

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AJINOMOTO CO., INC.,

Petitioner,

v.

ABTIS CO., LTD.

Patent Owner.

CASE: IPR2025-00283

U.S. PATENT NO. 11,896,675

DECLARATION OF DR. ZHAOHUI SUNNY ZHOU, PH.D.

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I. INTRODUCTION

1. I am submitting this declaration in support of Patent Owner AbTis Co., Ltd.'s ("AbTis") reply to Petitioner's Opposition to AbTis's Motion to Amend (Paper 25) in the above-captioned proceeding. I have previously submitted a declaration in this proceeding (Ex. 2004) in support of Patent Owner AbTis Co., Ltd.'s ("AbTis" or "Patent Owner") Motion to Amend (Paper 23). I have reviewed Petitioner's Opposition (Paper 25), Dr. Tumey's second declaration (Ex. 1059), the prior art references relied upon therein, and the Patent Trial and Appeal Board's ("PTAB") Preliminary Guidance (Paper 27). My qualifications, background, and experience are set forth in my prior declaration (Ex. 2004) and in my *Curriculum Vitae* (Ex. 2005), and I incorporate those disclosures here by reference.

II. DR. TUMEY'S DECLARATION FAILS TO OVERCOME THE ISSUES I NOTED PREVIOUSLY

A. Dr. Tumey Does Not Show A Clear Path To The Claimed Compounds

2. Dr. Tumey's opinions fall short in two respects. First, he fails to show that the prior art would lead a POSA to the concept of the claimed moieties in proposed substitute claims 14-16. Second, even if a POSA were to envision the claimed moieties, he fails to show that the prior art disclosed a successful route of synthesis for making the moieties that a POSA would pursue.

3. Dr. Tumey points to the background section of my original declaration, and asserts that it “[m]ischaracterizes” the state of the prior art by stating that, as of the priority date of the ’675 Patent, there was no single accepted or predictable path to achieving a desired antibody modification or conjugation outcome. *See* Ex. 1059 ¶ 3. The pertinent question is not whether some site-specific approaches existed, but whether a person of ordinary skill in the art (“POSA”) would have needed some motivation to pursue a particular path and reasonably expect it to succeed. I followed that background statement with a thorough analysis of why AbTis’s ’675 patent fully supports and enables the proposed substitute claims. The prior art cited by Dr. Tumey does not establish such a motivation or reasonable expectation for the moieties in the proposed substitute claims.

4. Dr. Tumey now relies on general review articles and platform-level chemistry discussions (e.g., Exs. 1041-1043)—some of which are after the priority date—to argue that site-specific conjugation was “predictable” *See* Ex. 1059 ¶ 4-7. He does not, however, provide any specific reasons why a POSA would combine these references with any of the references he relies on for obviousness (e.g., the PepTalk Presentation, Yamada, or Matsuda), and if they did so, why they would expect to succeed in making the claimed compounds.

5. Importantly, none of Ex. 1041, Ex. 1042, or Ex. 1043 discloses or evaluates the specific chemical modifications at issue here (e.g., norbornene- or

azide-modified lysine 248 structures with the claimed spacer configuration). At most, these references discuss high-level correlations (e.g., hydrophobicity, solvent exposure, or DAR distributions) derived from extensive experimental work. Correlation alone is not predictability of success for a specific chemistry.

6. Dr. Tumey's assertion that there was an "emerging consensus" that certain sites "reliably performed well regardless of conjugation chemistry" (*see* Ex. 1059 ¶ 4) is not supported by the cited literature. These papers dealt with specific optimization, platform development, and side-by-side comparisons of specific reactions, and do not teach the specific bioorthogonal click-chemistry groups, spacers, or lysine 248 site, but deal with other click-chemistry groups, spacers, and antibody conjugation sites.

7. The PepTalk Poster and PepTalk Presentation (together the "PepTalk References") similarly do not establish a method of making the claimed compounds, let alone a predictable one, as Dr. Tumey suggests. *See* Ex. 1059 ¶ 16. These materials reflect outcomes achieved by the AJICAP™ platform following proprietary development and optimization. The PepTalk References are high-level platform disclosures that highlight selected successful embodiments, not technical teachings that would allow a POSA to generalize across sites or predict outcomes for different chemical structures. Although lysine 248 is shown as an illustrative example, the PepTalk References do not state that lysine 248 is the only workable

site, nor do they establish that lysine 248 is optimal relative to other lysines. Notably, the PepTalk References reference new second generation technologies with additional potential lysine positions using placeholders such as “LysXXX” and “LysYYY” (*see, e.g.*, Ex. 1007, at 34), but do not identify those sites or disclose the corresponding structures, conjugation chemistries, reaction conditions, or comparative performance data. Such placeholder references signal the existence of undisclosed embodiments while intentionally withholding the information necessary to evaluate, reproduce, or compare them, and therefore do not constitute a complete technical teaching that a POSA could rely upon. Accordingly, neither the PepTalk Poster nor the PepTalk Presentation “provide[] predictable paths for achieving desirable conjugation outcomes” as Dr. Tumey asserts. Ex. 1059 ¶ 8. Again, the fact that Ajinomoto developed and promoted their second generation technology while the first generation was first disclosed to the public illustrated that outcomes of bioconjugation methodologies, let alone success, could not be predicted.

