

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AJINOMOTO CO., INC.
Petitioner

v.

ABTIS CO., LTD.
Patent Owner

IPR2025-0283
Patent No. 11,896,675

DECLARATION OF DR. LAWRENCE NATHAN TUMEY

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I, Lawrence Nathan Tumey, Ph.D., declare as follows:

I. INTRODUCTION

1. I am submitting this declaration in support of Petition Ajinomoto Co., Inc.'s response to AbTis's Motion to Amend ("Motion") in the above-captioned proceeding directed to review of U.S. Patent No. 11,896,675 ("the '675 Patent"). I have reviewed AbTis's Motion and the supporting Declaration of Dr. Zhaohui Sunny Zhou (EX2004). This Declaration is based on information currently available to me. I reserve the right to continue my investigation and analysis, which may include a review of documents and information not listed in this Declaration, including any documents and information that may be submitted by AbTis. I also reserve the right to expand or modify my opinions and conclusions as my investigation and study continues, and to supplement my opinions and conclusions in response to any additional information that becomes available to me. I also reserve the right to respond to any argument that AbTis may make in this proceeding.

2. The opinions stated in this declaration are based on the documents I have reviewed, listed herein, as well as my education, experience, and professional knowledge and judgment. I previously set forth my background, qualifications and compensation for this proceeding in my declaration dated December 23, 2024, which is incorporated herein.

II. Dr. Zhou Mischaracterizes the State of the Prior Art

3. I disagree with a number of the statements made by Dr. Zhou in his declaration (EX2004) concerning the state of the prior art. For example, Dr. Zhou states, “[t]here was no single accepted or predictable path to achieving a desired modification and/or conjugation outcome, and moreover, what specific outcomes are desirable or preferable.” EX2004, ¶37. Respectfully, I disagree with this assertion, and I note that Dr. Zhou fails to support this opinion with any citations to literature.

4. While there may not have been a “single accepted” path, there were certainly “predictable” paths to achieving desirably conjugation outcomes. Various robust methods for site-specific conjugation were known to provide a predictable drug to antibody ratio (“DAR”), reliable conjugation to a variety of payloads, and scalable conjugation chemistry. From 2016-2020, there was an emerging consensus that certain conjugation sites reliably performed well for a variety of antibodies, payloads, and linkers, and that certain conjugation approaches were routinely and predictably useful. *See* EX1041 (*AAPS Journal*, 2017, 19(4), 1123-1135); EX1042 (*ACS Medicinal Chemistry Letters*, 2016, 7(11), 977-982); EX1043 (*Molecular Cancer Therapeutics*, 2020, 19, 10, 2068-2078).

5. For example EX1041 explains that, as of 2017, there was a “shift towards site-specific conjugation technology” (*id.*, Abstract) which was “frequently shown to result in improved safety, exposure, and stability” (*id.*, at 1, right column).

In other words, site-specific conjugation technologies were known to provide desirable outcomes for ADCs made with such approaches. Further, EX1041 explains that “[i]n addition to their improved pharmacological properties, site-specific ADCs offer potential advantages in terms of regulatory burden due to the simplified bioanalytical strategy,” (*id.*) which would motivate people of ordinary skill to pursue site-specific conjugation approaches. EX1041 also notes that “a variety of site-specific conjugation technologies have been developed in recent years” and “success has been realized using each of these [] methods.” *Id.*, 2, left column.

6. EX1042 similarly discloses that, as of 2016, it was known that the “site of conjugation can play a critical role in addressing metabolic and PK liabilities of an ADC.” *Id.*, Abstract. EX1042 notes that “a clear correlation was identified between the hydrophobicity of an ADC and its susceptibility to metabolic enzymes” and suggested that “this study demonstrates that traditional medicinal chemistry strategies can be effectively applied to ADC programs.” *Id.* Specifically, the authors detailed a “two-pronged strategy” for predictably improving ADC conjugation and performance, and even suggested that the disclosed strategies were broadly applicable as “a timely reminder that the principles of small molecule medicinal chemistry can be effectively applied even to biotherapeutic programs such as ADCs.” EX1042, 5, right column.

7. EX1043 also “showcase[s a] platform approach in optimizing ADC design” and “[t]he design elements of identifying novel sites of conjugation employed in this study serve as a platform for developing optimized ADCs against other tumor-specific targets” and were shown to maximize “stability, efficacy, and safety for a four drug–antibody ratio (DAR) ADC.” EX1043, Abstract. By the time the ’675 Patent was filed, these papers (EX1041, EX1042, and EX1043) and others had established that certain sites within an antibody, such as the C-terminal end of the light chain, could reliably be used to make ADCs with desirable characteristics regardless of the conjugation chemistry, whereas other regions, such as the C-terminal end of the heavy chain, tended to perform comparatively poorly (even with multiple conjugation approaches). Thus, there was an emerging consensus that ADC properties could be “predicted” to some degree, and EX1041, EX1042, and EX1043 all disclose known, predictable approaches for achieving desirable conjugation outcomes that specifically suggest that the technologies used therein are broadly applicable for use in various ADCs.

8. The prior art cited in the Petition also contradicts Dr. Zhou’s assertion and shows that those of ordinary skill in the art were aware of predictable paths for achieving desirably conjugation outcomes. For example, the PepTalk Poster (EX1006) and PepTalk Presentation (EX1007) both explain the desirable and predictable outcomes achieved by the AJICAP™ platform. The PepTalk Poster touts

that AJICAP™ “can enable us to conjugate payloads with a native mAb chemically in site-specific manner” on Lysine 248 of an IgG Fc domain, and that the platform provides a “controlled DAR 2” and a “[w]ide drug-linker compatibility [and] reactive group compatibility.” *See* EX1006. The PepTalk Presentation similarly notes that AJICAP™ provides “[s]ite specific, controlled DAR 2” specifically at Lysine 248 (EX1007, 13-18), it shows the compatibility of various drug-linkers and reaction groups (*id.*, 20-27), and it even shows gram scale synthesis (*id.*, 28) to substantiate the claim of “[h]igh yields” and “ease to manufacture” (*id.*, 13, 33). In other words, prior to the filing date of the ’675 patent, people of ordinary skill in the art were aware that at least AJICAP™ and the methodologies discussed in EX1041-EX1043 provided predictable paths for achieving desirable conjugation outcomes.

9. Finally, I note that the mc-Val-Cit-PABC linker system was ubiquitous in the ADC space prior to the filing date of the ’675 patent, with approximately half of the FDA-approved ADCs using this system for conjugation of drug to antibody. EX1045; EX1046. This shows that the mc-Val-Cit-PABC linker system provided predictable and desirable results that were transferable across numerous antibody products.

10. In sum, Dr. Zhou’s statement that “[t]here was no ... predictable path to achieving a desired modification and/or conjugation outcome” (EX2004, ¶37) is demonstrably incorrect.

11. Dr. Zhou also states in paragraph 37 of his declaration that “[a]s of the priority date of the ’675 Patent (March 8, 2019), the field of antibody-drug conjugation (“ADC”) and site-specific protein modification was highly active but exceptionally complex and unpredictable, partially due to the lack of systematic studies and side-by-side comparison of different approaches.” Again, I disagree and note Dr. Zhou’s inability to produce any supporting citation for this statement.

12. As noted above, EX1041, EX1042, EX1043, PepTalk Poster (EX1006), and PepTalk Presentation (EX1007) all attest to the importance of site-specific conjugation for improving ADC properties, and each reference provides an approach for achieving predictable site-specific conjugation. *See, e.g.*, EX1041, Abstract; EX1042, Abstract; EX1043, Abstract; EX1006, Conclusion; EX1007, 13, 33.

13. Additionally, Dr. Zhou’s own publications contradict his assertion that “site-specific protein modification was highly active but exceptionally complex and unpredictable.” Like the references discussed above, EX1044, which was published December 18, 2020, indicates that “site-specific methods produce well-defined and more homogenous antibody conjugates, ensuring developability and clinical applications” (*id.*, Abstract) and notes that “[s]ite-specific methods offer advantages over their nonspecific counterparts in the conjugate’s properties and functions, such as enhanced plasma stability, increased tumor uptake, enhanced binding efficiency, less variability in dose studies, and a higher level of binding” (*id.*, 272, right column).

Dr. Zhou also cites multiple papers detailing “previously reported site-specific conjugation technologies,” including AJICAP™ (*id.*, 272, para. Spanning left and right columns), and most of these papers—i.e., cited references 22, 24, and 25 of EX1044—predate even the earliest claimed priority date for the ’675 Patent (March 8, 2019). Dr. Zhou further notes that “[a]s a general trend, the percentages of site-specific ADCs have been steadily increasing over the years, and is 100% in 2020,” (*id.*, 280, right column) which shows that the alleged complexity and unpredictability that Dr. Zhou references was not an impediment to clinical uptake and application of the technology.

