

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CSPC MEGALITH BIOPHARMACEUTICAL CO., LTD.,

Petitioner,

v.

SHANGHAI MIRACOGEN INC,

Patent Owner.

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Case No. IPR2025-00685

Patent No. 10,792,370

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

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

1. I have been retained by counsel for CSPC Megalith Biopharmaceutical Co., Ltd. (“Petitioner”). I understand that Petitioner is submitting a petition for inter partes review (“IPR”) of U.S. Patent No. 10,792,370 (“the ’370 patent,” attached as EX1001), which is assigned to Shanghai Miracogen Inc. (“Patent Owner”). It is my understanding that Petitioner is requesting that the United States Patent and Trademark Office (“USPTO”) cancel all claims of the ’370 patent as unpatentable. I submit this expert declaration in support of Petitioner’s IPR petition for the ’370 patent. I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

## **I. QUALIFICATIONS**

2. I received my BS in Genetics and Immunology in 2005 from the University of Aberdeen, Aberdeen, United Kingdom. I received my MS in Life Science in 2006 from the University of Edinburgh, Edinburgh, United Kingdom. I received my Ph.D. in Immunology in 2010 from the University of Edinburgh. I did my postdoctoral work at the Rockefeller University, New York City, USA, in the division of virology and antibody therapeutics.

3. I am currently employed by the Rockefeller University, where I am a Research Associate Professor. I was also a member of the American Association of Immunologists, New York Academy of Science, American Heart Association, and

WHO Expert Group for the development of preclinical models of COVID-19 disease.

4. I have over 15 years of research experience in the study of antibodies and FcR function in health and disease. My studies have demonstrated a critical role for IgG Fc-Fc $\gamma$ R interactions in the protective activity of antibodies against bacterial and viral pathogens, leading to the clinical development of Fc-optimized antibodies with improved effector function. Additionally, my research on the mechanisms by which antibodies contribute to dengue disease pathogenesis identified specific glycan changes at the IgG Fc domain as robust predictive biomarkers for symptomatic dengue disease. In addition, I have determined the *in vivo* immunological mechanisms by which Fc-Fc $\gamma$ R interactions drive dengue pathogenesis.

5. I have served as a scientific reviewer for many peer-reviewed scientific journals, including PLoS One, Journal of Experimental Medicine, Lung, Cell Reports, Cell Host & Microbe, International Archives of Allergy and Immunology, European Journal of Immunology, The Journal of Immunology, Nature Microbiology, Nature Communications, Frontiers in Immunology, Immunity, Cell Reports Medicine, iScience, EbioMedicine, and Scientific Reports.

6. I have also served as a grant reviewer for the National Cancer Institute, the National Institute on Aging, the Medical Research Council (MRC) (United

Kingdom), Deutsche Forschung Gemeinschaft (DFG) (Germany), and the Israeli Ministry of Innovation, Science and Technology (Israel).

7. Since 2012, I have been an invited speaker at various scientific meetings, including NIAID Workshop on Clinical Development of Broadly Neutralizing Antibodies (bnAbs) for HIV-1, 2022; EMBO Workshop on Antibodies and complement: Effector functions, therapies and technologies, 2016 Girona, Spain; PEGS Europe: Protein & Antibody Engineering Summit, 2017, Lisbon, Portugal; 2<sup>nd</sup> Next-Generation Antibodies and Protein Analysis 2017, Ghent, Belgium; NIAID Workshop on Mechanisms of Fc-Dependent, Antibody-Mediated Killing, Rockville, MD; Keystone Biobetters and Next-Generation Biologics: Innovative Strategies for Optimally Effective Therapies 2017, Snowbird, UT; and AIDS vaccine 2012 conference, Boston, MA.

8. Additional information regarding my education, experience, publications, awards and honors, patents, publications, and presentations is detailed in my curriculum vitae (**Appendix A**).

9. A list of the materials relied upon, in addition to my experience, education, and training, to provide the opinions contained in this declaration is listed below in Section III.

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

11. I have reviewed the '370 patent (EX1001) and relevant portions of its prosecution history at the USPTO (EXS1002, 1003). Specifically, I have reviewed the '370 patent and its prosecution history in relation to the asserted prior art and arguments at issue in the present IPR.

12. Based on my experience described above and contained in my CV, I have an established understanding of the relevant field in the relevant timeframe and the knowledge that would have been known by a person of ordinary skill in the art, as defined above and during the relevant time frame (on or before February 17, 2015 – the claimed priority date of the '370 patent).

## **II. SUMMARY OF OPINIONS**

13. I have been asked to consider whether claims 1-23 (the “Challenged Claims”) of the '370 patent are obvious in view of the references discussed in Section VII. The Challenged Claims are directed to 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.

14. In my opinion, claims 1-23 would have been obvious over a combination of U.S. Patent Application Publication No. 2015/071923 (“Wei” (EX1005)) and Chinese Patent Application Publication No. CN103772504 (“Liu (EX1007)).

15. In my opinion, claims 1-23 would have been obvious over a combination of International Patent Application Publication No. WO 2014/152199 (“Leanna” (EX1006)) and Liu in view of Wei.

16. Finally, there are no apparent secondary considerations supporting non-obviousness of the claims. I reserve the right to address any secondary considerations put forth by Patent Owner (e.g., unexpected results) in any later response to this declaration or the petition it accompanies.

### **III. MATERIALS RELIED UPON**

17. I have reviewed the Petition and supporting evidence. I have also reviewed all Challenged Claims of the '370 patent (claims 1-23), as well as the specification of the '370 patent and relevant parts of its file history, with particular attention to rejections by the Patent Examiner and the responses on behalf of the alleged inventors. I have examined the prior art references asserted against the '370

patent in the Petition. My opinions are based on my own knowledge, experience, and education and with further reference to the exhibits cited herein. I will use the exhibit numbers listed on the “Table of Exhibits” on pages v-vi of the Petition (Paper 1), which I have included for ease of reference below:

**LIST OF EXHIBITS**

<b>Exhibit</b>	<b>Description</b>
EX1001	U.S. Patent No. 10,792,370 to Hu (“the ’370 patent”)
EX1003	File History of U.S. Patent No. 10,792,370 Part 1
EX1004	File History of U.S. Patent No. 10,792,370 Part 2
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”)
EX1008	Certified English Translation of Chinese Patent Application Publication No. CN103772504 (“Liu”)
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)
EX1016	Kovtun & Goldmacher, <i>Cancer Lett.</i> , 255(2):232-40 (2007)
EX1017	Okeley, et al., <i>Clin Cancer Res.</i> , 16(3):888-97 (2010)
EX1018	Nagaria, et al., <i>Neoplasia</i> , 15(8):939-51 (2013)
EX1019	Perez, et al., <i>Drug Discovery Today</i> , 19(7): 869-881 (2014)

<b>Exhibit</b>	<b>Description</b>
EX1020	Alley, et al., <i>Curr Opin Chem Biol.</i> , 14(4):529-37 (2010)
EX1021	Younes, et al., <i>Nat Rev Drug Discov.</i> , 11(1):19-20 (2012)
EX1022	Hwang & Foote, <i>Methods.</i> , 36(1):3-10 (2005)
EX1023	Herbst & Shin, <i>Cancer.</i> , 94(5):1593-611 (2002)
EX1024	Martinelli, et al., <i>Clin Exp Immunol.</i> , 158(1):1-9 (2009)
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)
EX1028	Afar, et al., <i>Mol Cancer Ther.</i> , 3(8):921-32 (2004)
EX1029	Doronina, et al., <i>Bioconjug Chem.</i> , 17(1):114-24 (2006)
EX1030	Chinese Patent Application No. 201510085038.8 (“the ’038.8 Provisional”)
EX1031	De Goeij, et al., <i>Mol Cancer Ther.</i> , 14(5):1130-40 (2015)
EX1032	U.S. Patent No. 10,792,370 to Reilly, et al.
EX1033	Khan, et al., <i>World J Gastroenterol.</i> , 20(11):2979-94 (2014)
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”)

#### **IV. THE UNDERSTANDING APPLIED TO MY ANALYSIS**

18. In preparing and forming my opinions set forth in this declaration, I have been informed by counsel of relevant legal principles. I applied my understanding of those principles in forming my opinions. My understanding of those principles is summarized below. In performing my analysis and reaching my opinions and conclusions, I have been informed of and have been advised to apply

various legal principles relating to unpatentability, which I set forth herein. In setting forth these legal standards, it is not my intention to testify about the law. I only provide my understanding of the law, as explained to me by counsel, as a context for the opinions and conclusions I am providing.

19. I understand that my opinions regarding unpatentability are presented from the viewpoint of a person of ordinary skill in the art (“POSA” or “skilled artisan”) in the field of technology of the patent as of the patent’s priority date. In this declaration, my opinions are premised on the perspective of a POSA at the time of the earliest claimed priority date for the ’370 patent, which I have been informed for this proceeding is February 17, 2015. (EX1001 at 1.) To the extent Patent Owner asserts that the claims of the ’370 patent are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

20. I understand that in an IPR proceeding, claims should be construed as having their ordinary and customary meaning as understood by a POSA at the time of the invention. I understand that claims should be read in the context of the claim language of which they are a part. I further understand that the specification and file history can also inform the scope of the claims. If, after a review of this evidence, the construction is not apparent, I understand that extrinsic evidence, such as dictionary definitions, treatises, and trade journals, may be consulted to discern the meaning of a term. For terms where no construction is necessary, I have simply read

the terms according to their ordinary and customary meaning. My understandings herein are made in light of how a POSA in or around 2015 would view the ordinary and customary meaning of the claim terms. I reserve the right to supplement my Declaration should any claim terms be given different constructions.

21. I understand that a claim is anticipated if a single prior art reference discloses each and every limitation of the claimed invention. I understand that a limitation can be expressly disclosed by the reference or be inherent. I further understand that for a feature to be inherently disclosed, a POSA would understand the inherent feature would necessarily and inevitably be present when the teaching of the reference is practiced. That is, I understand that if a feature is not necessarily and inevitably present, it is not inherently disclosed.

22. I understand that a patent claim may be unpatentable for obviousness if the difference between the claimed subject matter and the prior art is such that the subject matter as a whole would have been obvious at the time the invention was made to a POSA. I understand that a finding of obviousness requires a determination of: (1) the scope and content of the prior art; (2) the difference(s) between the claimed invention and the prior art; and (3) the level of skill of the ordinary artisan in the pertinent art. I understand this analysis looks at whether the differences are such that the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

23. It is my understanding from counsel that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. It is my understanding that any need or problem known in the field of endeavor at the time of invention or addressed by the patent can provide a reason for combining prior art elements to arrive at the claimed subject matter. I understand that only a reasonable expectation of success is necessary to show obviousness.

24. My understanding is that the obviousness inquiry is not limited to just the prior art references being applied, but includes the knowledge and understanding of one of ordinary skill in the art. However, I understand that merely demonstrating that each element, independently, was known in the prior art is, by itself, insufficient to establish a claim was obvious. My understanding is that the test for obviousness is not whether the features of one reference can be incorporated into the structure of another reference, but rather what the combined teachings would have suggested to those of ordinary skill in the art. I further understand that a party seeking to invalidate a patent must show a person of ordinary skill in the art would have been motivated to combine the teachings of the prior art references to achieve the claimed invention.

25. I understand that a combination of old, familiar, or known elements used according to known methods is likely to be obvious when it does no more than yield predictable results. Predictable variations of a work from one field are likely to be obvious, even if the variation is in another field. For example, where a technique has been used to improve a device, use of the same technique to improve similar devices is a predictable variation and likely obvious. Likewise, if the use of prior art for improvements is simply done according to the prior art's established functions, a POSA has simply implemented a predictable variation. If there existed at the time of invention a known problem for which there was an obvious solution, a patent claim encompassing that solution is not patentable.

26. I further understand that any obviousness analysis must consider objective evidence of non-obviousness, where such evidence is present. I understand that objective evidence of non-obviousness includes (1) copying, (2) long-felt but unsolved need, (3) failure of others, (4) commercial success of the invention, (5) unexpected results created by the claimed invention, (6) unexpected properties of the claimed invention, (7) licenses showing industry respect for the invention, (8) skepticism of skilled artisans before the invention, (9) recognition of invention's advancement, and (10) contemporaneous invention by others or absence thereof. In general, there must be a connection between any of the factors and the claimed invention. For instance, the "commercial success" of a product practicing the

claimed invention is relevant to the obviousness analysis only if the commercial success is attributable to advantages from the use of the invention that were not available to the purchasing public before the invention was made.

27. I understand that a claim in a granted patent must be sufficiently supported by the original disclosure of the granted patent, read in the context of what one of ordinary skill in the art would have known at the time of the claimed invention. I understand that the basic inquiry for written description is whether the specification provides sufficient information for a skilled artisan to recognize that the named inventors possessed the full scope of the claimed invention. To satisfy the written description requirement for such claims, I understand that the specification must disclose either a representative number of species falling within the scope of the claimed genus or structural features common to the members of the genus such that one skilled in the art can “visualize or recognize” the members of the claimed genus. I understand that a disclosure to a species may be insufficient to demonstrate possession of a larger claimed genus. However, I understand the same disclosure in a prior art reference may be sufficient to render a claim to that genus obvious.

28. I also understand that claims must be enabled by the original disclosure of the patent. For the claims to be enabled, the information contained in the disclosure must be sufficient to inform those skilled in the relevant art how to make

and use the claimed invention without undue experimentation. I understand that the enablement requirement is separate and distinct from the written description requirement.

29. I understand that to establish priority to a previously filed patent application, the earlier application must describe the later-claimed invention in sufficient detail so that a POSA can clearly conclude that the inventor invented and had possession of each element of the claimed invention as of the earlier filing date being sought. I understand that this requires that the earlier disclosure must describe and enable every limitation of the later-claimed invention. I understand that a showing of possession of a single species may be insufficient to demonstrate that the inventor had possession of the larger genus. I understand that to establish possession of the larger genus may require a showing that, as of the earlier desired filing date, the inventor disclosed use of multiple species of the genus and/or that the inventor understood that each species of the genus would create the same result, i.e., could be substituted without modification.

30. Although the following analysis cites to particular pages, lines, paragraphs, or figures of many of the references discussed, these citations are intended to assist in understanding the various bases of my conclusions, and prior art teachings used to reach them. These citations are not intended to be an exhaustive recitation of every page, line number, or paragraph in which these teachings may be

found. Similar teachings or disclosures may be found at other pages, lines, figures, or paragraphs, as well as in other references, and it is to be understood that my opinions and statements are made in view of all of the references and teachings I have reviewed.

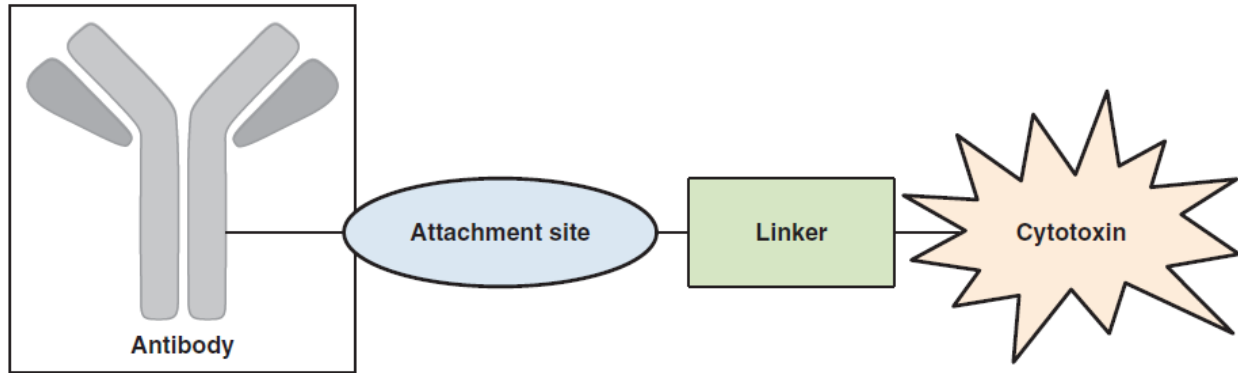
## **V. CLAIM CONSTRUCTION**

31. I understand that claims of a patent subject to IPR should be construed in accordance with the plain and ordinary meaning of such claim as understood by a POSA in view of the specification of the patent and the prosecution history pertaining to the patent.

## **VI. BACKGROUND AND STATE OF THE ART**

32. The '370 patent relates to antibody-drug conjugates (“ADCs”). In this Section, I present a brief overview of certain aspects of ADCs, such as anti-EGFR ADCs, that will assist in better understanding the '370 patent.

33. ADCs represent a new, important class of pharmaceutical therapeutics designed to harness the specificity of antibodies with the potency of small molecule therapeutics. The three main components of ADCs are an antibody, a linker, and a cytotoxic payload that is conjugated to the antibody via the linker, as shown in the figure below. (EX1015 at 1; EX1019 at 4.)



(EX1019 at 4.)

34. ADC technology is based on the principle that linking a cytotoxic drug to an antibody specific for an antigen more highly expressed on cancer cells could allow high doses of the cytotoxic drug to be specifically delivered to cancer cells, largely sparing normal tissues. (EX1020 at 1.) Compared with unconjugated antibodies that are efficacious against certain tumors, linking the antibody to a cytotoxic payload often provides increased efficacy and tumor eradication.

35. ADC research has revealed several factors that affect the likelihood of success. (EX1021.) First, the selected antigen should provide substantial tumor selectivity. (Id. at 19.) Second, the cytotoxic drug should be highly potent as only a small amount of the ADC will reach the target cells. (Id.) Third, linker technologies are needed that result in stability of the ADC in circulation while also permitting efficient release of the cytotoxic drug following its internalization into target cells or localization in the tumor. (Id.) Based on an improved understanding of these factors, several ADCs have been evaluated in clinical trials in various

cancers. (Id.)

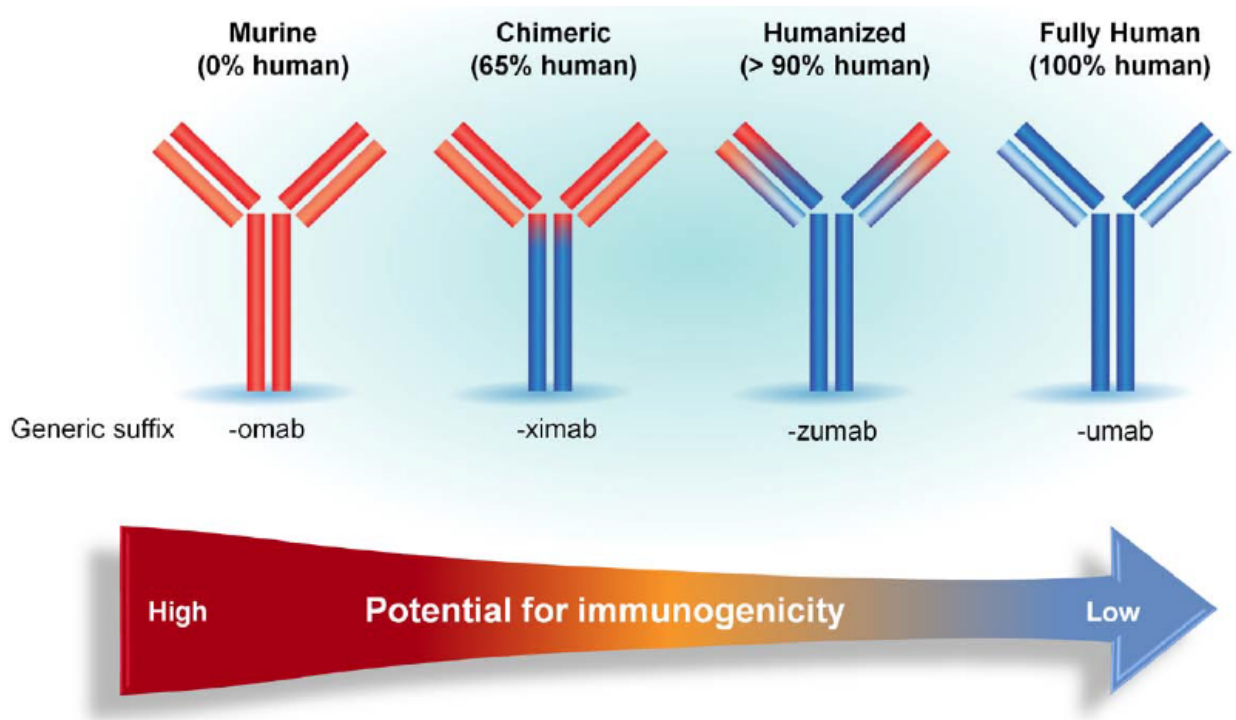
**A. Anti-EGFR Antibodies**

36. Antibodies are a foundational component of the immune system’s defense against both foreign agents (*e.g.*, viruses, bacteria) and aberrant self-made components of the body (*e.g.*, cancers and auto-immune diseases). Each antibody can recognize a specific target molecule called an antigen. Through binding to its specific antigen, an antibody can trigger additional biological processes to occur, depending on the biological context in which the binding occurs.