8. Dr. Tumey suggests that platform technologies such as AJICAP™ made site-specific chemistry completely predictable such that a POSA could, for example, make all of the billions of structures disclosed in Yamada. Ex. 1059 ¶ 16. That is simply not the state of the art. The existence of platform technologies such as AJICAP™, for example, do not demonstrate that particular site-specific chemistries were predictable. Rather, platforms are developed precisely because

small structural or mechanistic changes can materially affect reactivity, selectivity, yield, and stability and must be empirically optimized. Statements in the PepTalk References regarding broad applicability or “potential” across antibody isotypes are merely aspirational and outcome-oriented, and they do not disclose the chemistry-specific information necessary for a POSA to reasonably predict success for a particular modification. Far from being “logically nonsensical,” as Dr. Tumey writes (Ex. 1059 ¶ 16), my original declaration accurately reflects the state of antibody conjugation chemistry and platform technology at the relevant time that included a mix of successes and notable failures. Even the PepTalk References highlight the problems with first generation AJICAPTM technology that needed to be overcome in the second generation. *See* Ex. 1006; Ex. 1007 at 34. Dr. Tumey further argues that my opinions are contradicted by a 2020 publication of which I am a co-author titled, “Site-Specific Conjugation of Native Antibody” (Ex. 1044). *See* Ex. 1059 ¶ 14. That assertion is incorrect. Dr. Tumey points out that the paper discusses the success and increasing use of site-specific methods, but does not suggest that each such methods will work for any given conjugation. He does not point to anything in this paper that would motivate one to make the claimed compounds with a reasonable expectation of success in doing so. Nor does he explain why this reference would be combined with the PepTalk References, Yamada, or Matsuda.

9. Finally, Dr. Tumey mischaracterizes my statement that subtle changes in spacers or reactivity could profoundly affect outcomes. *See* Ex. 1059 ¶ 15. This is a well-established principle in bioconjugation and protein chemistry. Dr. Tumey’s own statement admits that there is a degree of unpredictability by saying “[w]hile changes in spacer and linker composition or reactivity can affect a reaction, this does not mean that the results are *always* unpredictable.” *Id.* More importantly, he does not connect any of these ideas to a concrete reason why a POSA would pursue the claimed compounds.

10. Dr. Tumey’s opinions rest on hindsight reconstruction of the claims, and his discussion of known methods and their uses is no substitute for prior art teachings of the components of the claimed compounds and specific reactions that would make them.

B. Dr. Tumey’s New Analyses Ignore Critical Gaps in Prior Art Disclosure and Contain Technical Errors

i. Dr. Tumey Shifts From His Flawed Reliance on Yamada’s Synthetic Scheme To Reliance On Other References That Is Also Flawed

11. In Dr. Tumey’s original declaration, he proceeded on a structure-by-structure, example-by-example analysis, which (erroneously) mapped each claim limitation to a specific purportedly disclosed embodiment in the prior art. *See generally* Ex. 1002. In contrast, Dr. Tumey’s second declaration tries to show

that making the claimed compounds would have been possible without providing a motivation to pursue them. But even his attempts at showing possible reactions suffer from technical errors.

12. In discussing several new references, Dr. Tumey does not account for the constraints imposed by the suitable conditions for conjugation that must be compatible with intact proteins, including antibodies. For example, Dr. Tumey proposes elimination reactions or related transformations and suggests that they would proceed under conditions “suitable for bioconjugation.” Ex. 1059 ¶ 60. However, the references he relies upon involve reaction conditions that a POSA would recognize as incompatible with maintaining antibody structures and functions. These include harsh conditions and reactive intermediates that are not protein-compatible. *See* Ex. 1057.

ii. Dr. Tumey Recasts Distinct Click-Chemistry Groups as Interchangeable

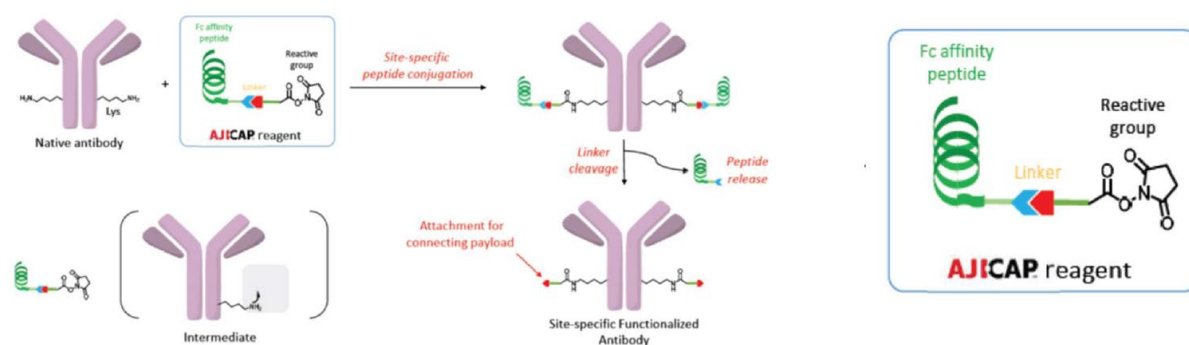
13. Dr. Tumey also relies on the mere existence of click chemistry substituents, and inapplicable synthetic procedures, to argue that a POSA would have made the claimed compounds. Ex. 1059 ¶¶ 4-9, 26-44, 54-63. That argument overlooks critical technical constraints.