14. Dr. Zhou’s publication (EX1044) also states that “systematic studies and side-by-side comparison[s]” had, in fact, been completed. EX1044 notes that “several recent side-by-side comparisons of site-specific and stochastic methods have demonstrated that site-specific approaches are more likely to achieve their desired properties and functions” (*id.*, Abstract). In fact, my own research lab was one such group that had specifically compared a new approach we were employing (known as “Q295”) in a side-by-side comparison with various other site-specific approaches. EX1047. This was common practice, and any time a researcher publishes a new method, it entirely expected that he or she will compare it to other “state of the art” methods to determine whether the new method is an improvement. Although EX1044 published after the earliest claimed priority date of the ’675 Patent

(though not before the filing date of U.S. Appl. No. 18/154,998, from which the '675 Patent issued) 95 of the 122 references cited in EX1044 as informing Dr. Zhou's perspective on the state of the art do pre-date the earliest priority claim of the '675 Patent (i.e., they were published before March 8, 2019). Accordingly, Dr. Zhou's statements in his declaration at paragraph 37 about the stifling complexity and unpredictability of the art are contradicted by his interpretation of the state of the art in his publication. EX1044.

15. In paragraph 38 of his declaration (EX2004), Dr. Zhou states “even subtle changes in spacer and linker composition or reactivity could profoundly affect reaction selectivity, yield, and stability (both chemical and physical), and the subsequent biological activities and immunogenicity in animals and humans, which means that results could not be readily predicted by experts, much less a POSA...” I disagree with the underlined portion of this statement. While changes in spacer and linker composition or reactivity can affect a reaction, this does not mean that the results are always unpredictable. To the contrary, EX1042 shows that traditional medicinal chemistry strategies—which would include consideration of linkers and spacers—can be effectively applied to ADC development (EX1042, Abstract, 5, right column) and EX1043 highlights specific design elements that have predictable effects on such properties (EX1043, Abstract). Further, there is wide consensus that particular features of an ADC are indeed predictable based on structure. For

example, there is an established correlation between ADC polarity and improved pharmacokinetics (EX1041; EX1048), solvent exposure of conjugation sites is correlated with rapid metabolism (EX1041; EX1042), and cleavable linkers have improved bystander activity (EX1049). Thus, even though “subtle changes in linker composition or reactivity” can affect ADC properties, many results are readily predictable by a person of ordinary skill in the art (“POSA”).

16. Finally, turning to paragraph 40 of his declaration (EX2004), Dr. Zhou states “the field was inherently non-predictable: small structural or mechanistic changes often resulted in dramatically different reactivity, selectivity, yield, and product stability.” In my opinion, this is yet another over-statement. For at least the reasons noted above, it is a categorical misstatement to allege that the field was inherently non-predictable. There were many well-established, predictable aspects of ADC development prior to the earliest claimed priority date of the ’675 Patent. Moreover, Dr. Zhou’s position is logically nonsensical. Companies develop “platform technologies”—like AJICAP™, as disclosed in the PepTalk Poster (EX1006) and PepTalk Presentation (EX1007)—precisely because they believe their technology is broadly applicable and will translate from one antibody to another. In fact, this is directly stated in PepTalk Presentation (EX1007), which states that AJICAP™ “has great potential for mAb isotypes: IgG1, 2, 4” and lists several examples of each (EX1007, 20). Dr. Zhou’s unsupported assertions about the level

of unpredictability in the field of ADCs is objectively inconsistent with the prior art of record and the general state of the art as of the filing date or earliest claimed priority date of the '675 Patent.

III. MODIFYING EXACTLY ONE HEAVY CHAIN OR MORE THAN TWO HEAVY CHAINS WOULD BE DIFFICULT

17. The specification¹ does not explain or provide a process that would reliably allow a skilled person to make an antibody with exactly one modified heavy chain or an antibody that has three or more modified heavy chains.

18. Rather, the Example titled “Synthesis and confirmation of structure of antibody containing first click-chemistry functional group in site-specific manner” (*see* EX2002, paras. [1272]-[1329]) describes modifying trastuzumab (an anti-HER2 IgG1) on the lysine at position 246 or 248 to modify both heavy chains of trastuzumab.

19. Those skilled in the art would understand that modification reactions such as those described in EX2002, paras. [1272]-[1329] could produce a trastuzumab molecule with one modified heavy chain, two modified heavy chains,

¹ References to “the specification” may refer to U.S. Appl. No. 18/154,998 (“the '998 application”), which ultimately issued as the '675 Patent, or U.S. Appl. No. 16/980,503 (“the '503 application”), which was the parent of the '675 Patent, because I understand that these specifications are effectively identical. However, for the purposes of this declaration, I will cite to the '503 application (EX2002) for consistency with how AbTis and Dr. Zhou cite to the specification.

or zero modified heavy chains. In other words, the reaction will make a mixture of products with differing numbers of modified heavy chains. Hence, it is commonly reported that an ADC will have a DAR that is represented by a range or signified by a number that is not a whole number (e.g., a DAR of 1.5 would suggest some ADCs with at least two drugs attached, some with one drug attached, some with zero, and some with potentially more than two). But here, AbTis reports in the specification full loading of the antibody (i.e., a DAR = 2, with both HC's fully modified).

20. Given this, it would require a tremendous amount of work to develop a process that *always* resulted in exactly one modified heavy chain, if it were possible at all.

21. Further, the '675 Patent defines "antibody" as referring to "an immunoglobulin molecule or a fragment thereof" including "naturally occurring immunoglobulins," such as IgG, IgM, IgA, IgE, and IgD, as well as encompassing "all recombinant proteins, fusion proteins, chimeric proteins, human immunoglobulins, non-human animal immunoglobulins, and the like, which have the same or similar structures." EX1001, 40:52-57; EX2002, ¶[0209]. Accordingly, the phrase "one or more modified heavy chain" logically extends to "antibodies" such as IgM that have five heavy chains, as well as other proteins that "have the same or similar structures," yet the specification fails to provide any evidence that AbTis possessed a method to produce a modified form of any antibody that has three

or more modified heavy chains, much less teach how to do so without requiring significant further experimentation.

**IV. THE PROPOSED SUBSTITUTE CLAIMS ARE NOT NOVEL OR
ARE OBVIOUS OVER THE PRIOR ART OF RECORD**

22. In my previous Declaration I discussed why I believe claim 11 was anticipated or obvious in view of several prior art references. My opinion remains that proposed substitute claims 14-16 are also anticipated and obvious.

A. Claims 14-16 Are Anticipated by the '959 Publication (EX1005).

23. As stated previously, I understand that, because the '675 Patent issued from the '998 Application, which itself is a continuation of the '503 Application, the '675 Patent and '503 Application share an identical specifications. Counsel has informed me that, as a result, if the proposed substitute claims lack written description support or enablement in the specification of the '675 Patent, then they also lack written description support or enablement in the identical specification of the '503 Application. I am informed that, in that case, the claims of the '675 Patent would not be entitled to claim priority to the September 14, 2020, filing date of the '503 Application, and would instead have a priority date no earlier than the '675 Patent's own filing date of January 16, 2023. It is my understanding that when the '675 Patent is afforded a priority date of January 16, 2023, the '959 Publication (EX1005) becomes prior art.

24. The '959 Publication discloses modified forms of trastuzumab with a lysine at position 248 that was modified to include the azide modification of proposed substitute claim 14, the norbornene modification of proposed claim 15, and the norbornene modification of proposed claim 16. EX1005, 222-241. Figures 56 and 57 of the '959 Publication show mass spectra of trastuzumab and a trastuzumab-azide complex, respectively. *Id.*, 32, 229, Figures 56, 57. The '959 Publication states that an azide is a bio-orthogonal click chemistry functional group. The '959 Publication discusses the procedure by which the modified trastuzumab-norbornene structures were confirmed in paragraphs 225 and Figures 44-47. Notably, Figure 43 shows “the structure of the final product” for trastuzumab-norbornene” that clearly corresponds to proposed substitute claim 15. *Id.*, 225.

25. While Dr. Zhou alleges that “Dr. Tumey agrees that the proposed substitute claims are supported by the original patent because he shows that support in contending that claim 11 is anticipated by the '959 Publication” (EX2004, ¶53), Dr. Zhou’s interpretation of my agreement is misplaced. I have been informed by counsel that anticipation (i.e., novelty) and “support” are two different legal standards with separate requirements. As noted above, I was not asked nor required to make a determination regarding “support” for the purposes of my prior testimony. Thus, my opinion that the '959 Publication anticipated claim 11 or now anticipates

proposed claims 14-16 is not an acknowledgement that the proposed substitute claims are supported.

