the heavy chain and light chain constant regions of BA03, which correspond to the SEQ ID NO:3 and SEQ ID NO:4 sequences claimed in the '370 patent (EX1008, [0133]; *see also* EX1002, 91.) Dr. Bournazos demonstrates that the sequences of heavy chain constant regions of BA03 in MYK-3 of the '370

patent (upper sequence) are identical to those of BA03 disclosed by Liu (lower sequence).

US370_SID3	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSQVHTEFPAVLQSS	60
LIU_BA03_SID42	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSQVHTEFPAVLQSS	60

US370_SID3	GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGG	120
LIU_BA03_SID42	GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGG	120

US370_SID3	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN	180
LIU_BA03_SID42	PSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYN	180

US370_SID3	STYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE	240
LIU_BA03_SID42	STYRVVSVITVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE	240
	*****;*****	
US370_SID3	MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW	300
LIU_BA03_SID42	MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW	300

US370_SID3	QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	330
LIU_BA03_SID42	QQGNVFSCSVMHEALHNHYTQKSLSLSPGK	330

(Id.)

Dr. Bournazos also shows that the sequences of the light chain constant regions of BA03 in MYK-3 of the '370 patent (upper sequence) are identical to those of BA03 disclosed by Liu (lower sequence).

US370_SID4	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD	60
LIU_BA03_SID43	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD	60

US370_SID4	SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	107
LIU_BA03_SID43	SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	107

(Id.)

Liu reports that BA03 had higher cytotoxic activity than cetuximab (Tables 2 and 3, Examples 4-7) and demonstrated the highest EGFR binding affinity among other humanized anti-EGFR antibodies studied, as well as inhibitory activity in blocking interactions between EGFR and EGF. (*See* EX1008, Examples 1-5, [00141]- [0146], Tables 1-3.) Liu further characterized BA03 to determine its ability to block EGFR phosphorylation (Example 6), Antibody-Dependent Cell-Mediated Cytotoxicity (“ADCC”) activity (Example 7), *in vitro* immunogenicity (Example 8), and *in vitro* anti-tumor activity against lung cancer, colorectal carcinoma, pancreatic carcinoma, and breast cancer (Example 9). More specifically, Liu reported that BA03 has stronger activity than cetuximab in inhibiting EGFR phosphorylation on A431 cells (Fig. 3). (*See id.*, [0148].) Liu also reported that BA03 showed, at both 0.1 µg/ml and 1 µg/ml, higher ADCC activity than cetuximab (Fig. 4). (*See id.*, [0150].) Liu also observed that BA03 had significantly lower immunogenicity compared to cetuximab (Fig. 5) and high anti-tumor activity against lung cancer, colorectal carcinoma, pancreatic carcinoma, and breast cancer. (*See id.*, [0152]- [0160], Table 4.)

D. Tikhomirov

Tikhomirov is a PCT application with an application number of WO/2015/000062 and a publication date of January 8, 2015. (EX1009, 1.) It is prior

art under 35 U.S.C. § 102(a) because it was published before the earliest possible filing date of the '370 patent and none of the exceptions of 35 U.S.C. § 102(b) apply.

Tikhomirov, entitled “EGFR Antibody Conjugates,” relates to ADCs that target EGFR-expressing cancer cells, and specifically identifies cetuximab conjugated with the auristatin (MMAE) anti-microtubule payload as a preferred embodiment. (*See id.*, Abstract, 16.) Indeed, Tikhomirov discloses a cetuximab ADC conjugated to the anti-microtubule toxin MMAE using the cleavable valine-citrulline linker. (*See id.*, FIG. 13.)

While Tikhomirov indicates that a non-cleavable linker is most desirable, it does not preclude the use of a cleavable linker. Consistently, Tikhomirov provides methods “useful to potentiate the anti-cancer activity of an EGFR antibody without potentiating the effect thereof on normal EGFR+ cells,” with the method comprising:

- (i) selecting, for conjugation, an EGFR antibody that is a full EGFR antagonist and competes with cetuximab for binding to EGFR;
- (ii) selecting, for delivery by the EGFR antibody, an anti-microtubule toxin;
- (iii) selecting, for coupling the selected EGFR antibody and the anti-microtubule toxin, **a linker**; and

producing an immunoconjugate that incorporates the linker between the antibody and the toxin, thereby providing an immunoconjugate having a cytotoxicity that is potentiated against EGFR+ disease cells and essentially not potentiated against normal EGFR+ keratinocyte cells.

(*Id.*, 5 (emphasis added).)

Tikhomirov discloses a pharmaceutical composition of EGFR antibody-based immunoconjugate in an amount cytotoxic to EGFR-positive cancer cells, and a pharmaceutically acceptable carrier, excipient, or stabilizer. (*See id.*, 8, 16.) Tikhomirov also states that ADCs as disclosed are useful in the treatment of a variety of cancers to inhibit the growth or proliferation of EGFR-positive cancer cells and tumors comprising them. (*See id.*, 19.) Tikhomirov states that ADCs are useful in the treatment of a variety of cancers to inhibit the growth or proliferation of EGFR-positive cancer cells and tumors comprising them, including hematopoietic cell cancers and solid tumors, including renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulvar, and thyroid cancers; hepatic carcinomas; sarcomas; glioblastomas; and various head and neck tumors; as well as leukemias and lymphoid malignancies. (*See id.*)

In Figure 13, Tikhomirov states that Cetux 2C9-MMAE—an ADC comprising cetuximab conjugated to MMAE by the valine-citrulline cleavable

linker—“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.” (*Id.*, 10, 11, 30.)

However, as explained by Dr. Bournazos, Figure 13 only contains a comparison between Cetux 2C9-MMAE, Cetux 2C9-DM1, certuximab-2C9 (without an anti-microtubule toxin payload), hIg-DM1 (non-binding ADC), and hIgG (non-binding and without anti-microtubule toxin payload). (EX1002, 103.) Thus, there is no head-to-head comparison in Figure 13 between Cetux 2C9-MMAE (with a cleavable linker) and cetuximab-SMCC-MMAE (or cetuximab-SMCC-DM1) (with a non-cleavable linker). (*See id.*) In addition, Dr. Bournazos points out that the experiment is missing a statistical comparison between the treatment groups to confirm there is a biologically meaningful effect. (*See id.*) Importantly, a POSA would have understood that the payloads (DM1 vs. MMAE) as tested have different cytotoxic activity against the selected cell lines, and thus, the Applicant’s interpretation of the data is problematic. (*See id.*) Moreover, the experiment is also missing important controls, such as payload alone and isotype with vc-MMAE. (*See id.*)

As Dr. Bournazos further explains, even assuming that there was a head-to-head comparison between ADCs with the same payload but different linkers, a POSA would have understood that any observation based on a single anti-EGFR

antibody (cetuximab), a single anti-microtubule payload (DM1), and a single non-cleavable linker (*i.e.*, SMCC) or a single cleavable linker (*i.e.*, valine-citrulline) could not be generally applied to other anti-EGFR antibodies, other linkers, and other payloads within the broad scope of the Challenged Claims, which literally cover any non-cleavable linker and any payload. (*Id.*, 104). Therefore, Dr. Bournazos concludes that Tikhomirov’s reasoning is flawed when it states that the “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,” and “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.” (EX1009, 30, 31 (emphasis added).)

Furthermore, Tikhomirov makes clear that its observation regarding toxicity against normal cells between a non-cleavable linker and a cleavable linker only applies to anti-microtubule payloads (*e.g.*, DM1). Indeed, Tikhomirov states that, “conjugates of cetuximab with cell-killing agents **other than anti-microtubule toxins, such as saporin**, were found, as expected, to have an attendant and significantly enhanced toxicity toward keratinocytes.” (*Id.*, 4 (emphasis added).) Thus, a POSA would have understood that Tikhomirov’s observation regarding toxicity issues with anti-EGFR ADCs would only apply to anti-microtubule payloads, and that whole classes of non-anti-microtubule payloads covered by the

Challenged Claims would not be expected to raise any toxicity concerns, regardless of whether a non-cleavable linker or a cleavable linker is used. (EX1002, 105.)