14. In Dr. Tumey’s original declaration, he treats azide, norbornene, tetrazine, DBCO, thiol, and aldehyde as distinct functional groups, and attempted to

show prior art disclosures specific to azide- and norbornene-substituted antibody conjugates. *See, e.g.*, Ex. 1002 ¶¶ 94-100 (azide); *id.* at ¶¶ 99, 119-120 (norbornene). By contrast, in Dr. Tumey's second declaration, Dr. Tumey does not try to show the specific bioorthogonal group in the prior art together with a method of making it, and instead tries to shortcut the disclosure step by asserting that once one click group is shown to work, a POSA would expect all other click groups to work in essentially the same way. Ex. 1059 ¶¶ 4-9, 26-44, 54-63. That approach directly contradicts his original analysis and is not supported by the cited references.

iii. Dr. Tumey's New Reaction Schemes Do Not Have Support in the Prior Art

15. First, at paragraph 57 of the declaration, Dr. Tumey refers to a generic reaction scheme disclosed in the PepTalk References. At paragraph 58, Dr. Tumey brings a new reaction scheme for making a norbornene-modified antibody defined in Claim 15; at paragraph 59, Dr. Tumey brings another new reaction scheme for making a norbornene-modified antibody defined in Claim 16; and similarly at paragraph 60, Dr. Tumey brings still new reaction schemes for making norbornene-modified antibodies defined in Claims 15 and 16. Dr. Tumey asserts that a POSA would readily envisage the reaction schemes from the following generic reaction scheme from PepTalk Poster and PepTalk Presentation.



16. However, PepTalk Poster and PepTalk Presentation do not disclose the specific linkers of the reaction schemes proposed by Dr. Tumey that correspond to the blue and red elements in the foregoing generic scheme. More specifically, while PepTalk Poster and PepTalk Presentation disclose that azide could be conjugated to a lysine terminal of an antibody, neither of them discloses norbornene at all. Further, even for azide, PepTalk Poster and PepTalk Presentation do not disclose it as part of an intermediate compound. Thus, a norbornene or azide precursor as the red element of an intermediate compound does not have any support in these prior art references. Moreover, neither PepTalk Poster nor PepTalk Presentation discloses -S-S- or -CF₂-SO₃- as the blue element in their reaction scheme. Therefore, the specific conjugated blue and red elements in these four reaction schemes in paragraphs 58-60 appear to be completely out of Dr. Tumey's imagination.

17. Additionally, Dr. Tumey relies on Chalker et al., "Methods for Converting Cysteine" (Ex. 1056) ("Chalker") to support the second reaction in the reaction schemes of paragraphs 58 and 59. Chalker discloses Scheme 17(c) at page

1674, in which a thiol group in cysteine is removed from a carbon backbone and a double bond is formed at the end of the backbone in dehydroalanine. However, Scheme 17(c) does not disclose, teach, or suggest forming a norbornene at all. Chalker discloses neither a norbornene precursor as part of the first and second compounds nor a norbornene structure as part of the third compound in its Scheme 17(c) or elsewhere.

18. Dr. Tumey applies Chalker's reaction scheme to norbornene without any teaching or suggestion in the reference that such an extension is appropriate. Importantly, a POSA would not assume that chemistry developed for one class of reactive thiol groups (converting cysteine to dehydroalanine) would automatically apply to norbornene or azide-modified lysines in an antibody context. Absent explicit teaching or significant experimental evidence, a POSA would not reasonably expect such chemistry to work with norbornene-modified lysines. In fact, I am not aware of any literature reference that reports the formation of norbornene or azide using the reagents listed in Chalker and highlighted in paragraphs 58 and 59 of Dr. Tumey's second declaration. *See* Ex. 1059 ¶¶ 58-59.

iv. Dr. Tumey's New Analyses and References Contain Technical Errors

19. Dr. Tumey's second declaration relies on Kirmse et al., "Destabilisierte 2-Norbornyl" (Ex. 1057) ("Kirmse") to support the second reaction in the reaction

schemes of Paragraph 60. However, Kirmse makes no reference to antibodies at all. It only discloses small molecule organic chemistry reactions. More importantly, a POSA would understand that the reaction conditions in Kirmse are incompatible with intact antibodies. *See* Ex. 2009 (Full Kirmse Reference in English translation provided by the journal), Table 1 (reproduced below).