B. Yamada Renders The Proposed Substitute Claims Obvious, Alone or in Combination with Matsuda

26. As explained in my prior declaration, Yamada discloses “A modified antibody comprising a bio-orthogonal click chemistry functional group, wherein the modified antibody comprises one or more modified heavy chain, wherein each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system.” EX1002, ¶¶271-272. Proposed replacement claims 14-16 have the same limitation and thus, it is my opinion that Yamada provides the same disclosure for claims 14-16 for the reasons I previously explained. *See* EX1002, ¶¶384-420; *see also* EX1009, FIG. 1-2, [0151]-[0153], [0581]-[0598], [0607], [1019] [1108]-[1109], [1944]-[1971]. Dr. Zhou does not appear to contest that Yamada discloses and specifically suggests modifying the heavy chain of an antibody at Lysine 248 with a bio-orthogonal click chemistry group, and that Yamada discloses azides and norbornene as suitable bio-orthogonal click chemistry groups (*see, e.g.*, EX2004, ¶89).

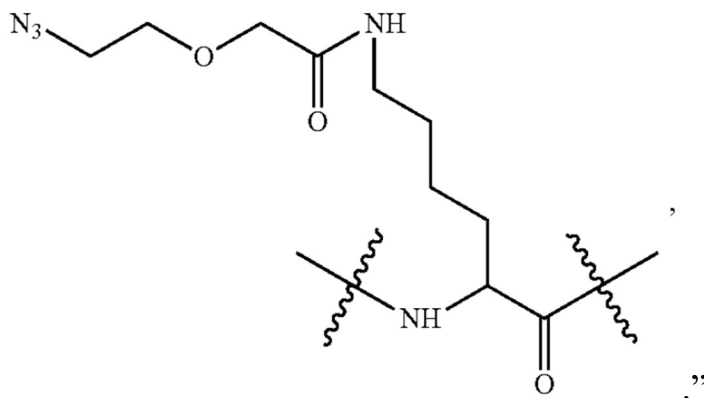
27. The only aspect of Yamada that AbTis and Dr. Zhou appear to disagree with is whether Formula (IV), reproduced below, would lead a POSA to the modified lysine structure now recited in proposed substitute claims 14-16.

L1-B-R'-T (IV)

For all of the reasons discussed in my previous declaration (*see* EX1002, ¶¶445-451), I believe that Yamada would have motivated a POSA to make the structures in proposed substitute claims 14-16 with a reasonable expectation of success.

28. More specifically, claim 14 recites:

“... wherein the modified lysine residue has following structure:



29. There is no dispute that Yamada teaches the necessary substituent groups so that Formula (IV) can produce the modified lysine of proposed substitute claim 14. This is an objective fact. Dr. Zhou takes issue with the number of possible combinations recited in Yamada and the alleged lack of motivation to combine the disclosed substituent groups to arrive at the claimed structure.

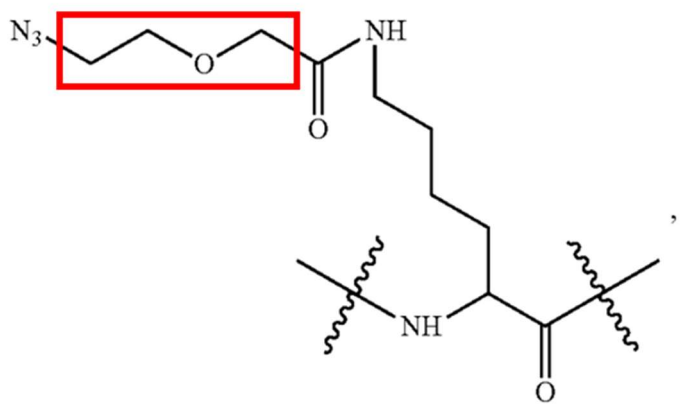
30. While Dr. Zhou states, “Yamada’s generalized schema does not disclose the claimed modified lysine residues to a POSA” and “Yamada’s Formula (IV) ($L_1-B-R'-T$) is a schematic representation comprising independently variable elements and does not identify the specific claimed combinations” (EX2004, ¶84), he cannot assert that the necessary substituent groups are missing. Rather, as explained in my prior declaration, there are at least two options for combining L_1 , B , R' , and T of the Formula (IV) to arrive at the structure of proposed substitute claim 14. EX1002, ¶450. So, although the completed structure is not disclosed, the component parts are all presented together in Yamada in a single section that specifically invites a POSA to combine the various disclosed substituents for L_1 , B , R' , and T . EX1009, ¶¶[0616]-[0639].

31. Dr Zhou also mistakenly assumes that Ajinomoto’s Petition was “working backward from Yamada” using “impermissible hindsight analysis” (EX2004, ¶84-85), but there was ample reason for a POSA to select an azide as the bio-orthogonal click chemistry group and a short alkyl linker, as discussed below.

32. Specifically, Yamada itself presents an azide at the beginning of the list of suitable biorthogonal functional groups (it is the third group listed), and azide-cycloalkyne click chemistry was among the most well-established and commonly utilized bio-orthogonal click reactions at the time the '675 Patent was filed (regardless of either the 2019 or 2023 filing date). (EX1050). Both the PepTalk

Poster (EX1006, “Capability of AJICAP™”) and PepTalk Presentation (EX1007, 20) also specifically teach using an azide as the biorthogonal functional group.

33. The linker/spacer component of the modified lysine is shown in the red box below:



I previously explained that “when an azide group” is used, the linker/spacer “would most likely be an alkyl or cycloalkyl.” EX1002, ¶¶256, 351, *see also* ¶¶267, 362. This is because a short alkyl linker/spacer would provide some flexibility, which can be helpful for subsequent reactions attaching a drug, and also because short alkyl spacers were commonly used for this type of modification. EX1048; EX1051. Indeed, both PepTalk Poster (EX1006, “Synthesis of Site-Specific ADC by AJICAP™”) and PepTalk Presentation (EX1007, 16) provide examples of short alkyl linkers/spacers (i.e., an ethyl linker/spacer), and Yamada also discloses multiple examples of similar short alkyl linkers/spacers (EX1009, p. 147-153, Examples 2-1, 2-2, 2-3, 11-3, 55, 59, and 63).

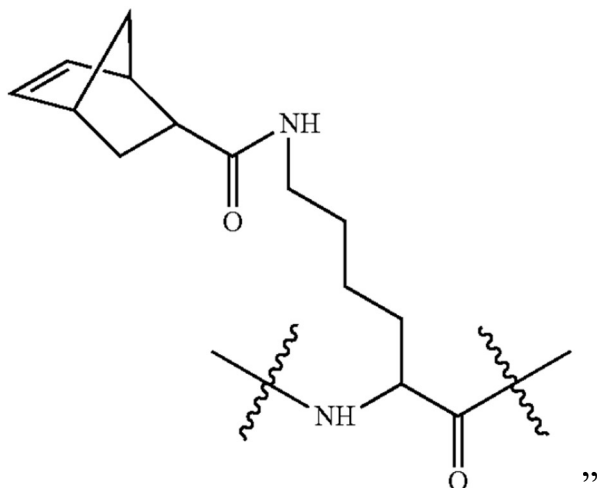
34. The linker/spacer of proposed substitute claim 14 also includes a heteroatom (e.g., an oxygen or “O”). When an oxygen is included in an ether, as shown in the structure of proposed claim 14, the oxygen is non-reactive. From a synthetic perspective, this is beneficial because that means the oxygen will be stable in a variety of reaction conditions. EX1048. Including an oxygen heteroatom was also known to be biologically beneficial, as it increases the polarity of the linker/spacer, which improves solubility. EX1052, 3535

35. Moreover, Yamada provides multiple options for inclusion of a heteroatom (including oxygen, specifically) within the linker/spacer component, as noted previously (EX1002, ¶453; EX1009, [0622], [0633]). When questioned about this during my deposition on October 17, 2025, I confirmed that “there are examples in Yamada where they successfully couple spacers with a beta heteroatom” (EX2006, 186:19-21; 188:17-19; 189:5-17), and even noted that Example 59 of Yamada specifically utilizes an oxygen as a heteroatom.

36. In sum, Yamada specifically disclosed short alkyl linker/spacers that can optionally include a heteroatom, and link/spacer constructs like these were commonly used at the time. Accordingly, I maintain that a person of ordinary skill would have been motivated to select from Yamada an azide as the terminal click chemistry group and a short alkyl linker including an oxygen heteroatom, thus arriving at the structure shown in proposed substitute claim 14.

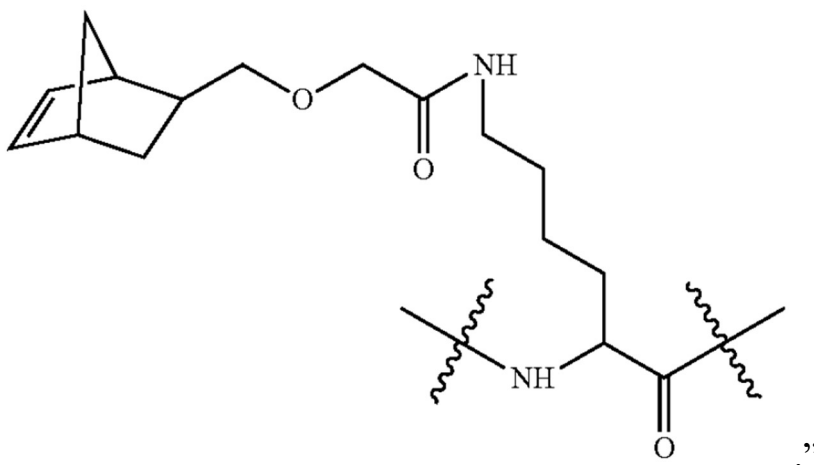
37. Next, proposed substitute claim 15 recites:

“... wherein the modified lysine residue has following structure:



and proposed substitute claim 16 recites:

“... wherein the modified lysine residue has following structure:



38. As with proposed substitute claim 14, Yamada teaches the necessary substituent groups so that Formula (IV) can be used to produce the modified lysine of proposed substitute claims 15 and 16. Also like proposed substitute claim 14,

there was ample motivation for a person of ordinary skill to prepare the modified lysines of proposed substitute claims 15 and 16 based on Yamada.