IX. PERSON OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art (“POSA”) at the time of the alleged invention would typically have had a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an MD with similar experience. A POSA would typically have had at least five years of experience with antibodies and antibody engineering, or access to other individuals with that knowledge and experience.

X. CLAIM CONSTRUCTION

For IPR proceedings, the Board applies the same claim construction standard set forth in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). *See* 83 Fed. Reg. 51,340-59 (Oct. 11, 2018). “[C]laim terms need only be construed ‘to the extent necessary to resolve the controversy.’” *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2001). Petitioner submits that no term of the Challenged Claims requires construction to resolve the challenges in this Petition.

XI. LEGAL STANDARDS

A. Standard For Instituting IPR

The Petition must be granted if it meets the threshold requirement of demonstrating that there is a “reasonable likelihood” that Petitioner would prevail as to at least one of the Challenged Claims. *See* 35 U.S.C. § 314(a) (2011). The

“reasonable likelihood standard is higher than mere notice pleading but...lower than the ‘preponderance’ standard to prevail...” *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 13 (PTAB Dec. 20, 2019) (precedential).

B. Standard for Obviousness under 35 U.S.C. § 103

The standard for obviousness, which forms the basis of Grounds 1-2 of the Petition, was set forth in *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). There, the Supreme Court emphasized that inventions arising from ordinary innovation, ordinary skill, or common sense should not be patentable. In that regard, a patent claim may be obvious if the combination of elements was obvious to try or there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent’s claims. In addition, when a reference is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 35 U.S.C. §103 likely bars its patentability.

C. Standard for Discretionary Denial under 35 U.S.C. §325(d)

When evaluating whether to exercise its discretion to deny institution of an IPR under Section 325(d), the PTAB applies a two-part test: “(1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office;

and (2) if either condition of the first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8 (PTAB Feb. 13, 2020) (precedential). In the first step, the PTAB considers the similarities and material differences between the asserted art and the prior art involved during prosecution. (*See id.*, 9.) If the first step is satisfied, the PTAB then goes to the second step and considers the extent to which the prior art was the basis for rejection, whether Petitioner has pointed out sufficiently how the Office erred in its evaluation of the prior art, and the extent to which additional evidence and facts presented in the petition justify reconsideration of the prior art or argument. (*See id.*, 10-11.)

Applied here, the PTAB should not exercise its discretion to deny institution because the grounds for the Petition are substantially different from the arguments that were overcome by Patent Owner during prosecution. For the reasons discussed in more detail below, Petitioner here relies on the Wei and Leanna references, which were never discussed by the Office or the Applicant during prosecution, and these references are not cumulative to the art identified by the Office during prosecution, namely, Tikhomirov. Unlike Tikhomirov, Wei and Leanna disclose anti-EGFR ADCs with cleavable linkers without any toxicity concerns associated with cleavable linkers. Moreover, as also discussed in more detail below, the Office erred when it

allowed the claims based on Applicant's arguments that (1) Tikhomirov "teaches away" from the use of cleavable linkers in anti-EGFR ADCs, and (2) Applicant's use of cleavable linkers in ADCs was an unexpected result. But for these errors, the Challenged Claims would not have issued. The PTAB should therefore decline to exercise discretionary denial under Section 325(d).

XII. EFFECTIVE FILING DATE

The effective filing date of the Challenged Claims is February 16, 2016, the date of the actual U.S. filing of the '370 patent. The Challenged Claims are not entitled to claim the benefit of the foreign Chinese application filing date of February 17, 2015, because that foreign application does not adequately describe the full scope of the Challenged Claims. The Challenged Claims cover ADCs, pharmaceutical compositions containing these ADCs, and methods of treatment administering these ADCs that cover all cleavable linkers and cytotoxic payloads. As Dr. Bournazos explains, the claim element "cleavable linker" represents a vast, diverse genus (*e.g.*, hundreds of thousands) of cleavable linkers, and the number of cleavable linkers that can be encompassed in this genus is astronomical. (EX1002, 165.) For example, cleavable linkers can include chemically labile (*e.g.*, hydrazones and disulfides) and protease-labile linkers, linkers that can be cleaved under different conditions (*e.g.*, pH, enzymes, reductive conditions), and linkers with different coupling functional handles. (EX1015.) Each of these groups of cleavable linkers can give rise to a

whole subgenus of cleavable linkers, thus further expanding the number of potential cleavable linkers covered by the Challenged Claims.

In sharp contrast, the foreign Chinese application only describes 3 peptide cleavable linkers: valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), and 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB), and one non-peptide cleavable linker: N-succinimidyl 4-(2-pyridylthio)valerate (SPP). (EX1030, 14; EX1035, 14; EX1003, 272.) As Dr. Bournazos concludes, these mere three cleavable linkers clearly are not a representative number of species falling within the scope of the large genus of cleavable linkers. (EX1002, 167.) The foreign application also fails to describe structural features common to the members of the large genus of cleavable linkers and fails to provide guidance as to how to predict any common structural features of this vast genus. (*See id.*)

“For a claim in a later-filed application to be entitled to the filing date of an earlier application under 35 U.S.C. § 120 (1994), the earlier application must comply with the written description requirement of 35 U.S.C. § 112(a).” *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed. Cir. 1998). The earlier applications, therefore, must “contain a written description of the invention, and of the manner and process of making and using it.” (*Id.*) A disclosure in any parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description

requirement; it must describe the claimed invention with all its limitations. (*See id.*; *see also* 35 U.S.C. § 112(a).)

Because the Chinese foreign application does not adequately describe the full scope of the Challenged Claims, the Challenged Claims are not entitled to priority from the filing of this foreign application.

However, even if the Challenged Claims are entitled to the February 17, 2015 filing date of the foreign Chinese application, the Petition should still be granted because all of the art supporting Grounds 1-2 would still be prior art under an effective filing date of February 17, 2015.

XIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Ground 1: There is a reasonable likelihood that at least Claims 1-23 are obvious over Wei and Liu

Claim 1:

The obviousness of claim 1 over Wei and Liu is demonstrated in the following claim chart.

Claim 1 of the '370 patent	Prior Art
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,	Wei discloses: An anti-EGFR antibody-drug conjugate (EX1005, [0229]), including the Y104D-Mc-vcPAB-MMAE ADC (<i>id.</i> , [0742], [1092]-[1141])) and a humanized version of this antibody, huY104D-MMAE ADC (<i>id.</i>), that comprises an anti-EGFR antibody (<i>e.g.</i> , Y104D,

<p>wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain,</p> <p>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.</p>	<p>huY104D) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (<i>id.</i>, [0742], [1092]-[1127], claims 27-40.)</p> <p>Liu discloses: A humanized anti-EGFR antibody BA03 comprising a heavy chain and a light chain (EX1008, Examples 1-5, [00141]-[0146], Tables 1-3), wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7 (<i>id.</i>, [0085], [0123], [0124]), and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14 (<i>id.</i>, [0108], [0123], [0124]).</p>
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As shown above, Wei and Liu teach each and every feature of claim 1.

Wei discloses anti-EGFR ADCs, including the Y104D-Mc-vcPAB-MMAE ADC (also referred to as Y104D-MMAE ADC) and a humanized version thereof, huY104D-Mc-vcPAB-MMAE ADC (also referred to as huY104D-MMAE ADC), that comprise a modified cetuximab antibody covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker. (EX1005, [1092]-[1127].) The Y104D antibody is a cetuximab variant “where the tyrosine (Y) at a position corresponding to position 104 is replaced with D [aspartic acid].” (*Id.*, [0660], Examples 1-2.) Example 18 of Wei discloses the formation of the Y104D-MMAE ADC, where Y104D was conjugated to MMAE via the cleavable linker

maleimidocaproyl-valine-citrulline-p-aminobenzyl linker (maleimidocaproyl-vcPAB) as described in Francisco *et al.* Blood 102:1458-1465 (2003). (*Id.*, [1103].) Example 20 of Wei describes that the Y104D-MMAE ADC and a humanized version of this cetuximab variant, huY104E-MMAE, were administered in breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors and were shown to exhibit strong anti-tumor response and tumor regression. (*See id.*, [1122-1127].)

Liu discloses the humanized anti-EGFR antibody BA03—an IgG1 isotype anti-EGFR antibody, which is the same BA03 antibody used in the '370 patent to generate its preferred embodiment MYK-3 ADC—and is a humanized cetuximab antibody. (EX1008, [0060]; EX1001, 18:3-6.) As discussed above, the heavy chain variable region, light chain variable region, heavy chain constant region, and light chain constant region sequences of the BA03 antibody disclosed in Liu are identical to those of the BA03 antibody used and claimed in the '370 patent to obtain the MYK-3 ADC. Thus, all the recited CDR sequences (SEQ ID NOs: 5-7 and 12-14) in claim 1 of the '370 patent are taught by Liu.

In addition, Liu discloses that among the disclosed humanized anti-EGFR antibodies, BA03 demonstrated the highest binding affinity to EGFR and inhibitory activity in blocking interactions between EGFR and EGF. (EX1008, Examples 1-5, [0141]-[0146], Tables 1-3.) Furthermore, BA03 demonstrates several advantageous

properties, including: (1) stronger EGFR phosphorylation inhibition than cetuximab (*id.*, [0148], FIG. 3); (2) higher ADCC activity than Erbitux (*id.*, [0150], FIG. 4); and (3) significantly lower immunogenicity compared to Erbitux (*id.*, [0152]-[0160], Table 4, FIG. 5).

1. A POSA would have been motivated to combine the teachings of Wei and Liu

A POSA clearly would have been motivated to combine the teachings of Wei and Liu to arrive at claim 1.

First, Liu discloses and claims the humanized version of cetuximab—BA03—and states that BA03 has numerous benefits over cetuximab, including stronger EGFR phosphorylation inhibition, higher ADCC activity, and significantly lower immunogenicity. (EX1008, [0148-0152].)

Second, both Wei and Liu disclose and characterize humanized anti-EGFR antibodies, which a POSA would recognize as having lower immunogenicity than murine and chimeric antibodies. (*Id.*; EX1005, [1116-1127].) In fact, as explained by Dr. Bournazos, the humanized anti-EGFR antibodies disclosed by these references are substantially identical, where Liu discloses a humanized cetuximab and Wei discloses a humanized cetuximab variant huY104D as part of the huY104D-MMAE ADC. (EX1002, 188.) Notably, the Y104D antibody of Wei differs from cetuximab by only one amino acid, out of several hundred. (*Id.*, 187.)

Third, Wei discloses an ADC containing the cetuximab variant Y104D attached to the MMAE cytotoxic payload with a vc cleavable linker, the same vc-MMAE linker payload disclosed as preferred embodiments in the '370 patent and covered by the Challenged Claims. (EX1005, [1103].) As Dr. Bournazos further explains, a POSA would have recognized that if ADCs with cleavable linkers were being made in the prior art using a modified version of the chimeric version of M225 (cetuximab variant Y104D, as shown by Wei), they would have been strongly motivated to create ADCs using the humanized version of M225 (BA03), because humanized antibodies had several advantages over chimeric antibodies, including lower immunogenicity, which Liu specifically discloses in detail. (*Id.*, 188.) In fact, as confirmed by Dr. Bournazos, Wei discloses a humanized version of its cetuximab variant ADC—huY104D-MMAE—which is substantially identical to the humanized cetuximab-vc-MMAE (MYK-3) disclosed as preferred embodiments in the '370 patent and claimed by the Challenged Claims. (*Id.*) Moreover, the humanized cetuximab variant ADCs of Wei exhibited reduced growth inhibition of **non-tumor** cells compared to the chimeric antibody at pH physiological pH (pH of the human body). (EX1005, [1139].) This would have provided even more motivation to create the humanized ADCs of claim 1 because humanized cetuximab variant ADCs were more selective in targeting tumor cells than chimeric ADCs. (*Id.*)

Fourth, it was this well-known progression of antibody engineering, from murine to chimeric to humanized antibodies, that compelled the Office to conclude that ADCs using the antibody of claim 1 were obvious over the prior art, since it correctly reasoned that a POSA “would have been motivated” to use the BA03 antibody in place of cetuximab in anti-EGFR ADCs “because the BA03 antibody 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.” (EX1003, 406-07.) The Office further reasoned that a POSA “would also be motivated to use the humanized BA03 antibody in place of cetuximab because BA03 has humanized framework regions, and because the N88 amino acid in the chimeric 225 antibody [cetuximab] is no longer present,” and thus the BA03 humanized antibody “would not cause hypersensitivity reactions in subjects”. (*Id.*, 407.) This reasoning—that the POSA would be motivated to replace cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu—was never even challenged, let alone overcome, by the Patent Owner during prosecution. (*See supra.* at VII.)

2. Petitioner’s grounds are substantially different from Patent Owner’s arguments raised during prosecution

Petitioner’s grounds are substantially different from those overcome by applicants during prosecution. For example, Patent Owner made the following arguments to overcome obviousness rejections:

- (a) the only reference cited in the office Action that discloses a linker used in forming an anti-EGFR ADC, D1 [Tikhomirov], focuses almost exclusively on non-cleavable linkers (*see especially* Abstract, the first sentence in the Summary of the Invention section on page 3),
- (b) D1 provides extensive disclosures and numerous examples of non-cleavable linkers (*see* pages 6, 13, and 14),
- (c) all the ADCs disclosed with experimental data in D1 uses a non-cleavable linker, SMCC, except that Cetux2C9-MMAE uses a cleavable linker, valine-citrulline (*see* Examples I to 4),
- (d) Example 4 of D1 shows that the cleavable linker, Cetux2C9-MMAE, is not favorable compared to a non-cleavable linker because this ADC with the cleavable linker had potentiated toxicity against normal cells (*see* Figure 13 and its description at the end of page 9), and
- (e) D1 states that “a safe anti-EGFR ADC **should** incorporate a strongly antagonistic anti-EGFR antibody

linked to an anti-microtubule payload by a **non-cleavable linker**” (*see* the last sentence of the first paragraph on page 30) (emphasis added).

(EX1004, 200.)

However, none of these points apply to the Wei and Leanna references that Petitioner herein relies upon to show that the prior art taught anti-EGFR ADCs, at least because: (a) Wei and Leanna do not focus exclusively on non-cleavable linkers but have working examples of ADCs using cleavable linkers (EX1005, [1103], [0751]; Ex 1006, Examples 1, 4); (b) while Wei and Leanna do disclose ADCs with non-cleavable linkers, these references also extensively discuss and teach ADCs with cleavable linkers, including the specific vc cleavable linker disclosed as a preferred embodiment and claimed in the '370 patent (EX1001, 5:25-6:65; EX1005, [0742], [1116]; EX1006, 8.); (c) substantial amounts of the experimental data in Wei and Leanna are directed to anti-EGFR ADCs using cleavable linkers (EX1005, Examples 18, 20-23; EX1006, Examples 1-3, 6); (d) nothing in Wei and Leanna would indicate to a POSA that cleavable linkers used in anti-EGFR ADCs are disfavored; and (e) Wei and Leanna teach that a “safe anti-EGFR ADC” can incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a **cleavable linker**, especially since these references have disclosures and claims of pharmaceutical compositions and methods of treatment

using these cleavable linker ADCs (EX1005, [0238]-[0239], [0442], claims 48-55, 58; EX1006, 15, 34-51, claims 8.)

3. The Office was misled in allowing the claims based on Patent Owner’s defective “teaching away” and unexpected results arguments

Moreover, to the extent that Applicant convinced the Office that Tikhomirov “teaches away” from the use of cleavable linkers in the Challenged Claims, this was material error affecting the patentability of the Challenged Claims.

As discussed above, while Figure 13 of Tikhomirov states that an ADC using a cleavable linker “potentiates its toxicity” against both normal cells and cancer cells while an ADC with a non-cleavable linker only “potentiates anti-cancer activity,” (EX1009, 10-11.) Dr. Bournazos points out many serious errors within Figure 13 that do not support Applicant’s “teaching away” arguments. (EX1002, 102-105.)

These include:

- Figure 13 only contains a comparison between Cetux 2C9-MMAE, Cetux 2C9-DM1, certuximab-2C9 (without anti-microtubule toxin payload), hIg-DM1 (non-binding ADC), and hIgG (non-binding and without anti-microtubule toxin payload). (*Id.*, 103.) Thus, there is no head-to-head comparison in Figure 13 between an ADC with a cleavable linker attached to a payload and an ADC with a non-cleavable linker attached to the same payload, such as Cetux 2C9-MMAE (with a cleavable linker) and cetuximab-

SMCC-MMAE (or cetuximab-SMCC-DM1) (with a non-cleavable linker).

(See id.)

- Figure 13 is missing a statistical comparison between the treatment groups and missing important controls, such as payload alone and isotype with vcMMAE, to confirm that there is a biologically meaningful effect. *(See id.)*
Without a statistical comparison and appropriate controls, a POSA would not be able to conclude that cleavable linkers were potentiating toxicity to normal cells.
- In reviewing Figure 13, a POSA would have recognized that the payloads (DM1 vs. MMAE) as tested have different cytotoxic activity against the selected cell lines, and thus, the interpretation of the data to suggest that cleavable linkers are not preferable to non-cleavable linkers is highly suspect. *(See id.)*
- Even assuming that there was a head-to-head comparison between ADCs with the same payload but different linkers, a POSA would have understood that a single observation based on a single anti-EGFR antibody cetuximab, a single anti-microtubule payload DM1, and a single non-cleavable linker (*i.e.*, SMCC) or a single cleavable linker (*i.e.*, valine-citrulline) would be insufficient evidence that all of the other anti-EGFR antibodies, other linkers, and other payloads within the broad scope of the Challenged Claims, which

literally cover any non-cleavable linker and any payload, would show the same or similar results.

- Tikhomirov makes clear that its observation regarding toxicity to normal cells between a non-cleavable linker and a cleavable linker only applies to anti-microtubule payloads (*e.g.*, DM1). (EX1009, 4 (“conjugates of cetuximab with cell-killing agents **other than anti-microtubule toxins, such as saporin**, were found, as expected, to have an attendant and significantly enhanced toxicity toward keratinocytes.”) (emphasis added)). Thus, a POSA would have understood that whole classes of non-anti-microtubule payloads covered by the Challenged Claims would not be expected to raise any toxicity concerns regarding cleavable linkers. (EX1002, 105.)

As a result, Dr. Bournazos concludes that a POSA would not have concluded from Tikhomirov that cleavable linkers posed problems compared to non-cleavable linkers when developing therapeutic ADCs. (*See id.*, 106.) Thus, to the extent the Office agreed with Applicant’s arguments regarding Tikhomirov during prosecution, this was material error allowing the claims to issue.

Moreover, Applicant’s “unexpected results” arguments are also erroneous. Specifically, Applicant argued that the results in Example 6 were unexpected because they purportedly showed that the MYK-3 ADC with a vc cleavable linker

had a lower EC50 value compared to the non-cleavable linker ADCs BA03-MC-MMAE and BA03-MCC-MMAE. (*See, e.g.*, EX1004, 298.)

However, as Dr. Bournazos explains, rather than being unexpected, the results of Example 6 were obvious. (EX1002, 191.) First, at the time of the filing of the '370 patent, there were multiple studies in several different targets, epitopes, cell lines, and antibodies demonstrating that the vc cleavable linker displays very potent efficacy both *in vitro* and *in vivo*, as well as favorable safety and stability, irrespective of the target and mAb used. (*Id.*) Therefore, the finding that MYK-3 demonstrated good efficacy was not unexpected.

Second, it was known in the art that drugs linked by cleavable linkers, such as vcMMAE, are more likely to retain cytotoxic efficacy because drugs conjugated through a cleavable linker are more likely metabolized into their original unconjugated form. (*Id.*, 192; *See* EX1016, 5-6.) For example, in contrast to a non-cleavable linker, an antibody conjugated with MMAE through a cleavable linker releases more potent MMAE drug, which can diffuse through the cell membrane and induce bystander killing of neighboring target cells. (*See* EX1016, 5-6; EX1017, 1-2.)

Third, the finding that neither MC-MMAE nor MCC-MMAE, which used non-cleavable linkers, have any activity was to be fully expected because the prior art taught that "MMAE, a protein-based anti-mitotic drug, is most potent in its native

form and is therefore poorly suited for derivatization with non-cleavable linkers” as shown in Example 6. (EX1002, 193; EX1015, 6.)

Fourth, even assuming *arguendo* that a POSA would consider the data of Example 6 to be unexpected (it was not not), those results were still obtained from an ADC based on a single anti-EGFR antibody BA03, a single cleavable vc linker, and a single cytotoxic agent, and therefore cannot support the patentability of the full scope of the vast genus (*e.g.*, hundreds of thousands) of ADCs covered by the Challenged Claims, as discussed above. (*See supra.* at XII; EX1002, 195.)

Since the purported unexpected result was obtained from a single ADC, MYK-3, a POSA would have understood that such a result cannot be generally applied to other ADC species covered by claim 1. Indeed, the '370 patent itself recognizes that “it is highly complex and unpredictable whether an antibody drug conjugate becomes a safe and effective drug depending on a variety of factors,” and these factors include “characteristics of small molecule drug: potency of the cytotoxicity of the small molecule drug, stability thereof in blood, and toxicity of the *in vivo* metabolites of the ADC containing the small molecule drug,” “characteristics of linker: whether the linker is cleavable or non-cleavable, and stability of the linker in blood,” and “characteristics of monoclonal antibody: specificity of the monoclonal antibody to the target antigen (preferably no cross-reaction with other proteins), stability of the monoclonal antibody, and whether the complex of the

monoclonal antibody and the target can be endocytosed into the cell.” (EX1001, 3:10-37.)

Thus, the purported unexpected results based on a single ADC would not adequately support the full scope of the vast genus of ADCs covered by claim 1. *See In re Peterson*, 315 F.3d 1325, 1329-31 (Fed. Cir. 2003) (data showing improved alloy strength with the addition of 2% rhenium did not evidence unexpected results for the entire claimed range of about 1-3% rhenium); *In re Grasselli*, 713 F.2d 731, 741 (Fed. Cir. 1983) (evidence presented to rebut an obviousness rejection comparing catalysts containing sodium with the prior art held insufficient to rebut the *prima facie* case because experiments limited to sodium were not commensurate in scope with the claims directed to alkali metals).

Finally, Applicant’s unexpected results arguments are based on the assumption that ADCs with cleavable linkers are disfavored, and therefore a POSA would not expect cleavable linker ADCs to be developed. However, this contradicts reality. At the filing of the Challenged Claims, there were only two FDA-approved ADCs—Mylotarg® (anti-CD33) and Adcetris® (anti-CD30)—for use in cancer treatments, yet **both** used cleavable linkers. (*See* EX1010, 3.) Currently, there are fourteen FDA-approved ADCs available, twelve of which use cleavable linkers. (*See id.*, 3-6.)

Thus, because the Patent Owner's unexpected results arguments are both factually and legally flawed, the Office was led into error by Patent Owner to the extent that the Office allowed the Challenged Claims based on these faulty arguments.

Therefore, claim 1 of the '370 patent would have been obvious over Wei and Liu.

Claim 2:

Claim 2 depends from claim 1 and recites that "FR1, FR2, FR3, FR4 of the variable region of the heavy chain of the anti-epidermal growth factor receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 8 to 11."

SEQ ID NOs: 8-11 are the respective amino acid sequences of FR1, FR2, FR3, and FR4 of the variable region of the heavy chain of the BA03 antibody. (EX1001, 18:1-36.)

As discussed above for claim 1, the '370 patent indicates that the "BA03 antibody of the present invention" was described in Liu. (*Id.*, 18:3-6.) Liu discloses that FR1, FR2, FR3, and FR4 of the variable region of the heavy chain of the anti-EGFR receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 8 to 11.

Accordingly, claim 2 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 3:

Claim 3 depends from claim 1 and recites that “FR1, FR2, FR3, FR4 of the variable region of the light chain of the anti-epidermal growth factor receptor antibody respectively comprise sequences as shown in SEQ ID NOs: 15 to 18.”

SEQ ID NOs: 15-18 are the respective amino acid sequences of FR1, FR2, FR3, and FR4 of the variable region of the light chain of the BA03 antibody. (*Id.*, 18:1-36.)

As discussed above for claims 1 and 2, the '370 patent indicates that the “BA03 antibody of the present invention” was described in Liu. (*Id.*, 18:3-6.) Thus, Liu discloses that FR1, FR2, FR3, and FR4 of the variable region of the light chain of the anti-EGFR antibody respectively comprise sequences as shown in SEQ ID NOs: 15 to 18.

Thus, claim 3 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 4:

Claim 4 depends from claim 1 and recites that “the heavy chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human IgG constant region, a human IgM constant region, a human IgA constant region, and a human IgD constant region.”

The BA03 antibody taught by Liu and the Y104D antibody disclosed in Wei have a human IgG1 constant region. (EX1008, [0037]; EX1005, [0558], [0559].)

Thus, claim 4 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 5:

Claim 5 depends from claim 4 and recites that “the IgG is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.”

As stated above for claim 4, the BA03 antibody taught by Liu and the Y104D antibody disclosed in Wei have a human IgG1 constant region. (EX1008, [0037]; EX1005, [0328]).

Thus, claim 5 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 4.

Claim 6:

Claim 6 depends from claim 4 and recites that “the constant region of the heavy chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 3.”

SEQ ID NO: 3 is the amino acid sequence of the constant region of the heavy chain of BA03. As discussed above for claim 1, the '370 patent indicates that the “BA03 antibody of the present invention” was described in Liu. (EX1001, 18:3-6.) Thus, Liu discloses that “the constant region of the heavy chain of the anti-epidermal

growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 3.”

Thus, claim 6 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 4.

Claim 7:

Claim 7 depends from claim 1 and recites, “the light chain of the anti-epidermal growth factor receptor antibody has a constant region selected from the group consisting of a human lambda constant region, and a human kappa constant region.”

Liu teaches that the BA03 antibody has a human kappa light chain constant region. (EX1008, [0037].) Similarly, Wei also teaches that the anti-EGFR antibody can be IgG1 antibody containing a human lambda light chain constant region. (EX1005, [0558], [0559].)

Thus, claim 7 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 8:

Claim 8 depends from claim 7 and recites, “the constant region of the light chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 4.”

SEQ ID NO: 4 is the amino acid sequence of the constant region of the light chain of the BA03 antibody. As discussed above with respect to claim 1, the '370 patent indicates that the "BA03 antibody of the present invention" was described in Liu. (EX1001, 18:3-6.) Thus, Liu discloses that "the constant region of the light chain of the anti-epidermal growth factor receptor antibody comprises an amino acid sequence as shown in SEQ ID NO: 4."

Thus, claim 8 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 7.

Claim 9:

Claim 9 depends from claim 1 and recites:

The antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1, which has a structure as shown in Formula I,

Ab-(L-D)_p Formula I

wherein:

Ab represents the anti-epidermal growth factor receptor antibody;

L represents a cleavable linker;

D represents the cytotoxic agent;

p represents 1-9.

Wei discloses that Y104D-MMAE ADC has an average drug antibody ratio (DAR) of 4, which falls within the recited range of 1-9. (*See* EX1005 at [1103].) Thus, a combination of Wei and Liu teaches an anti-EGFR ADC that can be represented by formula Ab-(L-D)_p, wherein Ab represents the anti-epidermal growth factor receptor antibody, L represents a cleavable linker, D represents the cytotoxic agent, and p represents 1-9.

Thus, claim 9 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 10:

Claim 10 depends from claim 9 and recites that “the cytotoxic agent is selected from the group consisting of chemotherapeutic agents, radioisotopes, antibiotics, enzymes, and biologically active peptides.”

Wei’s Y104D-MMAE ADC contains the cytotoxic agent MMAE, which is a chemotherapeutic agent that interferes with microtubule dynamics and GTP hydrolysis. (*See* EX1005, [0434].)

Thus, claim 10 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 9.

Claim 11:

Claim 11 depends from claim 10 and recites that “the cytotoxic agent is selected from the group consisting of Monomethyl auristatin E (MMAE),

Monomethyl auristatin F (MMAF), maytansinoid alkaloids, Calicheamicin, duocarmycin MGBA, doxorubicin, ricin, diphtheria toxin, I131, and tumor necrosis factors.”

As discussed above, Wei’s Y104D-MMAE ADC contains the cytotoxic agent MMAE.

Thus, claim 11 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 10.

Claim 12:

Claim 12 depends from claim 9 and recites that “the linker is selected from the group consisting of valine-citrulline (val-cit), alanine-phenylalanine (ala-phe), N-succinimidyl 4-(2-pyridylthio)valerate (SPP), and 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB).”

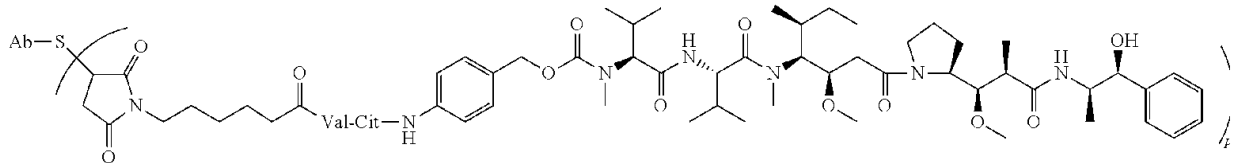
Wei’s Y104D-MMAE ADC contains the val-cit cleavable linker. (*See id.*, [1103].)

Thus, claim 12 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 9.

Claim 13:

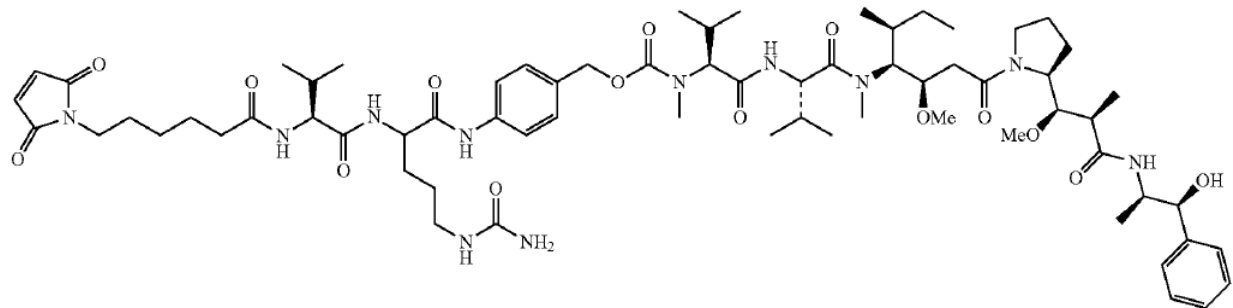
Claim 13 depends from claim 9 and recites:

The antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 9, which is:



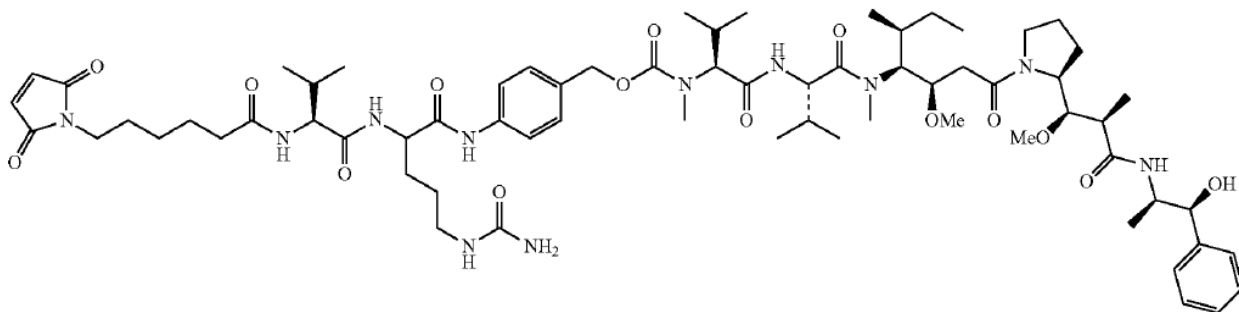
wherein Ab represents the anti-epidermal growth factor receptor antibody, p is 1-8.

Wei discloses the same chemical structure of the linker-drug payload of claim 13.



(See *id.*, [0740], [0742], [1102], [1103].)

Claim 40 of Wei also states:



Moreover, as discussed above, Wei discloses that Y104D-MMAE ADC has an average DAR of 4, which falls within the recited range of 1-9. (*See id.*, [1103].)

As a result, claim 13 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 9.

Claim 14:

Claim 14 depends from claim 9 and recites that “the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB).”

As stated above, Wei discloses Y104D-MMAE ADC, where Y104D “was conjugated to MMAE via the cleavable linker maleimidocaproyl-valine-citrulline-p-aminobenzyl linker (maleimidocaproyl-vcPAB-MMAE) as described in Francisco *et al.* Blood 102:1458-1465 (2003).” (*Id.*)

Thus, claim 14 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 9.

Claim 15:

Claim 15 depends from claim 1 and recites “[a] composition, which comprises the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1, optionally, further comprises at least one pharmaceutically acceptable carrier, diluent or excipient.”

Wei discloses that its ADCs can be formulated into “pharmaceutical compositions” comprising “a pharmaceutically acceptable carrier or excipient.” (*Id.*, [0238], [0861]-[0875].)

Accordingly, claim 15 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 16:

Claim 16 depends from claim 1 and recites “[a] method for treatment of a disease associated with epidermal growth factor receptor (EGFR), comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1.”

Wei discloses that its anti-EGFR ADCs “can be used for targeted delivery of cytotoxic or cytostatic agents, *i.e.*, drugs to kill or inhibit tumor cells expressing EGFR in the treatment of cancer,” and “such conjugates exhibit selectivity to tumor cells that are desired to be eliminated over non-diseased cells, and thereby do not result in unacceptable levels of toxicity to normal cells. Therefore, the conjugates achieve maximal efficacy with minimal toxicity and reduced side effects.” (*Id.*, [0666].) Wei further discloses that a pharmaceutical composition comprising its anti-EGFR ADCs can be used in “methods of treating a condition responsive to treatment with an anti-EGFR antibody in a subject, including administering to the

subject a pharmaceutically effective amount of a pharmaceutical composition provided herein,” including “conditions that are responsive to treatment with an anti-EGFR antibody include a tumor, such as a solid tumor, cancer or metastasis, particularly when the tumor expresses EGFR.” (*Id.*, [0239].)

Thus, claim 16 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 17:

Claim 17 depends from claim 16 and recites that “the disease associated with epidermal growth factor receptor (EGFR) is a tumor associated with overexpression of EGFR.”

As discussed above, Wei discloses that its ADCs can be used to treat a solid tumor having overexpression of EGFR. (*Id.*, [0239], [0442].)

Thus, claim 17 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 18:

Claim 18 depends from claim 1 and recites “[a] method for inhibiting tumor angiogenesis, delaying tumor progression, inhibiting tumor growth, or inhibiting tumor cell proliferation, comprising: administering to a subject in need a therapeutically effective amount of the antibody-drug conjugate or the pharmaceutically acceptable salt thereof according to claim 1.”

Wei discloses methods for treating a subject comprising administering a therapeutically effective amount of an anti-EGFR ADC, wherein the subject has a disorder, such as a tumor, a cancerous condition, a precancerous condition, and any condition related to or resulting from hyperproliferative cell growth to alleviate the symptoms and/or tumor progression. (*See id*; *see also id.*, [0441]-[458], [1086]-[1127], claims 48 and 58.) Wei also states that treating “means that the subject’s symptoms are partially or totally alleviated, or remain static following treatment,” and prevention of worsening of symptoms or progression of a cancer. (*Id.*, [0443].)

Thus, claim 18 is obvious for the reasons stated herein and for the reasons set forth above with respect to claim 1.

Claim 19:

Claim 19 depends from claim 18 and recites that “the tumor is selected from colon cancer, rectal cancer, head and neck cancer, lung cancer, ovarian cancer, cervical cancer, bladder cancer, esophageal cancer, breast cancer, renal cancer, prostate cancer, gastric cancer, pancreatic cancer and brain glioma.”

Wei discloses that “[ex]emplary tumors that can be treated” by its ADC inventions “are those that overexpress EGFR. Some tumors observed to overexpress EGFR that can be treated include, but are not limited to, colorectal and head and neck tumors, especially squamous cell carcinoma of the head and neck, brain tumors

such as glioblastomas, and tumors of the lung, breast, pancreas, esophagus, bladder, kidney, ovary, cervix, and prostate.” (*Id.*, [0903].)

Thus, claim 19 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1 and 19.

Claim 20:

Claim 20 depends from claim 17, which depends from claim 16, and recites, that for the claimed method of treatment of administering a therapeutically effective amount of the antibody-drug conjugate, “the tumor is a tumor with KRAS gene mutation.”

Wei discloses that the Y104D-MMAE and huY104D-MMAE were tested in breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors, and that these ADCs “exhibit a strong anti-tumor response in KRAS mutated, EGFR+ tumor model” and that “[t]he anti-tumor response of each of the tested antibodies achieves tumor growth regression.” (*Id.*, [1116]-[1127].)

Thus, claim 20 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1, 16, and 17.

Claim 21:

Claim 21 depends from claim 17, which depends from claim 16, and recites, that for the claimed method of treatment of administering a therapeutically effective

amount of the antibody-drug conjugate, “the tumor is a tumor with BRAF gene mutation.”

As discussed above, Wei discloses that the Y104D-MMAE and huY104D-MMAE ADCs were tested in breast cancer xenograft models (MDA MB 231M TNBC) and exhibited a strong anti-tumor response and achieved tumor growth regression. As of the earliest possible effective filing date of the Challenged Claims, it was known that the MDA MB 231M TNBC tumors tested with Wei’s ADCs are BRAF-mutated tumors. (EX1018, 939, 942 (“MDA-MB-231 (KRASG13D and BRAF-G464V mutations”).))

Thus, claim 21 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1, 16, and 17.

Claim 22:

Claim 22 depends from claim 19, which depends from claim 18, and recites, that for the claimed method of treatment of administering a therapeutically effective amount of the antibody-drug conjugate, “the tumor is a tumor with KRAS gene mutation.”

As discussed above, Wei discloses that the Y104D-MMAE and huY104D-MMAE were tested in breast cancer xenograft models (MDA MB 231M TNBC) of KRAS-mutated tumors. (EX1005, [1127].)

Thus, claim 22 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1, 18, and 19.

Claim 23:

Claim 23 depends from claim 19, which depends from claim 18, and recites, that for the claimed method of treatment of administering a therapeutically effective amount of the antibody-drug conjugate, “the tumor is a tumor with BRAF gene mutation.”

As discussed above, it was known that the MDA MB 231M TNBC tumors tested with Wei’s Y104D-MMAE and huY104D-MMAE are BRAF-mutated tumors. (*See* EX1018, 939, 942.)

Thus, claim 23 is obvious for the reasons stated herein and for the reasons set forth above with respect to claims 1, 18, and 19.

B. Ground 2: There is a reasonable likelihood that at least Claims 1-23 are obvious over Leanna and Liu in view of Wei

Claim 1:

The obviousness of claim 1 over Leanna and Liu in view of Wei is demonstrated in the following claim chart.

Claim 1 of the '370 patent	Prior Art
1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody	Leanna discloses: An anti-EGFR antibody-drug conjugate, including Antibody 1-vc-MMAE ADC that comprises a humanized anti-EGFR antibody (<i>i.e.</i> , Antibody 1) covalently

<p>covalently linked to a cytotoxic agent via a cleavable linker,</p> <p>wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain,</p> <p>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.</p>	<p>linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (EX1006, 34).</p> <p>Liu discloses: A humanized anti-EGFR antibody BA03 comprising a heavy chain and a light chain (EX1008, Examples 1-5, [00141]-[0146], Tables 1-3), wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7 (<i>id.</i>, [0085], [0123], [0124]), and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14 (<i>id.</i>, [0108], [0123], [0124]).</p> <p>Wei provides further motivation to combine the anti-EGFR ADCs of Leanna with the Liu, which discloses the BA03 antibody claimed in the Challenged Claims.</p> <p>Wei discloses the Y104D-Mc-vcPAB-MMAE ADC, containing a modified cetuximab antibody (<i>i.e.</i>, Y104D) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (EX1005, [0742], [1092]-[1141]). In view of Wei, a POSA would have been motivated to combine the humanized ADC of Leanna with a modified (humanized) cetuximab antibody – BA03 – as taught by Liu, to arrive at the Challenged Claims.</p>
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As shown above, the combination of Leanna and Liu in view of Wei teaches each and every feature of claim 1.

Leanna discloses ADCs comprising an anti-EGFR antibody and a cytotoxic agent, such as MMAE or MMAF. (EX1006, 1, 5, 6.) Leanna discloses that MMAE is conjugated to the antibody via a cleavable valine-citrulline (vc) linker. (*Id.*, 8.) Leanna specifically discloses an Antibody 1-vc-MMAE ADC. (*Id.*, 26.) Antibody 1 is a humanized IgG1 isotype anti-EGFR antibody previously disclosed in WO2011/041319 and US20110076232. (*Id.*)

As discussed above, Liu discloses a humanized anti-EGFR antibody called BA03—an IgG1 isotype anti-EGFR antibody, which is the same BA03 antibody used in the '370 patent to generate its preferred embodiment MYK-3 ADC—and is a humanized cetuximab antibody. (EX1008, [0060]; EX1001, 18:3-6.)

A POSA clearly would have been motivated to combine the teachings of Leanna and Liu in view of Wei to arrive at claim 1.

First, Leanna discloses anti-EGFR ADCs with the cleavable linker vc—covered by claim 1 and disclosed as a preferred embodiment of the '370 patent. (EX1006, 50-60.) At the time of the invention, there were only two FDA-approved anti-EGFR antibodies for therapeutic use, one of which was cetuximab. (EX1014.)

Second, as discussed above, Liu discloses and claims a humanized version of cetuximab—BA03—and states that BA03 has numerous benefits over cetuximab,

including higher ADCC activity and significantly lower immunogenicity. (EX1008, [0141-0160].)

Third, both Leanna and Liu disclose humanized anti-EGFR antibodies, which a POSA would recognize as having lower immunogenicity compared to murine and chimeric antibodies. (*Id.*; EX1006, 26, 34.) Moreover, Wei discloses a humanized cetuximab variant huY104D as part of the huY204D-MMAE ADC. (EX1005, Example 20.)

Fourth, Wei's Y104D-MMAE ADC contains the cetuximab variant Y104D attached to the MMAE cytotoxic payload with a vc cleavable linker, the same vc-MMAE linker payload disclosed as preferred embodiments in the '370 patent and covered by the Challenged Claims. (*Id.*, [0740], [0742], [1103].) As Dr. Bournazos explains, POSAs would have recognized that if ADCs with cleavable linkers were being made in the prior art using a modified version of the chimeric version of M225 (cetuximab variant Y104D, as shown by Wei), they would have been strongly motivated to create ADCs using the humanized version of M225 (BA03), because humanized antibodies had several advantages over chimeric antibodies, including lower immunogenicity, which Liu specifically discloses in detail. (EX1002, 188.)

Fifth, as discussed above, a POSA would have recognized the standard progression of antibody engineering, from murine to chimeric to humanized antibodies, which was the primary basis for the Office to conclude that ADCs using

the claimed antibody of claim 1 were obvious over the prior art. (*See supra.* at VI.) The Office was correct when it found that a POSA “would have been motivated” to replace the BA03 antibody in place of cetuximab ADCs “because the BA03 antibody 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.” (EX1003, 406-07.) As noted above, this reasoning—that the POSA would be motivated to replace cetuximab in prior-art ADC references with the humanized cetuximab antibody of Liu—was never challenged by Patent Owner during prosecution. (*See supra.* at VII.)

Moreover, for all the reasons stated above with respect to Ground 1, Petitioner’s grounds here are substantially different from Patent Owner’s arguments raised during prosecution, and the Office was led into material error by allowing the claims based on Patent Owner’s “teaching away” and unexpected results arguments. (*See supra* at XIII.A.3.)

Therefore, claim 1 of the ’370 patent would have been obvious over Leanna and Liu in view of Wei.

Claim 2:

For the reasons discussed above with respect to claim 1 of Ground 2 and claim 2 of Ground 1, claim 2 is also obvious.

Claim 3:

For the reasons discussed above with respect to claim 1 of Ground 2 and claim 3 of Ground 1, claim 3 is also obvious.

Claim 4:

For the reasons discussed above with respect to claim 1 of Ground 2 and claim 4 of Ground 1, claim 4 is also obvious.

Claim 5:

Antibody 1 taught by Leanna has a human IgG1 constant region. (*See* EX1006, 26.) Thus, for this reason, and the reasons discussed above with respect to claims 1 and 4 of Ground 2 and claim 5 of Ground 1, claim 5 is also obvious.

Claim 6:

For the reasons discussed above with respect to claims 1 and 4 of Ground 2 and claim 6 of Ground 1, claim 6 is also obvious.

Claim 7:

For the reasons discussed above with respect to claim 1 of Ground 2 and claim 7 of Ground 1, claim 7 is also obvious.

Claim 8:

For the reasons discussed above with respect to claims 1 and 7 of Ground 2 and claim 8 of Ground 1, claim 8 is also obvious.

Claim 9:

Leanna teaches the Antibody 1-vc-MMAE ADC that has an average DAR of 3.85, which falls within the recited range of 1-9. (EX1006, 34, 51, FIG. 1.) Thus, for this reason, and the reasons discussed above with respect to claim 1 of Ground 2 and claim 9 of Ground 1, claim 9 is also obvious.

Claim 10:

Leanna teaches the Antibody 1-vc-MMAE ADC containing the cytotoxic agent MMAE that is a chemotherapeutic agent. (*Id.*, 30-31.) Thus, for this reason, and the reasons discussed above with respect to claims 1 and 9 of Ground 2 and claim 10 of Ground 1, claim 10 is also obvious.

Claim 11:

For the reasons discussed above with respect to claims 1, 9, and 10 of Ground 2 and claim 11 of Ground 1, claim 11 is also obvious.

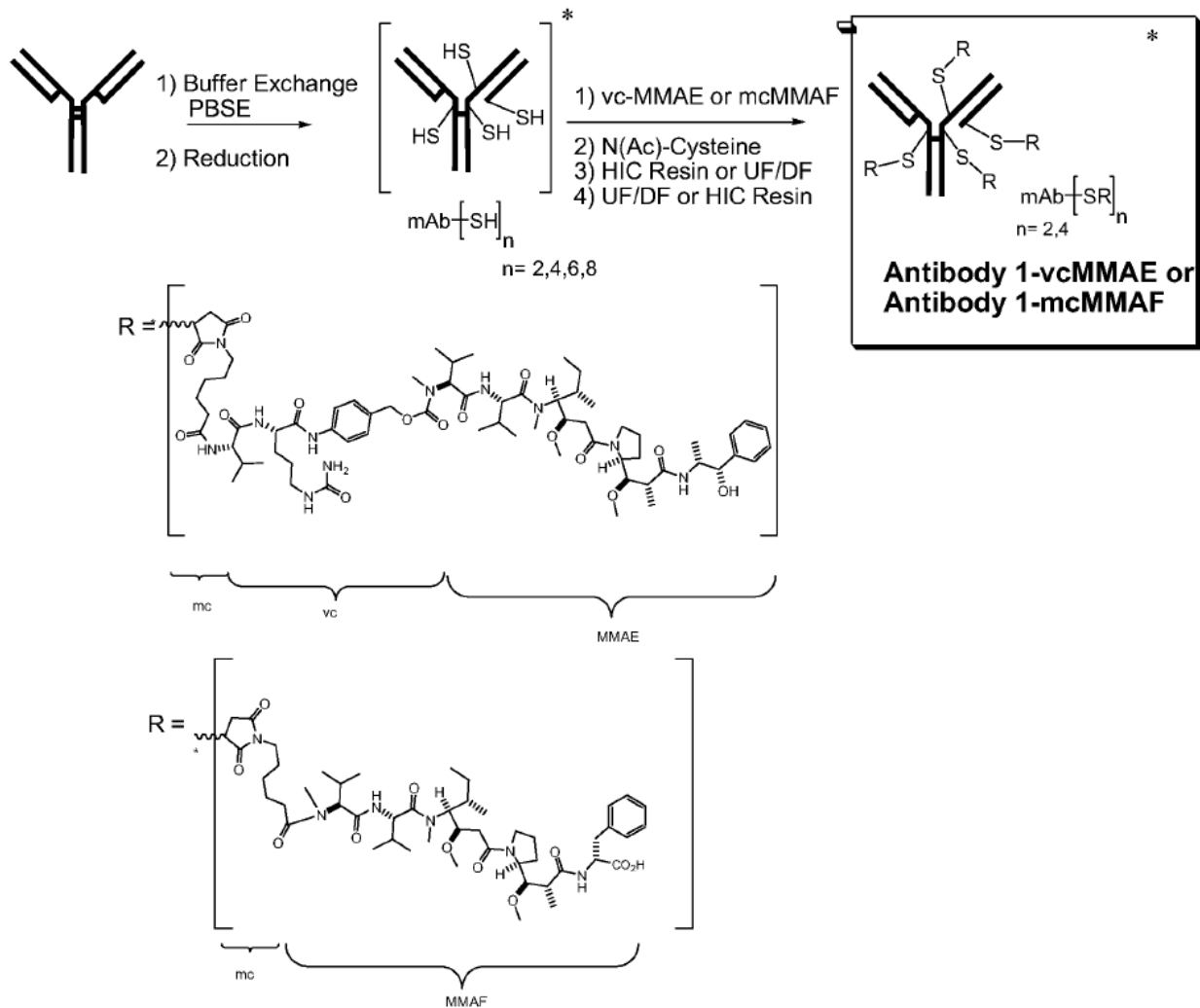
Claim 12:

Leanna teaches the Antibody 1-vc-MMAE ADC containing the cleavable val-cit linker. (*Id.*, 34, 51, FIG. 1.) Thus, for this reason, and the reasons discussed above with respect to claims 1 and 9 of Ground 2 and claim 12 of Ground 1, claim 12 is also obvious.

Claim 13:

Leanna teaches the Antibody 1-vc-MMAE ADC (more specifically, Antibody 1-MC-vc-PAB-MMAE) as depicted in Leanna Figure 1. The chemical structure of

the linker-drug is identical to the recited chemical structure of claim 13. Moreover, Leanna discloses that the average DAR for Antibody 1-vcMMAE was 3.85. (*Id.*, 51.)



Thus, for this reason, and the reasons discussed above with respect to claims 1 and 9 of Ground 2 and claim 13 of Ground 1, claim 13 is also obvious.

Claim 14:

Leanna teaches the Antibody 1-MC-vc-PAB-MMAE ADC. (EX1006, FIG. 1.) Thus, for this reason, and the reasons discussed above with respect to claims 1 and 9 of Ground 2 and claim 14 of Ground 1, claim 14 is also obvious.

Claim 15:

Leanna teaches pharmaceutical compositions containing the active ingredient (ADC) can further include a pharmaceutically acceptable excipient, carrier, buffer, stabilizer, or other materials well known to those skilled in the art. (*Id.*, 37-38.) Thus, for this reason, and the reasons discussed above with respect to claim 1 of Ground 2 and claim 15 of Ground 1, claim 15 is also obvious.

Claim 16:

Leanna discloses methods for treating a subject comprising administering a therapeutically effective amount of an anti-EGFR ADC, wherein the subject has a disorder, such as a tumor, a cancerous condition, a precancerous condition, and any condition related to or resulting from hyperproliferative cell growth. (*Id.*, 36.) Thus, for this reason, and the reasons discussed above with respect to claim 1 of Ground 2 and claim 16 of Ground 1, claim 16 is also obvious.

Claim 17:

Leanna discloses ADCs used to treat a solid tumor having overexpression of EGFR and to treat a subject having an advanced solid tumor likely to overexpress EGFR. (*Id.*, 15, 35-36.) Thus, for this reason, and the reasons discussed above with

respect to claims 1 and 16 of Ground 2 and claim 17 of Ground 1, claim 17 is also obvious.

Claim 18:

Leanna discloses methods for treating a subject comprising administering a therapeutically effective amount of an anti-EGFR ADC, wherein the subject has a condition from hyperproliferative cell growth to alleviate tumor progression. (*Id.*, 34-36.) Thus, for this reason, and the reasons discussed above with respect to claim 1 of Ground 2 and claim 18 of Ground 1, claim 18 is also obvious.

Claim 19:

Leanna teaches that the treated cancer of the claimed method is selected from the group consisting of non-small cell lung cancer, lung cancer, colon cancer, head and neck cancer, breast cancer, squamous cell tumors, anal cancer, skin cancer, and vulvar cancer. (*Id.*, 15, 35-36.) Thus, for this reason, and the reasons discussed above with respect to claims 1 and 18 of Ground 2 and claim 19 of Ground 1, claim 19 is also obvious.

Claim 20:

For the reasons discussed above with respect to claims 1, 16, and 17 of Ground 2 and claim 20 of Ground 1, Claim 20 is obvious.

Claim 21:

For the reasons discussed above with respect to claims 1, 16, and 17 of Ground 2 and claim 21 of Ground 1, Claim 21 is obvious.

Claim 22:

For the reasons discussed above with respect to claims 1, 18, and 19 of Ground 2 and claim 22 of Ground 1, Claim 22 is obvious.

Claim 23:

For the reasons discussed above with respect to claims 1, 18, and 19 of Ground 2 and claim 23 of Ground 1, Claim 23 is obvious.

XIV. CONCLUSION

Based on the foregoing, Petitioner requests institution of IPR for claims 1-23 of the '370 patent based on the grounds specified in the Petition.

Dated: March 3, 2025

By: /Joe Chen/
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Counsel for Petitioners

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of Claims 1–23 of U.S. Patent No. 10,792,370 contains, as measured by the word-processing system used to prepare this paper, 13,952 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: March 3, 2025

By: /Joe Chen/

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Reg. No. 70,066

Counsel for Petitioners

CERTIFICATE OF SERVICE

I hereby certify that on March 3, 2025, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of Claims 1–23 of U.S. Patent No. 10,792,370 to be served by Federal Express on the Patent Owner at the following correspondence address of record as listed on the USPTO’s Patent Center website:

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