Table 1. Distribution of products upon solvolysis of the triflates **6** and **8**.

Educt	Conditions	3	7	5	<i>exo : endo</i>
<i>endo</i> -Series					
6a	Dioxane-H ₂ O (1 : 1), 80°C	8.6	91.2	0.2	—
6a	CF ₃ CO ₂ H, CF ₃ CO ₂ Na, 110°C	1.9	96.1	2.0	—
6b	Dioxane-H ₂ O (1 : 1), 100°C	1.3	98.7	—	—
6b	HCO ₂ H, HCO ₂ Na	trace	> 99	—	—
<i>exo</i> -Series					
8a	Dioxane-H ₂ O (7 : 3), 80°C	69.0	5.3	25.7	0.21
8a	Dioxane-H ₂ O (1 : 1), 80°C	71.8	6.4	21.7	0.29
8a	Dioxane-H ₂ O (3 : 7), 80°C	60.0	14.4	25.6	0.56
8a	CF ₃ CO ₂ H, CF ₃ CO ₂ Na, 80°C	58.1	36.6	5.3	6.85
8b	Dioxane-H ₂ O (1 : 1), 100°C	> 99	trace	—	—
8b	HCO ₂ H, HCO ₂ Na, 100°C	36.3	62.4	1.3	48
8b	CF ₃ CO ₂ H, CF ₃ CO ₂ Na, 65°C	59.2	40.7	trace	> 100

Ex. 2009, Table 1.

20. All temperatures reported in Kirmse are substantially higher than those tolerated by antibodies (e.g., 100 °C for **8b**, which was the only condition that led to a clean product in high yield), and moreover, the solvent systems include cosolvent concentrations that would degrade, denature or destabilize antibody structures. While antibodies can tolerate limited amounts of certain cosolvents and acids/bases, the levels disclosed in this reference are far outside what would be considered

acceptable for bioconjugation of antibodies. A POSA would therefore understand that the chemistry in this reference would not translate to the claimed chemical context due to the fundamental chemical properties, reactivities, and conditions. In addition, Dr. Tumey's comments regarding pH are incorrect. *See* Ex. 1059 ¶ 60. The pH ranges required to promote these elimination reactions are not compatible with maintaining antibody stability and Fc integrity. In addition, the norbornenes disclosed in Kirmse were heavily substituted (i.e., four substituents), and in comparison, only mono-substituted norbornenes are in AbTis's claims. As noted in Kirmse, "The presence of four fluorine atoms or four trifluoromethyl groups at C-5 and C-6 should intensify the electron deficiency". In other words, these substituents markedly alter the reactivities of the systems. As such, a POSA would not expect the reactions with heavily substituted norbornenes described in Kirmse could be applied for the mono-substituted norbornenes in AbTis' claims. In sum, these are the wrong reactants operating under the wrong conditions for antibody bioconjugation.

21. As another example, Dr. Tumey's discussion of elimination reactions (i.e., fluorinated sulfonate esters) illustrates this problem again. Dr. Tumey invokes difluoro-substituted systems and suggests that they would operate under bioconjugation-compatible conditions. From a chemical standpoint, this is incorrect. Difluoro-substituted systems are less reactive than the trifluoro-analogs

that were described in Kirmse; as such, difluoro-substituted systems generally require even higher temperatures or harsher conditions to undergo elimination. Dr. Tumey does not specify reaction temperatures or conditions in his declaration, but a POSA would recognize that elimination reactions of this type are not compatible with the mild, aqueous conditions required to preserve antibody structures and functions. Put plainly, Dr. Tumey relies on the wrong reactant under the wrong conditions.

v. Dr. Tumey's References "Predictability" References Do Not Teach Toward The Claimed Compounds But To Other Alternatives

22. Moreover, several of the references Dr. Tumey cites as evidence of predictability explicitly describe their results as surprising or as representing significant improvements over prior methods (*see, e.g.*, Ex. 1058). In Mullapudi et al., "Resin-Supported Site-Specific Antibody" (Ex. 1058) ("Mullapudi") for example, the authors report that common reductants reduce interchain disulfides (e.g., in the first generation AJICAP™ technology) and then describe a newly developed series that shows significant improvement. That disclosure confirms that earlier methods had problems and that the improved outcomes were not predictable. Moreover, Mullapudi does not teach the conjugation at Lys-248, the claimed spacer configuration, norbornene or azide. This lack of disclosure cannot be overcome by Dr. Tumey's assertion that making the claimed structures would have been routine

or expected because a POSA would have no motivation to make them, let alone a reasonable expectation of success when the reference does not address them in any disclosed synthesis.

23. Importantly, Mullapudi is not prior art to the '675 Patent and therefore does establish that a POSA would have known any of the conclusions Dr. Tumey suggests at the time of the claimed invention. Dr. Tumey's reliance on such references further underscores the hindsight nature of his analysis.