39. Norbornene is repeatedly described in Yamada as a suitable bio-orthogonal click chemistry group for modifying the lysine at position 248. EX1009, ¶¶[0627], [0778], [1458], [1491]. Like azide-cycloalkyne click chemistry, norbornene-tetrazine click chemistry was also well-established and commonly used in bio-orthogonal click reactions at the time the '675 Patent was filed (regardless of whether the 2019 or 2023 filing date is provided). For example, EX1053 states “The copper-free click chemistry reaction between norbornene and tetrazine species is known to proceed in a rapid, reliable and selective manner under mild conditions” and “[d]ue to these attractive properties, this reaction has recently been explored as a generally applicable method of bioconjugation.” Because of its simple, reliable, and bio-orthogonal chemistry, similar Diels-Alder reactions had successfully been used to create ADCs prior to the filing date of '675 Patent (regardless of whether the 2019 or 2023 filing date is provided). EX1054; EX1055. Thus, prior to the filing date of the AbTis patent, a person of ordinary skill would have had ample reason to select norbornene as the bio-orthogonal click chemistry group for modifying lysine 248, as disclosed in Yamada.

40. With respect to the linker/spacer component, the structure in proposed substitute claim 15 has no linker/spacer, and the structure in proposed substitute

claim 16 has a short alkyl chain with an oxygen heteroatom, similar to the linker/spacer used in claim 14.

41. As discussed during my deposition, there is an implicit motivation to keep molecules simple, a la Occam's razor. EX2006, 152:8-22. As a result, a person of ordinary skill preparing a modified lysine with a norbornene as the terminal bio-orthogonal click chemistry group would logically start by preparing the simplest structure, which is the structure recited in proposed substitute claim 15. This structure, which lacks a spacer/linker, would serve as the standard of comparison (i.e., control) to determine the functional impact of adding a spacer/linker. In other words, there is always a logical and implicit need to begin one's development with the simplest modification and then iterate and develop from there. Accordingly, there was a motivation for a person of ordinary skill to prepare the modified lysine of proposed substitute claim 15.

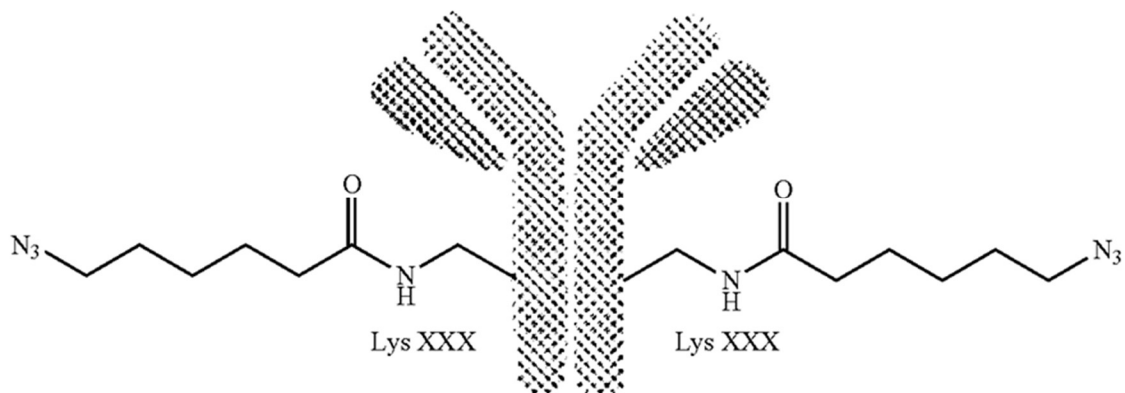
42. With respect to the modified lysine and the linker structure shown in proposed substitute claim 16, all of the motivations discussed above with respect to proposed substitute claim 14 apply. Namely, an oxygen heteroatom, particularly an oxygen ether, can provide synthetic and biological benefits to the linker/spacer (EX1048; EX1052, 3535), and Yamada provides multiple options for inclusion of a heteroatom (including oxygen, specifically) in the linker/spacer (EX1002, ¶453;

EX1009, [0622], [0633]). Thus, a person of ordinary skill would have been motivated to prepare a short alkyl linker/spacer like the one in proposed claim 16.

43. For at least the reasons discussed above, Yamada renders proposed substitute claims 14-16 obvious on its own, given the knowledge and motivations of those ordinarily skilled in the art.

44. If Matsuda is further considered with Yamada the case for obviousness becomes even stronger. In particular, Matsuda discloses Example 5-2-1, shown below, where the bio-orthogonal click chemistry functional group is a terminal azide and the spacer/linker is nearly very similar to the spacer/linker of proposed substitute claim 14, with the only differences being one extra carbon in the spacer/linker of Matsuda's Example 5-2-1 and the claimed spacer linker having an oxygen in the beta position.

5-2-1



EX1011, p. 92. Although the particular lysine residue in these examples is not identified, Matsuda discloses that modification of lysine residue 248 is preferable. *Id.*, [0146], [0329]. Matsuda likewise discloses norbornene as a suitable bio-

orthogonal click chemistry group that—like thiols or azides—can be used to modify the lysine at position 248. *Id.*, [0593], [0739]. Thus, while Matsuda is not necessary to render the proposed substitute claims obvious, it further illustrates that those of ordinary skill in the art were already preparing antibodies with a modified lysine at position 248 that included modifications that were similar to and suggestive of the modified lysines now recited in proposed substitute claims 14-16.

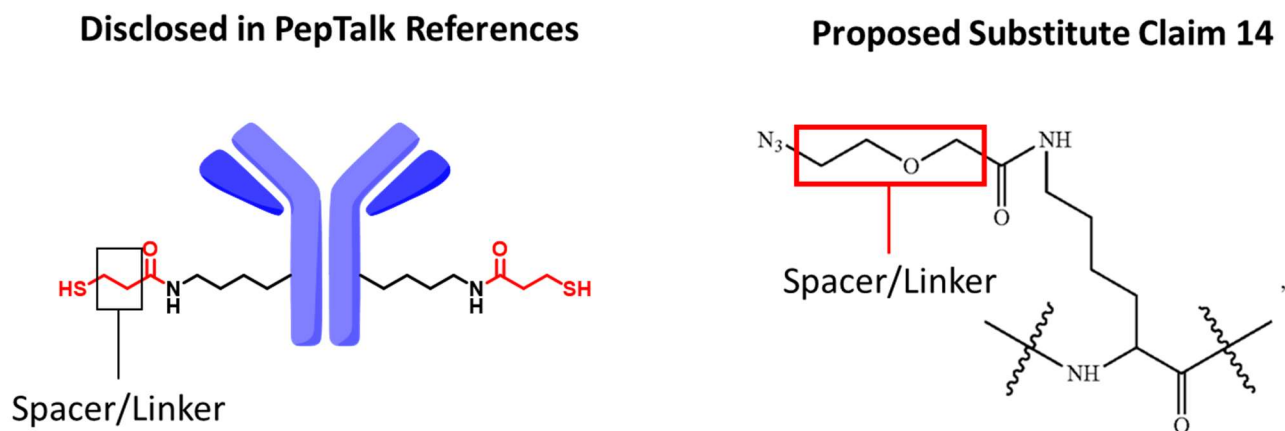
C. PepTalk Poster and PepTalk Presentation Further Render the Proposed Substitute Claims Obvious

45. In my prior declaration I explained why claim 11 would have been obvious in view of the PepTalk Poster (EX1006) or PepTalk Presentation (EX1007) in view of Yamada. For the same reasons, I believe that proposed substitute claims 14-16 are obvious over this combination of references.

46. As noted above, Yamada discloses the modified lysine structures recited in proposed substitute claims 14-16 vis-à-vis the available combinations taught for Formula (IV), and a person of ordinary skill would be motivated to select either an azide or norbornene click chemistry group and the short spacers/linkers recited in each of the proposed substitute claims. The PepTalk Poster and Presentation further support the obviousness of these claims.