37. Antibodies are typically composed of four polypeptide chains: two longer, identical “heavy chains” and two shorter, identical “light chains.” The four chains typically pair up to form two arms in a characteristic “Y” shape, and variability in the antibody structure is well-documented.

38. Therapeutic antibody development often starts by inducing an antibody response in rodents, such as mice, whose antibody-producing cells can be further manipulated to isolate specific antibody clones against a specific target antigen. However, antibodies generated in mice, when administered to humans, are often attacked by the human body’s own immune system, negating their efficacy, as they are rapidly cleared from circulation. Chimeric antibodies have been engineered where the murine (mouse) constant regions of the antibody are replaced by human constant regions to render the antibody “more human” so as to prevent a human

immune response. A further progression of antibody engineering is humanization, where only the complementarity determining regions (“CDRs”) of the antibody variable regions are of mouse origin, and the rest of the antibody is derived from human sequences. Fully human and humanized antibodies have a lower risk of inducing an immune response in humans than murine or chimeric antibodies. (EX1022 at 1.) A spectrum progressing from a fully mouse antibody to a chimeric antibody to a humanized antibody to a fully human antibody is represented below, where the red portions are of mouse origin, and the blue portions are of human origin.



(EX1034 at 4.)

39. EGFR (also known as HER1 or ErbB1) is a member of the epidermal

growth factor (“EGF”) family of receptor tyrosine kinases. Human EGFR is a 170 kDa transmembrane receptor encoded by the c-erbB protooncogene. (EX1023.) The sequence of human EGFR is available at SwissProt database entry P00533.

40. EGFR is a cell membrane growth factor receptor characterized by tyrosine kinase activity that plays a crucial role in the control of key cellular transduction pathways in both normal and cancerous cells. (EX1024 at 1.) EGFR is overexpressed in a variety of cancers, including head and neck, breast, lung, colorectal, prostate, kidney, pancreatic, ovarian, brain, and bladder cancer. (Id.) EGFR regulates numerous cellular processes via tyrosine kinase-mediated signal transduction pathways, including activation of signal transduction pathways that control cell proliferation, differentiation, cell survival, apoptosis, angiogenesis, mitogenesis, and metastasis. (EX1025.)

41. The function of EGFR depends on the formation of EGFR – EGFR homodimers or heterodimers following binding of an EGFR-selective ligand. (EX1024 at 1.) Known activating ligands for EGFR include epidermal growth factor (EGF), transforming growth factor- $\alpha$  (TGF- $\alpha$ ), amphiregulin, and neuregulin. (Id.) The binding of EGFR and ligand results in conformational changes that allow the activation of EGFR tyrosine kinase and the phosphorylation of specific tyrosine residues within the EGFR intracellular carboxyl-terminal domain. (Id.) Phosphorylated tyrosine residues serve as docking sites for several signaling

proteins, ultimately stimulating cell proliferation, loss of differentiation, invasion, angiogenesis, and blocking of apoptosis. (Id.)

42. Anti-EGFR monoclonal antibodies in clinical use generally bind to the extracellular domain of EGFR. (Id.) They compete for receptor binding by occluding the ligand-binding region, thereby blocking ligand-induced EGFR tyrosine kinase activation. (Id. at 1-2.) To date, two anti-EGFR monoclonal antibodies, panitumumab and cetuximab, are currently in widespread use in anti-cancer therapies. (Id. at 2.)

43. Cetuximab (also known as C225 or Erbitux, marketed by Eli Lilly) is an immunoglobulin (“Ig”) G1 human–murine chimeric counterpart of the murine monoclonal antibody M225. (Id.) It binds to EGFR with a significantly higher affinity compared to the native ligands EGF and TGF- $\alpha$ . (Id.) Binding of cetuximab to EGFR promotes receptor internalization and subsequent degradation without receptor phosphorylation and activation. (Id.) This results in receptor down-regulation, reducing the availability of EGFR on the cell surface and preventing activation of EGFR-associated downstream signaling pathways. (Id.) Cetuximab also binds to the mutant EGFR receptor variant EGFRvIII, inducing internalization of antibody-receptor complexes and a significant reduction in phosphorylated EGFRvIII. (Id.)

44. Panitumumab (also known as Vectibix, marketed by Amgen) is a fully

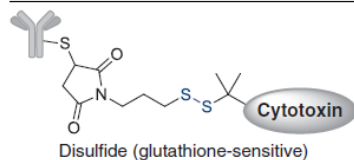
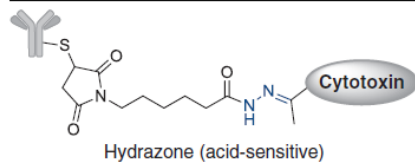
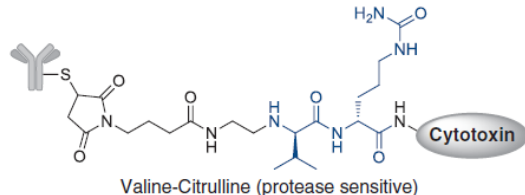
human IgG2 monoclonal antibody targeting the extracellular domains of EGFR. (Id. at 3.) It offers effective therapy with a minimal frequency of allergic reactions or anaphylaxis. (Id.) Panitumumab is well-tolerated. Its main toxic effect is dermatological, but this has not reportedly reached grade 4 severity in clinical trials. (Id.) Because of its structure (i.e., fully human antibody), infusion-related reactions are minimal. (Id.)

## **B. Linkers**

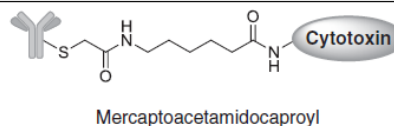
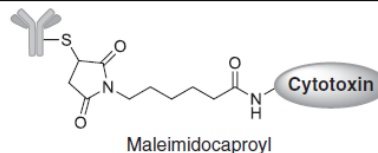
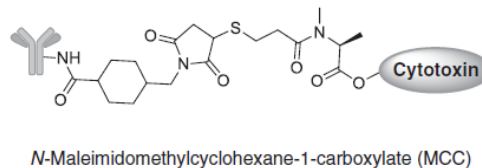
45. Linkers and their conjugation chemistry play an important role in determining how a drug is released from an ADC. (EX1015.) Cleavable linkers are reactive to physiological stimuli, such as low pH, high glutathione concentrations, and proteolytic cleavage, whereas non-cleavable linkers rely on degradation of the ADC within the lysosome after internalization. (Id. at 6.) Some examples of ADC drug linkers are shown below. (EX1019 at 6.)

## Examples of ADC drug linkers

### Cleavable linkers



### Noncleavable linkers



46. One of the advantages of protease-sensitive cleavable linkers over non-cleavable linkers is called the bystander effect. Solid tumors often express the target antigen in a heterogeneous fashion, and some ADCs may kill bystander cells irrespective of their antigen expression, in addition to killing antigen-expressing cells. (EX1016.) However, the bystander effect can be affected by differences between parent drugs and potential ADC metabolites. (EX1015 at 6.) Conjugated drugs that are not released in their original unconjugated form may suffer decreased efficacy, which is often seen with conjugation through non-cleavable linkers. (Id. at 8.) Indeed, monomethyl auristatin E (“MMAE”), a protein-based anti-mitotic drug which is most potent in its native form, is poorly suited for derivatization with a non-cleavable linker. (Id. at 6.)

47. The bystander cytotoxicity possessed by some cleavable linkers may

enhance the potency of ADCs against solid tumors that express the antigen in a heterogeneous fashion, or when there are physical barriers to ADC access to all cells of a solid tumor. (Id.) While the bystander effect can add collateral toxicity to normal tissues, this collateral toxicity may be mitigated by the inherent resistance of non-dividing cells to cytotoxic drugs. (Id.)

**a. Cleavable Linkers**

48. Cleavable linkers include chemically labile (e.g., hydrazones and disulfides) and protease-labile linkers. (EX1015 at 7-8.) These cleavable linkers are designed to be stable in the circulation and only release toxic payloads following internalization of the ADC, due to differences between the extracellular and intracellular microenvironments. (Id.) Hydrazones are selectively cleavable under acidic conditions, such as those found in the lysosome, because they have a significantly longer plasma half-life at pH 7 than pH 5. (Id. at 7.) Disulfide bridges utilize a cellular-reducing environment. After internalization and degradation, disulfide bridges can release drugs in lysosomes. (Id.)

49. Enzymatically cleavable linkers have gained significant attention in ADC development due to their superior plasma stability and release mechanism. (Id. at 8.) They provide ADCs with plasma stability comparable to that of non-cleavable linkers while boasting a more defined method of drug release compared to disulfide-linked or acid-labile linkers. (Id.)

50. The most commonly used enzymatically cleavable linker is the valine-citrulline (“Val-Cit” or “vc”) dipeptide linker combined with the self-immolative spacer p-aminobenzyl alcohol (“PAB”), also known as “vc-PAB.” (Id.) The vc-PAB linker is hydrolyzed by the cysteine protease cathepsin B in lysosomes following endocytosis. (EX1026.) Cleavage of an amide-linked PAB triggers a 1,6-elimination of carbon dioxide and concomitant release of the free drug in a parent amine form. (EX1015 at 8.) A comparison of the potency of the auristatin derivative MMAE linked by a Val-Cit linker to another dipeptide linker, Phe-Lys, and a hydrazone linker shows that the Val-Cit linker is significantly more stable than the Phe-Lys linker and the hydrazone linker in human plasma. (Id.)

51. ADCs conjugated with MMAE through a cleavable vc linker (referred to herein as “vc-MMAE”) have shown good stability, efficacy, and safety in several studies. For example, Brentuximab vedotin (also known as Adcetris, marketed by Seattle Genetics); a CD30-specific ADC conjugated with vcMMAE, is the first ADC that couples the targetability of monoclonal antibodies (“mAbs”) with the potent cytotoxicity of small molecule drugs and desirable pharmacokinetic (“PK”) profiles. (EX1021.) Its single-agent activity in patients with Hodgkin’s lymphoma in a post-ASCT setting is equivalent to that of multi-agent combination chemotherapy, but with a much lower toxicity profile. (Id. at 20.)

52. Mao et al. present a pre-clinical study describing the development and

preclinical evaluation of an ADC against EphB2 (called MMAE-vc-2H9) using vcMMAE payloads. (EX1027.) The results demonstrate specificity and efficacy of MMAE-vc-2H9 in *in vivo* tumor growth models, with no overt signs of drug-related toxicity in mice. (Id. at 7.)

53. Doronina et al. also report that an anti-CD30 antibody-valine-citrulline (vc)-MMAE ADC was much more stable in buffers and plasma than anti-CD30 ADCs containing a hydrazone of 5-benzoylvaleric acid-AE ester (AEVB). (EX1026.) The anti-CD30 antibody-valine-citrulline (vc)-MMAE ADC demonstrates high *in vitro* efficacy and specificity, and *in vivo* anti-tumor activity and safety. (See Id. at, e.g., Figs 3-5 and Table 1.) In addition, Afar et al. characterized an anti-TMEFF2 ADC, Pr1-vcMMAE, and report this ADC huPr1-vcMMAE is well-tolerated and can safely and effectively inhibit the growth of two distinct and aggressive prostate cancer xenograft models. (EX1028.)

#### **b. Non-cleavable Linkers**

54. Non-cleavable linked ADC linkers require antibody degradation within lysosomes following ADC internalization to release cytotoxic payload derivatives. The payload from non-cleavable linked ADCs remains covalently bonded to the linker via the residues to which the linkers are conjugated. (EX1029.) This payload derivative then subsequently kills the target cells.

55. As discussed above, non-cleavable linked ADCs can suffer decreased

efficacy due to the lack of additional efficacy from bystander effects. (EX1015 at 6.) One mechanism underlying the decreased efficacy of non-cleavable linked ADCs is that drugs bearing charged amino acids resulting from antibody degradation have decreased membrane permeability, limiting their ability to kill nearby cells. (Id.)

### **C. Cytotoxic Payloads**

56. The criteria for selecting an ADC payload include solubility, amenability to conjugation, and stability. (EX1015 at 8.) Lipophilic drugs can readily pass through cell membranes and, therefore, have a greater potential to escape the lysosome after release. (Id.) A potential payload must also be sufficiently soluble to allow for conjugation to the antibody in aqueous buffers. (Id.) The low solubility of many candidate payloads may be balanced by hydrophilic linkers, such as those containing sulfonates or poly(ethylene glycol). (Id.)

57. Many potent drugs require modifications to incorporate chemically functional handles necessary for conjugation. (Id.) However, such modifications can have deleterious effects on drug action. (Id.) Also, conjugated drugs not released as the free parent form may suffer decreased efficacy, which often is the case for drugs conjugated through non-cleavable linkers. (Id.) Self-immolative linkers such as PAB facilitate the release of appended drugs back to the original unconjugated form. (Id.) In addition, following conjugation, the payload must

remain stable in circulation, through cellular processing and release, to reach the cytosolic target. (Id.) Acid-sensitive drugs may be degraded in the lysosome prior to reaching the target site, and disulfide-, alkene-, and epoxide-containing drugs may be reduced or transformed by cellular enzymes. (Id.) For such drugs, additional protection and modifications may be needed. (Id.)

58. Derivatives of auristatin, maytansinoid, calicheamicin, durcomycin, pyrrolbenzodiazepines, and amanitin are currently being used as payloads. Currently, the majority of ADC payloads in clinical studies fall into two categories: anti-mitotic and DNA-damaging. (Id.) The two most recently approved ADCs, containing trastuzumab or brentuximab, both contain anti-mitotic payloads (i.e., maytansinoid and MMAE, respectively). (Id.) Additional anti-mitotic drugs investigated as ADC payloads include taxanes and vinca alkaloids. (Id.) DNA-damaging drugs, including duocarmycin, pyrrolbenzodiazepine, calicheamicins, and doxorubicin, have also been explored as ADC payloads. (Id.)

## **VII. OVERVIEW OF PRIOR ART AND STATE OF THE ART REFERENCES**

### **A. US20150071923A1 (“Wei”)**

59. U.S. Patent Application No. 14/485,620 to Ge Wei et al., entitled “Modified anti-epidermal growth factor receptor antibodies and methods of use thereof,” was filed on September 12, 2014 and published on March 12, 2015 as US20150071923A1 (“Wei”). (EX1005 at 1.) Wei claims priority to International

Patent No. PCT/US2014/055526, filed on September 12, 2014 and U.S. Provisional Application No. 61/960,253, filed on September 12, 2013. (Id. at 2.) I was informed that Wei is prior art at least because it has an effective filing date earlier than the earliest possible claimed priority date of the '370 patent.

60. Wei discloses anti-EGFR antibodies that are modified cetuximab antibodies, as well as ADCs containing the modified cetuximab antibodies. (EX1005 at ¶¶ [0009], [0010], [0229].) Cetuximab (C225, also known and marketed as Erbitux) refers to an anti-EGFR antibody that is a human-mouse chimeric monoclonal antibody. (Id. at ¶ [0328].) Cetuximab was derived from the mouse anti-EGFR antibody M225 by replacing the non-human constant region of M225 with the human IgG1 constant region. (Id. at ¶¶ [0490], [0496].) C225 also contains a human kappa light chain constant region. (Id.) Wei states that cetuximab is an exemplary anti-EGFR antibody that it “is approved for the treatment of recurrent or metastatic head and neck cancer, colorectal cancer, and other diseases and conditions” and that can also be used “in the treatment of other diseases or conditions involving overexpression of EGFR or aberrant signaling or activation of EGFR.” (Id. at ¶ [0009].) Wei also states that because anti-EGFR antibodies can bind to EGFR in healthy cells and tissues, it limits the dosages of cetuximab. (Id.)

61. Wei discloses 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. at ¶¶ [0010], [0036].) 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. at ¶ [0660], Examples 1-2.)

62. Wei states that these cetuximab variants “exhibit greater activity (binding affinity) under conditions of acidic pH, such as present in a tumor microenvironment, than under conditions of neutral pH, such as exists in non-tumor tissue.” (Id. at ¶¶ [0010], [0476].) Wei further states that, “By 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. at ¶ [0011].)

63. Wei also discloses an ADC represented by the formula: Ab-(L)q-(targeted agent)m, where q is 0 or more and m is at least 1. (Id. at ¶ [0665].) Wei teaches that the target agent is “a therapeutic moiety, such as a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.” (Id. at ¶ [0230].) Wei further discloses that “the therapeutic moiety is a maytansine derivative that is a maytansinoid, such as ansamitocin or mertansine (DM1); an auristatin or a functional peptide analog or derivative thereof, such as monomethyl auristatin E (MMAE) or F (MMAF).” (Id. at ¶ [0231].)



reduced tumor growth” compared to the vehicle control in the mouse model, especially at higher doses where the tumor growth regressed back to baseline volume, as shown in Table 39. (Id. at ¶ [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	

(Id., Table 39.)

67. In particular, Wei discloses the results of *in vivo* studies of the Y104D-MMAE and huY104D-MMAE ADCs in a HT29 tumor xenograft model and a MDA-MB-231M human breast tumor xenograft model, both of which are KRAS-mutated, EGFR-positive tumor models. (Id. at ¶¶ [1116]-[1127], Example 20.) The KRAS-mutated tumors are shown to be resistant to cetuximab. (Id. at ¶¶ [1102]-[1127], Table 41.) 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 with the humanized version of the ADC also exhibited a strong anti-tumor response and tumor regression, as shown in Tables 44 and 45. (Id. at ¶¶ [1122]-[1127], below)

TABLE 44

Breast Tumor Growth Following huY104D-MMAE Treatment						
Time (Days)	Vehicle	Y104D- MMAE	huY104D-MMAE			
			10 mg/kg	3 mg/kg	6 mg/kg	10 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	huY104D-MMAE			
			10 mg/kg	3 mg/kg	6 mg/kg	10 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	huY104E-MMAE			
			10 mg/kg	3 mg/kg	6 mg/kg	10 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

68. Wei thus concludes that, “These 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, “The anti-tumor response of each of the tested antibodies achieves tumor growth regression.” (Id. at ¶ [1127].) Notably, Wei also states that at a physiological pH (e.g., pH 7.4), the humanized ADCs exhibited reduced growth inhibition of non-tumor cells compared to the chimeric ADC.

69. 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. at ¶ [0666].)

70. In addition, Wei discloses that its anti-EGFR ADCs can be used for treating a condition responsive to treatment with an anti-EGFR antibody in a subject. (Id. at ¶ [0239].) Wei further discloses that “conditions responsive to treatment with an anti-EGFR antibody” refers to any disease or condition that is associated with or caused by aberrant EGFR signaling or overexpression of EGFR and that “EGFR-associated diseases or conditions or conditions responsive to treatment with an anti-

EGFR antibody include cancers, such as, but not limited to, colorectal cancer, squamous cell cancer of the head and neck and non-small-cell lung cancer.” (Id. at ¶ [0442].)

71. In addition to disclosing these ADCs, Wei also discloses “pharmaceutical compositions that include any of the modified anti-EGFR antibodies, antigen-binding fragments, or conjugates provided herein and a pharmaceutically acceptable carrier or excipient” and which “can be formulated as a gel, ointment, liquid, suspension, aerosol, tablet, pill, powder or lyophile, and/or can be formulated for systemic, parenteral, topical, oral, mucosal, intranasal, subcutaneous, aerosolized, intravenous, bronchial, pulmonary, vaginal, vulvovaginal, esophageal, or oroesophageal administration.” (Id. at ¶ [0238].)

72. Wei also discloses “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. at ¶ [0239].)

73. Wei 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. at ¶¶ [0441-458], [1086]-

[1127], claims 48 and 58.) Wei also 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. at ¶ [0903].)

**B. WO2014152199A1 (“Leanna”)**

74. International Patent Application No. PCT/US2014/027062 to Marvin Robert Leanna et al., entitled “Antibody drug conjugate (ADC) purification,” was filed on March 14, 2014 by AbbVie Inc. and was published on September 25, 2014 as WO2014152199A1 (“Leanna”). I understand that Leanna is prior art at least because it was published before the earliest possible claimed priority date of the ’370 patent. I am also aware that Leanna was included in an Information Disclosure Statement (“IDS”) dated August 14, 2017 but was not discussed in the office actions issued by the USPTO during prosecution of the ’370 patent. (EX1003 at 102.)