24. In sum, Dr. Tumey's new references do not provide a motivation to pursue the specific chemical structures recited in the proposed substitute claims, nor does it provide a reasonable expectation of success in pursuing them. Rather, it is my opinion that the prior art cited by Dr. Tumey demonstrates that site-specific conjugation and antibody modification were active areas of research and development involving significant experimentation. They do not demonstrate that a POSA would have been motivated to make the specific claimed modified lysine structures, and even if a POSA were so motivated, that one would succeed under antibody-compatible conditions. Ultimately, Dr. Tumey's second declaration relies on generalized principles, non-protein chemistry, and post-hoc reasoning, rather than chemistry-specific teachings that would have provided a reasonable expectation of success for the claimed embodiments.

III. THE PRIOR ART DOES NOT TEACH OR DISCLOSE THE CLAIMED MOIETIES

25. Dr. Tumey's cited references do not disclose the moieties claimed in the proposed substitute claims, either expressly or inherently, nor do they provide a POSA with sufficient technical guidance to arrive at those moieties without impermissible hindsight.

A. Dr. Tumey Has Not Provided Prior Art Disclosing the Claimed Moieties

26. Dr. Tumey maintains that Yamada in combination with Matsuda renders the proposed substitute claims obvious. Ex. 1059 ¶ 26. I still disagree with Dr. Tumey's opinion.

27. Dr. Tumey does not provide a disclosure of the structures of the claimed moieties, as a whole or in parts, even though he is presenting new references. He admits that Yamada and Matsuda do not disclose the three claimed moieties as a whole, stating that "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 L1, B, R', and T." Ex. 1059 ¶ 30. But he also does not show disclosure in parts. While he points to the click chemistry groups, azide and norbornene, in Yamada, he does not provide any reason to select those from among any of the others disclosed.

28. He also does not show a teaching or reason to target lysine 248 for conjugation. He points to the PepTalk Poster and PepTalk Presentation as disclosing it, but does not identify a reason to target it, let alone a preference for it. In fact, his own article that he cites targets a different conjugation site, Q295 (a glutamine residue that is chemically distinct from a lysine residue). *See* Ex. 1047. The references Dr. Tumey cites do not teach toward substituting lysine 248.

29. The most pronounced deficiency is that Dr. Tumey has not shown a single reference disclosing any of the spacer groups on any of the moieties in the proposed substitute claims. The spacer groups connect the bioorthogonal group to the lysine, and are -C-C-O-C-, a bond -, and -C-O-C- in claims 14, 15, and 16, respectively. Without disclosure of a specific one of them, he reasons that “‘when an azide group’ is used, the linker/spacer ‘would most likely be an alkyl or cycloalkyl’ 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.” Ex. 1059 ¶ 33. In other words, he admitted himself that alkyl or cycloalkyl linker/spacers, not ether linkages, are the most likely choices. Furthermore, he ignores that Matsuda also taught away from (β)-heteroatoms, and ether oxygen specifically. And for claim 15, which only has a bond (i.e., no spacer), his rationale that one would choose a spacer for flexibility no longer holds, and he instead relies

on “Occam’s Razor” instead of a particular disclosure. Ex. 1059 ¶ 41. The only place he shows the claimed structures is in the proposed substitute claims themselves. *Id.* ¶¶ 33, 37. That appears to be the same kind of hindsight he presented in his first declaration. His self-contradictions, nonetheless, highlight that a POSA would not have a preconceived notion of which substituents to choose from and which one would be more likely to succeed for specific applications and desired outcomes.

30. In other words, Dr. Tumey fails to show that each of the parts were present in the prior art, let alone why a POSA would select and then combine them.

B. A POSA Would Understand Yamada’s Disclosures as Limited by Yamada’s Reaction Scheme

31. Dr. Tumey maintains that Yamada in combination with Matsuda renders the proposed substitute claims obvious. Ex. 1059 ¶ 26. I disagree with Dr. Tumey’s opinion.

32. Dr. Tumey admits, “the completed structure is not disclosed” (i.e., the claimed modified lysine residues) in Yamada. Ex. 1059 ¶ 30. But, Dr. Tumey alleges that “component parts are all presented together in Yamada in a single section that specifically invites a POSA to combine the various disclosed substituents for L1, B, R’, and T.” Ex. 1059 ¶ 30. I disagree with Dr. Tumey’s opinion.

33. A POSA would not read Yamada's compound disclosures in isolation from Yamada's disclosed reaction scheme. Yamada presents its compounds within the framework of Formula IV and the accompanying synthetic steps, which define how intermediates are formed and how final antibody conjugates are produced. A POSA would therefore understand Yamada's disclosed compounds as limited to what can actually be synthesized using Yamada's taught chemistry. Absent an express suggestion to do so, which is not disclosed in Yamada, abandoning the disclosed synthetic framework and importing chemistry from other sources would not be considered routine or obvious.