47. With respect to proposed substitute claim 14, both the PepTalk Poster (EX1006, “Capability of AJICAP™”) and PepTalk Presentation (EX1007, 20)

specifically suggest an azide as the biorthogonal functional group to modify the lysine at position 248, and indicate that it is a substitute for a thiol group like the one shown in the modified antibody depicted below. Both references also disclose a modified antibody in which the lysine at position 248 has a short alkyl spacer/linker that differs from the spacer/linker of proposed substitute claim 14 only with respect to the oxygen ether, as shown below:

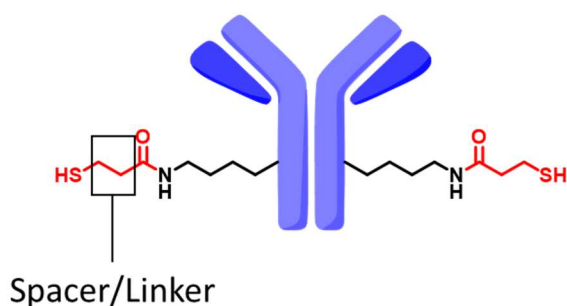


EX1006, “Synthesis of Site-Specific ADC by AJICAP™”; EX1007, 16. Those skilled in the art would understand that incorporation of an oxygen in the spacer/linker can provide synthetic benefits by incorporating a non-reactive group into the linker and biological benefits, such as improved solubility. EX1048; EX1052, 3535. Yamada provides multiple options for inclusion of a heteroatom (including oxygen, specifically) within the linker/spacer (EX1002, ¶453; EX1009, [0622], [0633]). Thus, there was an express suggestion in Yamada to explore the use of a heteroatom in the linker, and a person of ordinary skill view PepTalk Poster or

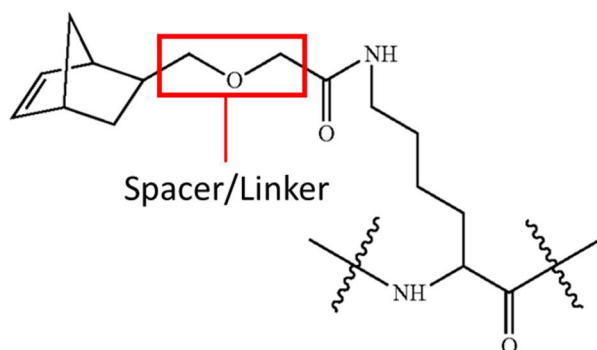
PepTalk Presentation with Yamada would be motivated to alter the spacer/linker in PepTalk Poster or PepTalk Presentation with an oxygen heteroatom given the known benefits. Thus, taken together with Yamada, these references clearly suggest preparing the modified lysine structure now recited in proposed substitute claim 14, and a person of ordinary skill would be motivated to make it.

48. The same holds true for proposed substitute claims 15 and 16. While PepTalk Poster and PepTalk presentation do not explicitly disclose norbornene as a suitable bio-orthogonal click chemistry group, the practical utility of norbornene in this context was well-established (EX1053), and Yamada explicitly suggests it. Moreover, the spacer/linker exemplified in the PepTalk Poster and PepTalk Presentation is even more similar to the spacers/linkers recited in proposed substitute claims 15 and 16. EX1006, “Synthesis of Site-Specific ADC by AJICAP™”; EX1007, 16. With proposed substitute claim 15, the bio-orthogonal click directly attached to the lysine without a spacer/linker instead of the simple two carbon linker provided in the PepTalk references. Thus, the arrangement recited in proposed claim 15 is one of the only ways the modified lysine disclosed in the PepTalk Poster and PepTalk Presentation could be further simplified. With proposed substitute claim 16, the linker is two carbon atoms and an oxygen in the beta position:

Disclosed in PepTalk References



Proposed Substitute Claim 16



EX1006, “Synthesis of Site-Specific ADC by AJICAP™”; EX1007, 16. Thus, the only difference between the arrangement recited in proposed claim 16 and the modified lysine disclosed in the PepTalk Poster and PepTalk Presentation is a single oxygen atom, which a person skilled in the art would have reason to incorporate, as noted above. EX1048; EX1052, 3535.

49. In sum, PepTalk Poster and PepTalk Presentation disclose azides and other commonly utilized bio-orthogonal click chemistry groups for modifying a lysine at position 248 of an antibody, and one of the exemplified modified lysines has a spacer/linker that is highly similar to the structures now claimed by AbTis. Accordingly, AbTis’s selection of the claimed components, which are all disclosed and suggested in Yamada, represent nothing more than substituting known components for utilization in the same contexts within which they were all disclosed. Arriving at the structures recited in proposed substitute claims 14-16 based on the PepTalk References and Yamada was not a matter of reverse engineering or

hindsight, but rather an obvious iteration of the information disclosed and a matter of routine selection.

**V. DR. ZHOU’S INTERPRETATION OF PEPTALK POSTER AND
PEPTALK PRESENTATION IS STRAINED**

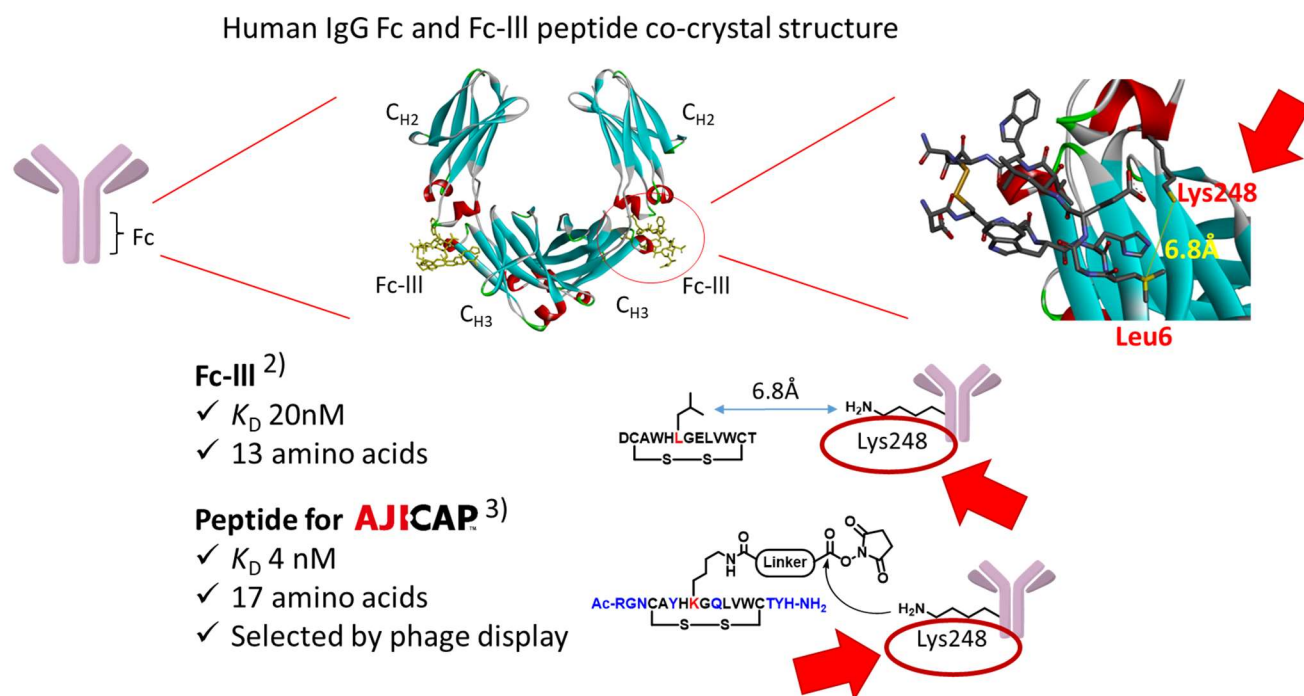
50. In his declaration, Dr. Zhou asserts that “[w]hile the PepTalk Poster mentions ‘lysine residue 248’ as an example, it does not state that it is the exclusive lysine binding site, let alone the exclusive site on the antibody” and he therefore reasons that “[a] POSA would understand that when the PepTalk Poster says ‘Determine Target Lysine Residue’ it means that a lysine other than lysine 248 may be determined as the target.” EX2004, ¶57. He also states that the PepTalk Poster, “provides no indication that lysine 248 is preferred.” *Id.* Dr. Zhou similarly asserts with respect to the PepTalk Presentation that “[w]hile the PepTalk Presentation mentions ‘lysine residue 248’ as an example, it does not state that it is the exclusive lysine conjugation site, let alone the only site on the antibody that AJICAP could target. *Id.*, ¶71.