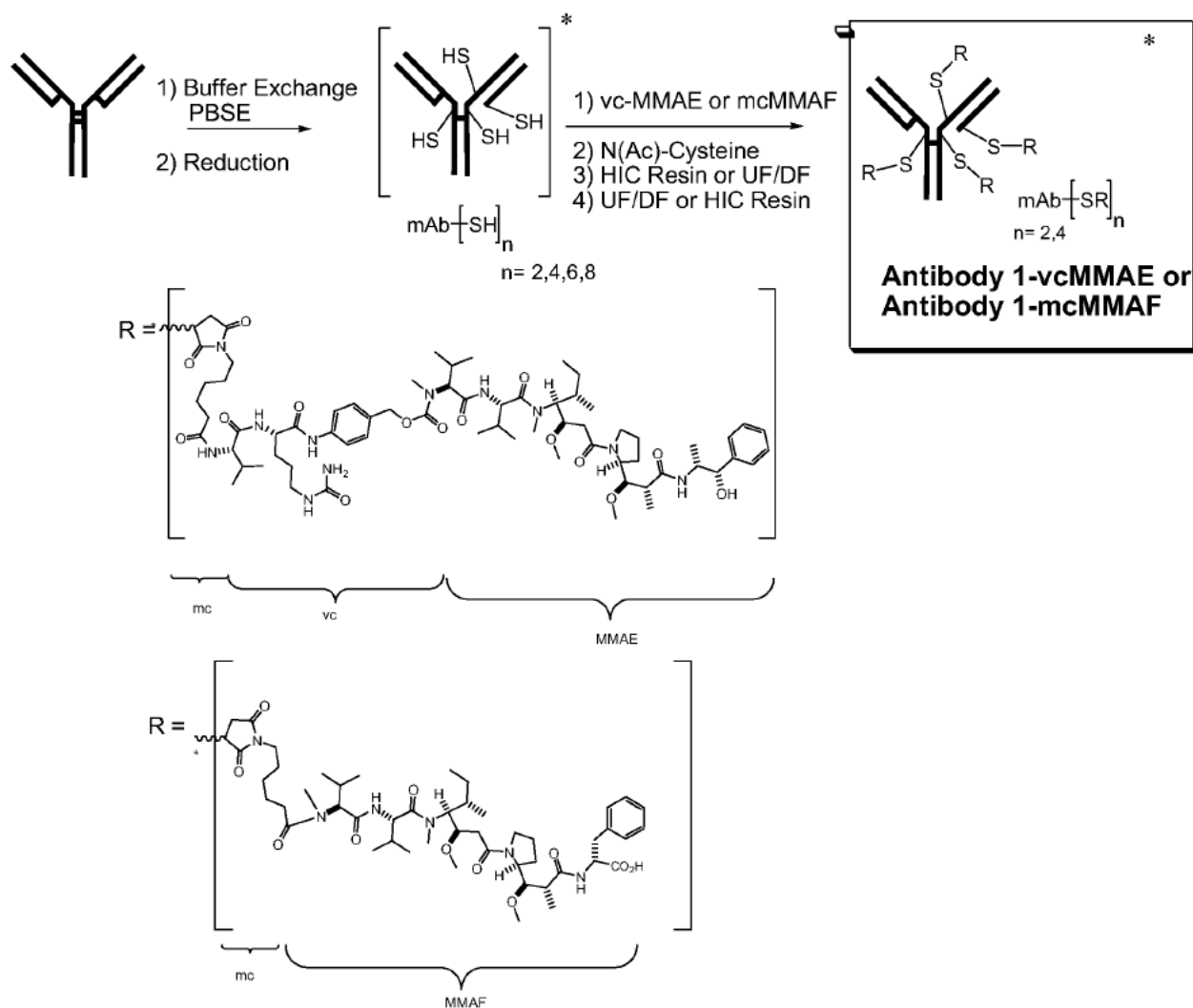
75. Leanna discloses ADCs comprising an anti-EGFR antibody and an auristatin, such as MMAE or MMAF. (EX1006 at Abstract, 3:1-5, 4:25-31, 32:1-8.) Auristatins represent a group of dolastatin analogs that have generally been shown to possess anticancer activity by interfering with microtubule dynamics and GTP hydrolysis, thereby inhibiting cellular division. (Id. at 28:12-29:3.) As a specific

embodiment, Leanna discloses that MMAE is conjugated to the antibody via a cleavable valine-citrulline (vc) linker to form a linker-drug designated as “vc-MMAE.” (Id. at 6:6-8.)

76. Leanna states that anti-EGFR antibodies suitable for use in accordance with current compositions and methods are typically monoclonal and can include, for example, chimeric (e.g., having a human constant region and mouse variable region), humanized, or human antibodies; single chain antibodies; or the like. The immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2) or subclass of immunoglobulin molecule. (Id. at 24:8-18.)

77. As an example, Leanna discloses Antibody 1-vc-MMAE ADC, which was generated by covalently linking Antibody 1 to one or more MMAE molecules using a cleavable valine citrulline linker, as shown in Figure 1. (Id. at 32:1-18.) The average Drug to Antibody Ratio (DAR) for Antibody 1-vcMMAE was 3.85. (Id. at 49: 22-27.)

78. The Antibody 1-vc-MMAE ADC is depicted in Figure 1 (reproduced below). Based on the chemical structure depicted in Figure 1, I understand that the linker drug is MC-vc-PAB (p-aminobenzylcarbamoyl).



(Id., FIG. 1.)

79. Antibody 1 is a humanized anti-EGFR antibody, which was previously described in WO 2011/041319 and US20110076232 (see, e.g., antibody sequence of Figure 55). (Id. at 24:14-17.) 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 VH and/or VL sequence has been altered to be more “human-like,” i.e., more similar to human

germline variable sequences. (Id. at 11:14-26.) 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. (Id.)

80. In Examples 1-3, Leanna describes detailed processes for preparing the Antibody 1-vc-MMAE ADC (Example 1), purification of the ADC (Example 2), and scaling up of batch purification of the ADC (Example 3). (Id. at 48:1-58:15.) In particular, Example 1 describes conjugation of an antibody to an auristatin to form an antibody drug conjugate (ADC), specifically the conjugation of MMAE to anti-EGFR Antibody 1. (Id. at 48:1-50:5.) Generation of the Antibody 1 ADC with reduced drug loads of vc-MMAE molecules per antibody, involved a partial reduction of the mAb followed by reaction with Val-Cit-MMAE (vcMMAE) to complete the conjugation. (Id.) Reduction of Antibody 1 was achieved using tricarboxyethyl phosphine (“TCEP”). (Id.) Leanna indicates that recombinant monoclonal Antibody 1 was produced by a transfected Chinese hamster ovary cell line. Following antibody purification, Antibody 1 was then partially reduced by the addition of TCEP. (Id.) To conjugate the thiols of Antibody 1, Val-Cit-MMAE (vc-MMAE), Val-Cit was added to the antibody solution to a final vc-MMAE:reduced

Cysteine (Cys) molar ratio of 1.15. (Id.) The conjugation reaction was carried out in the presence of 10% v/v DMSO and allowed to proceed at 20°C for 45 minutes. (Id.) Analytical analysis of the reaction mixture was accomplished by hydrophobic interaction chromatography-high-performance liquid chromatography (HIC-HPLC) using a TSKgel Butyl-NPR column. (Id.)

81. Leanna also describes methods for purifying anti-EGFR antibody-vc-MMAE ADCs. (Id. at 14:1-23:26.) Following production and purification of an antibody from an expression system (e.g., a mammalian expression system), the antibody is reduced and coupled to a drug through a conjugation reaction. (Id.) The method further includes adding a hydrophobic resin to an ADC mixture such that undesired ADCs, i.e., higher drug loaded ADCs, bind the resin and can be selectively removed from the mixture. (Id.) The purification process can be performed using a batch purification method, a circulation process, or a flow through process. (Id.) In particular, Example 2 describes a practical, scalable batch purification process of an ADC (Antibody 1-vc-MMAE) using hydrophobic resin. (Id. at 50:7-56:16.) Example 3 describes a large-scale batch purification of the ADC. (Id. at 56:18-58:15.)

82. 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. at 6:11-22, 32-47.) 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. at 35:20-36:3.)

83. 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. at 32:27-34:14.) 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. at 13:1-30, 33:14-34:22.) In particular, Leanna 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. (Id.)

**C. CN103772504A (“Liu”)**

84. Chinese Patent Application No. CN201210406288.3A to Jie Liu, entitled “Humanized antibody against epidermal growth factor receptor and application thereof,” was filed on October 17, 2012 by Shanghai JMT Biotechnology

Co Ltd and was published on May 7, 2014 as CN103772504A (“Liu”). I understand that Liu is prior art at least because it was published before the earliest possible claimed priority date of the ’370 patent. I am also aware that Liu was discussed in the office actions issued by the USPTO during prosecution of the ’370 patent.

85. Liu discloses that humanized anti-EGFR antibodies have lower immunogenicity and higher target binding activity, such that the antibodies have stronger biological activity and *in vitro* and *in vivo* antineoplastic activity. (EX1008 at Abstract.) Liu states that compared with a human-mouse chimeric antibody, the humanization of anti-EGFR antibodies as disclosed further reduced the immunogenicity of the antibodies, strengthened antigen recognition activity and anti-knurl function *in vivo* and *in vitro* simultaneously, and had better potential applicability in clinical practice. (Id. at ¶ [0001].)

86. In the Background Technology section, Liu reviewed the two known anti-EGFR antibodies, cetuximab (also known as Erbitux or C225 antibody; a human mouse chimeric antibody generated from the mouse source antibody M225) and panitumumab (also known as Victibix; a humanized antibody). (Id. at ¶¶ [0003], [0004].) For cetuximab, Liu states that the human mouse chimeric antibody C225 adopts human IgG1  $\kappa$  and the variable region of the mouse source monoclonal antibody M225. (Id. at ¶ [0003].) It has reduced immunogenicity compared to M225, retains binding affinity to EGFR, is capable of blocking interactions between

EGFR and ligands such as EGF and TGF $\alpha$ , and suppresses phosphorylation and downstream signal transduction, thereby inhibiting growth of tumor cells, inducing apoptosis and reducing generation of matrix metalloproteinase and VEGF. (Id.) However, Liu notes that in addition to the side effects associated with skin and mucus membranes, cetuximab still has immunogenicity and is prone to induce immunogenic reactions, causing it to be eliminated from the system. (Id.) Regarding panitumumab, Liu states that panitumumab is a fully humanized monoclonal anti-EGFR antibody and an IgG2 antibody. (Id. at ¶ [0004].) Compared to an IgG1 antibody, the IgG2 antibody has significantly lower biological activity, such as complement-dependent cytotoxicity (“CDC”) activity and Antibody-dependent cellular cytotoxicity (“ADCC”). (Id.) Moreover, the IgG2 antibody has lower stability, which may be the main reason why panitumumab did not show clear superiority over the chimeric antibody cetuximab. (Id.)

87. To address the need for a humanized anti-EGFR antibody that has lower immunogenicity, better efficacy, and fewer side effects, Liu reported BA03, BB03, BC03, and BD03 humanized anti-EGFR antibodies, which have a human IgG1 heavy chain constant region and a human kappa light chain constant region. (Id. at ¶¶ [0037], [0060].) Among these humanized anti-EGFR antibodies, BA03 demonstrated the highest binding affinity to EGFR as well as inhibitory activity in blocking interactions between EGFR and EGF. (Id. at Examples 1-5, ¶¶ [0141]-

[0146], Tables 1-3.) Liu further characterized BA03 to determine its ability to block phosphorylation of EGFR (Example 6), ADCC activity (Example 7), *in vitro* immunogenicity (Example 8), and *in vitro* anti-tumor activity against lung cancer, colorectal carcinoma, carcinoma of the pancreas, and breast cancer (Example 9). More specifically, Liu reported that BA03 has stronger activity than Erbitux in inhibiting phosphorylation of EGFR on A431 cells (Fig. 3). (Id. at ¶ [0148].) BA03 also showed, at both 0.1 µg/ml and 1 µg/ml, higher ADCC activity than Erbitux (Fig. 4). (Id. at ¶ [0150].) Liu also observed that BA03 had significantly lower immunogenicity compared to Erbitux (Fig. 5) and higher anti-tumor activity against lung cancer, colorectal carcinoma, carcinoma of the pancreas, and breast cancer. (Id. at ¶¶ [0152]-[0160], Table 4.)

88. Liu also discloses the sequences of BA03 as follows:

Heavy chain variable region (SEQ ID NO: 5)

QVQLQESGPGLVKPSSETLSLTCTVSGFSLSNYDVH  
WVRQAPGKGLEWLGVIWSSGNTDYNTPTSLTI  
SVDTSKNQFSLKLSSVTAADTAVYYCARALDYD  
YEFAYWGQGTLVTVSS

(Id. at ¶¶ [0085], [0123], [0124].)

Light chain variable region (SEQ ID NO: 13)

EIVLTQSPDFQSVTPKEKVTITCRASQSIGTNIHWY  
QQKPDQSPKLLIKYASESISGIPSRFSGSGSGTDFTL  
TINSLEAEDAATYYCQQNNEWPTSFGQGTKLEIK

(Id. at ¶¶ [0108], [0123], [0124].)

Heavy chain human IgG1 Fc (SEQ ID NO: 42)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP  
VTVSWNSGALTSQVHTFPAVLQSSGLYSLSSVTV  
PSSSLGTQTYICNVNHKPSNTKVDKRVKPKCDKT  
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT  
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE  
EQYNSTYRVVSVITV L HQDWLNGKEYKCKVSNKA  
LPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQV  
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVL  
DSDGSFFLYSKLTVDKSRWQQGNV FSCSVMHEAL  
HNHYTQKSLSLSPGK

(Id. at ¶ [0133].)

Light chain constant region (SEQ ID NO: 43)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE  
AKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSS  
TLT LSKADY EKHKVYACEVTHQGLSSPVTKSFNR  
GEC

(Id. at ¶ [0135].)

89. I understand that in several Office Actions, including the Non-final Office Action dated April 4, 2019, the USPTO found that Liu teaches the sequence of the heavy chain variable region of BA03 (SEQ ID NO: 5), which comprises SEQ ID NO: 5-7 of the heavy chain CDRs and SEQ ID NOs: 8-11 of the framework regions FR1, FR2, FR3, and FR4 as recited in the Challenged Claims of the '370 patent. (EX1003 at 405.) The USPTO also found that the kappa light chain of the constant region (SEQ ID NO: 43) is identical to SEQ ID NO: 4 as recited in claim 4 of the '370 patent, and that the IgG1 Fc fragment (SEQ ID NO: 42) is identical to SEQ ID NO: 3 as recited in claim 3 of the '370 patent. (Id.)

90. I was asked to confirm the above findings made by the USPTO, particularly whether the BA03 antibody used to generate the MYK-3 ADC has identical heavy chain and light chain variable regions as well as heavy chain and light chain constant regions. To that end, I compared the amino acid sequences of the heavy chain variable region (SEQ ID NO: 5) and the light chain variable region (SEQ ID NO: 13) of BA03 disclosed by Liu respectively to those of the heavy chain variable region (SEQ ID NO: 1) and the light chain variable region (SEQ ID NO: 2) of BA03 used in MYK-3 of the '370 patent using Clustal Omega<sup>1</sup>. As shown in the sequence alignments below, the sequences of the heavy chain and light chain variable regions of BA03 in MYK-3 of the '370 patent are identical to those of BA03 disclosed by Liu.