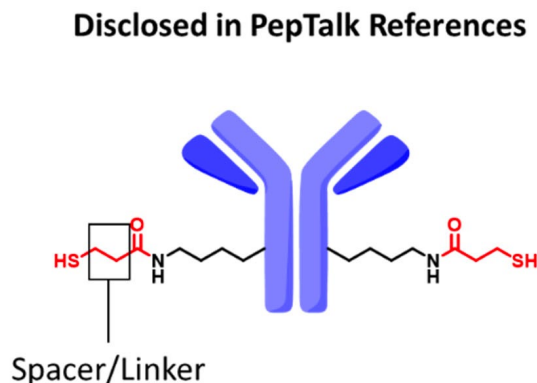
34. Because Yamada does not disclose a reaction scheme capable of producing the ether-containing spacer and specific modified lysine structures recited in proposed substitute claims 14-16, a POSA would not understand Yamada to disclose or teach those compounds.

C. Matsuda Teaches Away From the Claimed Moieties

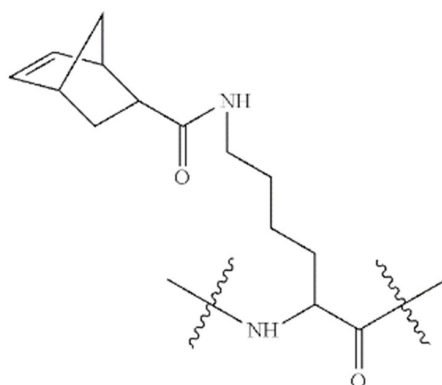
35. As I explained in my original declaration (Ex. 2004), Matsuda teaches away from incorporating beta (β)-heteroatom (e.g., ether-oxygen) substituents in the linker used to modify lysine 248, which are the very types of spacers recited in proposed substitute claims 14 and 16. Ex. 2004 ¶ 106–110. This is still my opinion, and Dr. Tumey has not presented any evidence or arguments that contradict my opinion. In his second declaration, Dr. Tumey stated that Yamada and Matsuda

utilize an oxygen as a heteroatom; however, none of these is an ether-oxygen and/or at the beta (β)-position as specified in the AbTis proposed substitute claims. In other words, all oxygens are not equal, and neither are their positions on the molecules. The -C-C-O-C- and -C-O-C- spacers in compounds 14 and 16, respectively, are precisely to the sorts of spacers that Matsuda taught away from. There is nothing in Yamada, Matsuda, the PepTalk References, or any of Dr. Tumey's new references that would lead a POSA to change the -C-C- spacer Dr. Tumey points to in the PepTalk References to the spacers of claims 14 and 16.

36. Another erroneous assumption by Dr. Tumey is stated on page 23 of Petitioner's Opposition: "For claim 15, one of the only ways the structure in the PepTalk References could be simplified is by removing the two carbon linker entirely, which a POSA would have been motivated to do. EX1059, ¶48-49, 41." The figure is reproduced below.



Ex. 1059 ¶ 48.



Proposed Substitute Claim 15

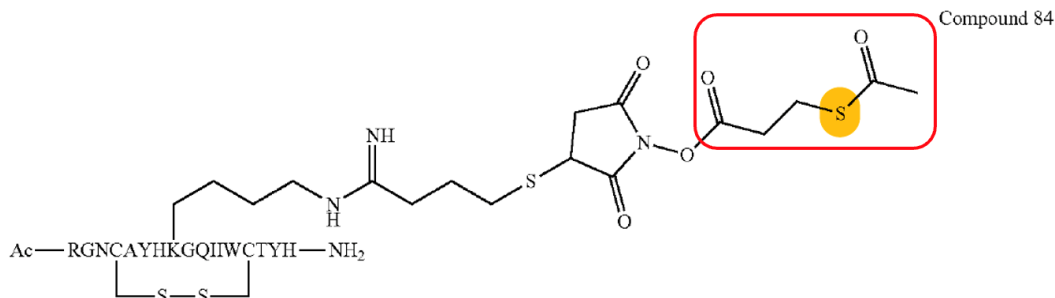
37. First, “removing the two carbon linker entirely” does not lead to claim 15 (shown above), and instead affords a structure depicted in the following scheme. The resulting function group (R-NH-C(=O)-SH) is referred to as N-alkylmonothiocarbamate in some literature.



38. Its chemical instability is worth noting. As reported in Muller-Litz (Ex. 2010, Zeitschrift für Chemie, 1980, 20 (11), 416-417; English translation of title by the Chemical Abstract Service (CAS): Decomposition of iso-butylammonium N-alkylmonothiocarbamates in weakly acidic and neutral aqueous solutions), such compounds rapidly decomposed in aqueous solutions, for instance, with a half-life less than 30 minutes (i.e., 1,800 seconds) at pH 7.47 and 25 C, and even shorter at lower pH's. As such, contrary to Dr. Tumey's statement that “For claim 15, one of

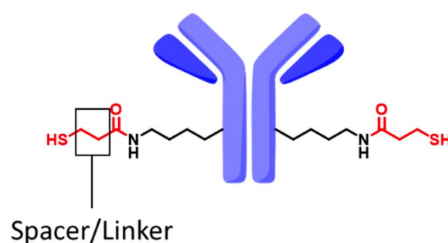
the only ways the structure in the PepTalk References could be simplified is by removing the two carbon linker entirely, which a POSA would have been motivated to do[.]” a POSA would recognize the chemical instability of the proposed structures in aqueous solutions, and would avoid using such chemistry for bioconjugation. Moreover, notwithstanding the chemical instability of the resulting functional group proposed by Dr. Tumey, he also failed to provide the corresponding reagents and conditions that would lead to the formation of the proposed functional groups, if it would even be possible under the suitable bioconjugation conditions.