51. While Dr. Zhou acknowledges that “there is an example functionalizing trastuzumab at Lys248,” he claims that because this example included a different spacer and different bio-orthogonal group (thiol) than the claims “it teaches away from the claimed modified residue.” *Id.* I disagree with Dr. Zhou’s interpretation of

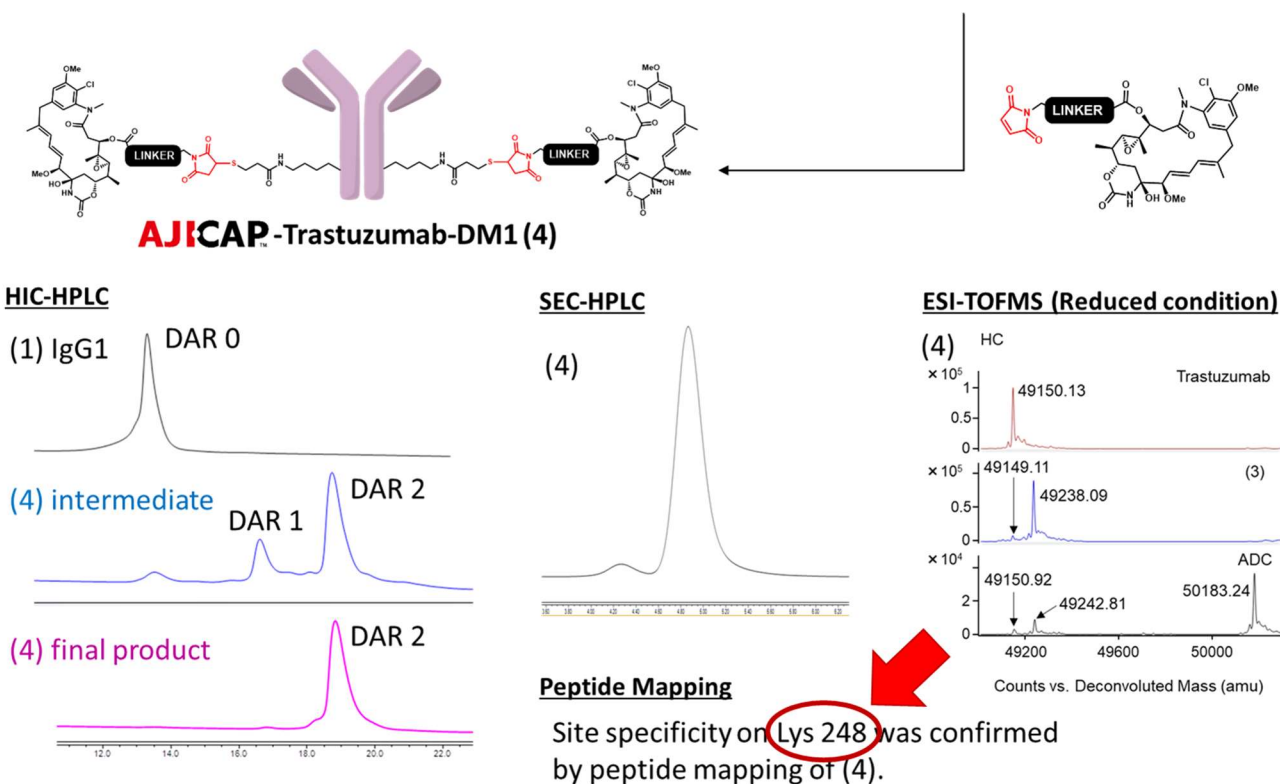
these references, and I find his interpretation to be so far strained that I do not find it to be a credible reading of the PepTalk Poster or PepTalk Presentation.

52. PepTalk Poster does not merely “mention[] ‘lysine residue 248.’” Rather, the lysine at position 248 is the only residue that is discussed. As Dr. Zhou notes, lysine 248 is explicitly identified under the heading “2. Determine Target Lysine Residue” as shown below with markings to indicate the multiple disclosures:

2. Determine Target Lysine Residue



Similarly, the section titled “3. Synthesis of Site-Specific ADC by AJICAP™” provides a specific example of modifying trastuzumab at lysine 248, as shown below:



The modified trastuzumabs with conjugations at lysine 248 were then tested under the “Results” section and the results show that these ADCs had improved effectiveness against cancer models both *in vitro* and *in vivo* (see Results 3. *In Vitro* Cytotoxicity and 5. Mouse Xenograft Model) without an increase in systemic toxicity (see Results 6, Safety Study in Rats). Even if other sites could be targeted for modification, it is clear from PepTalk Poster that lysine 248 is a “preferred” target site for modification, given that lysine 248 is the only residue that is discussed, used, and tested, with those tests showing that modification of the lysine 248 site provided desirable results. Similarly, PepTalk Presentation does much more than “mention[] ‘lysine residue 248’ as an example.” Like PepTalk Poster, lysine 248 is the only

specific position discussed in PepTalk Presentation (*see* EX1007, 14, 18, 24), and the PepTalk Presentation includes actual examples of modifying trastuzumab at this position with the same positive results (*id.*, 17-18, 22-27).

53. While it is true that the AJICAP™ platform could be used to modify other amino acids, this does not—in any way—detract from the focus on lysine 248 in the PepTalk Poster and PepTalk Presentation. Given this position is repeatedly highlighted in both references, no other position is mentioned, and the ADCs disclosed in these references repeatedly include a modification at lysine 248, neither reference provides a person of ordinary skill any reason to avoid modifications at this site. Rather, it strains credulity for Dr. Zhou to allege that one would consider other modifications in view of the repeated discussion of lysine 248 and positive empirical data. Given the successful modifications at this position disclosed within PepTalk Poster and PepTalk Presentation, a person of ordinary skill would have been motivated to continue making additional or alternative modifications at this site.

**VI. A PERSON OF ORDINARY SKILL COULD PREPARE THE
MODIFIED LYSINES RECITED IN PROPOSED SUBSTITUTE
CLAIMS 14-16**

54. While Dr. Zhou acknowledges in his declaration that all of the constituent parts of the structures recited in the proposed substitute claims can be

found within Yamada's Formula (IV), he asserts that preparing the structures is "scientifically infeasible." EX2004, ¶98. More specifically, Dr. Zhou alleges:

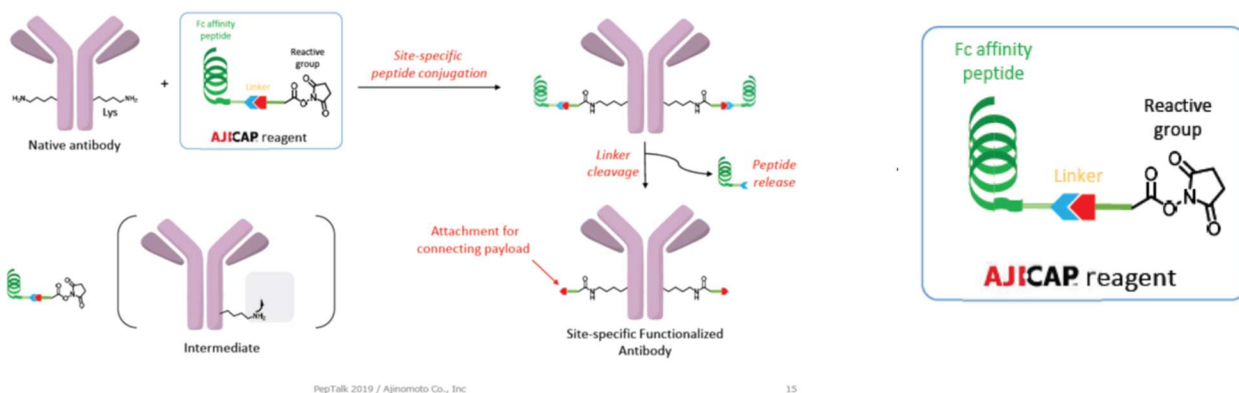
Yamada's Figure 2 and the description of the L cleavage process to form L₁ make clear that L represents a temporary, cleavable linker fragment, not a retained reactive moiety. To obtain the claimed azide- or norbornene-modified lysine residues as Dr. Tumey suggests, L₁ itself would have to result in cleavage of L. A POSA would have recognized that once L is cleaved, it no longer exists as part of the conjugate; it cannot, therefore, function as the retained azide or norbornene handle required by the claimed structures. In other words, Dr. Tumey's opinion assumes that the cleavage step both cleaves and simultaneously preserves the same functional group, which is logically contradictory and chemically impossible.

EX2004, ¶102.

55. Clearly Dr. Zhou's pronouncement that construction of the claimed structures is "scientifically infeasible" is incorrect because AbTis has apparently prepared a modified version of trastuzumab with each of the claimed structures. Therefore, the synthesis itself is not "scientifically infeasible," nor would a person of ordinary skill have viewed it as such prior to the earliest claimed priority date of the '675 Patent.

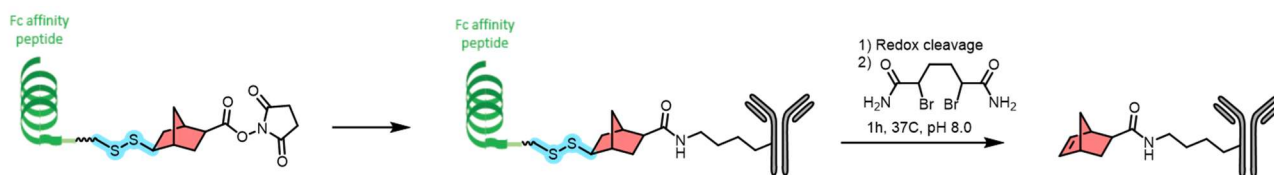
56. Although Yamada's synthesis scheme in Figure 2 could not be used to prepare the structures now recited in proposed substitute claims 14-16, a person of ordinary skill in the art would have understood that Figure 2 of Yamada was not the *only* possible approach for preparing a modified lysine.