'370 patent BA03 heavy chain variable region (SEQ ID NO: 1) vs. Liu's  
BA03 heavy chain variable region (SEQ ID NO: 5):

```

US370_SID1      QVQLQESGPGLVKPSSETLSLTCTVSGFSLSNYDVHWVRQAPGKGLEWLGVIWSSGNTDYN  60
LIU_BA03_SID5  QVQLQESGPGLVKPSSETLSLTCTVSGFSLSNYDVHWVRQAPGKGLEWLGVIWSSGNTDYN  60
*****

US370_SID1      TPFTSRLTISVDTSKNQFSLKLSVTAADTAVYYCARALDYYDYEFAYWGQGLVTVSS  119
LIU_BA03_SID5  TPFTSRLTISVDTSKNQFSLKLSVTAADTAVYYCARALDYYDYEFAYWGQGLVTVSS  119
*****

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<sup>1</sup> Clustal Omega is a public multiple sequence alignment tool available at <https://www.ebi.ac.uk/Tools/msa/clustalo/> (Sievers F, *et al.* Molecular Systems Biology 7 Article number: 539)

'370 patent BA03 heavy chain variable region (SEQ ID NO: 2) vs. Liu's

BA03 heavy chain variable region (SEQ ID NO: 13):

US370_SID2	EIVLTQSPDFQSVTPKEKVTITCRASQSIGTNIHWYQQKPDQSPKLLIKYASESISGIPS	60
LIU_BA03_SID13	EIVLTQSPDFQSVTPKEKVTITCRASQSIGTNIHWYQQKPDQSPKLLIKYASESISGIPS	60
	*****	
US370_SID2	RFSGSGSGTDFTLTINSLEAEDAATYYCQQNNEWPTSFQGQTKLEIK	107
LIU_BA03_SID13	RFSGSGSGTDFTLTINSLEAEDAATYYCQQNNEWPTSFQGQTKLEIK	107
	*****	

91. I also compared the amino acid sequences of the heavy chain constant region (IgG1 Fc; SEQ ID NO: 42) and the light chain constant region (SEQ ID NO: 43) of BA03 disclosed by Liu to those of the heavy chain constant region (SEQ ID NO: 3) and the light chain constant region (SEQ ID NO: 4) of BA03 used in MYK-3 of the '370 patent using Clustal Omega. As shown in the sequence alignments below, the sequences of the heavy chain and light chain constant regions of BA03 in MYK-3 of the '370 patent are identical to those of BA03 disclosed by Liu.

'370 patent BA03 heavy chain constant region (SEQ ID NO: 3) vs. Liu's

BA03 heavy chain constant region (SEQ ID NO: 42):

US370_SID3	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSS	60
LIU_BA03_SID42	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSQVHTFPAVLQSS	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
	*****	

'370 patent BA03 light chain constant region (SEQ ID NO: 4) vs. Liu's BA03 light chain constant region (SEQ ID NO: 43):

US370_SID4	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD	60
LIU_BA03_SID43	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD	60
	*****	
US370_SID4	SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	107
LIU_BA03_SID43	SKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	107
	*****	

92. The above sequence analysis results are also consistent with the statement in the '370 patent that, "The antibody BA03 of the present invention was BA03 as described in the Chinese invention patent application CN103772504A, and its preparation method could be seen in Example 3 of this patent application."

(EX1001 at 18:3-6.) I understand that the Chinese invention patent application CN103772504A refers to Liu as discussed above.

**D. WO2015000062A1 (“Tikhomirov”)**

93. International Patent Application No. PCT/CA2014/000543 to Ilia Alexandre Tikhomirov et al., entitled “EGFR antibody conjugates,” was filed on July 4, 2014 by Avidbiologics Inc. and was published on January 8, 2015 as WO2015000062A1 (“Tikhomirov”). I understand that Tikhomirov is prior art at least because it was published before the earliest possible claimed priority date of the ’370 patent. I am also aware that Tikhomirov was discussed in the office actions issued by the USPTO during prosecution of the ’370 patent.

94. Tikhomirov describes anti-EGFR ADCs comprising anti-EGFR antibodies, such as cetuximab or panitumumab, conjugated to a microtubule damaging agent, such as a maytansinoid. (EX1009 at 1.) Tikhomirov states that a goal was to provide a method for potentiating the cytotoxicity of an EGFR antibody toward diseased cells selectively such that potentiation of toxicity toward normal cells was essentially avoided. (Id. at 4.)

95. Tikhomirov states that, “Immunoconjugates having this property require the selection of an EGFR antibody that is a full antagonist, a toxin that is an anti-microtubule agent, and a linker that most desirably is not cleavable.” (Id. at 5.) While Tikhomirov indicates that a non-cleavable linker is most desirable, it does not

preclude the use of a cleavable linker. Consistently, Tikhomirov provides a method “useful to potentiate the anti-cancer activity of an EGFR antibody without potentiating the effect thereof on normal EGFR+ cells,” and the method comprises:

- (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. (emphasis added).)

96. Tikhomirov discloses ADCs comprising cetuximab conjugated with an anti-microtubule toxin (e.g., MMAE) through a non-cleavable linker (e.g., N-succinimidyl 4-(maleimidomethyl)cyclohexanecarboxylate (“SMCC”)), or a cleavable linker (i.e., valine-citrulline). (Id. at 7, 10, 14 and Fig. 13.) Cetuximab is commercially available from Eli Lilly and Company under the trade name Erbitux®. Cetuximab is a recombinant human/mouse chimeric IgG1 antibody that binds specifically to the extracellular domain of wtEGFR. (Id. at 12.)

97. 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. (Id. at 8, 16.)

98. 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+ cancer cells and tumors comprising them. (Id. at 19.) Tikhomirov discloses a method for treating a subject presenting with an EGFR-positive cancer cell, comprising administering the ADC to the subject in an amount cytotoxic to the EGFR-positive cancer cell. (Id. at 8.) 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. (Id. at 19.)

99. Tikhomirov discloses that conditions or disorders to be treated include benign or malignant tumors (e.g., renal, liver, kidney, bladder, breast, gastric, ovarian, colorectal, prostate, pancreatic, lung, vulva, and thyroid); hepatic carcinomas; sarcomas; glioblastomas; and various head and neck tumors; leukemias and lymphoid malignancies. (Id.) Tikhomirov discloses that the antibody or bivalent fragment is used in the treatment of such cancer cells that express EGFRvIII. (Id.)

100. Example 4 of Tikhomirov reports results with partial antagonist EGFR monoclonal antibody (i.e., J2989A, 6-LC) ADCs and full/strong antagonistic EGFR monoclonal antibody (e.g., panitumumab). (Id. at 30, 31.) Specifically, Figure 9 shows that a partial antagonist EGFR antibody, designated J2989A, has an activity that is potentiated on normal keratinocytes when conjugated to DM-1. (Id.) Figure

10 shows, similarly, that another partial antagonist antibody, designated 6-LC (a substitution variant of cetuximab having lower relative affinity for EGFR), has activity that is also potentiated at normal keratinocytes when conjugated to DM-1. (Id.) Figure 11 shows that the effect of panitumumab on keratinocytes is not potentiated on keratinocytes when conjugated to DM1, while the anticancer effect of the conjugate is potentiated dramatically (Figure 12). (Id.)

101. Tikhomirov also states that Figure 13 shows 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. at 10, 11, 30.)

102. I am aware that Patent Owner argued that one of ordinary skill in the art would not have been motivated by the cited references to use a cleavable linker to arrive at the ADC based on a statement in Tikhomirov – “a safe anti-EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker.” (EX1004 at 200.) However, as will be further discussed below, the teaching by Tikhomirov with respect to the distinction between cleavable linkers and non-cleavable linkers is very limited and based on a flawed experimental design. Thus, it should not be generalized to a large number of ADCs within the scope of the Challenged Claims.

103. First, 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). However, 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). In addition, the experiment is missing a statistical comparison between the treatment groups to confirm there is a biologically meaningful effect. Notably, the payloads (DM1 vs. MMAE) as tested have different cytotoxic activity against the selected cell lines; thus, the interpretation of data is problematic. Moreover, the experiment is also missing important controls, such as payload alone and isotype with vcMMAE.

104. Second, Tikhomirov's statement is based on a single experiment presented in Figure 13. A POSA would have understood that any observations obtained from a *single* anti-EGFR antibody, a *single* cleavable linker, and a *single* cytotoxic drug MMAE in the single experiment presented in Figure 13 are not generalizable to *all* cleavable linkers and *all* cytotoxic drugs as claimed in the Challenged Claims.

105. Third, even assuming that Tikhomirov's statement "a safe anti-EGFR ADC should incorporate a strongly antagonistic anti-EGFR antibody linked to an anti-microtubule payload by a non-cleavable linker" is correct, it is only limited to

an anti-microtubule payload linked to a strongly antagonistic anti-EGFR antibody. (EX1009 at 31.) In fact, Tikhomirov makes clear that its observation, with regard to toxicity against normal cells between a non-cleavable linker and a cleavable linker, only applies to anti-microtubule payloads. (Id.) 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. at 4 (emphasis added).) Thus, a POSA would have understood that the observation made with regard to safety of anti-EGFR ADCs would not apply to all types of payloads (e.g., non-anti-microtubule payloads) covered by the Challenged Claims, whether a non-cleavable linker or a cleavable linker is used. Therefore, in my opinion, Patent Owner’s argument that one of ordinary skill in the art would not have been motivated by the cited references to use a cleavable linker to arrive at the ADC is incorrect.

106. Contrary to Tikhomirov’s statement, as discussed above in Section VI, cleavable linkers, such as vcMMAE, have been used in many ADCs that demonstrate good stability, superior efficacy, and safety profiles. Therefore, a POSA would also have been motivated to use a cleavable linker in an anti-EGFR ADC.

## VIII. OVERVIEW OF THE '370 PATENT

### A. The Specification and Claims of the '370 patent

107. I have read the '370 patent, titled “Antibody-drug conjugate,” and reviewed the relevant portions of the prosecution history of the '370 patent (EXS1003, 1004). The '370 patent issued from U.S. Non-Provisional Patent Application No. 15/550,995 (“the '995 Application”), filed on February 16, 2016, which is a national stage application of International Application No. PCT/CN2016/073844, filed on February 16, 2016, which claims the benefit of Chinese Application No. 201510085038.8, filed on February 17, 2015. (EX1001 at 1:1-10.) The cover page of the '370 patent lists Chaohong Hu as the sole inventor and Shanghai Miracogen Inc as the Applicant and Assignee. (Id. at 1.)

108. The background of the '370 patent recognizes “it is highly complex and unpredictable whether an antibody drug conjugate becomes a safe and effective drug depending on a variety of factors.” (Id. at 3:10-37.) These factors include:

1) characteristics of target: whether a target antigen can be internalized or not, the expression level of the target antigen, differentials of expression level of target antigen between cancer cells and normal cells, and whether the target antigen has a extracellular domain (ECD) that is soluble in blood;

2) 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;

3) 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;

4) characteristics of linker: whether the linker is cleavable or non-cleavable, and stability of the linker in blood;

5) ADC characteristics: whether the complex of ADC and target antigen can be internalized or not, stability of ADC in blood, linker used and number of chemical drugs conjugated to the ADC, the balance between cancer killing activity of ADC and its toxicity.

(Id. (emphases added.))

109. The '370 patent describes and characterizes an anti-epidermal growth factor receptor (EGFR) antibody drug conjugate called MYK-3 that was generated from the monoclonal antibody BA03 and the linker-drug vc-MMAE. (Id. at Abstract, 18:61-19:50.) The '370 patent indicates that BA03 was disclosed in prior Chinese Patent Application CN103772504A. (Id. 18:3-59.)

110. The sequence of the variable region of the heavy chain of MYK-3 ADC was:

QVQLQESGPGLVKPSETLSLTCTVSGFSLSNYDVH  
WVRQAPGKGLEWLGVIWSSGNTDYNTTPFTSRLTI  
SVDTSKNQFSLKLSSVTAADTAVYYCARALDYYD  
YEFAYWGQGLVTVSS

(SEQ ID NO: 1)

wherein the underlined parts were CDR1 (SEQ ID NO: 5), CDR2 (SEQ ID NO: 6), CDR3 (SEQ ID NO: 7), respectively; the non-underlined parts were FRI (SEQ ID NO: 8), FR2 (SEQ ID NO: 9), FR3 (SEQ ID NO: 10), FR4 (SEQ ID NO: 11), respectively.

(Id. at 18:11-22.)

111. The sequence of the variable region of the light chain of MYK-3 ADC

was:

EIVLTQSPDFQSVTPKEKVTITCRASQSIGTNIHWY  
QQKPDQSPKLLIKYASESISGIPSRFSGSGSGTDFTL  
TINSLEAEDAATYYCQQNNEWPTSFGQGTKLEIK

(SEQ ID NO: 2)

wherein the underlined parts were CDR1 (SEQ ID NO: 12), CDR2 (SEQ ID NO: 13), CDR3 (SEQ ID NO: 14), respectively; the non-underlined parts were FR1 (SEQ ID NO: 15), FR2 (SEQ ID NO: 16), FR3 (SEQ ID NO: 17), FR4 (SEQ ID NO: 18), respectively.

(Id. at 18:23-36.)

112. The sequence of the constant region of the heavy chain of MYK-3 ADC

was:

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP  
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTV  
PSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKT  
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT  
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE  
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK  
ALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQ  
VSLTCLVKGFIYPSDIAVEWESNGQPENNYKTTPPV

LDS DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA  
LHNHYTQKSLSLSPGK

(SEQ ID NO: 3)

(Id. at 18:40-51.)

113. The sequence of the constant region of the light chain of MYK-3 ADC was:

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE  
AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS  
TLTSLKADYEEKHKVYACEVTHQGLSSPVTKSFNR  
GEC

(SEQ ID NO: 4)

(Id. at 18:54-69.)

114. Example 1 of the '370 patent describes preparation of an ADC from monoclonal antibody BA03 and the linker-drug vc-MMAE. (Id. at 18:61-19:50, FIG. 1.) The resulting ADC was referred to as MYK-3, having an average drug load drug/antibody ratio (DAR) of 4.1. (Id.) Example 2 describes *in vitro* evaluation of the cell growth inhibitory activity of MYK-3 on several cell lines (i.e., DiFi, HT-29, A549, U87-MG, and LoVo) using the BA03 monoclonal antibody as a control. (Id. 19:53-20:35, FIGs. 2-6.)

115. Example 3 describes an *in vivo* xenograft test of MYK-3 at 1 mg/kg and 5 mg/kg in mice, with the unconjugated BA03 monoclonal antibody and human IgG-vcMMAE non-binding ADC as controls. (Id. at 20:37-21:19, FIGs. 7-8.) It reports

effects of monoclonal antibody and ADC (i.e., MYK-3) on body weight of mice of an HT-29 colon cancer xenograft model. (Id.) However, it does not report effects of ADCs with non-cleavable linkers. (Id.)

116. Example 4 describes inhibitory activities of MYK-3, the monoclonal antibody BA03, and BA03+ equimolar vcMMAE on the growth of colorectal cancer cells (DiFi). (Id. at 21:21-67, FIG. 9.) Example 5 describes the inhibitory activity of MYK-3 at three doses (i.e., 0.3 mg/kg, 1 mg/kg, and 3 mg/kg) on the growth of transplanted tumors of the KRAS mutant colon cancer cell LoVo in nude mice, with Erbitux monoclonal antibody and anti-CD20 mAb-vcMMAE non-binding ADC as controls. (Id. 22:26-24:5, FIG. 10.)

117. Example 6 describes a comparison of inhibitory activity on cells *in vitro* between MYK-3 and BA03-MC-MMAE and BA03-MCC-MMAE. (Id. at 22:1-24:6, FIGs. 11-12.)

118. The '370 patent has one independent claim (claim 1) and 22 dependent claims (claims 2-23).

119. Independent claim 1 of the '370 patent recites:

1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker, wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and

the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.

120. Claim 2 depends from claim 1 and recites, “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.”

121. Claim 3 depends from claim 1 and recites, “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.”

122. Claim 4 depends from claim 1 and recites, “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.”

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

124. Claim 6 depends from claim 4 and recites, “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.”

125. 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.”

126. 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.”

127. 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)<sub>p</sub> 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.

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

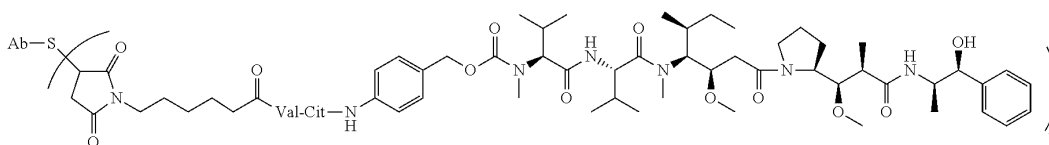
129. Claim 11 depends from claim 10 and recites, “the cytotoxic agent is selected from the group consisting of Monomethyl auristatin E (MMAE), Monomethyl auristatin F (MMAF), maytansinoid alkaloids, Calicheamicin,

duocarmycin MGBA, doxorubicin, ricin, diphtheria toxin, I131, and tumor necrosis factors.

130. Claim 12 depends from claim 9 and recites, “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).”

131. 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.

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

133. 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.”

134. 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.”

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

136. 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.”

137. Claim 19 depends from claim 18 and recites, “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.”

138. Claim 20 depends from claim 17 and recites, “the tumor is a tumor with KRAS gene mutation.”

139. Claim 21 depends from claim 17 and recites, “the tumor is a tumor with BRAF gene mutation.”

140. Claim 22 depends from claim 19 and recites, “the tumor is a tumor with KRAS gene mutation.”

141. Claim 23 depends from claim 19 and recites, “the tumor is a tumor with BRAF gene mutation.”

## **B. The Prosecution History of the '370 patent**

142. The '995 Application that issued as the '370 patent was filed on February 16, 2016 with 34 claims, including independent claim 1 that recited:

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

(EX1003 at 36).

143. In a preliminary amendment dated August 14, 2017, claims 1, 17-22, and 29-34 were canceled, and claims 2, 5, 7-12, 15, 16, 23-25, 27, and 28 were amended. (Id. at 101.) Specifically, claim 2 was rewritten as an independent claim and to incorporate the limitations of canceled claim 1. (Id at 96.) The amendment to claim 2 is reproduced below:

2. (Currently Amended) An antibody-drug conjugate, a pharmaceutically acceptable salt thereof, a solvate thereof or a solvate of the salt, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent~~The antibody drug conjugate, (he~~

~~pharmaceutically acceptable salt thereof, the solvate thereof or the solvate of the salt according to claim 1,~~ 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 or mutants thereof, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14 or mutants thereof.

(Id.)

144. Claims 5, 7-12, 15, 16, 23-25, 27, and 28 were amended to address informalities and remove multiple dependencies. (Id. at 101.) Claims 35 and 36 were newly added. (Id.) Claim 35 depends from claim 26 and recites, “the tumor is a tumor with KRAS gene mutation.” (Id. at 100.) Claim 36 depends from claim 26 and recites, “the tumor is a tumor with BRAF gene mutation.” (Id.)

145. On April 4, 2019, the USPTO issued a Non-final Office Action, rejecting all the pending claims (i.e., claims 2-16, 23-28, and 35-36) under multiple grounds. (Id. at 395.) In particular, claims 11 and 12 were rejected under 35 U.S.C. § 112(d) as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. (Id. at 396.) Claims 11, 12, and 14 were rejected under 35 U.S.C. § 112(b) as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor. (Id. at 397.)

146. Claims 2-16, 23-28, 35, and 36 were also rejected under 35 U.S.C. § 112(a) as failing to comply with the enablement requirement because the claimed subject matter was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (Id. at 398.) In particular, the USPTO rejected the cytotoxic agents “nanoparticles,” “cytokines,” “interleukins,” and “chemokines” recited in claims 11 and 12 as non-enabling at least because the specification lacks any objective evidence that nanoparticles without an attached cytotoxic moiety, cytokines, interleukins, and chemokines, when internalized by the conjugate and binding to EGFR on a target cell would exert a toxic effect on the target cell. (Id.) The USPTO also rejected the subject matter relating to a solvate of the antibody conjugates of claims 2-16, 23-28, 35, and 36 as non-enabling at least because the specification fails to provide any teachings for how to make the solvate of the antibody conjugates. (Id. at 399.) The USPTO further rejected the subject matter in claims 23, 24, 27, and 28 relating to a method for prophylaxis of disease associated with EGFR comprising administering a prophylactically effective amount of the antibody-drug conjugate as non-enabling. (Id.) The USPTO states that the specification fails to teach: (a) how to predict when a diseased cell expressing EGFR will occur in a human or a non-experimental animal such that the antibody conjugate can be injected prior to disease occurrence; and (b) how a “prophylactically effective

amount” of the antibody conjugate differs from a “therapeutically effective amount.  
(Id.)

147. Claims 2-16, 23-28, 35, and 36 were rejected under 35 U.S.C. § 112(a) as failing to comply with the written description requirement, particularly with regard to (a) “mutants thereof” in regard to the EGFR antibody recited in claims 2-6 and 8 encompass; (b) a sequence with an identity of greater than 70%, for example, greater than 75%, 80%, 85%, 90%, 95%, or 99% to the sequence as shown in SEQ ID NO: 3 or 4 recited in claims 7 and 9; and (c) a solvate of the antibody conjugates.  
(Id. at 400.)

148. Claims 2-14, 16, and 23-26 were rejected under 35 U.S.C. § 103 as being obvious over Tikhomirov in view of Liu, Brand et al. *Cancer Biology & Therapy*. 2011. Vol. 11. pp. 777-792 (“Brand”), and Chung et al. *New England Journal of Medicine*, 2008. Vol. 358, pp. 1109-1117 (“Chung”). (Id. at 402.) In particular, the USPTO stated that Tikhomirov teaches a method for treating a subject presenting with a tumor that responds to treatment with a full antagonist EGFR antibody, wherein treatment therewith elicits by keratinocytes the improvement comprising treating said subject with the full antagonist EGFR antibody in a form conjugated with an anti-microtubule toxin, whereby the tumor response to treatment with conjugated antibody is enhanced essentially without enhancing the adverse keratinocyte response to treatment, relative to treatment with naked antibody alone.

(Id. at 403-404.) The USPTO also stated that Tikhomirov teaches full antagonist EGFR antibodies (e.g., cetuximab) conjugated to an anti-microtubule toxin (e.g., MMAE) via a non-cleavable linker (e.g., maleimidocaproyl (MC)) or a cleavable linker (e.g., a linker incorporating valine-citrulline such as Cetux-2C9-MMAE). (Id.) Brand teaches that cetuximab, also known as C225, is the chimeric version of the murine antibody M225, and Chung teaches that among 76 cetuximab-treated subjects, 25 had hypersensitivity reactions to the drug, and that most of the subjects having hypersensitivity reactions had pre-existing IgE antibodies to galactose-a-1,3-galactose which is present on the Fab portion of the cetuximab heavy chain. (Id. at 405.) Finally, the USPTO pointed out that Liu teaches four humanized versions of the murine M225 antibody comprising a human IgG1 Fc fragment and a kappa light chain, termed BA03, BB03, BC03, and BD03. (Id.) Liu teaches the sequences of the heavy chain and light chain variable regions of BA03 (SEQ ID NOs: 5 and 13), which are identical to SEQ ID NOs: 1 and 2, respectively, as described in the '995 Application. Liu also teaches the sequences of the heavy chain and light chain CDRs (SEQ ID NOs: 5-7 and 12-14) and framework regions (FR1, FR2, FR3, and FR4; SEQ ID NOs: 8-11) of BA03 as described in the '995 Application. (Id. at 405-6.) The USPTO also provided the sequence alignments to show that Liu teaches the sequence of the heavy chain constant (SEQ ID NO: 3) region and that of the light chain constant region (SEQ ID NO: 4) of BA03. (Id.) Liu further teaches that the

BA03 and BD03 antibodies have higher binding affinity, stronger ligand blocking ability and stronger inhibitory activity against surface EGFR than Erbitux/cetuximab, and that BB03 and BC03 have binding affinity and ligand blocking abilities that are similar to that of Erbitux. (Id. at 406.) The USPTO concluded that:

It would have been prima facie obvious as of the effective filing date to use the BA03 antibody in place of cetuximab in the conjugates and methods of using the conjugates of Tikhomirov. One of skill in the art would have been motivated to do so because the BA03 antibody is a full length antibody that is an antagonist of EGFR as demonstrated by Liu and has higher binding affinity and ligand blocking abilities than cetuximab. One of skill in the art would also be motivated to use the humanized BA03 antibody in place of cetuximab because the BA03 has humanized framework regions, and because the N88 amino acid in the chimeric 225 antibody is no longer present. Thus, one of skill in the art would know that the humanized 225 antibody of Liu BA03 would not carry galactose-a-1,3-galactose on N88 within FR3, and the antibody would not cause hypersensitivity reactions in subjects having pre-existing IgE antibodies to galactose-a-1,3-galactose.

(Id. at 406-7.)

149. The USPTO also rejected claims 2-16 and 23-26 under 35 U.S.C. § 103 as being unpatentable over Tikhomirov, Liu, and Chung and further view of Chari et al., *Angewandte Chemie*, 2014, Vol. 53. pp. 3796-3827 (“Chari”). (Id. at 407.) In regard to claim 15, the USPTO stated that Chari teaches a Mal-caproyl-val-cit-PAB-MMAE linkable derivative of MMAE, and the linkage to a mAb, wherein cleavage

at the citrulline induces the self-immolation of the p-amino benzoate to release free MMAE. (Id.) Chari teaches that the interchain disulfides can be fully or partially reduced by a mild reducing agent to give a distribution of antibody species with two to eight free thiol groups which react with a maleimide comprising auristatin derivative to give conjugates with an average of four auristatins linked per antibody. Chari teaches that with the auristatin MMAF, the val-cit linked MMAF can be up to 10 times more potent on some cell types versus the MMAF with a non-cleavable linker. Claims 2-14, 16, 23-27, and 35 were rejected under 35 U.S.C. § 103 as being unpatentable over Tikhomirov, Liu, and Chung, and further in view of Lievre et al., Cancer Research. 2006. Vol. 66. pp. 3992-3995 (“Lievre”). (Id. at 408.) In regard to claims 27 and 35, the USPTO stated that Lievre teaches that patients with KRAS tumors are resistant to cetuximab and that whatever the expression level of EGFR is, the presence of the KRAS mutation is associated with a downstream activation of the Ras/MAPK pathway leading to cell proliferation that cannot be significantly inhibited by cetuximab, because cetuximab acts upstream of the K-ras protein. (Id.)

150. Claims 2-14, 16, 23-26, 28, and 36 were rejected under 35 U.S.C. § 103 as being unpatentable over Tikhomirov, Liu, and Chung and further in view of DiNicolantonio et al., Journal of Clinical Oncology, 2008, Vol. 26. pp. 5705- 5712 (“DiNicolantonio”). (Id.) In regard to claims 28 and 36, the USPTO stated that DiNicolantonio teaches that patients with BRAF mutated EGFR expressing tumors

did not respond to cetuximab and that the therapeutic effect of cetuximab could be restored if administered with a BRAF inhibitor such as sorafenib or other compounds targeting BRAF or its downstream effectors. (Id. at 409.)

151. In its response dated July 1, 2019, the Applicant made the following amendments to independent claim 2:

2. (Currently Amended) An antibody-drug conjugate, a pharmaceutically acceptable salt thereof, ~~a solvate thereof~~ or a solvate of the salt, 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 ~~or mutants thereof~~, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14 ~~or mutants thereof~~.

(EX1004 at 129.)

152. Claim 13 was canceled, and new claim 37 reciting “thereof according to claim 10, wherein the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB)” was added. (Id. at 131, 134.) In response to the § 103 rejections against claims 2-14, 16, and 23-26, the Applicant argued that one of ordinary skill in the art would have been motivated to use a cleavable linker in generating an anti-EGFR ADC in view of Tikhomirov. (Id. at 137.) The Applicant asserted that Tikhomirov focuses on non-cleavable linkers, although it acknowledges that Tikhomirov also discloses Cetux2C9-MMAE, which uses the

cleavable linker valine-citrulline (see Examples 1 to 4). (Id. at 138.) The Applicant also argued that Example 4 of Tikhomirov suggests that a cleavable linker is not favorable compared to a non-cleavable linker due to the fact that the resulting ADC had potentiated toxicity against normal cells. (Id.)

153. The Applicant further argued that the claimed ADCs exhibited unexpectedly superior properties as demonstrated in Example 6 of the present application. (Id. at 139.) Specifically, the Applicant stated that Example 6 compares the inhibition activities against cancer cells *in vitro* between MYK-3 (containing a cleavable linker) and BA03-MC-MMAE and BA03-MCC-MMAE (both containing a non-cleavable linker), and Figure 12 shows that MYK-3 has a lower EC50 value compared to BA03-MC-MMAE and BA03-MCC-MMAE. (Id.)

154. On October 18, 2019, the USPTO issued a Final Office Action, rejecting claims 2-12, 14-16, 23-28, 35, and 36 under 35 U.S.C. § 112(a) as failing to comply with the enablement requirement with regard to the subject matter relating to a salt of the claimed antibody conjugates. (Id. at 148.) Claims 2-16, 23-28, 35, and 36 were also rejected under 35 U.S.C. § 112(a) as failing to comply with the written description requirement, particularly with regard to (a) the subject matter relating to a salt of the claimed antibody conjugates, and (b) a sequence with an identity of greater than 70%, or greater than 75%, 80%, 85%, 90%, 95%, or 99% to the sequence as shown in SEQ ID NO: 3 or 4 recited in claims 7 and 9. (Id. at 150.)

155. The USPTO maintained the rejections against claims 2-12, 14, 16, and 23-26 under 35 U.S.C. § 103 as being obvious over Tikhomirov in view of Liu, Brand, and Chung. (Id. at 157.) The USPTO also maintained the §103 rejections against claim 15 over Tikhomirov in view of Liu, Brand, and Chung and further in view of Chari, against claims 27 and 35 over Tikhomirov in view of Liu, Brand, and Chung and further in view of Lievre, and against claims 28 and 36 over Tikhomirov in view of Liu, Brand, and Chung and further in view of DiNicolantonio. (Id. at 158-59.)

156. The USPTO reiterated the fact that Tikhomirov teaches anti-EGFR ADCs (e.g., a cetuximab-based anti-EGFR ADC) using a non-cleavable linker (e.g., MC linker) or a cleavable linker (e.g., a valine-citrulline linker). (Id. at 159-60.) In response to the Applicant's arguments that Tikhomirov teaches a cleavable linker as being a non-preferred embodiment of the antibody conjugates, the USPTO contended, by citing to M.P.E.P § 2123 II:

**Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments.** *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). **“A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.”** *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994).

Furthermore, “[t]he prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure

does not criticize, discredit, or otherwise discourage the solution claimed ...” *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1/46 (Fed. Cir. 2004).

(Id. at 160 (emphases added).)

157. With regard to the purported unexpected results associated with MYK-3 using a cleavable valine-citrulline linker asserted by the Applicant, the USPTO contended that:

Poison et al. (Cancer Research, 2009, Vol. 69, pp. 2358-2364) teach that antibody drug conjugates with cleavable linkers have broad efficacy and are relatively insensitive to target biology compare[d] to ADCs with a non-cleavable “MCC” linker (pages 2359-2360, bridging sentence). **Thus it was not unexpected that the antibody conjugates of Tikhomirov et al. having non-cleavable linkers were not that much more cytotoxic to k eratinocytes than the free antibody. Further, it was not unexpected that the antibody-MMAE conjugate with a valine-citrullene linker of the instant invention was more cytotoxic against cells bearing the target antigen than the corresponding antibody conjugates having a non-cleavable linker.**

(Id. (emphases added).)

158. In its response dated December 16, 2019, the Applicant made a minor amendment to independent claim 2 to remove “or a solvate of the salt.” (Id. at 231.) Claims 7 and 9 were amended to specify that the sequence identity is greater than 90%. (Id. at 232) To address the § 103 rejections against claims 2-12, 14, 16, and 23-26, the Applicant continued to argue that Tikhomirov discloses the valine-

citruiline cleavable linker as a non-favorable linker compared to a non-cleavable linker and that the claimed ADCs are unexpectedly superior to ADCs comprising non-cleavable linkers based on the results demonstrated by a single ADC, MYK-3. (Id. at 203.)

159. On January 17, 2020, the USPTO issued a Non-final Office Action, maintaining the rejections against claims 7 and 9 under 35 U.S.C. § 112(a) as failing to comply with the written description requirement and also rejecting claims 2-12, 14-16, 23-26, and 37 under 35 U.S.C. § 103 as being unpatentable over Tikhomirov in view of Liu, Brand, Chung, and Doronina et al., *Cancer Research*, 2006, Vol. 17, pp. 114-124 (“Doronina”). (Id. at 242-43.) Regarding the § 103 rejections, in addition to restating the teachings of Tikhomirov, Liu, Brand, and Chung, the USPTO stated that Doronina teaches that the mechanisms of drug release from an antibody conjugate having a non-cleavable linker involves complete degradation of the antibody and that drugs released from antibody drug conjugates utilizing non-cleavable linkers may be released in a modified form, and that many drugs lose activity as a result of the modification. (Id. at 247.) The USPTO further stated that Doronina concludes that the use of non-cleavable linkers may not be uniformly applicable for the linking of any drug to a targeting antibody because of the inability of all drugs to retain activity when released in a modified form. (Id.) Notably, Doronina teaches a cAC10-L1-MMAE conjugate having a cleavable linker and a

cAC10-L4-MMAE conjugate having a non-cleavable linker, wherein the conjugate with the cleavable linker has a potency of over 270 times that of the conjugate with the non-cleavable linker when tested on target cells *in vitro* (page 120. Table 3). (Id.) Accordingly, the USPTO concluded that it would have been obvious to use a cleavable linker rather than a non-cleavable linker in cases where the linked drug loses activity as a result of modification of the released drug, such as MMAE, in view of the teachings of Doronina regarding loss of drug activity as a result of degradation of the ADC resulting in release of a modified form of the drug that is not active. (Id. at 248.)

160. In its response dated March 26, 2020, the Applicant appeared to argue that the teaching of Doronina is not applicable because it relates to an anti-CD30 ADC. (Id. at 299-300.)

161. On July 18, 2020, the USPTO issued a Notice of Allowance without stating specific reasons for allowance, and indicated that claims 2-12, 14-16, 23-28, and 35-37 were allowed. (Id. at 311.)

### **C. The Priority Date of the '370 patent**

162. I understand that under the “Cross-reference to Related Application” of the '370 patent, the '995 Application from which the '370 patent was issued is a national phase application of International Application No. PCT/CN2016/073844, filed on February 16, 2016, which claims the benefit of Chinese Application No.

201510085038.8, filed on February 17, 2015 (“the ’038.8 Provisional” (EX1030, EX1035)).

163. I was told that to establish priority, the earlier application must describe the later-claimed invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought—which I understand to mean that the earlier disclosure must describe and enable the later-claimed invention with all of its limitations. I further understand that a plan to obtain or achieve the claimed invention in the future is insufficient to show possession at the time of filing.

164. I was asked to evaluate whether the ’038.8 Provisional sufficiently describes and enables the full scope of the Challenged Claims of the ’370 patent. Claim 1 of the ’370 patent 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 at 33:2-12 (emphasis added).) Claim 1 only specifies the sequences of the anti-EGFR antibody,

failing to specify any structural or functional features of the recited “cleavable linker” or “cytotoxic agent.” A POSA would have understood that claim 1 is extremely broad and covers various cleavable linkers and cytotoxic agents and various combinations of cleavable linkers and cytotoxic agents.

165. In particular, the recited “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. 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 claim 1 of the '370 patent. As with claim 1, claims 2-11 and 15-23 of the '370 patent also fail to further define the cleavable linker.

166. I have been informed that a provisional application can provide sufficient written description to support the full scope of a claim to this type of genus if the disclosure of the provisional application describes a representative number of species falling within the scope of the claimed invention or structural features common to the members of the claimed invention such that a POSA could visualize

or recognize its members. In my opinion, the '038.8 Provisional does not satisfy any of these requirements.

167. Indeed, the '038.8 Provisional only describes three 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 at 14;.EX1035 at 14) These mere four cleavable linkers are nowhere close to a representative number of species falling within the scope of the large genus of cleavable linkers. Nor does the '038.8 Provisional describe structural features common to the members of the large genus of cleavable linkers or provide guidance as to predict the common structural features.

168. Therefore, it is my opinion that the '038.8 Provisional does not provide sufficient written description to support the large and diverse genus of cleavable linkers as recited in claims 1-11 and 15-23 of the '370 patent.

169. Nor is the large genus of cleavable linkers enabled by the '038.8 Provisional. As recognized by the '370 patent, "it is highly complex and unpredictable whether an antibody drug conjugate becomes a safe and effective drug depending on a variety of factors." (EX1001 at 3:10-37.) One such factor according to the '370 patent is "characteristics of linker: whether the linker is cleavable or non-cleavable, and stability of the linker in blood." (Id.) Thus, the claimed cleavable

linker represents a diverse and unpredictable genus of cleavable linkers that requires substantive experimentation to assess the efficacy and safety of ADCs. Yet, the guidance in the '038.8 Provisional with regard to cleavable linkers is extremely limited. The '038.8 Provisional contains just three working examples (Examples 1-3), and all that is tested in Examples 1-3 is a single cleavable linker, valine-citrulline (val-cit). (EX1030 at 27-30; EX1035 at 28-32) Importantly, the '038.8 Provisional does not even compare the efficacy and safety of an ADC having a cleavable linker with that of an ADC having a non-cleavable linker.

170. As mentioned above, since the '038.8 Provisional does not describe structural features common to all species of the genus of cleavable linkers or provide sufficient guidance, identifying cleavable linkers falling within the very broad scope of the claimed genus requires substantial trial and error by constructing and characterizing a large number of candidate ADCs.

171. Thus, at least for the recited genus of cleavable linkers, a POSA would recognize that the '038.8 Provisional does not sufficiently describe and enable the full scope of claims 1-11 and 15-23 of the '370 patent.

172. I find that the '038.8 Provisional is similarly deficient in providing sufficient written description and enablement for the recited genus of cytotoxic agents. Similar to “cleavable linker,” the recited “cytotoxic agent” also represents a vast, diverse genus (e.g., hundreds of thousands) of cytotoxic agents. Cytotoxic

agents can include various classes of anti-tumor drugs, including alkylating agents, plant alkaloids, anti-tumor antibiotics, antimetabolites, and topoisomerase inhibitors, among others. (EX1035.) Auristatin, maytansinoid, calicheamicin, durcomycin, pyrrolbenzodiazepines, and amanitin are currently being used as payloads. (EX1015 at 8.) Each of these groups of cleavable linkers can give rise to entire subgenera of cytotoxic agents, thus further expanding the number of potential cytotoxic agents covered by claim 1 of the '370 patent. As with claim 1, claims 2-10, 12, and 14-23 of the '370 patent also fail to further define the cytotoxic agent.

173. Indeed, the '038.8 Provisional only describes MMAE, MMAF, maytansinoid alkaloids (e.g., Maytansine DM1, Maytansine DM4), Calicheamicin, duocarmycin MGBA, doxorubicin, ricin, diphtheria toxin and other toxins, I-131, interleukins, tumor necrosis factors, chemokines and nanoparticle as examples of cytotoxic agents. (EX1030 at 13-14; EX1035 at 14.) As recognized by the '370 patent, “it is highly complex and unpredictable whether an antibody drug conjugate becomes a safe and effective drug depending on a variety of factors.” (EX1001 at 3:10-37.) One such factor according to the '370 patent is “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.” (Id.) These limited examples are far from a representative number of species falling within the claimed scope of the large genus of cytotoxic

agents. Indeed, based on the small number of examples of cytotoxic agents, a POSA would not have envisaged cytotoxic agents having desirable characteristics that fall within the scope of the recited genus. Nor does the '038.8 Provisional describe structural features common to all members of the large genus of cytotoxic agents or provide guidance as to predict any such common structural features.

174. Furthermore, the large genus of cytotoxic agents claimed is not enabled by the '038.8 Provisional. As stated above, the characteristics of cytotoxic agents contribute to the complexity and unpredictability of safety and efficacy of ADCs. However, the guidance provided by the '038.8 Provisional for a POSA to make and use the claimed ADCs is very limited. The '038.8 Provisional does not describe the common structural features of cytotoxic agents required to obtain safe and efficacious ADCs. In fact, the only three working examples (Examples 1-3) in the '038.8 Provisional are all related to a single cytotoxic agent, MMAE. Given that different cytotoxic agents have different characteristics and complexity, and the unpredictability of the safety and efficacy of ADCs, a POSA would have to resort to significant experimentation by identifying cytotoxic agents falling within the very broad scope of the claimed genus and constructing and characterizing a large number of candidate ADCs.

175. Thus, at least for the recited genus of cytotoxic agents, a POSA would recognize that the '038.8 Provisional does not sufficiently describe and enable the full scope of claims 1-10, 12, and 14-23 of the '370 patent.

176. Therefore, it is my opinion that a POSA would recognize that at least claims 1-12 and 14-23 of the '370 patent are not entitled to the filing date of February 17, 2015 of the '038.8 Provisional.

## **IX. UNPATENTABILITY OF THE '370 PATENT**

177. As explained below, in my opinion, claims 1-23 of the '370 patent would have been obvious over the references discussed below and a POSA's general knowledge before the effective filing date of the '370 patent.

### **A. GROUND 1: CLAIMS 1-23 WOULD HAVE BEEN OBVIOUS OVER WEI AND LIU**

178. As discussed below, in my opinion, claims 1-19 would have been obvious in view of the state of the art and a POSA's general knowledge before the effective filing date of the '370 patent, in particular, Leanna and Liu. The teachings of Leanna and Liu are detailed above in Section VII.

#### **1. Claim 1**

179. Independent claim 1 recites:

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

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

180. SEQ ID NOs: 5-7 and 12-14 are the respective amino acid sequences of heavy chain and light chain CDRs of the BA03 antibody. (EX1001 at 18:1-31.)

181. In my opinion, claim 1 would have been obvious over Wei and Liu. A comparison between the ADC of claim 1 and the teachings of Leanna and Liu is provided in the chart below:

Claim 1 of the '370 patent	Prior Art
<p>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,</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><b>Wei</b> discloses: An anti-EGFR antibody-drug conjugate (EX1005 at [0229]), including the Y104D-Mc-vcPAB-MMAE ADC (id. at [0742], [1092]-[1141])) and a humanized version of this antibody, huY104D-MMAE ADC (id.), that comprises an anti-EGFR antibody (e.g., Y104D, huY104D) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (id. at [0742], [1092]-[1127], claims 27-40.)</p> <p><b>Liu</b> discloses: A humanized anti-EGFR antibody BA03 comprising a heavy chain and a light chain (EX1008 at 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</p>

	NOs: 5 to 7 (id. at [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 (id. at [0108], [0123], [0124]).
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182. As can be seen from the above chart, a combination of Wei and Liu teaches each and every feature of claim 1.

183. Wei discloses anti-EGFR ADCs, including the Y104D-Mc-vcPAB-MMAE ADC (also referred to as Y104D-MMAE ADC) and its humanized version, huY104D-Mc-vcPAB-MMAE ADC (also referred to as huY104D-MMAE ADC), which comprise a modified cetuximab antibody covalently linked to the cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker. (EX1005 at ¶¶ [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. at ¶ [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 (“Mc-vcPAB”). (Id. at ¶ [1103].)

184. Example 20 of Wei describes the results of in vivo studies of the Y104D-MMAE and huY104D-MMAE ADCs in a HT29 tumor xenograft model and a MDA-MB-231M human breast tumor xenograft model, both of which are

KRAS mutated, EGFR-positive tumor models. (Id. at ¶¶ [1116]-[1127], Example 20.) Wei concludes that, “These 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, “The anti-tumor response of each of the tested antibodies achieves tumor growth regression.” (Id. at ¶ [1127].)

185. Liu discloses and characterizes a humanized anti-EGFR antibody called BA03 – an IgG1 isotype anti-EGFR antibody and a humanized cetuximab antibody, which is the same BA03 antibody used in the ’370 patent to generate its preferred embodiment, the MYK-3 ADC. (EX1008 at ¶ [0060]; EX1001 at 18:3-6.) As discussed above at Section VII, the sequences of heavy chain variable regions, light chain variable regions, heavy chain constant regions, and light chain constant regions 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.

186. 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. at Examples 1-5, ¶¶ [0141]-[0146], Tables 1-3.) Furthermore, BA03 demonstrates

several advantageous properties of BA03, including: (1) a stronger activity than Erbitux in inhibiting phosphorylation of EGFR (id. at ¶ [0148], FIG. 3); (2) a higher ADCC activity than Erbitux (id. at ¶ [0150], FIG. 4); and (3) significantly lower immunogenicity compared to Erbitux (id. at ¶¶ [0152]-[0160], Table 4, FIG. 5).

187. In my opinion, a POSA would have been motivated to combine the teachings of Wei and Liu to arrive at the Challenged claims. Wei discloses a modified cetuximab antibody Y104D that differs from cetuximab by only one amino acid, out of several hundred. Wei recognizes that “humanized antibodies exhibit reduced immunogenicity as compared to cetuximab” and discloses a humanized cetuximab variant huY104D for forming the huY104D-MMAE ADC. (EX1005 at ¶¶ [0501], [1116].) Liu discloses and characterizes the BA03 antibody—a humanized version of cetuximab, and states that BA03 has several advantages over cetuximab, including stronger activity in inhibiting phosphorylation of EGFR, higher ADCC activity, and significantly lower immunogenicity. (EX1008 at Examples 1-5, Tables 1-4, and FIGs. 3-5.) The humanized anti-EGFR antibodies disclosed by these references are substantially identical.

188. Moreover, Wei discloses the huY104D-MMAE ADC containing the humanized cetuximab variant huY104D linked to the cytotoxic payload MMAE with a vc cleavable linker, which has the same vc-MMAE linker-payload disclosed as preferred embodiments in the '370 patent and covered by the Challenged Claims.

(EX1005 at ¶¶ [0742], [1116]; EX1001 at 5:25-6:65.) Since Wei teaches that ADCs with cleavable linkers were made using a modified version of the human mouse chimeric version of M225 (e.g., cetuximab variant Y104D), a POSA would have been strongly motivated to create ADCs using the humanized version of M225 (such as Liu's BA03 antibody), because both Wei and Liu recognize humanized antibodies had several advantages over chimeric antibodies, including reduced immunogenicity compared to cetuximab. (EX1005 at ¶¶ [0501], [1116]; EX1008 at Examples 1-5, Tables 1-4, and FIGs. 3-5.) In fact, 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. Notably, Wei teaches that its humanized cetuximab variant ADCs exhibited more selective killing of tumor cells by reducing growth inhibition of non-tumor cells compared to the chimeric antibody at physiological pH. (EX1005 at ¶ [1139].) Thus, Wei provides further motivation for a POSA to create ADCs with a humanized anti-EGFR antibody, such as BA03.

189. Therefore, for at least the above reasons, claim 1 would have been obvious over Wei and Liu.

190. I am aware of the unexpected result arguments presented by Patent Owner during prosecution of the '370 patent. (See, e.g., EX1004 at 139.)

Specifically, Patent Owner argued that based on the results in Example 6, MYK-3 has a lower EC50 value compared to BA03-MC-MMAE and BA03-MCC-MMAE. (Id.)

191. In my opinion, the result in Example 6 is not unexpected. First, the argument presented by Patent Owner that “the effect of the linker type on the efficacy of ADCs is different” is not supported by experimental evidence. (Id. at 205.) By contrast, 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 selected cleavable linker (Val-Cit) displayed very potent efficacy both *in vitro* and *in vivo*, as well as favorable safety profile and stability. (See, e.g., EXS1026, 1027, 1028.) All these studies support that the linker has potent efficacy irrespective of the target and mAb used. Therefore, the finding that MYK-3 demonstrated good efficacy is not unexpected.

192. Second, it was known in the art that drugs linked by cleavable linkers, such as vcMMAE, are more likely to have the bystander effect (see Section VI) and anti-EGFR mAbs conjugated to vcMMAE show potent antitumor activity *in vivo* and *in vitro*. (See, e.g., EXS1031, 1032).

193. Furthermore, the finding that neither MC-MMAE nor MCC-MMAE have any activity is nothing unexpected. As discussed in Section VI, McCombs et al. mention specifically 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.”** (EX1015 at 6.) Thus, it is expected that only vcMMAE will be active, but not the non-cleavable linkers, despite all three variants having the same degree of labeling.

194. Thus, in my opinion, the unexpected results arguments based on the comparison in Fig. 12 of the '370 patent between BA03-vc-MMAE, BA03-MC-MMAE, and BA03-MCC-MMAE are seriously flawed.

195. Even assuming there is an unexpected result, in my opinion, the result obtained from an ADC based on a single anti-EGFR antibody BA03, a single cleavable valine citrulline (vc) linker, and a single cytotoxic agent cannot support the full scope of the vast genus (e.g., hundreds of thousands) of claimed ADCs that do not specify the cleavable linker and the cytotoxic agent.

196. As a POSA would have understood, the recited “cleavable linker” represents a vast, diverse genus of cleavable linkers. 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 at 7-8.) Each of these groups of cleavable linkers also represents a large subgenus of cleavable linkers, thus further expanding the number of potential cleavable linkers covered by claim 1 of the '370 patent.

197. Similarly, the recited “cytotoxic agent” also represents a vast, diverse genus of cytotoxic agents. Cytotoxic agents can include various classes of anti-tumor drugs, including alkylating agents, plant alkaloids, anti-tumor antibiotics, antimetabolites, and topoisomerase inhibitors, among others. Auristatin, maytansinoid, calicheamicin, durcomycin, pyrrolbenzodiazepines, and amanitin are currently being used as payloads. (EX1015 at 8.) Each of these groups of cleavable linkers also represents a large subgenus of cytotoxic agents, thus further expanding the number of potential cytotoxic agents covered by claim 1 of the ’370 patent.

198. Moreover, ADCs can be formed from any combination of any of the large number of cleavable linkers and any of the large number of cytotoxic agents, resulting in an astronomical number of ADCs covered by claim 1 of the ’370 patent. The number of ADCs is at least a combinatorial product of multiplication of the number of cleavable linkers and the number of cytotoxic agents. For example, if there are 500 cleavable linkers in the cleavable linker genus and 500 cytotoxic agents in the cytotoxic agent genus, there would be at least 250,000 ADCs. A POSA would have understood that the number would be even larger when the number of possible anti-EGFR antibodies is additionally considered.

199. Since the purported unexpected result was obtained from a single ADC, MYK-3, a POSA would have understood that such a result cannot be generalizable to other ADC species covered by claim 1 of the ’370 patent. Indeed, the ’370 patent

itself recognizes “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 at 3:10-37.)

200. Therefore, in my opinion, 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 of the '370 patent.

201. I understand that no additional secondary considerations were asserted during prosecution. I reserve the right to address any secondary considerations set forth by Patent Owner in any later response to this declaration or the petition it accompanies.

## **2. Claim 2**

202. In my opinion, claim 2 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 2 depends from claim 1 and recites “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.”

203. 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 at 18:1-36.)

204. As discussed above for claim 1, the '370 patent indicates that the “BA03 antibody of the present invention” was described in Liu. (Id. at 18:3-6.) Thus, 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.

205. Accordingly, claim 2 of the '370 patent would have been obvious to a POSA over the prior art.

## **3. Claim 3**

206. In my opinion, claim 3 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 3 depends from claim 1 and recites, “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.”

207. 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. at 18:1-36.)

208. 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. at 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.

209. Accordingly, claim 3 of the '370 patent would have been obvious to a POSA over the prior art.

#### **4. Claim 4**

210. In my opinion, claim 4 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 4 depends from claim 1 and recites, “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.”

211. The BA03 antibody taught by Liu has a human IgG1 constant region. (EX1008 at ¶ [0037].) Similarly, the Y104D (or huY104D) antibody taught by Wei also contains a human IgG1 constant region at least because cetuximab has a human IgG1 constant region. (EX1005 at ¶¶ [0558], [0559].)

212. Accordingly, claim 4 of the '370 patent would have been obvious to a POSA over the prior art.

### **5. Claim 5**

213. In my opinion, claim 4 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 4. Claim 5 depends from claim 4 and recites, “the IgG is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.”

214. As stated above for claim 4, both the Y104D (or huY104D) antibody taught by Wei and the BA03 antibody taught by Liu have a human IgG1 constant region. (EX1008 at ¶ [0037]; EX1005 at ¶¶ [0558], [0559].)

215. Accordingly, claim 5 of the '370 patent would have been obvious to a POSA over the prior art.

### **6. Claim 6**

216. In my opinion, claim 6 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 4. Claim 6 depends from claim 4 and recites, “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.”

217. 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 at 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.”

218. Accordingly, claim 6 of the '370 patent would have been obvious to a POSA over the prior art.

## **7. Claim 7**

219. In my opinion, claim 7 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

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

221. Accordingly, claim 7 of the '370 patent would have been obvious to a POSA over the prior art.

### **8. Claim 8**

222. In my opinion, claim 8 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 7. 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.”

223. SEQ ID NO: 4 is the amino acid sequence of the constant region of the light chain of the BA03 antibody. As discussed above for claim 1, the '370 patent indicates that the “BA03 antibody of the present invention” was described in Liu. (EX1001 at 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.”

224. Accordingly, claim 8 of the '370 patent would have been obvious to a POSA over the prior art.

### **9. Claim 9**

225. In my opinion, claim 9 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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)<sub>p</sub> 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.

226. Wei teaches an ADC represented by the formula: Ab-(L)<sub>q</sub>-(targeted agent)<sub>m</sub>, where q is 0 or more and m is at least 1. (EX1005 at ¶ [0665].) Wei also discloses the final conjugated product Y104D-Mc-VcPAB-MMAE (also referred to as Y104D-MMAE) had a drug:antibody (DAR) ratio of approximately 4 as assessed by hydrophobic interaction chromatography. (Id. at ¶ [1103].)

227. Thus, a combination of Wei and Liu teaches an anti-EGFR ADC that can be represented by formula Ab-(L-D)<sub>p</sub>, 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.

228. Accordingly, claim 9 of the '370 patent would have been obvious to a POSA over the prior art.

## **10. Claim 10**

229. In my opinion, claim 10 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9. Claim 10 depends from claim 9 and recites, “the cytotoxic agent is selected from the group consisting of chemotherapeutic agents, radioisotopes, antibiotics, enzymes, and biologically active peptides.”

230. Wei teaches that the cytotoxic agent is “a therapeutic moiety, such as a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.” (EX1005 at ¶ [0230].) Wei further discloses that “the therapeutic moiety is a maytansine derivative that is a maytansinoid, such as ansamitocin or mertansine (DM1); an auristatin or a functional peptide analog or derivative thereof, such as monomethyl auristatin E (MMAE) or F (MMAF).” (Id. at ¶ [0231].)

231. Accordingly, claim 10 of the '370 patent would have been obvious to a POSA over the prior art.

## **11. Claim 11**

232. In my opinion, claim 11 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 10. Claim 11 depends from claim 10 and recites, “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.”

233. Wei further discloses that the cytotoxic agent is “an auristatin or a functional peptide analog or derivative thereof, such as monomethyl auristatin E (MMAE) or F (MMAF).” (Id. at ¶ [0231].)

234. Accordingly, claim 11 of the ’370 patent would have been obvious to a POSA over the prior art.

## **12. Claim 12**

235. In my opinion, claim 12 of the ’370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9. Claim 12 depends from claim 9 and recites, “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).”

236. Wei teaches the Y104D-Mc-vcPAB-MMAE ADC that contains a MC-vc-PAB linker. (Id. at ¶¶ [0740], [1103], claim 40.)

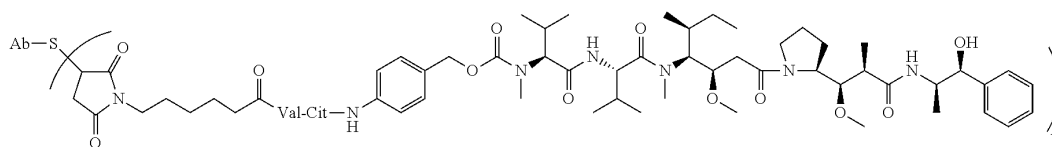
237. Accordingly, claim 12 of the ’370 patent would have been obvious to a POSA over the prior art.

### 13. Claim 13

238. In my opinion, claim 13 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9.

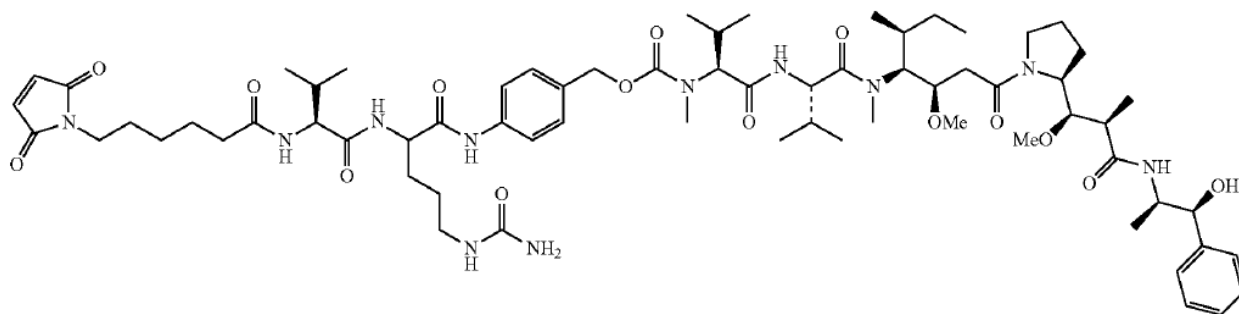
Claim 13 depends from claim 9 and recites:

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.

239. Wei teaches the Y104D-Mc-vcPAB-MMAE ADC contains a MC-vc-PAB-MMAE linker-drug, which is represented by the following structure:



(Id. at ¶¶ [0740], [0742], [1103], claim 40.)

240. Furthermore, as stated above, Y104D-Mc-VcPAB-MMAE as disclosed by Wei had a drug: antibody (DAR) ratio of approximately 4, which falls within the recited range of 1-9. (Id. ¶ [1103].)

241. Accordingly, claim 13 of the '370 patent would have been obvious to a POSA over the prior art.

#### **14. Claim 14**

242. In my opinion, claim 14 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9. Claim 14 depends from claim 9 and recites, “the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB).”

243. As stated above, Wei teaches the Y104D-Mc-vcPAB-MMAE ADC contains a MC-vc-PAB linker. (Id. at ¶¶ [0740], [1103], claim 40.)

244. Accordingly, claim 14 of the '370 patent would have been obvious to a POSA over the prior art.

#### **15. Claim 15**

245. In my opinion, claim 15 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

246. Wei teaches pharmaceutical compositions that include the anti-EGFR conjugates as disclosed and “a pharmaceutical acceptable carrier or excipient.” (Id. at ¶¶ [0238], [0861]-[0875].)

247. Accordingly, claim 15 of the '370 patent would have been obvious to a POSA over the prior art.

### **16. Claim 16**

248. In my opinion, claim 16 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

249. Wei teaches 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.” (EX1005 at ¶ [0666].) Wei also 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. at ¶ [0239].)

250. Accordingly, claim 16 of the '370 patent would have been obvious to a POSA over the prior art.

### **17. Claim 17**

251. In my opinion, claim 17 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 16. Claim 17 depends from claim 16 and recites, “the disease associated with epidermal growth factor receptor (EGFR) is a tumor associated with overexpression of EGFR.”

252. As stated above, Wei teaches that its anti-EGFR ADCs can be used for treating a condition responsive to treatment with an anti-EGFR antibody in a subject. (Id. at ¶ [0239].) Wei further teaches that “conditions responsive to treatment with an anti-EGFR antibody” refers to any disease or condition that is associated with or caused by aberrant EGFR signaling or overexpression of EGFR and that “EGFR-associated diseases or conditions or conditions responsive to treatment with an anti-EGFR antibody include cancers, such as, but not limited to, colorectal cancer,

squamous cell cancer of the head and neck and non-small-cell lung cancer.” (Id. at ¶ [0442].)

253. Accordingly, claim 17 of the ’370 patent would have been obvious to a POSA over the prior art.

### **18. Claim 18**

254. In my opinion, claim 18 of the ’370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

255. Wei teaches methods for treating a subject comprising administering a therapeutically effective amount of a pharmaceutical composition comprising an anti-EGFR ADC, wherein 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. at ¶¶ [0441-458], [1086]-[1127], claims 48 and 58.)

256. Accordingly, claim 18 of the ’370 patent would have been obvious to a POSA over the prior art.

## 19. Claim 19

257. In my opinion, claim 19 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 18. Claim 19 depends from claim 18 and recites, “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.”

258. Wei teaches that “conditions responsive to treatment with an anti-EGFR antibody” refers to any disease or condition that is associated with or caused by aberrant EGFR signaling or overexpression of EGFR and that “EGFR-associated diseases or conditions or conditions responsive to treatment with an anti-EGFR antibody include cancers, such as, but not limited to, colorectal cancer, squamous cell cancer of the head and neck and non-small-cell lung cancer.” (Id. at ¶ [0442].) Wei also 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. at ¶ [0903].)

259. Accordingly, claim 19 of the '370 patent would have been obvious to a POSA over the prior art.

## **20. Claim 20**

260. 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.”

261. Wei discloses the results of in vivo studies of the Y104D-MMAE and huY104D-MMAE ADCs in a HT29 tumor xenograft model and a MDA-MB-231M human breast tumor xenograft model, both of which are KRAS mutated, EGFR-positive tumor models. Wei reported 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. at ¶¶ [1116]-[1127].)

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

## **21. Claim 21**

263. 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.”

264. As discussed above, Wei discloses that the results of in vivo studies of the Y104D-MMAE and huY104D-MMAE ADCs in a MDA-MB-231M human breast tumor xenograft model and shows that these ADCs exhibited a strong anti-tumor response and achieved tumor growth regression. (Id. at ¶¶ [1116]-[1127].) The HT29 tumor xenograft model and MDA-MB-231M human breast tumor xenograft model are known to have BRAF gene mutation. (EX1033 at 1; EX1018 at Abstract (“MDA-MB-231 (KRASG13D and BRAF-G464V mutations”).)

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

## **22. Claim 22**

266. 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.”

267. As discussed above, Wei discloses that the Y104D-MMAE and huY104D-MMAE ADCs exhibited a strong anti-tumor response and achieved tumor growth regression based on the results of in vivo studies of these ADCs in a HT29 tumor xenograft model and a MDA-MB-231M human breast tumor xenograft

model, both of which are KRAS-mutated, EGFR-positive tumor models. (EX1005. at ¶¶ [1116]-[1127].)

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

### **23. Claim 23**

269. 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.”

270. As discussed above, the HT29 tumor xenograft model and the MDA-MB-231M human breast tumor xenograft model are known to have BRAF gene mutations. (See EX1033 at 1; EX1018 at Abstract, 4.)

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

### **B. GROUND 2: CLAIMS 1-23 WOULD HAVE BEEN OBVIOUS OVER LEANNA AND LIU IN VIEW OF WEI**

272. As discussed below, in my opinion, claims 1-23 would have been obvious in view of the state of the art and a POSA’s general knowledge before the effective filing date of the ’370 patent, in particular, Leanna and Liu in view of Wei. The teachings of Leanna, Liu, and Wei are detailed above in Section VII.

## 1. Claim 1

273. Independent claim 1 recites:

**Claim 1:** An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker, wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain, wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.

274. SEQ ID NOs: 5-7 and 12-14 are the respective amino acid sequences of heavy chain and light chain CDRs of the BA03 antibody. (EX1001 at 18:1-31.)

275. In my opinion, claim 1 would have been obvious over Leanna and Liu in view of Wei. A comparison between the ADC of claim 1 and the teachings of Leanna and Liu in view of Wei is provided in the chart below:

<b>Claim 1 of the '370 patent</b>	<b>Prior Art</b>
1. An antibody-drug conjugate or a pharmaceutically acceptable salt thereof, comprising an anti-epidermal growth factor receptor antibody covalently linked to a cytotoxic agent via a cleavable linker, wherein the anti-epidermal growth factor receptor antibody comprises a heavy chain and a light chain,	<b>Leanna</b> discloses: An anti-EGFR antibody-drug conjugate, including Antibody 1-vc-MMAE ADC that comprises a humanized anti-EGFR antibody (i.e., Antibody 1) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (EX1006 at 32:1-18).  <b>Liu</b> discloses: A humanized anti-EGFR antibody BA03 comprising a heavy chain and a

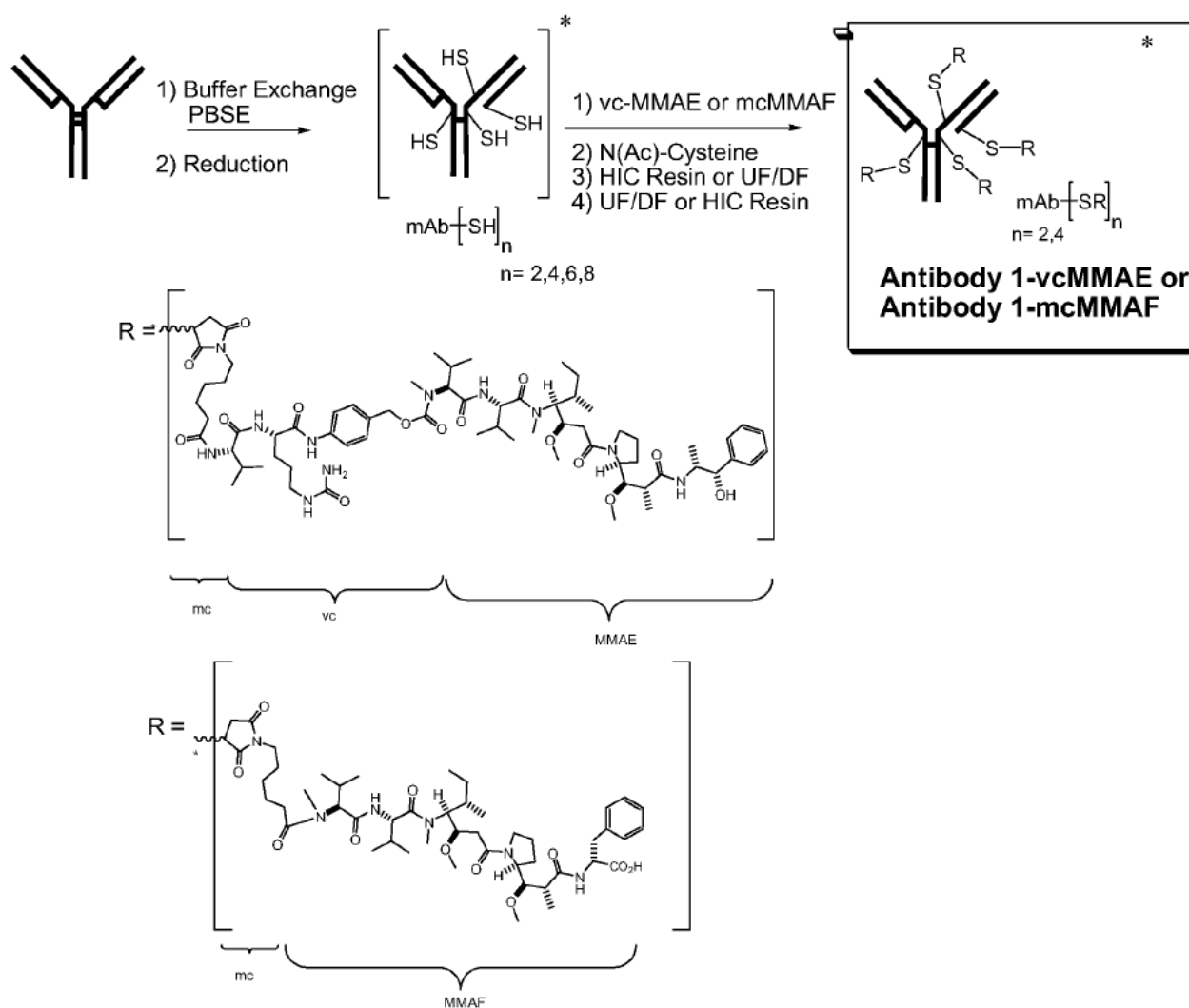
<p>wherein the heavy chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 5 to 7, and the light chain has a variable region comprising CDR1, CDR2 and CDR3 having sequences as shown in SEQ ID NOs: 12 to 14.</p>	<p>light chain (EX1008 at Examples 1-5, [00141]-[0146], 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 (id. at [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 (id. at [0108], [0123], [0124]).</p> <p><b>Wei</b> 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.e., Y104D) covalently linked to a cytotoxic agent MMAE via a cleavable valine-citrulline (vc) linker (EX1005 at [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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276. As can be seen from the above chart, a combination of Leanna and Liu in view of Wei teaches each and every feature of claim 1.

277. Leanna discloses ADCs comprising an anti-EGFR antibody and a cytotoxic agent, such as MMAE or MMAF. (EX1006 at Abstract, 3:1-5, 4:25-31.)

Leanna discloses that MMAE is conjugated to the antibody via a cleavable valine-citrulline (vc) linker. (Id. at 6:6-8.)

278. In particular, Leanna discloses an Antibody 1-vc-MMAE ADC. (Id. at 24:8-18.) Antibody 1 is a humanized IgG1 isotype anti-EGFR antibody that was previously disclosed in WO 2011/041319 and US20110076232. (Id. at 26.) The Antibody 1-vc-MMAE ADC is depicted in Figure 1 (reproduced below):



279. Leanna also discloses detailed processes for preparing the Antibody 1-vc-MMAE ADC (Example 1), purification of the ADC (Example 2), and scaling up of batch purification of the ADC (Example 3). (Id. at 48:1-58:15.)

280. 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. (EX1008 at ¶ [0060]; EX1001 at 18:3-6.) Indeed, the '370 patent states that, “The antibody BA03 of the present invention was BA03 as described in the Chinese invention patent application CN103772504A, and its preparation method could be seen in Example 3 of this patent application.” (EX1001 at 18:3-6.) CN103772504A is referred to as “Liu” in this declaration. As described in Section VII above, through sequence alignment analysis, I confirmed that the sequences of the heavy chain variable region, light chain variable region, heavy chain constant region, and light chain constant region of the BA03 antibody disclosed in Liu are identical to those of the BA03 antibody used 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.

281. In addition, Liu also 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 at

Examples 1-5, ¶¶ [00141]-[0146], Tables 1-3.) Furthermore, Liu demonstrates several advantageous properties of BA03, including: (1) a stronger activity than Erbitux in inhibiting phosphorylation of EGFR (id. at ¶ [0148], FIG. 3); (2) a higher ADCC activity than Erbitux (id. at ¶ [0150], FIG. 4); and (3) significantly lower immunogenicity compared to Erbitux (id. at ¶¶ [0152]-[0160], Table 4, FIG. 5).

282. In view of Liu's teachings, a POSA would have been motivated to modify the Antibody 1-vc-MMAE ADC disclosed in Leanna by replacing the humanized anti-EGFR antibody Antibody 1 with another humanized anti-EGFR antibody, such as BA03, having demonstrated superior properties in multiple aspects to arrive at the claimed ADC. A POSA would also have had a reasonable expectation of success in such a modification, because Leanna teaches detailed processes for preparing the Antibody 1-vc-MMAE ADC (Example 1), purification of the ADC (Example 2), and scaling up of batch purification of the ADC (Example 3). (EX1006 at 48:1-58:15.)

283. Moreover, Wei discloses a Y104D-Mc-vcPAB-MMAE ADC containing the cetuximab variant Y104D covalently linked to the cytotoxic agent MMAE via a cleavable linker vcPAB, which contains the same linker-drug (vc-PAB-MMAE) as in the preferred embodiments disclosed by the '370 patent and as covered by the Challenged Claims. Wei further discloses that Y104D-Mc-vcPAB-MMAE ADCs exhibited a strong anti-tumor response and achieved tumor

growth regression. (EX1005 at ¶¶ [1116]-[1127].) In view of Wei's disclosure that a modified cetuximab had been used in its Y104D-Mc-vcPAB-MMAE ADC with cleavable linkers and the anti-tumor activity of the Y104D-Mc-vcPAB-MMAE ADC, a POSA would have been motivated to generate anti-EGFR ADCs using the humanized cetuximabBA03 antibody, because humanized antibodies, such as BA03, had several advantages over chimeric antibodies, including lower immunogenicity, as specifically disclosed by Liu.

284. Therefore, for at least the foregoing reasons, claim 1 of the '370 patent is obvious at least over the references discussed above.

## **2. Claim 2**

285. In my opinion, claim 2 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 2 depends from claim 1 and recites "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."

286. 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 at 18:1-36.)

287. As discussed above for claim 1, the '370 patent indicates that the "BA03 antibody of the present invention" was described in Liu. (Id. at 18:3-6.)

Thus, 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.

288. Accordingly, claim 2 of the '370 patent would have been obvious to a POSA over the prior art.

### **3. Claim 3**

289. In my opinion, claim 3 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 3 depends from claim 1 and recites, “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.”

290. 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. at 18:1-36.)

291. 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. at 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.

292. Accordingly, claim 3 of the '370 patent would have been obvious to a POSA over the prior art.

#### **4. Claim 4**

293. In my opinion, claim 4 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. Claim 4 depends from claim 1 and recites, “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.”

294. Both the BA03 antibody taught by Liu and Antibody 1 taught by Leanna have a human IgG1 constant region. (EX1008 at ¶ [0037]; EX1006 at 26.)

295. Accordingly, claim 4 of the '370 patent would have been obvious to a POSA over the prior art.

#### **5. Claim 5**

296. In my opinion, claim 4 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 4. Claim 5 depends from claim 4 and recites, “the IgG is selected from the group consisting of IgG1, IgG2, IgG3 and IgG4.”

297. As stated above for claim 4, both the BA03 antibody taught by Liu and Antibody 1 taught by Leanna have a human IgG1 constant region. (EX1008 at ¶ [0037]; EX1006 at 26.)

298. Accordingly, claim 5 of the '370 patent would have been obvious to a POSA over the prior art.

## **6. Claim 6**

299. In my opinion, claim 6 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 4. Claim 6 depends from claim 4 and recites, “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.”

300. 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 at 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.”

301. Accordingly, claim 6 of the '370 patent would have been obvious to a POSA over the prior art.

## **7. Claim 7**

302. In my opinion, claim 7 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

303. Liu teaches that the BA03 antibody has a human kappa light chain constant region. (EX1008 at ¶ [0037].)

304. Accordingly, claim 7 of the '370 patent would have been obvious to a POSA over the prior art.

## **8. Claim 8**

305. In my opinion, claim 8 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 7. 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.”

306. SEQ ID NO: 4 is the amino acid sequence of the constant region of the light chain of the BA03 antibody. As discussed above for claim 1, the '370 patent indicates that the “BA03 antibody of the present invention” was described in Liu. (EX1001 at 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.”

307. Accordingly, claim 8 of the '370 patent would have been obvious to a POSA over the prior art.

### **9. Claim 9**

308. In my opinion, claim 9 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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)<sub>p</sub> 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.

309. Leanna teaches the Antibody 1-vc-MMAE ADC that has an average Antibody Ratio (DAR) of 3.85, which falls within the recited range of 1-9. (EX1006 at 32:1-18, 49:22-27, FIG. 1.) Thus, a combination of Leanna and Liu teaches an anti-EGFR ADC that can be represented by formula Ab-(L-D)<sub>p</sub>, 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.

310. Accordingly, claim 9 of the '370 patent would have been obvious to a POSA over the prior art.

#### **10. Claim 10**

311. In my opinion, claim 10 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9. Claim 10 depends from claim 9 and recites, “the cytotoxic agent is selected from the group consisting of chemotherapeutic agents, radioisotopes, antibiotics, enzymes, and biologically active peptides.”

312. Leanna teaches the Antibody 1-vc-MMAE ADC containing the cytotoxic agent MMAE that is a chemotherapeutic agent shown to possess anticancer activity by interfering with microtubule dynamics and GTP hydrolysis. (EX1006 at 28:12-29:3.)

313. Accordingly, claim 10 of the '370 patent would have been obvious to a POSA over the prior art.

#### **11. Claim 11**

314. In my opinion, claim 11 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 10. Claim 11 depends from claim 10 and recites, “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.”

315. Leanna teaches the Antibody 1-vc-MMAE ADC containing the cytotoxic agent MMAE. (Id. at 32:1-18, 49:22-27, FIG. 1.)

316. Accordingly, claim 11 of the '370 patent would have been obvious to a POSA over the prior art.

## **12. Claim 12**

317. In my opinion, claim 12 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9. Claim 12 depends from claim 9 and recites, “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).”

318. Leanna teaches the Antibody 1-vc-MMAE ADC containing the cleavable valine-citrulline (val-cit; vc) linker. (Id. at 32:1-18, 49:22-27, FIG. 1.)

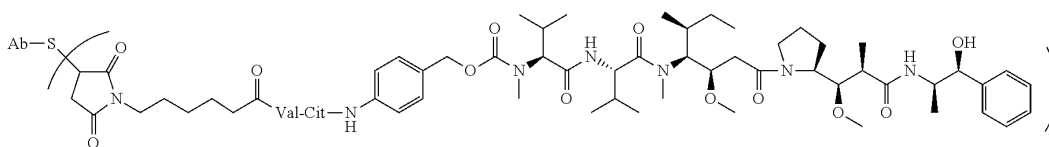
319. Accordingly, claim 12 of the '370 patent would have been obvious to a POSA over the prior art.

### 13. Claim 13

320. In my opinion, claim 13 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9.

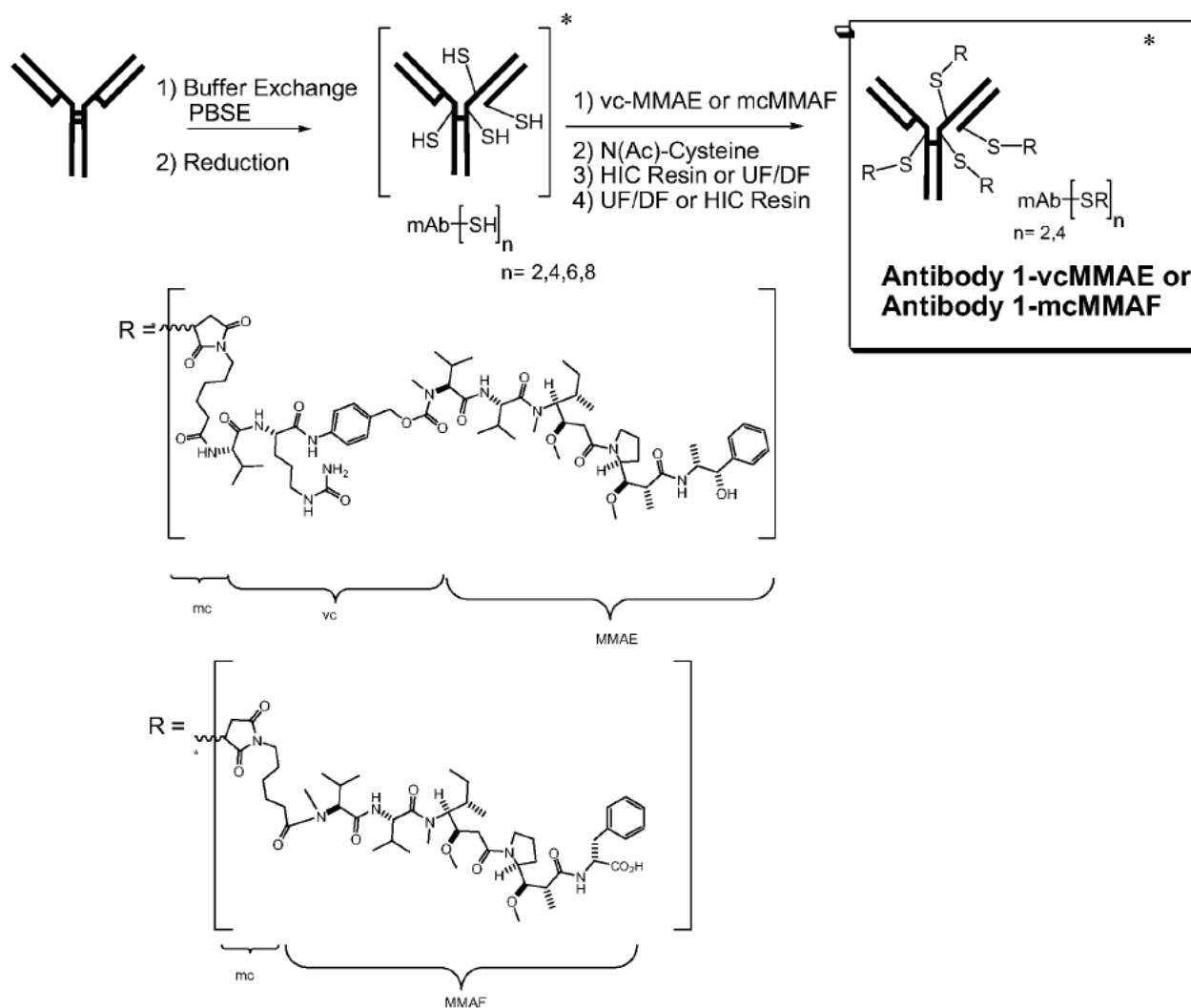
Claim 13 depends from claim 9 and recites:

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.

321. Leanna teaches the Antibody 1-vc-MMAE ADC (more specifically, Antibody 1-MC-vc-PAB-MMAE) as depicted in Figure 1 of Leanna. The chemical structure of the linker-drug is identical to the recited chemical structure of claim 13. The average Drug to Antibody Ratio (DAR) for Antibody 1-vcMMAE was 3.85. (Id. at 49: 22-27.)



322. Accordingly, claim 13 of the '370 patent would have been obvious to a POSA over the prior art.

#### 14. Claim 14

323. In my opinion, claim 14 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 9. Claim 14 depends from claim 9 and recites, "the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzoyloxycarbonyl (MC-vc-PAB)."

324. As stated above, Leanna teaches the Antibody 1-vc-MMAE ADC (more specifically, Antibody 1-MC-vc-PAB-MMAE). (Id. at FIG. 1.)

325. Accordingly, claim 14 of the '370 patent would have been obvious to a POSA over the prior art.

### **15. Claim 15**

326. In my opinion, claim 15 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

327. 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. at 35:20-36:3.)

328. Accordingly, claim 15 of the '370 patent would have been obvious to a POSA over the prior art.

### **16. Claim 16**

329. In my opinion, claim 16 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

330. 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. (Id. at 34:9-14.)

331. Accordingly, claim 16 of the '370 patent would have been obvious to a POSA over the prior art.

### **17. Claim 17**

332. In my opinion, claim 17 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 16. Claim 17 depends from claim 16 and recites, “the disease associated with epidermal growth factor receptor (EGFR) is a tumor associated with overexpression of EGFR.”

333. 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. at 13:1-30, 33:14-34:22.)

334. Accordingly, claim 17 of the '370 patent would have been obvious to a POSA over the prior art.

### **18. Claim 18**

335. In my opinion, claim 18 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claim 1. 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.”

336. 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 tumor progression. (Id. at 32:27-34:14.)

337. Accordingly, claim 18 of the '370 patent would have been obvious to a POSA over the prior art.

### **19. Claim 19**

338. In my opinion, claim 19 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1 and 18.

Claim 19 depends from claim 18 and recites, “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.”

339. Leanna teaches that 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. at 13:1-30, 33:14-34:22.)

340. Accordingly, claim 19 of the '370 patent would have been obvious to a POSA over the prior art.

## **20. Claim 20**

341. In my opinion, claim 20 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 16, and 17. Claim 20 depends from claim 17 and recites, “the tumor is a tumor with KRAS gene mutation.”

342. As discussed in Ground 1 above with respect to claim 20, Wei discloses the results of *in vivo* studies of the Y104D-MMAE and huY104D-MMAE ADCs in a HT29 tumor xenograft model and a MDA-MB-231M human breast tumor xenograft model, both of which are KRAS-mutated, EGFR-positive tumor models.

Wei reported 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.” (EX1005 at ¶¶ [1116]-[1127].)

343. Accordingly, claim 20 of the ’370 patent would have been obvious to a POSA over the prior art.

## **21. Claim 21**

344. In my opinion, claim 21 of the ’370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 16, and 17. Claim 21 depends from claim 17 and recites, “the tumor is a tumor with BRAF gene mutation.”

345. As discussed in Ground 1 above with respect to claim 21, Wei discloses that the results of in vivo studies of the Y104D-MMAE and huY104D-MMAE ADCs in an MDA-MB-231M human breast tumor xenograft model and shows that these ADCs exhibited a strong anti-tumor response and achieved tumor growth regression. (Id. at ¶¶ [1116]-[1127].) The MDA-MB-231M human breast tumor xenograft model is known to have BRAF gene mutations. (See EX1018 at Abstract (“MDA-MB-231 (KRASG13D and BRAF-G464V mutations)”)).

346. Accordingly, claim 21 of the ’370 patent would have been obvious to a POSA over the prior art.

## **22. Claim 22**

347. In my opinion, claim 22 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 18, and 19. Claim 22 depends from claim 19 and recites, “the tumor is a tumor with KRAS gene mutation.”

348. As discussed in Ground 1 above with respect to claim 22, Wei discloses that the Y104D-MMAE and huY104D-MMAE ADCs exhibited a strong anti-tumor response and achieved tumor growth regression based on the results of in vivo studies of these ADCs in a HT29 tumor xenograft model and a MDA-MB-231M human breast tumor xenograft model, both of which are KRAS-mutated, EGFR-positive tumor models. (EX1005 at ¶¶ [1116]-[1127].)

349. Accordingly, claim 22 of the '370 patent would have been obvious to a POSA over the prior art.

## **23. Claim 23**

350. In my opinion, claim 23 of the '370 patent would also have been obvious in view of the prior art as discussed above with respect to claims 1, 18, and 19. Claim 23 depends from claim 19 and recites, “the tumor is a tumor with BRAF gene mutation.”

351. As discussed in Ground 1 above with respect to claim 23, the HT29 tumor xenograft model and the MDA-MB-231M human breast tumor xenograft

model are known to have BRAF gene mutations. (See EX1033 at 1; EX1018 at Abstract, 4.)

352. Accordingly, claim 23 of the '370 patent would have been obvious to a POSA over the prior art.

## **X. CONCLUSION**

353. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

354. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Signature:  \_\_\_\_\_

Stylianios Bournazos, Ph.D.

Date: 02/27/2025

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### **Education**

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<b>BSc (Hons) in Genetics – Immunology (First Class Honors)</b> University of Aberdeen, Aberdeen, United Kingdom	2002 – 2005
<b>MSc (by Research) in Life Sciences (with Distinction)</b> University of Edinburgh, Edinburgh, United Kingdom	2005 – 2006
<b>PhD in Immunology</b> University of Edinburgh, Edinburgh, United Kingdom	2006 – 2010
<b>Postdoctoral Training</b> The Rockefeller University, New York, NY	2010 – 2015

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### **Positions and Appointments**

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2021 – present	<b>Research Associate Professor</b> , The Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York, NY
2023 – 2024	<b>Visiting Scientist</b> , Università della Svizzera Italiana Institute for Research in Biomedicine, Bellinzona, Switzerland
2016 – 2021	<b>Research Assistant Professor</b> , The Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York, NY
2015 – 2016	<b>Research Associate</b> , The Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York, NY
2013 – 2015	<b>Postdoctoral Fellow</b> , The Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York, NY
2010 – 2013	<b>Postdoctoral Associate</b> , The Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York, NY
2006 – 2010	<b>Graduate Research Fellow</b> , MRC Center for Inflammation Research, Edinburgh, United Kingdom
2006 – 2009	<b>Clinical Research Assistant</b> , Department of Cardiology, NHS Lothian Royal Infirmary of Edinburgh, United Kingdom
2005 – 2006	<b>MSc Research Student</b> , University of Edinburgh/British Heart Foundation Center for Cardiovascular Science, Edinburgh, United Kingdom
2004 – 2005	<b>Undergraduate Research Fellow</b> , University of Aberdeen, United Kingdom

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## Honors and Awards

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University of Aberdeen Brenda Page Memorial Prize in Genetics 2005  
British Heart Foundation MSc/PhD Fellowship 2005-2009  
University of Edinburgh Center for Cardiovascular Science Travel Fellowship 2005  
Biochemical Society Student Travel Grant 2008  
IUBMB-FEBS Travel Bursary 2008  
British Heart Foundation Travel Fellowship 2008, 2009  
NIH-Northeast Biodefense Center (NBC) Career Development Award 2011  
American Heart Association Founders Affiliate Postdoctoral Research Fellowship 2013  
amfAR Mathilde Krim Fellowship in Basic Biomedical Research 2014  
Gilead Sciences HIV Scholar Award 2017  
Wellcome Trust Discovery Award 2024

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## Patents

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### *Issued and pending applications*

US 62/262,091 WO2017096221A1 "Bispecific anti-HIV broadly neutralizing antibodies"  
Stylianos Bournazos, Michel C. Nussenzweig, Jeffrey V. Ravetch

US 16/424,639 US20190300621A1 "Human IgG Fc domain variants with improved effector function"  
Jeffrey V. Ravetch, Stylianos Bournazos

US 17/617,901 "Antibodies and methods for treatment of viral infections"  
Jeffrey V. Ravetch, Stylianos Bournazos

US 63/160,054 "Diagnosis and treatment of dengue virus infection"  
Stylianos Bournazos, Jeffrey V. Ravetch

US 22/19,743 "Glycoform specific nanobodies and methods of use"  
Stylianos Bournazos, Jeffrey V. Ravetch, Kevin Kao, Aaron Gupta

US 63/584,527 "Methods of using CU-43 Fc fusion constructs"  
Eric Sundberg, Diego Sastre, Jonathan Du, Stylianos Bournazos, Jeffrey Ravetch

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## Academic Activities

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### *Mentoring*

Member of the thesis committee of Ms Cindy Rodriguez, PhD candidate from the MSK-Hunter College graduate program, 2017 – 2024

Served as the graduate student mentor and supervisor for the following graduate rotation students and undergraduate trainees:

- Max Chomet, 1<sup>st</sup> year rotation student from the Cornell University graduate school (Department of Immunology), 05/2013 – 09/2013
- Harlan Pietz, MD-PhD Student, Weill Cornell/Rockefeller/Sloan Kettering, Tri-Institutional MD-PhD Program, 05/2017 – 08/2017
- Noah Perlmutter, visiting BS student from Washington University in St. Louis, 06/2018 – 07/2018
- Kevin Kao, MD-PhD Student, Weill Cornell/Rockefeller/Sloan Kettering, Tri-Institutional MD-PhD Program, 07/2018 – 12/2022
- Aaron Gupta, MD-PhD Student, Weill Cornell/Rockefeller/Sloan Kettering, Tri-Institutional MD-PhD Program, 07/2018 – 12/2022

- William Doyle, PhD Student, Rockefeller University graduate program, 01/2023 – 03/2023
- James Hopkins, PhD Student, Rockefeller University graduate program, 01/2024 – 03/2024

### **Editorial**

Associate Editor – *Frontiers in Immunology*

Ad-hoc reviewer – *Annals of Epidemiology, Autoimmunity Reviews, Cell Host & Microbe, Cell Reports, Cell Reports Medicine, EBioMedicine, Epigenetics, European Journal of Immunology, Frontiers in Immunology, Heliyon, Immunity, International Archives of Allergy and Immunology, iScience, JCI Insight, Journal of Clinical Investigation, Journal of Experimental Medicine, Journal of Immunological Methods, Lung, mAbs, mBio, Nature, Nature Communications, Nature Immunology, Nature Microbiology, Nature Protocols, PLoS One, Proceedings of the National Academy of Sciences, Science, Scientific Reports, The Journal of Immunology, Trends in Molecular Medicine*

### **Grant Reviewer**

National Cancer Institute:

Member of the Special Emphasis Panel/Scientific Review Group ZCA1 GRB-I (A) 08/2020

National Institute on Ageing:

Member of the Special Emphasis Panel/Scientific Review Group ZAG1 ZIJ-U (J1) 01/2021

National Institute of Allergy and Infectious Diseases:

Member of Special Emphasis Panel/Scientific Review Group ZAI1 RK-M (C3) 08/2023

Member of NIH Study section AIRT 03/2024

Member of Special Emphasis Panel/Scientific Review Group ZAI1 LG-M (M1) 03/2024

Member of NIH Study section VPI 06/2024

Member of the NIH Study section ZRG1 DCAI 81 11/2024

Member of NIH Study section IRID 12/2024

Member of NIH Study section VPI 03/2025

New York State Biodefense Commercialization Fund 2023-2024

Deutsche Forschungsgemeinschaft (DFG), Germany 2021

Medical Research Council (MRC), United Kingdom 2022

Israeli Ministry of Innovation, Science and Technology, Israel 2022

Singapore Ministry of Education 2024

### **Invited speaker at scientific meetings**

AIDS vaccine 2012 conference, Boston, MA. 2012

8<sup>th</sup> CAVD (The Collaboration for AIDS Vaccine Discovery) meeting, Seattle, WA. 2013

Keystone HIV Vaccines, Olympic Valley, CA. 2016

6<sup>th</sup> International Conference on Osteoimmunology: Interactions of the Immune and Skeletal Systems, Chania, Greece. 2016

HIVR4P 2016 / Canadian Alliance Coordinating Office, Chicago, IL. 2016

11<sup>th</sup> CAVD (The Collaboration for AIDS Vaccine Discovery) meeting, Seattle, WA. 2016

Keystone Biobetters and Next-Generation Biologics: Innovative Strategies for Optimally Effective Therapies, Snowbird, UT. 2017

NIAID Workshop on Mechanisms of Fc-Dependent, Antibody-Mediated Killing, Rockville, MD. 2017

2<sup>nd</sup> Next-Generation Antibodies and Protein Analysis, Gent, Belgium. 2017

PEGS Europe: Protein & Antibody Engineering Summit, 2017, Lisbon, Portugal. 2017

Gilead Research Scholars Day, San Francisco, CA. 2018

EMBO Workshop on Antibodies and complement: Effector functions, therapies and technologies, Girona, Spain. 2018

PEGS: the essential protein engineering summit, Boston MA. 2019

NIAID Workshop on Genetically Engineered Mouse Models to Accelerate HIV Vaccine Development, 2021

WHO Expert Group for the development of preclinical models of COVID-19 disease, 2021

NIAID Workshop on Clinical Development of Broadly Neutralizing Antibodies (bNAb) for HIV-1, 2022

### Memberships

Member, British Society for Immunology 2005

Member, Biochemical Society (UK) 2005

Member of the Scottish Cardiovascular Forum 2005

Organizing committee member, Biochemical Society – Dynamic Cell Conference, Edinburgh, UK 2009

New York Academy of Science – Science Alliance for Postdocs and Graduate Students 2010

Member, American Heart Association 2012

Member, American Association of Immunologists 2016

Member, New York Academy of Science 2016

Organizing committee member, NIAID Workshop on Genetically Engineered Mouse Models to Accelerate HIV Vaccine Development, 2021

Member, WHO Expert Group for the development of preclinical models of COVID-19 disease, 2020

Member of the Foundation for the National Institutes of Health (FNIH) working group on antibody effector function. 2021-2023

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## **Bibliography**

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### Research Articles

Bournazos S, Rennie J, Hart SP, Dransfield I. (2008) Choice of anticoagulant critically affects measurement of circulating platelet-leukocyte complexes. *Arterioscler Thromb Vasc Biol.* 28(1):e2-3.

Bournazos S, Rennie J, Hart SP, Fox KA, Dransfield I. (2008) Monocyte functional responsiveness after PSGL-1-mediated platelet adhesion is dependent on platelet activation status. *Arterioscler Thromb Vasc Biol.* 28(8):1491-1498.

Bournazou I, Pound JD, Duffin R, Bournazos S, Melville LA, Brown SB, Rossi AG, Gregory CD. (2009) Apoptotic human cells inhibit migration of granulocytes via release of lactoferrin. *J Clin Invest.* 119(1):20-32.

Bournazos S, Hart SP, Chamberlain LH, Glennie MJ, Dransfield I. (2009) Association of Fcγ receptor IIa (CD32a) with lipid rafts regulates ligand binding activity. *J Immunol.* 182(12):8026-8036.

McColl A, Bournazos S, Franz S, Perretti M, Morgan BP, Haslett C, Dransfield I. (2009) Glucocorticoids induce protein S-dependent phagocytosis of apoptotic neutrophils by human macrophages. *J Immunol.* 183(3):2167-2175.

Bournazos S, Fahim A, Hart SP. (2009) Identification of fibrocytes in peripheral blood. *Am J Respir Crit Care Med.* 180(12):1279.

Bournazos S, Bournazou I, Murchison JT, Wallace WA, McFarlane P, Hirani N, Simpson AJ, Dransfield I, Hart SP. (2010) Fcγ receptor IIIb (CD16b) polymorphisms are associated with susceptibility to idiopathic pulmonary fibrosis. *Lung.* 188(6):475-481.

Bournazos S, Grinfeld J, Alexander KM, Murchison JT, Wallace WA, McFarlane P, Hirani N, Simpson AJ, Dransfield I, Hart SP. (2010) Association of FcγRIIa R131H polymorphism with idiopathic pulmonary fibrosis severity and progression. *BMC Pulm Med.* 10:51

Bournazos S, Bournazou I, Murchison JT, Wallace WA, McFarlane P, Hirani N, Simpson AJ, Dransfield I, Hart SP. (2011) Copy number variation of *FCGR3B* is associated with susceptibility to idiopathic pulmonary fibrosis. *Respiration*. 881(2):142-149.

Smith P, DiLillo DJ, Bournazos S, Li F, Ravetch JV. (2012) Mouse model recapitulating human Fcγ receptor structural and functional diversity. *Proc Natl Acad Sci USA*. 109(16):6181-6186.

Pietzsch J, Gruell H, Bournazos S, Donovan BM, Klein F, Diskin R, Seaman MS, Bjorkman PJ, Ravetch JV, Ploss A, Nussenzweig MC. (2012) A mouse model for HIV-1 entry. *Proc Natl Acad Sci U S A*. 109(39):15859-15864.

Klein F, Halper-Stromberg A, Horwitz JA, Gruell H, Scheid JF, Bournazos S, Mouquet H, Spatz LA, Diskin R, Abadir A, Zang T, Dorner M, Billerbeck E, Labitt RN, Gaebler C, Marcovecchio P, Incesu RB, Eisenreich TR, Bieniasz PD, Seaman MS, Bjorkman PJ, Ravetch JV, Ploss A, Nussenzweig MC. (2012) HIV therapy by a combination of broadly neutralizing antibodies in humanized mice. *Nature* 492(7427):118-122.

Gruell H, Bournazos S, Ravetch JV, Ploss A, Nussenzweig MC, Pietzsch J. (2013) Antibody and antiretroviral pre-exposure prophylaxis prevent cervicovaginal HIV-1 infection in a transgenic mouse model. *J Virol*. 87(15):8535-8544.

Bournazos S, Chow SK, Abboud N, Casadevall A, Ravetch JV. (2014) Human IgG Fc domain engineering enhances antitoxin neutralizing antibody activity. *J Clin Invest*. 124(2):725-729.

Halper-Stromberg A, Lu CL, Klein F, Horwitz JA, Bournazos S, Nogueira L, Eisenreich TR, Liu C, Gazumyan A, Schaefer U, Furze RC, Seaman MS, Prinjha R, Tarakhovsky A, Ravetch JV, Nussenzweig MC. (2014) Broadly neutralizing antibodies and viral inducers decrease rebound from HIV-1 latent reservoirs in humanized mice. *Cell* 158(5):989-999.

Bournazos S, Klein F, Pietzsch J, Seaman MS, Nussenzweig MC, Ravetch JV. (2014) Broadly neutralizing anti-HIV-1 antibodies require Fc effector functions for in vivo activity. *Cell* 158(6):1243-1253.

Wang TT, Maamary J, Tan GS, Bournazos S, Davis CW, Krammer F, Schlesinger SJ, Palese P, Ahmed R, Ravetch JV. (2015) Anti-HA glycoforms drive B cell affinity selection and determine influenza vaccine efficacy. *Cell* 162(1):160-169.

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Rodriguez C, Sarrett SM, Sebastiano J, Delaney S, McGlone SA, Hosny MM, Thau S, [Bournazos S](#), Zeglis BM. (2024) Exploring the Interplay Between Radioimmunoconjugates and Fcγ Receptors in Genetically Engineered Mouse Models of Cancer. *ACS Pharmacol Transl Sci*. 7(11):3452-3461.

### **Review Articles**

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Pincetic A, [Bournazos S](#), DiLillo DJ, Maamary J, Wang TT, Dahan R, Fiebiger BM, Ravetch JV. (2014) Type I and type II Fc receptors regulate innate and adaptive immunity. *Nat Immunol*. 15(8):707-716.

[Bournazos S](#), DiLillo DJ, Ravetch JV. (2015) The role of Fc-FcγR interactions in IgG-mediated microbial neutralization. *J Exp Med*. 212(9):1361-1369.

[Bournazos S](#), Ravetch JV. (2015) Fcγ receptor pathways during active and passive immunization. *Immunol Rev*. 268(1):88-103.

Lewis GK, Pazgier M, Evans DT, Ferrari G, [Bournazos S](#), Parsons MS, Bernard NF, Finzi A. (2017) Beyond viral neutralization. *AIDS Res Hum Retroviruses* 33(8):760-764.

Bournazos S, Ravetch JV. (2017) Anti-retroviral antibody FcγR-mediated effector functions. *Immunol Rev.* 275(1):285-295.

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Bournazos S, Wang TT, Dahan R, Maamary J, Ravetch JV. (2017) Signaling by antibodies: recent progress. *Annu Rev Immunol.* 35:285-311.

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Wang TT, Bournazos S, Ravetch JV. (2018) Immunological responses to influenza vaccination: lessons for improving vaccine efficacy. *Curr Opin Immunol.* 53:124-129.

Bournazos S, Gupta A, Ravetch JV. (2020) The role of IgG Fc receptors in antibody-dependent enhancement. *Nat Rev Immunol.* 20(10):633-643.

Pihlstrom N, Bournazos S. (2023) Engineering strategies of Anti-HIV antibody therapeutics in clinical development. *Curr Opin HIV AIDS.* 18(4):184-190.

Edgar JE, Bournazos S. (2024) Fc-FcγR interactions during infections: From neutralizing antibodies to antibody-dependent enhancement. *Immunol. Rev.* doi.org/10.1111/imr.13393

### **Book Chapters**

Bournazos S, DiLillo DJ, Ravetch JV. (2014) Humanized mice to study FcγR function. *Curr Top Microbiol Immunol.* 382:237-248.

Bournazos S, Wang TT, Ravetch JV. (2016) The role and function of Fcγ Receptors on myeloid cells. *Microbiol Spectr.* 4(6).

Bournazos S. (2019) IgG Fc Receptors: Evolutionary Considerations. *Curr Top Microbiol Immunol.* 423:1-11.

Ravetch JV, Bournazos S, (2023) Fc Receptors, *Molecular Biology of B Cells* 3<sup>rd</sup> Edition, Ed. Honjo T, Reth M, Radbruch A, Alt F, Martin A, Academic Press

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## **Research Funding**

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### **Current Support**

311543/Z/24/Z (Bournazos, PI) 11/15/24 – 11/14/30  
Wellcome Trust Discovery Award  
Characterization of the immunological mechanisms that drive chronic chikungunya disease pathogenesis.  
Role: Principal Investigator

R01AI137276 (Bournazos, PI) 09/01/18 – 08/31/28  
National Institute of Allergy and Infectious Diseases (NIAID)  
Mechanisms of antibody-dependent enhancement during dengue infection.  
Role: Principal Investigator

R01CA244327 (Bournazos, PI) 07/01/20 – 06/30/25  
National Cancer Institute (NCI)  
Novel transgenic mouse models addressing outstanding translational barriers in antibody-based therapeutics.  
Role: Principal Investigator

IPR2025-00685  
CSPC EX1002

R01-AI145870 (Ravetch/Palese, PI) 06/18/19 – 05/31/29  
National Institute of Allergy and Infectious Diseases (NIAID)  
Development of vaccination strategies to elicit broadly protective immunity against influenza.  
Role: Co-Investigator

Collaborative Influenza Vaccine Innovation Centers (Ahmed/Krammer, PI) 09/10/19 – 09/09/26  
National Institute of Allergy and Infectious Diseases (NIAID)  
CRUIVV: Center for Research, Universal Influenza Virus Vaccines.  
Role: Co-Investigator

R01-AI153441 (Ravetch/Anthony, PI) 07/01/20 – 06/30/25  
National Institute of Allergy and Infectious Diseases (NIAID)  
Examining IgG4 sialylation as a gain of function post-translation modification in IgG4-related disease.  
Role: Co-Investigator

Sponsored Research Agreement (Ravetch, PI) 12/23/22 – 05/23/25  
Vir Biotechnology  
Assessing SARS-CoV-2 mRNA-vaccine responses and durability  
Role: Co-Investigator

INV-073059 (Ravetch, PI) 05/01/24 – 04/30/25  
Bill and Melinda Gates Foundation  
Engineered Fc fusion immunogens for the induction of broad and durable immunity  
Role: Co-Investigator

SNF Institute for Global Infectious Disease Research (Coller/Bournazos, PI) 07/01/24 – 06-30/25  
Development of novel transgenic mouse strains for the study of immune-related thrombotic events and  
IgG responses upon infection or vaccination  
Role: Principal Investigator

CTSA Pilot Award (Bournazos, PI) 06/01/24 – 05/31/25  
Novel mouse strains for the development of human antibody therapeutics and the study of human  
antibody function  
Role: Principal Investigator

**Previous Support**

Robertson Therapeutic Development Fund (Bournazos, PI) 12/01/23 – 11/30/24  
Development of IgG Fc glycan-specific nanobody-based therapeutics against viral and chronic  
inflammatory diseases  
Role: Principal Investigator

INV-001905 (Weiner/Ravetch, PI) 11/01/21 – 10/31/24  
Bill and Melinda Gates Foundation  
DNA/EP to Evaluate the Vaccinal Effect  
Role: Co-Investigator

INV-035597 (Ravetch, PI) Bill and Melinda Gates Foundation Early events and role of FcR pathways in immunity to mRNA vaccines. Role: Co-Investigator	07/29/21 – 07/31/24
U19AI111825 (Ravetch, PI) National Institute of Allergy and Infectious Diseases (NIAID) Integrating innate and adaptive pathways in vaccine responses. Role: Principal Investigator (Animal Core), Co-Investigator (Project 1)	04/01/14 – 03/31/24
3R01AI145870-02S1 (Ravetch, PI) National Institute of Allergy and Infectious Diseases (NIAID) Evaluation of the FcγR mechanisms in the antibody-dependent enhancement of SARS-CoV-2 infection Role: Co-Investigator	07/01/20 – 06/30/22
R01-AI129795 (Ravetch/Nussenzweig, PI) National Institute of Allergy and Infectious Diseases (NIAID) Optimization of Fc effector activity of anti-HIV antibodies to target HIV reservoir. Role: Co-Investigator	07/01/17 – 06/30/22
3U19AI111825-07S1 (Ravetch, PI) National Institute of Allergy and Infectious Diseases (NIAID) Characterization of the antibody responses elicited upon SARS-CoV-2 infection. Role: Co-Investigator	04/01/20 – 03/31/22
Thwarting Influenza with RNA-powered Modulators (ThIRM) (Santagelo, PI) Defense Advanced Research Projects Agency (DARPA) Thwarting Influenza with RNA-powered Modulators. Role: Co-Investigator	04/01/19 – 08/31/21
R01-AI137276-02S1 (Bournazos, PI) National Institute of Allergy and Infectious Diseases (NIAID) Mechanisms of antibody-dependent enhancement of SARS-CoV-2 infection. Role: Principal Investigator	05/18/20 – 08/31/21
SP008-SC007 A01 (Bournazos, PI) University of Alabama at Birmingham via NIAID Modulating the antibody response to vaccination through targeting the CD40 axis. Role: Principal Investigator	04/01/19 – 03/31/21
FastGrants Development of novel mouse strains for the study of COVID-19 Role: Co-Principal Investigator	05/01/20 – 10/31/20
OPP1188461 (Ravetch, PI) Bill and Melinda Gates Foundation Enhancing IgG transfer to prevent perinatal infections. Role: Co-Investigator	11/27/17 – 05/31/20

U19-AI109946 (Palese, PI) National Institute of Allergy and Infectious Diseases (NIAID) Mechanisms of Fc-dependent, broad-spectrum, humoral immunity against influenza. Role: Co-Investigator	04/01/14 – 03/31/19
Gilead (Bournazos, PI) Development and evaluation of anti-HIV-1 antibodies with potent cytotoxic activity against HIV-1 infected cells. Role: Principal Investigator	06/01/17 – 05/31/19
U01-AI115651 (Ravetch, PI) National Institute of Allergy and Infectious Diseases (NIAID) Dengue virus infection in India. Role: Co-Investigator	02/01/15 – 01/31/20
Robertson Therapeutic Fund (Ravetch, PI) Pre-clinical development of immune complex-based immunogens to increase the breadth of the seasonal influenza vaccination. Role: Co-Investigator	11/01/18 – 10/31/20
W31P4Q-14-1-0010 (Ahmed, PI) Defense Advanced Research Projects Agency (DARPA) Development of antibody therapeutics against Ebola; Project 3: Mechanisms of IgG-Mediated Protection Against Ebola Virus. Role: Co-Investigator	09/22/14 – 12/31/17
Investment ID INV-023152 Bill and Melinda Gates Foundation COVID-19: Hamster FcyR evaluation Role: Co-Investigator	04/12/20 – 03/15/21
amfAR Mathilde Krim Fellowship (Bournazos, PI) American Foundation for AIDS research (amfAR) Optimization of anti-HIV-1 antibodies for prevention and therapy. Role: Principal Investigator	07/01/16 – 06/30/17
CCHI Pilot Project U19-AI111825-03 (Bournazos, PI) National Institute of Allergy and Infectious Diseases (NIAID) The role of IgG3 in immunity. Role: Principal Investigator	04/01/16 – 03/31/17
amfAR Mathilde Krim Fellowship (Bournazos, PI) American Foundation for AIDS research (amfAR) Fc effector activity of anti-HIV-1 broadly neutralizing antibodies. Role: Principal Investigator	10/01/14 – 09/30/16
Postdoctoral Fellowship 13POST14100003 (Bournazos, PI) American Heart Association (Founders Affiliate)	01/01/13 – 09/30/14

The immunomodulatory role of Fc effector pathways in the protection against atherosclerosis.

Role: Principal Investigator

Career Development Award (Bournazos, PI)

03/01/11 – 01/01/13

Northeast Biodefense Center/National Institute of Allergy and Infectious Diseases (NIAID)

Role of Fc $\gamma$  receptors in antibody-mediated protection against microbial infection.

Role: Principal Investigator

PhD Fellowship FS/05/119/19568 (Bournazos, PI)

10/01/05 – 08/30/09

British Heart Foundation, UK.

Molecular mechanisms of the regulation of immune complex binding to neutrophil CD32.

Role: Principal Investigator