39. In addition, Dr. Tumey also made another erroneous interpretation of Yamada and Matsuda. For instance, on page 23 of Petitioner’s Opposition, it states that “For claim 16, there was motivation to alter the linker to include an oxygen heteroatom (EX1059, ¶48, 67; EX1048, EX1052), and both Yamada and Matsuda disclosed examples of heteroatoms in the linker (EX1009, [0622], [0633]; EX1011, [1154], [1161]-[1168]).” Paragraphs [1161]-[1168] in Matsuda describe the bioconjugation using compound 84 (its structure is shown here, box and annotations are added for clarity).



Ex. 1011, ¶ [1161]-[1168].

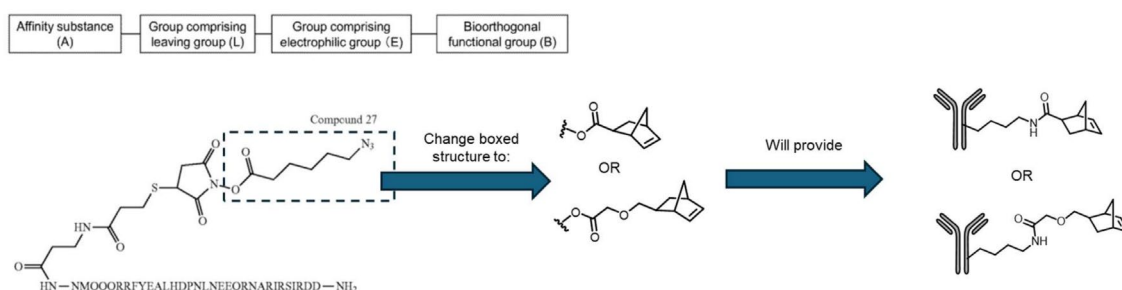
40. The resulting conjugate from compound 84 has the following structure as depicted in the inserted scheme, which does not contain any heteroatom in the linker at all.



Ex. 1059 ¶ 48.

41. For clarity, the thiol group (R-SH) is the bioorthogonal click group, not part of the linker. In sum, Dr. Tumey's analysis is erroneous.

42. Moreover, Dr. Tumey tries to explain that a POSA would ignore Matsuda's teaching away, and proceed to make each of the claimed compounds using the reaction scheme in Matsuda's Figure 1. *See* Ex. 1059 ¶ 62. His suggestion, however, appears to be pure hindsight because it begins by stating "Figure 1 of Matsuda is extremely similar to the synthetic methods described in the '675 patent." *Id.* Then, he shows an excerpt from Matsuda Figure 1 and says "simple substitutions" would readily allow a POSA to use the synthesis in Matsuda's Figure 1.



Ex. 1059 ¶ 62. Of course, the “simple substitutions” are to include the claimed spacers and bioorthogonal groups of proposed substitute claims 15 and 16 on the electrophilic group in the reaction to obtain the claimed compounds. He does not provide any reason why a POSA would pursue such compounds from among all of the possibilities other than hindsight. Next, even assuming a POSA might consider such options, a POSA also could not predict the outcome. And once more, Dr. Tumey ignores the teach-away of Matsuda about the lack of progress of conjugation with the (β)-heteroatom in the spacers, including the ether spacer. In addition, as Matsuda and literature have demonstrated again and again, once the chemistry of a conjugation reagent is altered, the reaction may not proceed at all; and even if it proceeds, may occur at a different residue or multiple sites (e.g., Lys 246 and/or Lys 248; LysXXX and/or LysYYY as described in the PepTalk References). Last but not least, a new reaction or technology may also suffer from unforeseen side reactions. For instance, Dr. Tumey’s own laboratory has addressed reactions “impacting the intrachain disulfides” on the antibody, i.e., generating undesirable

free thiols at sites, as with the first generation of AJICAP™ technology. *See, e.g.*, Ex. 1058 at 1957 (2 of 14).

43. Dr. Tumey says that a POSA would second-guess Matsuda's clear teaching that (β)-heteroatoms did not progress, without providing any reason why one would do so. Ex. 1059 ¶ 65-67. He suggests that a POSA would modify the conditions in Matsuda "[a]llowing a longer reaction time, increasing the pH, or increasing the temperature," which "*might* lead the reaction to proceed." *Id.* ¶ 66. Here, in paragraphs 66 and 67 Dr. Tumey is picking and choosing the portions of Matsuda a POSA would rely on and the portions a POSA would second guess. This is not the way a POSA would treat the reference. As for paragraph 66, Matsuda is *clear* and *categorical* about (β)-heteroatoms, and Dr. Tumey points to no apparent flaw in the disclosure that would cause a POSA to question that. Moreover, the increased reaction times, pH, and temperature are conditions that a POSA would understand would in all likelihood increase the degradation (such as deamidation of asparagine), denaturation and aggregation of both the antibody and the resulting conjugate itself, and he points to nothing that would show which changes (what reaction time, what temperature, or what pH) a POSA would make. To put it plainly, proteins and antibodies are delicate molecules; for instance, heating a protein solution at 100 °C or even a lower temperature lead to protein aggregation and loss of functions. For paragraph 67, the other examples in Matsuda and Yamada that Dr.

Tumey points to are not spacers with ether oxygen at the β position. Dr. Tumey's efforts to overcome Matsuda's teaching are unpersuasive.

IV. THE PROPOSED SUBSTITUTE CLAIMS SATISFY 35 U.S.C. § 112

44. I understand that Ajinomoto has asserted that the '675 patent does not meet certain written requirements. I have reviewed those assertions and respond to them below.

A. Full Scope Enablement and Written Description

45. I understand that Ajinomoto has asserted that the term "the modified antibody comprises one or more heavy chain" is broad relative to the examples in the specification, and "[i]t 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." Pet. Opp'n, 4. I disagree in several respects.

46. A POSA would understand the claim itself to limit the modified antibodies to those with lysine at position 248. Therefore, there is no overbreadth problem.

47. With regard to modifying the antibody at only one heavy chain, the claim reflects the practical reality of modifying antibodies. They result in DARs that are not always whole numbers, e.g., "DAR: 1.6~2.0 (Q-TOF, HIC)" and "DAR: 1.9 (Q-TOF), 1.8 (HIC)." (Ajinomoto's PepTalk Presentation slides 17 and 28, respectively). These different DAR values also highlight the intrinsic variabilities

of bioconjugation even if the same method is implemented, as the DAR values are affected by multiple factors, such as duration of the bioconjugation reactions. For example, a preparation that has an average DAR of approximately 1.0 may reflect a mixture of antibody molecules containing one modified heavy chain while others contain no modified heavy chains. Such preparations (i.e., preparations with an average DAR of approximately 1.0) are commonly referred to in practice as “DAR1.” Similarly, preparations having an average DAR of approximately 1.8 may reflect typical reaction product distributions including modified antibodies that contain two modified heavy chains while others contain fewer than two modified heavy chains. Such preparations (i.e., preparations with an average DAR of approximately 1.8) are commonly referred to in practice as “DAR2.” Even Ajinomoto’s own PepTalk Presentation presents DARs that are not whole numbers. Ex. 1007 at 28. Of note, nonetheless, Ajinomoto claimed whole numbers on multiple occasions, for instance, “controlled DAR 2” on slide 33 of the PepTalk Presentation and also the PepTalk Poster. *See* Ex. 1007 at 13, 33; Ex. 1006. Dr. Tumey’s understanding appears to be the same as well. Ex. 1059 ¶ 19.

B. Indefiniteness

48. I understand that Ajinomoto has asserted that there is ambiguity as to the number of bioorthogonal click chemistry groups in the proposed substitute

claims, and that a POSA would not know how many were within the scope of the claims. I disagree with this as well.

49. When read as a whole, each proposed substitute claim could not be understood as describing a modified lysine structure containing a bio-orthogonal click chemistry group and a separate bio-orthogonal click chemistry functional group elsewhere. Rather, a POSA would understand that the preamble describes the moiety generally, and that the specific description is below it. The specific description requires only one bioorthogonal click chemistry group.

V. UNEXPECTED PROPERTIES

50. Dr. Tumey asserts that the modified lysine structures recited in proposed substitute claims 14-16 lack unexpected technical benefits and merely constitute “ordinary alternatives” that a person of ordinary skill in the art could readily envisage based on the PepTalk Poster, PepTalk Presentation, Yamada, or combinations thereof. I disagree with Dr. Tumey’s opinion.

51. None of those references discloses or suggests the specific modified lysine structures recited in claims 14-16, and Dr. Tumey identifies no teaching directing a POSA to select those particular modifications from among the numerous possible alternatives. In my opinion, the complete absence of any such disclosure in the cited art is inconsistent with the assertion that these structures were routine or commonly utilized. Moreover, Matsuda affirmatively directs the skilled artisan

away from modification at the claimed lysine position and instead promotes different conjugation strategies. For these reasons, characterizing the claimed structures as “ordinary alternatives” reflects hindsight reconstruction rather than the teachings of the prior art.

Dated: March 6, 2026

A handwritten signature in black ink, appearing to read 'Zhaohui Sunny Zhou', is written over a horizontal line.

Dr. Zhaohui Sunny Zhou