57. For example, both the PepTalk Poster and PepTalk Presentation include the following general scheme for modifying the lysine at position 248:



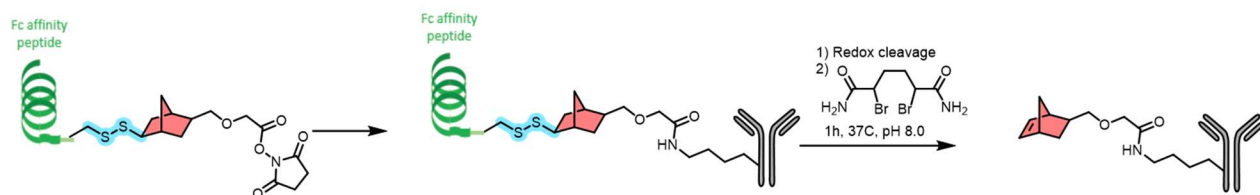
Utilizing the same blue- and red-coded coloring scheme for the illustrated linker group, I have provided below multiple feasible synthesis schemes for preparing the claimed modified lysines.

58. First, using a simple and common redox reaction like the one exemplified in PepTalk Poster and PepTalk Presentation (EX1007, 16), a person of ordinary skill would readily envisage the following scheme:

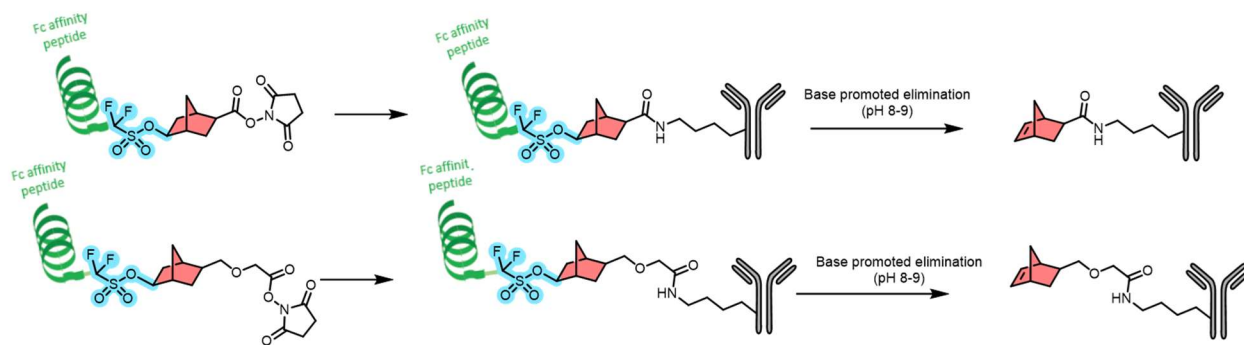


In this reaction, the middle step is consistent with the type of intermediate prepared in Yamada's Figure 2, but differs by utilizing a disulfide reduction followed by a desulfurization to result in cleavage of the norbornene group, thus producing the modified lysine of proposed substitute claim 15. This reaction has strong literature precedent, as evidence by EX1056.

59. Following the same synthetic scheme and simply changing the spacer element to incorporate an oxygen could be used to produce the modified lysine of proposed substitute claim 16:



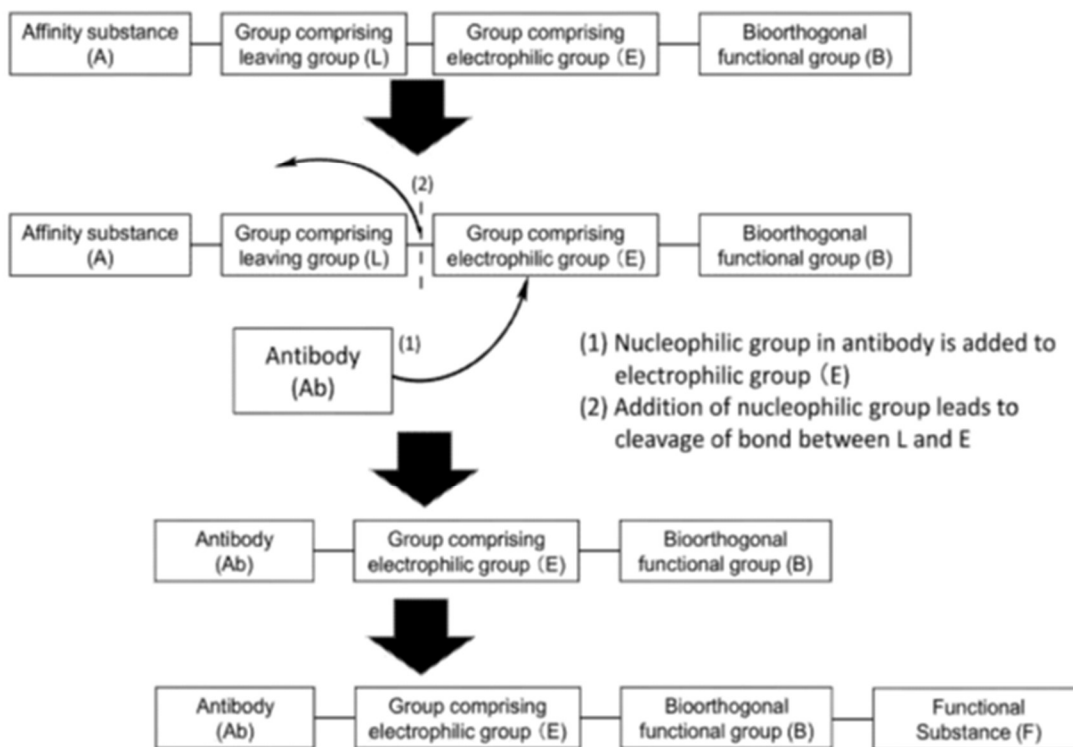
60. The above schemes represent only one possible method of preparation. Other methods could easily be envisioned by one skilled in the art. For example, a base-promoted elimination reaction, as shown in the scheme below, has precedent in the literature for the synthesis of substituted norbornenes. *See* EX1057. After modification of Lys248 by the indicated NHS-ester (on the left), the intermediate sulfonate would be subjected to base-promoted elimination conditions to convert the shown norbornane into a norbornene under pH and conditions that are suitable for bio-conjugation.



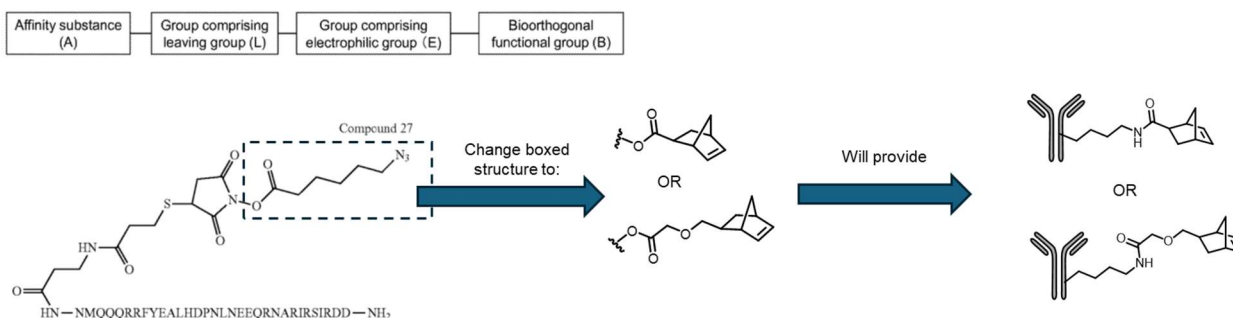
61. As noted above, PepTalk Poster, PepTalk Presentation, and Yamada teach the components of the modified lysines recited in the proposed substitute claims, and these references suggest combining these elements. *See* Section V discussion above. A person of ordinary skill in the art would have been motivated to select azide or norbornene groups and short acyl linkers for all of the reasons discussed above. *Id.* With this in mind, I believe a person of ordinary skill would also have reasonably expected to be able to make these compounds, regardless of synthetic scheme disclosed in Figure 2 of Yamada, because the knowledge and skill in the art was such that a person of ordinary skill would have been aware of numerous other potential synthetic routes that could produce the desired compounds, as shown above.

62. Moreover, the synthetic scheme disclosed in Figure 1 of Matsuda is extremely similar to the synthetic methods described in the '675 Patent, with both reactions using electrophilic intermediate to produce the modified lysine. For convenience, Figure 1 of Matsuda is reproduced below:

FIG. 1



Below, I have excerpted Part (2) of the reaction to show the simple substitutions that would readily allow a person of ordinary skill to use the synthesis disclosed in Matsuda's Figure 1:



For example, if we take “Compound 27” of Matsuda (*see* EX1011, [1018]), this compound includes the Affinity substance (A), Group comprising a leaving group (L), Group comprising an electrophilic group (E), and a Bio-orthogonal functional group (B), as described in Part (2) of Figure 1. I also note that Compound 27 includes an azide bio-orthogonal click chemistry group and a short acyl linker, which differs from the structure in proposed substitute claim 14 by being one carbon shorter and having an oxygen (O) in the beta position. Thus, only nominal changes would need to be made to the linker portion of Compound 27 for this intermediate to produce the modified lysine of proposed substitute claim 14. Similarly, as shown in the schematic above, simple substitutions of the displayed norbornene-containing groups would allow one to produce the modified lysines of proposed substitute claims 15 and 16.

63. Thus, Matsuda further evidences that the creation of the modified lysine structures in proposed substitute claims 14-16 was clearly feasible prior to even the earliest claimed priority date of the '675 Patent. A person of ordinary skill in the art therefore would have been entirely undeterred any potential incompatibility with Figure 2 of Yamada because other suitable synthetic strategies were part of the common knowledge in the art (*see* EX1056; EX1057) and at least one suitable approach was already provided in Matsuda as well (*see* EX1011, Figure 1; [1018]). Accordingly, I believe a person of ordinary skill in the art that would have been

motivated to create the modified lysine structures in proposed substitute claims 14-16, and he or she would have reasonably expected to be able to do so.

VII. MATSUDA DOES NOT “TEACH AWAY” FROM THE INCORPORATION OF HETEROATOMS

64. Dr. Zhou asserts that “Dr. Tumey failed to acknowledge that Matsuda expressly *teaches away* from incorporating beta (β)-heteroatoms (e.g., ether-oxygen) substituents in the linker used to modify lysine 248.” EX2004, ¶106 (emphasis original). I disagree with his characterization, and in my opinion, Matsuda does not “teach away” from the use of a beta (β)-heteroatom.

65. I have been informed that the prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives and that a reference does not teach away if it merely expresses a general preference for an alternative invention but does not criticize, discredit or otherwise discourage investigation into the invention claimed. Here, Dr. Zhou argues that Matsuda teaches away from including a beta (β)-heteroatom in the linker/spacer component of a modified lysine because Matsuda reported that two disclosed structures—compounds 26 and 60—that included a beta (β)-heteroatom “had not progressed” after incubation. EX2004, ¶107 citing EX1011 ¶¶[1014], [1023], [1150]-[1152].

66. First, as noted during my deposition, Matsuda’s indication that a reaction “had not progressed” does not necessarily mean that the reaction did not

work at all. Rather, it could simply mean that the reaction did not perform as well as they were hoping or that the reaction had not completed within the limited time allowed for the test. Specifically, the experiment involving compound 26 was only allowed to incubate for 16h at pH 7.2 and 37°C. The conditions used for compound 60 are not even disclosed (though they are presumably similar). Allowing a longer reaction time, increasing the pH, or increasing the temperature, among any number of other potential optimizing adjustments, might lead the reaction to proceed. It is and was common practice to optimize reaction conditions for conjugations, but that was not done (or at least not shown) in Matsuda. For instance, EX1058 shows a series of experiments with about 30 different reaction conditions for ADC conjugation; some “failed” (i.e., achieved a DAR of 0.6), but with careful optimization, the authors of EX1056 were able achieve full loading (i.e., a DAR of 2). *See* EX1058, Table 1. Further, these examples in Matsuda were designed to be comparative and show whether some drug linkers worked better than others for introducing an azide into the targeted lysine residue under similar conditions. For instance, the same reaction conditions were used for Example 6 (paras. [1080], [1083], [1086]) and Example 9 (para. [1180]), illustrating that Matsuda was interested in seeing the effect of changing the linker, not whether the use of any given linker was synthetically possible. Given the lack of reaction optimization for compound 26, the lack of disclosure of reaction conditions for compound 60, and

the numerous changes that could be made to potentially improve the reaction, the “Comparative Example” in paras. [1150]-[1152] of Matsuda cannot properly be considered evidence that linkers with oxygen beta heteroatoms “failed” to work altogether or that such heteroatoms should always be avoided.

67. Second, even if compounds 26 and 60 were a “failure” (and I do not agree that these compounds “failed” given the lack of empirical data on yield of these reactions), one cannot generalize that all beta (β)-heteroatoms will perform similarly in all structures based on these two results. Matsuda does not teach that having an oxygen in the beta position will always result in failure, much less in the context of the specifically claimed modified lysines. As I noted above, Yamada includes examples in which a beta (β)-heteroatom was incorporated into the linker/spacer, and these examples worked fine. EX1009, [0622], [0633]. Additionally, Matsuda compound 84 [1154] and 85 [1166] both contain a gamma-heteroatom and were each successfully loaded onto an antibody [1161-1168]. This is also seen in Yamada Tables 3-5, Examples 2-1 (gamma heteroatom), 2-2 (gamma heteroatom), 2-3 (gamma heteroatom), 11-1 (gamma heteroatom), 11-2 (gamma heteroatom), 53 (gamma heteroatom), 56 (gamma heteroatom), 57 (beta heteroatom), 58 (gamma heteroatom), 59 (beta heteroatom), 60 (beta heteroatom), 61 (gamma heteroatom), and 62 (gamma heteroatom). Thus, Matsuda in no way discredits the general concept of incorporating a heteroatom, in general, or a beta

(β)-heteroatom, specifically, in the linker/spacer, particularly in view of other references like Yamada. Therefore, I do not view Matsuda's disclosure as a "teaching away."

**VIII. THE MODIFIED LYSINES RECITED IN PROPOSED SUBSTITUTE
CLAIMS 14-16 DO NOT POSSESS UNEXPECTED PROPERTIES**

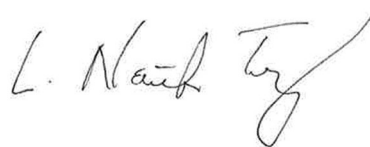
68. To my knowledge, neither AbTis nor Dr. Zhou has proffered any alleged evidence that the modified lysine structures recited in proposed substitute claims 14-16 possess any unexpected technical benefits or functions. Rather, they appear to be ordinary alternatives to known and commonly utilized structures that a person of ordinary skill could readily envisage based on the teachings of PepTalk Poster, PepTalk Presentation, Yamada, or a combination thereof.

X. CONCLUSION

69. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent & Trademark Office. I also recognize that I may be subject to cross-examination in the 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.

70. I hereby declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct, and that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true. I understand that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. § 1001).

Executed on January 21st, 2026



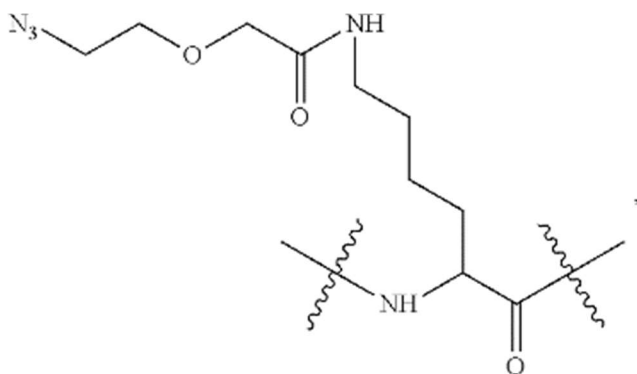
Lawrence Nathan Tumey

Appendix A

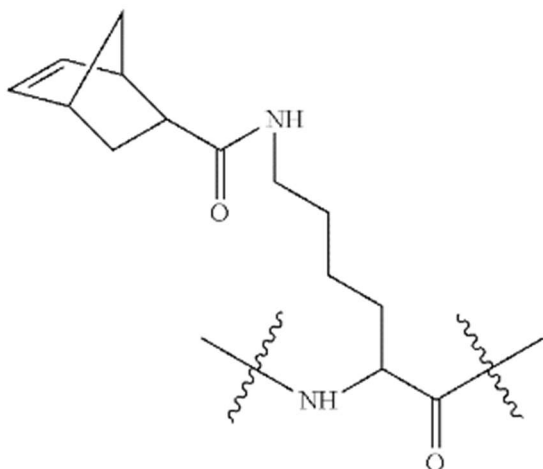
Proposed Substituted Claims

Proposed Substitute Claims of U.S. Patent No. 11,896,675

14. A modified antibody comprising bio-orthogonal click chemistry functional group,
wherein the modified antibody comprises one or more modified heavy chain,
wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and
wherein the modified lysine has the following structure:



15. A modified antibody comprising bio-orthogonal click chemistry functional group,
wherein the modified antibody comprises one or more modified heavy chain,
wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and
wherein the modified lysine has the following structure:



16. A modified antibody comprising bio-orthogonal click chemistry functional group,
wherein the modified antibody comprises one or more modified heavy chain,
wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and
wherein the modified lysine has the following structure:

