

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 ZHAOHUI SUNNY ZHOU, PH.D.

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I, Dr. Zhaohui Sunny Zhou, declare as follows:

1. I have been retained in this matter by K&L Gates LLP on behalf of Patent Owner, AbTis Co., Ltd. (“AbTis” or “Patent Owner”) as an independent technical expert concerning the petition for *inter partes* review of AbTis’ U.S. Patent No. 11,896,675 (“the ’675 Patent”), filed by Ajinomoto Co., Inc. (“Ajinomoto” or “Petitioner”).

2. The opinions contained in this declaration are mine, and mine alone. No part of my compensation for my time in this proceeding is tied to, or contingent on, any opinion or outcome of this proceeding.

I. QUALIFICATIONS

3. My expertise is in therapeutic applications of bioorganic and protein chemistry, with a focus on peptide and protein drug modalities, including extensive experience in bioconjugation, generally, and antibody-drug conjugates (ADCs), specifically.

4. Since 2007, I am a Professor in the Department of Chemistry and Chemical Biology at Northeastern University, Boston, MA. I am also a Faculty Fellow of the Barnett Institute for Chemical and Biological Analysis. I am an advisor and coordinator with the Industry PhD program. I hold a position as Affiliated Faculty with the Bioengineering and Biology departments at Northeastern University. I have held faculty appointments from 2000 to the present. My research

over the last 35 years has involved pioneering work in the areas of polypeptides and proteins. This research involved peptide and protein chemistry, analysis, engineering, and therapeutic development, and includes extensive work on peptide and protein drugs (e.g., ADCs).

5. I graduated from Peking University, Beijing, China, earning a B.S. in Organic Chemistry in 1990. In my undergraduate studies, I worked in the laboratory of Professor Quing-Zhong Zhou in the Department of Chemistry, and my research was focused on polymer chemistry and phase transfer catalysis. Subsequently, from 1990-1991, I worked as a scientist and research associate for Dr. Qi-Pin Gao in the Department of Medicinal Chemistry and Formulation, Academy of Traditional Chinese Medicine & Materia Medica, Changchun, Jilin, China. My work as a research assistant focused on natural product isolation, analysis and derivatization, e.g., polysaccharide (carbohydrate)-drug conjugates.

6. I subsequently earned a Ph.D. in Bioorganic Chemistry in 1997 from The Department of Chemistry and Molecular Biology, The Skaggs Institute of Chemical Biology, The Scripps Research Institute, La Jolla, California. I obtained my Ph.D. under Professor Donald Hilvert (currently at the Federal Institute of Technology (ETH) Zurich, Honggerberg, Switzerland). My Ph.D. research focused on catalytic antibodies for pericyclic reactions, cofactor-dependent oxidations and

reductions, medium effects in enzyme catalysis, and artificial enzymes for peptide and protein synthesis.

7. From 1997-2000, I was a Research Fellow in the laboratory of Professor Rowena G. Matthews at the University of Michigan, Ann Arbor, Michigan. My research efforts were focused on biochemical and biophysical studies of metallo-enzymes. From 2000-2006 I was an Associate Professor with tenure (2006) and Assistant Professor in the Department of Chemistry, Associate Member, School of Molecular Biosciences; Graduate Faculty, Program in Pharmacology and Toxicology; Faculty of the NIH Biotechnology Training Program on Protein Chemistry, Washington State University, Pullman, Washington.

8. In 2007 I began my current role as a Professor in the Department of Chemistry and Chemical Biology at Northeastern University, Boston, MA. From 2019-2021, I also worked as a Visiting Professor in Dermatology at Massachusetts General Hospital (MGH), and a Visiting Scientist at the Wellman Center for Photomedicine, Harvard Medical School, Boston, MA, working with Professor Tayyaba Hasan.

9. Currently, my laboratory (aka “SunnyLand”) applies protein chemistry, analysis and engineering to biology and medicine. One program is “Hybrid Modality Engineering of Proteins” – a platform to introduce noncanonical chemical moieties and/or scaffolds into peptides and proteins to confer novel functions (modes of

action) otherwise unavailable via recombinant technology. One application is the conditional release and activation of conjugated therapeutics (i.e., prodrugs), such as by light (photomedicine). The second is to devise chemo-enzymatic methodologies to characterize protein post-translational modifications (PTMs), such as crosslinking, isoaspartic acid formation (asparagine deamidation), S-adenosyl-methionine (AdoMet or SAM)-dependent methylations, as well as, unknown PTMs and analytical artifacts. In my research efforts with my laboratory, I often collaborate with biologists and clinicians alike, investigating the biological effects and critical attributes of protein pharmaceuticals. Over the past two decades, I have been actively collaborating with and consulting for more than 20 biopharma companies, including Abbott/AbbVie, Amgen, Dragonfly, Morphic and Takeda. Since 2020, I have been a co-founder and advisor of NIRa Biosciences (now a subsidiary of Alys Pharmaceuticals) with the support of venture capital (VC) fund. The work at NIRa centers on antibody-drug conjugates (ADC) that can be activated by light. The new platform for photoimmunotherapy is deployed toward immuno-dermatology and immuno-oncology, providing spatially defined, cell-targeted therapy.

10. I have over 70 research publications and my work has been published in numerous journals well-known within the field of peptide and protein therapeutics, such as *Antibody Therapeutics*, *Bioconjugate Chemistry*, *ChemMedChem*, *mAbs*, *Journal of Pharmaceutical Sciences*, and *Pharmaceutical*

Research. I have been named as an inventor on 12 patents and applications, all in the field of enzymes, polypeptides, and proteins, including their synthesis, bioconjugation, design and therapeutic applications. In addition to publishing my own research, I also serve as an editor or member of the editorial board of the journals *mAbs*, *Molecules*, *Antibody Therapeutic and Bioconjugation Insights*. Moreover, I have designed and been teaching several advanced courses on the development of peptide and protein therapeutics, such as Protein Chemistry, and Chemistry and Design of Protein Pharmaceuticals. Last but not least, I am also a frequent speaker and workshop instructor at various biopharma companies and conferences, such as ADC world series, Bioprocessing Summit, PEGs Summit, and PepTalk.

II. BACKGROUND OF PETITION

11. I understand that Ajinomoto (“Ajinomoto”) and its expert, Dr. L. Nathan Tumey, have submitted papers in this proceeding arguing that original Claims 1-13 (Ex. 1002) are unpatentable under the United States Patent and Trademark Office’s *inter partes* review standard of a preponderance of the evidence. I provide certain technical opinions regarding the scope and content of the prior art, including how those skilled in the art as of 2019 would have understood certain references, the industry as a whole, and what factors were driving innovation in this space.

12. In forming the opinions expressed below, I have considered the documents listed above, the relevant legal standards as provided to me by my counsel, and my own knowledge and expertise. My opinions are offered from the perspective of a person of ordinary skill in the art, as that term is defined, as of March 8, 2019.

13. I understand that Dr. Tumey has already provided his opinions in Exhibit 1002; however, if he is permitted to offer additional opinions, I reserve my right to respond to those should I be asked to do so.

III. LEGAL STANDARDS

14. Although I am not a lawyer, I have been advised on the relevant legal principles by AbTis's counsel and have used them as a basis for my opinions.

A. Claims and Their Meaning to a POSA

15. I understand that the claims within a patent set forth what the inventors have presented as their inventions. I understand that claims can be independent or dependent form. Dependent claims reference independent claims and add requirements.

16. I have been informed and understand that terms in the patent claims must be read as they would have been understood by a person of ordinary skill in the art ("POSA") at the time of the claimed invention, which for this case I have been

asked to assume is March 8, 2019, and which I understand is the date Dr. Tumey and the Petition use as the priority date of the '675 Patent.

17. I understand that a POSA is a person to which the claimed subject matter pertains with the capability of understanding the scientific and engineering principles applicable to the pertinent art. I understand that the following factors may be considered in determining the level of ordinary skill:

- the type of problems encountered in the art;
- prior art solutions to those problems;
- the speed with which innovations are made;
- the sophistication of the technology; and
- the educational level of active workers in the field.

I also understand that not every factor may be present and that one or more factors may predominate others.

18. Dr. Tumey opines that a POSA would have had specialized knowledge in the field of antibody-drug conjugates, including (1) a PhD degree in organic chemistry, biochemistry, medicinal chemistry, and/or pharmacology, along with at least 1-2 years of relevant applied research and/or industry experience in the field of antibodies or antibody-drug conjugates, or, alternatively, (2) a Master's or Bachelor's degree in one of the aforementioned fields with at least 3-5 years, or 5-7

years, respectively, of relevant applied research and/or industry experience in the field of antibodies or antibody-drug conjugates.

19. In forming my opinions for this declaration, I have used the perspective of one of ordinary skill in the art as defined above. My opinions, however, would not be affected if a POSA is defined as someone who has slightly more or slightly less experience than described above.

B. Specification

20. I understand that there are other parts of a patent, including the abstract, the figures of a patent, the background of the invention, the summary of the invention, and the detailed description of the invention. I understand that these portions often are collectively referred to as the “specification” of a patent. I understand that technically the claims are part of the specification, but that referring to the “specification” typically means referring to the written description of the inventions rather than the claims.

C. Prosecution History

21. I understand that the correspondence back and forth between the representative of the applicant, and the U.S. Patent and Trademark Office, leading up to the issuance of a patent is called the “file history” or “prosecution history.” I understand that the claim language, specification, and file history are referred to as “intrinsic evidence” or “the intrinsic record.”

D. Burden of Proof

22. I understand that, unlike at the district court, patents subject to *inter partes* review, such as this proceeding, are not presumed to be valid, such that a lower burden of proof is used to judge the patentability of challenged claims. Unlike the district court’s “clear and convincing” burden, here, a “preponderance of the evidence” burden exists.

E. Anticipation

23. I understand that a patent claim is invalid as “anticipated” by a single “prior art” reference if the reference discloses every single element of the claim with sufficient precision and detail to establish that the subject matter of the claim existed in the prior art. In particular, I understand that it is not sufficient to establish that all of the elements are collectively disclosed within the four corners of a particular document. Instead, the operative question is whether a person of ordinary skill would have understood the elements as being arranged as in the claim itself. I also understand that a prior art reference cannot “anticipate” a patent claim unless that reference enables one of ordinary skill in the art to make and use what is disclosed without undue experimentation. Thus, if the reference does not enable one of ordinary skill to make or use each and every claim limitation, then the claim cannot be “anticipated” by the reference.

24. I understand that a prior art reference can disclose a given claim element actually or inherently.

25. In the case of actual disclosure, I understand that a person of ordinary skill would need to have understood that the disclosure corresponds to the claim element in question. I also understand that such disclosure may be implicit rather than explicit. For example, prior art need not use the same words as the claimed invention. However, I understand that ambiguous references do not anticipate.

26. In the case of alleged “inherent” anticipation, I understand that the claim element in question must necessarily be present when practicing the described technology even though the prior art reference itself contains no express description of the element in question. In particular, I understand that “possibilities or probabilities” are not sufficient to establish inherency. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. Instead, the essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question.

F. Obviousness

27. I understand that a patent claim may describe an invention that was new (i.e., not anticipated by any prior art reference), but nevertheless be invalid for “obviousness” if the differences between the patented subject matter and the prior

art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time of the invention was made.

i. Motivation to Combine

28. I further understand that an invention is not obvious just by demonstrating that each of its elements was, independently, known in the prior art. To prove that an invention is obvious, I understand that it can be important to point to a reason or reasons, such as a teaching, suggestion, or motivation, that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does; however, I further understand that a teaching, suggestion, or motivation need not be explicitly set forth in a reference itself. I understand that this is because inventions in most (if not all) instances rely upon building blocks already known, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known; therefore, it can be important to point to such a reason or reasons. I understand that in identifying such a reason, the analysis need not require precise teachings in the prior art directed to the specific subject matter of the challenged claim. However, I further understand there must be some reason articulated that supports why a POSA (defined below) would have made the proposed modification, and that the reason must be rooted in the prior art time.

29. I understand that it will often be necessary for a court, the PTAB, or a finder of fact to look to interrelated teachings of multiple patents and the background knowledge possessed by a person having ordinary skill in the art in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. I understand that any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed. I understand that when a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. I understand that the combination of familiar elements according to known methods may be obvious when it does no more than yield predictable results.

30. I also understand that a claim is not invalid as obvious if it is more than the predictable use of prior art elements according to their established functions.

31. Further, I understand that while predictability is a touchstone of obviousness, the concept of a “predictable result” under the law refers not only to the expectation that prior art elements are capable of being combined, but also that the combination would have arrived at the challenged claims.

32. I also understand that if the prior art “teaches away” from combining known elements in the manner claimed by the invention at issue, discovering a successful way to combine them is less likely to be obvious. In particular, I

understand that a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant, or would understand based on the reference that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. Likewise, I understand that similar subject matter may not be sufficient motivation for a person of skill in the art to combine references if the references have conflicting elements.

33. Further, I understand that even if a reference does not necessarily “teach away,” the reference's statements regarding preferences are relevant to a finding regarding whether a person of ordinary skill would have had reason to combine that reference with another reference.

ii. Reasonable Expectation of Success

34. I understand that an invention is not rendered obvious simply on the basis of two or more different disclosures that collectively disclose all of the claimed elements. In other words, an invention is not obvious just because all of the elements that comprise the invention may have been known in the prior art. Instead, a person of ordinary skill in the art must have had both a reason to pursue the proposed combination and a reasonable expectation of success in pursuing the possibility that

turns out to succeed and is claimed. In particular, I understand that knowledge of a goal does not itself render achievement of that goal obvious.

35. I also understand that determining whether or not a claimed invention would have been obvious requires assessing facts related to (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, (3) the level of ordinary skill in the art, and (4) any objective evidence (“secondary considerations”) of non-obviousness. I understand that this is known as consideration of the “Graham Factors.”

iii. Hindsight

36. I also understand that one must be cautious and resist the temptation to rely on hindsight reasoning when attempting to combine references to suggest that a claim may be obvious. It is important to analyze validity based on the perspective of a POSA at the time of the invention, which for this case I have been asked to assume is March 8, 2019, and which I understand is the date Dr. Tumey and the Petition use as the priority date of the '675 Patent. I understand that impermissible hindsight occurs when a petitioner uses knowledge of the claimed invention gleaned from the subject patent itself, rather than only prior art that existed before, to argue obviousness. I also understand that objective indicia (or “secondary considerations”) of non-obviousness or obviousness may be particularly probative and helpful in

avoiding hindsight. I have not been asked to analyze any secondary considerations as part of this declaration.

IV. BACKGROUND OF THE TECHNOLOGICAL FIELD AT THE TIME OF THE '675 PATENT

37. As 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. Researchers across industry and academia were exploring diverse strategies to achieve site-selective modification of antibodies and other proteins, including enzymatic methods, and chemical conjugation approaches targeting lysine, cysteine, or other amino-acid residues. There 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.

38. Scientists in this field routinely experimented with different structural formats and reaction schemes, each having distinct advantages and limitations. As reflected in the art cited by Petitioner, approaches varied widely in terms of the reactive handle used for step-wise conjugation (e.g., azide, alkyne, thiol, aldehyde), the site and amino acid residue of modification (e.g., lysine, cysteine, tyrosine, or tryptophan), and the linker chemistry (e.g., ester, amide, and/or ether). The cited art

illustrates that researchers explored numerous strategies, related and unrelated, often with differing rationales and outcomes, underscoring that there was no predictable or uniform path to success. For example, 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, and the cited references are largely devoid of specific teachings that would guide a POSA toward any particular combination of reactive group, residue, or linker with a reasonable expectation of success.

39. Petitioner, Ajinomoto Co., Inc.'s AJICAP platform is one example of a development using its own set of conjugation reagents and linkers. AJICAP was designed for site-specific lysine modification using peptide-based affinity reagents, but it was only one of many competing technologies being investigated during this period (i.e., 2019). Other groups were pursuing unrelated technologies, including transglutaminase (TGase)-mediated conjugation, engineered cysteine chemistry (e.g., ThioMab). These competing methods highlight that there was no standardized or universally accepted route to achieve selective modification in antibodies. Further, at the time of the '675 Patent's priority date, Ajinomoto was still developing and refining its AJICAP chemistry. The technology disclosed in its PepTalk Poster

and related materials reflected ongoing experimental investigation, not an established or routine practice. For example, in the PepTalk Presentation, while Ajinomoto first introduced its first generation platform, it already mentioned that a second generation was under development. A POSA would have understood that these approaches remained exploratory, and that achieving selective modification, particularly at specific lysine residues such as lysine 248, was not a matter of routine optimization but one of significant uncertainty.

40. Moreover, the field was inherently non-predictable: small structural or mechanistic changes often resulted in dramatically different reactivity, selectivity, yield, and product stability. Moreover, given the structural diversity and highly variable chemo-physical properties of antibodies, a POSA could not predict with confidence whether a modification that succeeded for one antibody would also succeed for another, or whether a given linker chemistry (such as an ether-containing spacer as opposed to a non-ether-containing spacer) would maintain subsequent reactivity (e.g., steric accessibility) or stability once conjugated to the antibody.

41. This is true even in the context of synthetic compounds. Specifically, even when a compound could be made synthetically, it did not follow that it could be used successfully in a bioconjugation reaction. The distinction between synthetic feasibility and functional conjugation performance is critical. For example, Matsuda's β -heteroatom linkers could be synthesized, yet failed to achieve

conjugation to antibodies under physiological conditions or compatible conditions for protein modifications. *See, e.g.*, Ex. 1011, ¶¶[1014], [1023], [1150]-[1152]. In contrast, the '675 Patent chemical moieties (though chemically related in concept) successfully form stable, site-specific conjugates. This demonstrates that predicting which structural modifications would work was not possible without actual experimentation.

42. Importantly, Dr. Tumey's testimony underscores this unpredictability. In his deposition, Dr. Tumey did not identify any reasonable expectation of success that a POSA would have had in arriving at or using the claimed compounds. While he speculated that the compounds might be synthetically feasible, he did not opine that they would perform as intended in selective lysine modification. His testimony, in fact, reflects the uncertainty typical of this field—acknowledging that one might attempt such chemistry but without confidence in whether it would succeed.

43. Thus, as of March 2019, researchers like those at AbTis were still navigating among numerous experimental routes, trying to determine which conjugation chemistries could achieve site-selective, stable, and reproducible modification of antibodies. AbTis's achievement of the claimed chemical moieties, which are demonstrated to work and to yield stable lysine 248 conjugates, reflects a non-obvious advance in a field characterized by uncertainty, experimentation, and

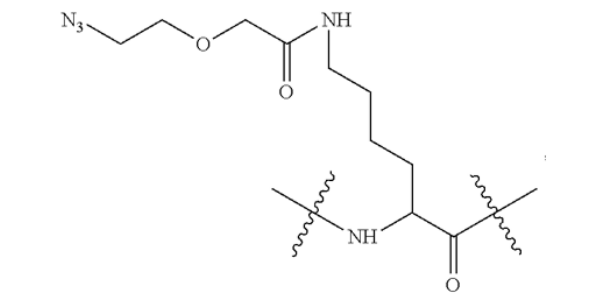
lack of predictability, and equally important, lack of clear direction of what specific modifications are desirable or preferable.

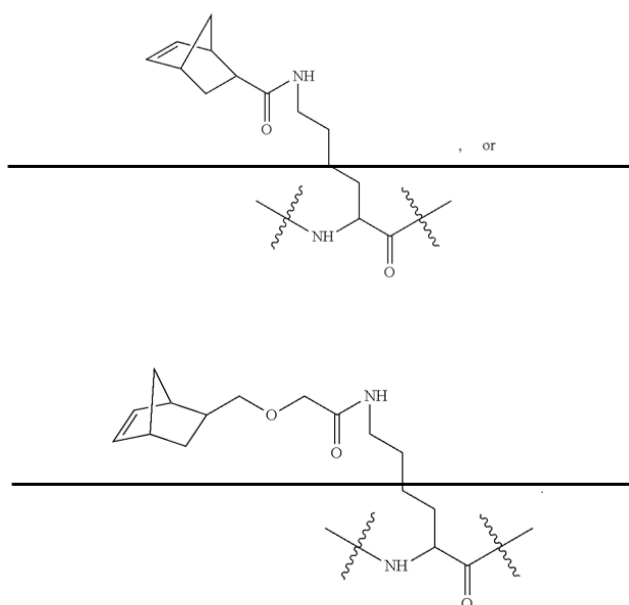
V. OVERVIEW OF PROPOSED SUBSTITUTE CLAIMS

44. Proposed substitute independent claims 14, 15, and 16 (collectively, the “Proposed Substitute Claims”) separate the alternative compounds previously recited in a single Markush group into individual species, without expanding the overall claim scope.

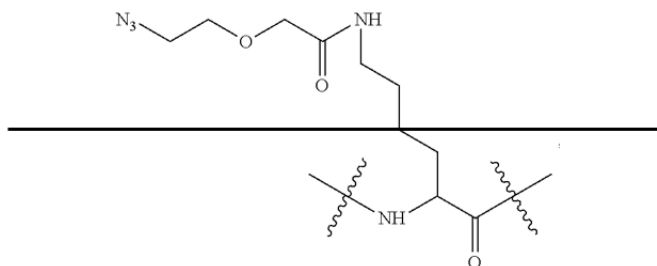
14. (Proposed substitute for original claim 11) ~~[[The]]~~A modified antibody of claim 1 comprising a bio-orthogonal click chemistry functional group,
wherein the modified antibody comprises one or more modified heavy chain,
wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and

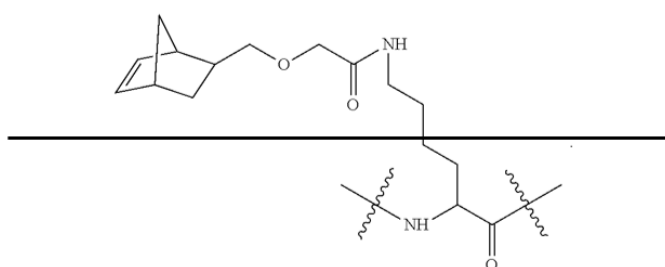
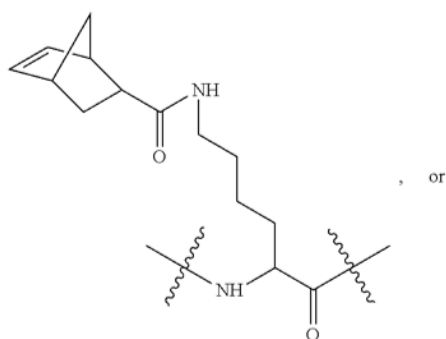
wherein the modified lysine residue has following structure:



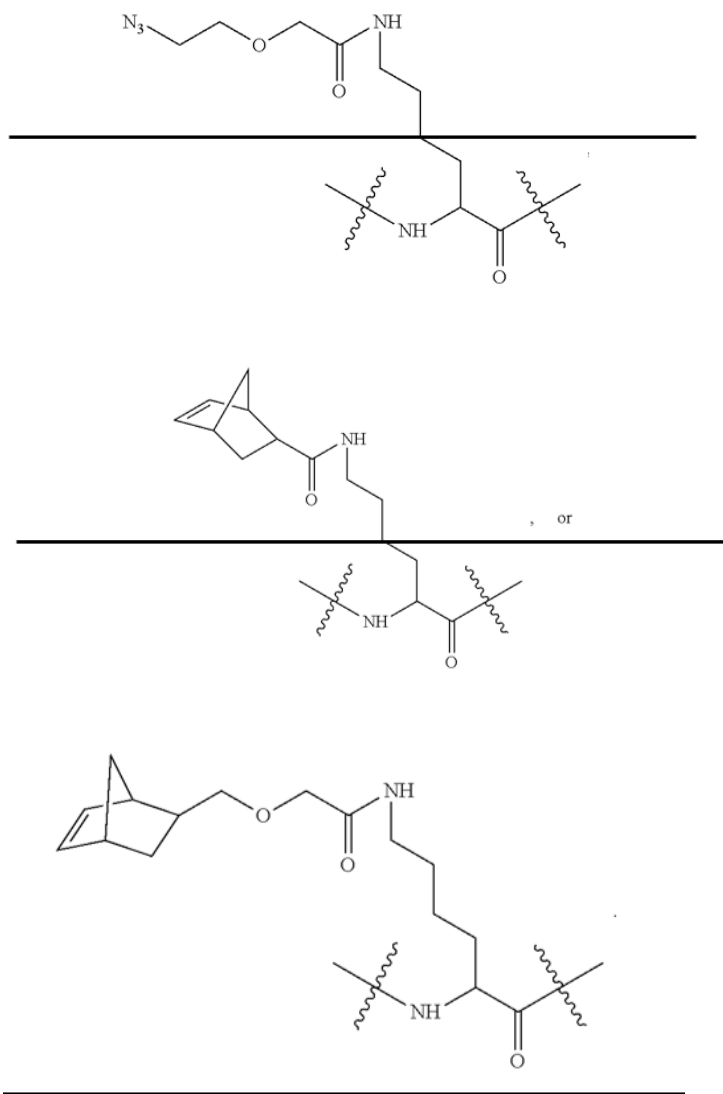


15. (Proposed substitute for original claim 11) ~~[[The]]~~ A modified antibody
~~of claim 1~~ comprising a bio-orthogonal click chemistry functional group,
wherein the modified antibody comprises one or more modified heavy chain,
wherein each of the modified heavy chain comprises a modified lysine residue
at 248 position of heavy chain amino acid sequence, wherein the 248 position is
determined by an EU numbering system, and
 wherein the modified lysine residue has following structure:





16. (Proposed substitute for original claim 11) ~~[[The]]~~A modified antibody
~~of claim 1~~ 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, and
 wherein the modified lysine residue has following structure:



45. Each Proposed Substitute Claim incorporates the limitations of original dependent claim 11 (which depended from disclaimed independent claim 1) while making two changes: (1) removal of the negative limitation carried over from claim 1, and (2) replacement of the three-member Markush group in original claim 11 with an affirmative limitation directed to one of the three single moieties in original claim 11.

46. Disclaimed claim 1 included a negative limitation stating that “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy, carboxyl, thiol, amino, or aldehyde groups.” When incorporated into dependent claim 11, this negative limitation did not affect the scope of the claim, because claim 11 already recited specific chemical moieties by their structure, such that they inherently exclude other functional groups. Specifically, the structural limitations in original claim 11 completely define the scope of the modified lysine residues. The negative limitation therefore provided no additional limitation, but was superfluous given claim 11’s more narrow structural limitations.

VI. OPINIONS

A. The Proposed Substitute Claims are Supported by the Original Disclosure

47. I have been asked to analyze the disclosure of U.S. App. Ser. No. 16/980,503 (“the ’503 Application”) (Ex. 2002), which qualifies as the “original disclosure” of the ’675 Patent because the application that issued as the ’675 Patent is a continuation of the ’503 Application, to determine whether it supports substituted claims 14, 15, and 16. It is my opinion that proposed substitute independent claims 14, 15, and 16 each derive from original claim 11 and are supported by the same written description in the specification, including at least the

embodiments shown in Formulas 5-2, 6-2, and 8-2, and Figures 15, 19, 21-22, and 42-43.

48. Specifically, each proposed substitute claim describes a modified antibody in which the Fc heavy-chain lysine residue at position 248 (EU numbering) is covalently modified with a specific attachment with a terminal bio-orthogonal click-chemistry functional group. The specification describes targeted transfer of a chemical functional group to lysine 248. *See, e.g.*, Ex. 2002 ¶[0008] (“[T]he present invention provides technology for specifically transferring a chemical functional group to lysine 248 in the antibody.”).

49. The specification describes the subject matter of the proposed substitute claims in a stepwise manner: beginning with a click-chemistry functional group substituted small-molecule intermediate, progressing through an Fc-targeting intermediate, and culminating in the antibody.

50. In my opinion, these disclosures demonstrated that the inventors possessed and enabled a POSA to make and use antibodies modified at Lys-248 by the three claimed substituents recited in substitute claims 14 (azide), 15 (norbornene), and 16 (norbornene with a spacer). The specification repeatedly defines antibodies bearing a “first chemical functional group” or “first click-chemistry functional group” covalently attached to the antibody, denoted as “R1'-Ab” or “H1-Ab.” *See, e.g.*, Ex. 2002 ¶¶[0395]–[0396], [0399]–[0400], [0406]. The

R1 moiety is expressly identified as a click-chemistry functional group that may be selected from an azide or a norbornene. *See, e.g.*, Ex. 2002 ¶¶[0406], [0518].

51. The '998 Application also specifies the spacer group through which the click-chemistry functional groups (azide or norbornene) are attached, as illustrated in Figures 15, 19, 21-22, and 42-43. The specification provides that D1, D2, and D3 may be “any alkylene, alkenylene, or alkynylene.” Ex. 2002 ¶[0450]. This disclosure supports the claimed spacer structures—namely, the covalent connection between the bio-orthogonal functional group (azide or norbornene) and the lysine residue at position 248—by defining the D1/D2/D3 spacer elements as short carbon-chain linkers that bridge the functional group to the antibody. *See* Ex. 2002 ¶¶[0448], [0450]–[0451].

52. Regarding the proposed substitute claims, Claim 14 (azide) is supported, for example, in at least ¶¶[0008], [0009], [0012]–[0016], [0228]–[0242], [0573]–[0597], and [0383]–[0400], and in Figures 21–22. Additionally, Claim 15 (norbornene, short/“no” spacer as claimed) is supported by the '503 Application in at least ¶¶[0383]–[0400] and Figures 15, 17, and 43. And Claim 16 (norbornene, ether-linked spacer as claimed) is supported by the '503 Application in at least ¶¶[0394]–[0414], [1344], and Figure 19.

B. The '959 Publication Is Not Prior Art to the Substitute Claims and Cannot Anticipate Them

53. 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. Ex. 1002, ¶¶ 174-182. He shows that each and every limitation of claim 11, and therefore, substitute claims 14, 15, and 16, are present in the '959 Publication disclosure, which is identical to the original patent, the '503 Application. *Id.*

54. The '503 Application was filed three days before the '959 Publication, and fully supports proposed substitute claims 14, 15, and 16. Therefore, the '959 Publication is not prior art to the substitute claims, and cannot anticipate them.

C. The Proposed Substitute Claims Are Patentable Over the Additional Art Dr. Tumey Cites

i. PepTalk Poster and Yamada (Ground 3) Do Not Render Obvious the Proposed Substitute Claims

55. Dr. Tumey opines that The PepTalk Poster (Ex. 1006) combined with Yamada (Ex. 1009) render claim 11 obvious. Ex. 1002, ¶280. For at least the reasons that follow, I disagree with Dr. Tumey's opinion.

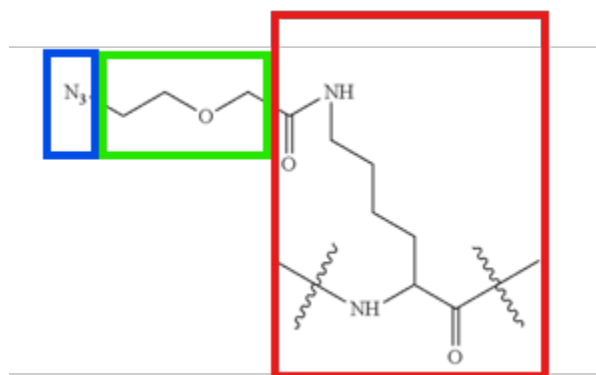
a. The PepTalk Poster Does Not Disclose Each Element of the Proposed Substitute Claims

56. Dr. Tumey states that The PepTalk Poster (Ex. 1006) "discloses modified antibodies in which lysine residue 248 is modified to include a click-

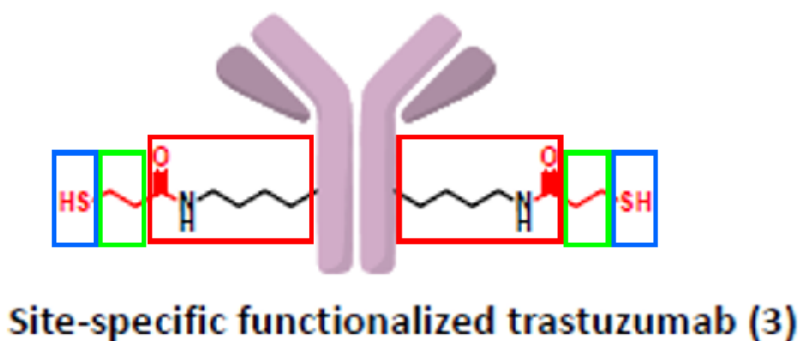
chemistry functional group at its terminal end, including an azide.” Ex. 1002, ¶193. However, Dr. Tumey fails to note that the PepTalk Poster *does not disclose* each limitation of claim 11. It likewise does not disclose each limitation of proposed substitute claims 14, 15, and 16.

57. While 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. 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. Ex. 1006 at number 2. The PepTalk Poster discusses “Capability of AJICAP” as being to “Lys residue,” not specifically lysine 248, and provides no indication that lysine 248 is preferred or offers any particular advantage. Thus, although lysine 248 may be targeted specifically, so can other sites. The PepTalk Poster does not teach why one would choose lysine 248 over other lysines or over alternative reactive residues such as tyrosine or tryptophan. Nor does the PepTalk Poster identify any structural or functional benefit of modifying lysine 248 relative to other sites. Especially when considered alongside Yamada’s generalized conjugation framework discussed below, the PepTalk Poster’s disclosure reflects only that multiple sites are possible—not that lysine 248 is preferred or advantageous—and thus would not have motivated a POSA to select lysine 248 for modification using the claimed bio-orthogonal substituents.

58. Moreover, the PepTalk Poster does not disclose, teach, or suggest the specific structures recited in proposed substitute claims 14-16, and would not have provided a POSA with a reason or expectation to arrive at the claimed Lys-248-modified antibodies. In particular, the claimed structural moieties have three components: a terminal bioorthogonal group (blue), a spacer (green), and a lysine 248 residue (red) to which the spacer is attached.



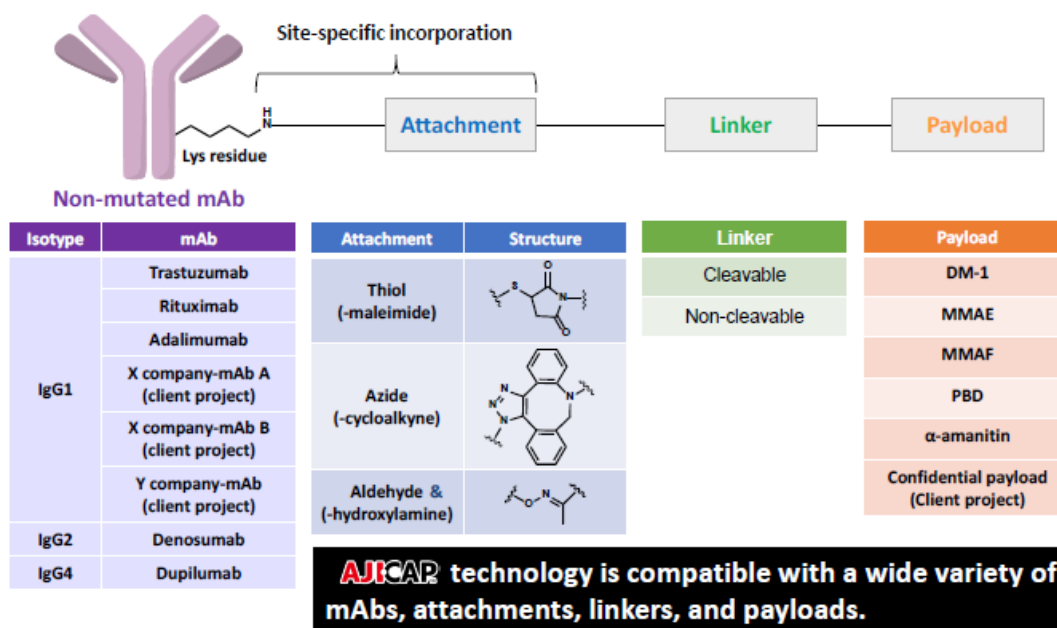
59. The PepTalk Poster does not specify any spacer preference at all, and only has an example of an alkylene spacer.



Id. at 16 (terminal bioorthogonal group is shown in blue; spacer is shown in green; lysine 248 residue, to which the spacer is attached, is shown in red).

60. Therefore, the PepTalk Poster does not disclose any compounds having the specific spacers recited in proposed substitute claims 14-16. Indeed, Dr. Tumey does not identify disclosure in the PepTalk Poster that includes an ether-linked spacer connecting the reactive functional group to the lysine residue, as required by claims 14 and 16, nor does he identify a direct (no-spacer) attachment as required by claim 15. Indeed, Dr. Tumey admits that the “PepTalk Poster depicts a *generalized* process for modifying an antibody[.]” Ex. 1002, ¶ 196 (emphasis added).

61. Further, proposed claims 14-16 require a specific bio-orthogonal functional group (e.g., azide or norbornene) is attached to the terminal end of the spacer opposite the lysine. The PepTalk Poster refers to these bioorthogonal groups as one part of a two-part “Attachment” to which the drug “Payload” is attached to the unspecified “Lys residue” via a “Linker.”

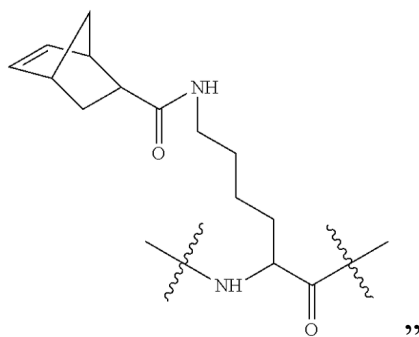


62. The PepTalk Poster discloses an azide bioorthogonal group, but that means little outside the context of the spacer to which it is attached or the lysine site two which it is bound. There is no preference stated for azide over the thiol or aldehyde groups, and therefore, a POSA would not select azide, let alone the remainder of the claimed chemical moiety based on the PepTalk Poster.

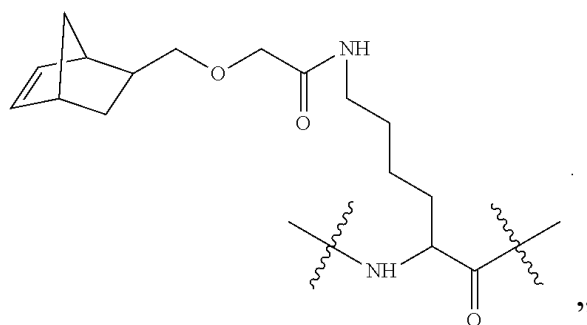
63. Accordingly, a POSA would not have understood the PepTalk Poster as teaching or suggesting modified lysine residue of claims 11 or 14-16.

b. The PepTalk Poster Does Not Teach or Suggest the Claimed Norbornene Chemical Moiety

64. The PepTalk Poster does not teach or suggest the use of norbornene as a modified lysine residue, and Dr. Tumey does not contend otherwise. As a result, the PepTalk Poster does not render obvious the claimed “modified lysine residue [that] has following structure:



(Proposed Substitute Claim 15), or the claimed “modified lysine residue [that] has following structure



(Proposed Substitute Claim 16).

65. There is no disclosure in the PepTalk Poster that teaches or suggests the substitution of norbornene for those other groups, or that such modification would be feasible at a lysine residue, much less at Lys-248.

66. Therefore, even setting aside the absence of site-specific lysine teaching discussed above, the PepTalk Poster fails to disclose or suggest the claimed structural features ((i) the ether spacer or no-spacer and (ii) the norbornene substituents) that distinguish proposed substitute claims 14-16. A POSA would recognize that these claimed structural combinations are absent from, and not reasonably suggested by, the PepTalk Poster.

67. Finally, the PepTalk Poster concludes with a discussion of a forthcoming, improved, second-generation AJICAP technology that is disclosed as having numerous advantages, but is not disclosed in detail. A POSA would have been dissuaded from using the current AJICAP technology based on the disclosed shortcomings and impending obsolescence.

68. For these reasons and the reasons set forth addressing Yamada below, substitute claims 14-16 are not obvious over PepTalk Poster in view of Yamada.

ii. PepTalk Presentation and Yamada (Ground 5) Do Not Render Obvious the Proposed Substitute Claims

69. Dr. Tumey opines that The PepTalk Presentation (Ex. 1007) combined with Yamada (Ex. 1009) render claim 11 obvious. Ex. 1002, ¶375. For at least the reasons that follow, I disagree with Dr. Tumey’s opinion.

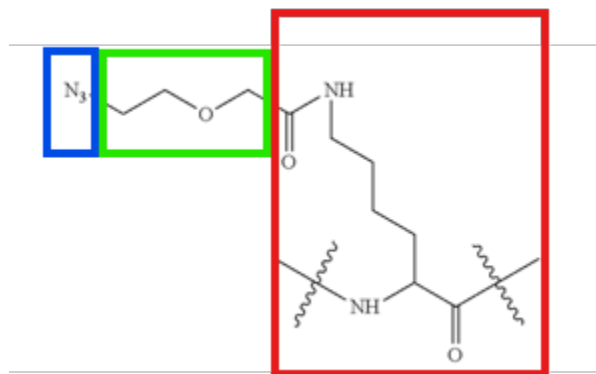
a. The PepTalk Presentation Does Not Disclose Each Element of the Proposed Substitute Claims

70. Dr. Tumey states that The PepTalk Presentation (Ex. 1007) “like the PepTalk Poster, discloses modified antibodies in which lysine residue 248 is modified to include a click-chemistry functional group at its terminal end, including an azide.” Ex. 1002, ¶289. Dr. Tumey fails to note, however, that the PepTalk Presentation does not disclose each limitation of claim 11. It likewise does not disclose each limitation of proposed substitute claims 14, 15, and 16.

71. While 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. *See* Ex. 1007 at 16-18, A POSA would understand that when the PepTalk Presentation says “Background of Affinity Peptide and Reaction Concept of AJICAP” it means that a lysine other than lysine 248 may be determined as the target. Ex. 1007 at 14. The PepTalk Presentation

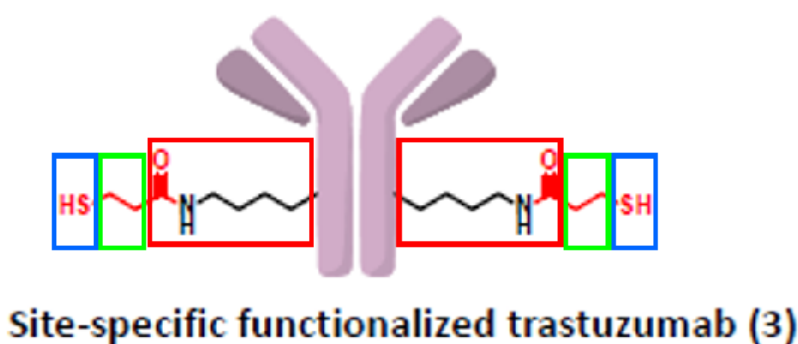
discusses “Strategy of AJICAP” as being to “Lys residue” without specifying lysine 248. *Id.* at 15. While there is an example functionalizing trastuzumab at Lys248, that example is with a different spacer and different bioorthogonal group (thiol) than the claims. *Id.* at 16. In other words, as a whole, it teaches away from the claimed modified residue.

72. Moreover, the PepTalk Presentation does not disclose, teach, or suggest the specific structures recited in proposed substitute claims 14-16, and would not have provided a POSA with a reason or expectation to arrive at the claimed Lys-248-modified antibodies. In particular, the claimed structural moieties have three components: a terminal bioorthogonal group (blue), a spacer (green), and a lysine 248 residue (red) to which the spacer is attached.



73. The PepTalk Presentation does not specify any spacer preference at all, and only has an example of an alkylene spacer. *Id.* at 16. As discussed above in Section VI.C.i.a, while the PepTalk Presentation mentions lysine 248 as one possible modification site, it also makes clear that other lysine residues, and even other

reactive amino acids such as tyrosine or tryptophan, can likewise be targeted. The PepTalk Presentation provides no explanation for why lysine 248 would be selected over these alternatives, nor does it attribute any structural or functional advantage to conjugation at that site. *See* Section VI.C.i.a. As a result, the PepTalk Presentation would not have motivated a POSA to specifically select lysine 248 for modification using the claimed bio-orthogonal substituents.

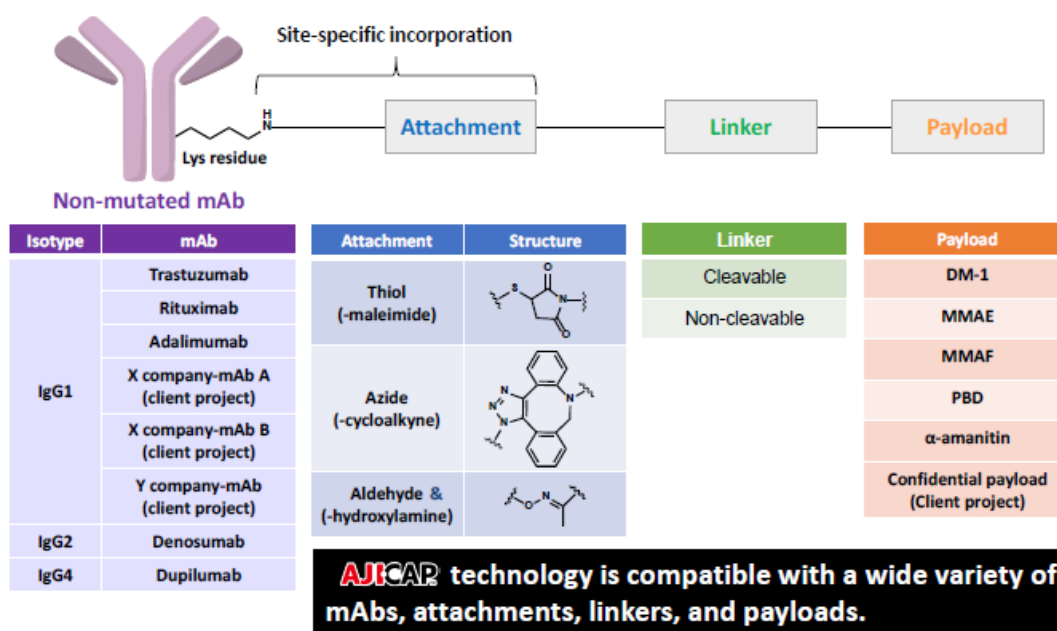


Id. at 16 (terminal bioorthogonal group is shown in blue; spacer is shown in green; lysine 248 residue, to which the spacer is attached, is shown in red).

74. Therefore, the PepTalk Presentation does not disclose any compounds having the specific spacers recited in proposed substitute claims 14-16. Indeed, Dr. Tumey does not identify disclosure in the PepTalk Presentation that includes an ether-linked spacer connecting the reactive functional group to the lysine residue, as required by claims 14 and 16, nor does he identify a direct (no-spacer) attachment as required by claim 15. Indeed, Dr. Tumey admits that the “PepTalk Poster depicts

a *generalized* process for modifying an antibody[.]” Ex. 1002, ¶291 (emphasis added).

75. Further, proposed claims 14-16 require a specific bio-orthogonal functional group (e.g., azide or norbornene) is attached to the terminal end of the spacer opposite the lysine. The PepTalk Presentation refers to these bioorthogonal groups as one part of a two-part “Attachment” to which the drug “Payload” is attached to the unspecified “Lys residue” via a “Linker.” *Id.* at 20.

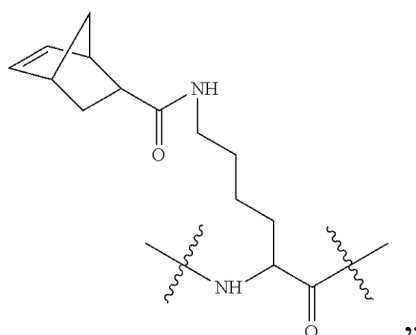


76. The PepTalk Presentation discloses an azide bioorthogonal group, but that means little outside the context of the spacer to which it is attached or the lysine site two which it is bound. There is no preference stated for azide over the thiol or aldehyde groups, and therefore, a POSA would not select azide, let alone the remainder of the claimed chemical moiety based on the PepTalk Presentation.

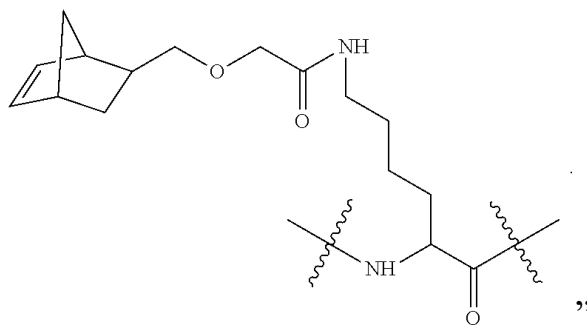
77. Accordingly, a POSA would not have understood the PepTalk Presentation as teaching or suggesting modified lysine residue of claims 11 or 14-16.

b. The PepTalk Presentation Does Not Teach or Suggest the Claimed Norbornene Chemical Moiety

78. The PepTalk Presentation does not teach or suggest the use of norbornene as a modified lysine residue, and Dr. Tumey does not contend otherwise. As a result, the PepTalk Presentation does not render obvious the claimed “modified lysine residue [that] has following structure:



(Proposed Substitute Claim 15), or the claimed “modified lysine residue [that] has following structure



(Proposed Substitute Claim 16).

79. There is no disclosure in the PepTalk Presentation that teaches or suggests the substitution of norbornene for those other groups, or that such modification would be feasible at a lysine residue, much less at Lys-248.

80. Therefore, even setting aside the absence of site-specific lysine teaching discussed above, the PepTalk Presentation fails to disclose or suggest the claimed structural features ((i) the ether spacer or no-spacer and (ii) the norbornene substituents) that distinguish proposed substitute claims 14-16. A POSA would recognize that these claimed structural combinations are absent from, and not reasonably suggested by, the PepTalk Presentation.

81. Finally, the PepTalk Presentation concludes with a discussion of a forthcoming, improved, second-generation AJICAP technology that is different than disclosed to have numerous advantages, but is not disclosed in detail. In other words, Ajinomoto admitted itself that its first-generation technology had numerous limitations that required further development. As such, a POSA would have been dissuaded from using the current AJICAP technology based on the disclosed shortcomings and impending obsolescence.

82. For these reasons and the reasons set forth addressing Yamada below, substitute claims 14-16 are not obvious over PepTalk Presentation in view of Yamada.

iii. Yamada, Alone or in Combination of the PepTalk Poster or the PepTalk Presentation, Fails to Render the Proposed Substitute Claims Obvious

a. A POSA Would Not Have Been Motivated to Modify the PepTalk Poster or PepTalk Presentation with Yamada

83. Dr. Tumey relies on Yamada in Grounds 3 (with PepTalk Poster), 5 (with PepTalk Presentation), and 7 (Yamada alone). I have been informed by counsel that Yamada was before the examiner during prosecution, and that the examiner never rejected the claim that issued as claim 11 (original claim 66) over Yamada; instead, that claim was objected to solely for dependency issues, and was ultimately allowed after amendments to the independent claims. In my opinion, this history is consistent with the structural distinctions between original claim 11 and Yamada's generalized conjugates.

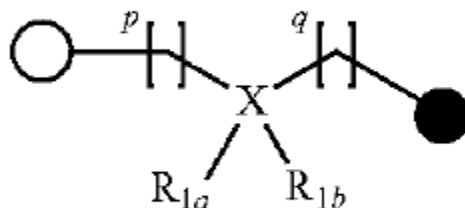
84. **First**, Yamada's generalized schema does not disclose the claimed modified lysine residues to a POSA. Yamada's Formula (IV) ($L_1-B-R'-T$) is a schematic representation comprising independently variable elements and does not identify the specific claimed combinations. Petitioner selects various definitions (e.g., separate lists for L_1 , B , and R') from Yamada to reconstruct the claimed species. In my opinion, beginning with the claimed modified lysine residues and working backward from Yamada, picking and choosing among billions of options is

inconsistent with how a POSA would read Yamada and is an impermissible hindsight analysis.

85. This hindsight assembly is particularly apparent because Yamada's generic formula encompasses an extraordinary number of theoretical combinations of linkers and reactive groups. Each variable of Formula (IV) (L1-B-R'-T) is defined to include dozens of potential atoms, chains, and functional groups, yielding potentially billions of distinct possibilities.

86. Dr. Tumey points to ¶¶[582]-[639], [1465], [1470], [1472], and [1480] to piece together the variables of Formula (IV). Ex. 1002 ¶¶272-280, 367-375, and 446-454. But Dr. Tumey provides no reason for choosing any particular option at any variable based on the prior art, and the options are numerous.

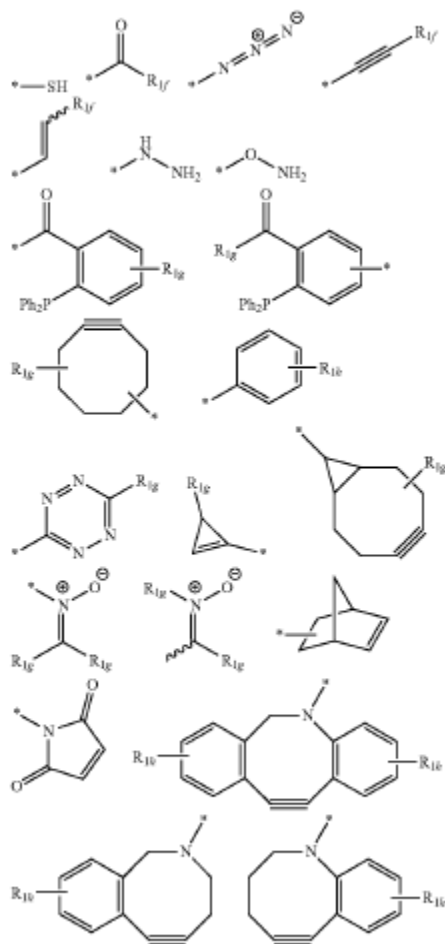
87. For example, for Formula (IV) (L1-B-R'-T), Yamada discloses that L1 can be variable C1 or variables C1-Lb, wherein Lb is a divalent group and C1 is a bioorthogonal group or a group other than a bioorthogonal group. Ex. 1009 ¶¶[616]-[622]. Putting aside that C1 can be anything under that definition, and assuming it is a bioorthogonal functional group, there are still many possibilities for it. Lb is represented by the formula:



wherein p is any integer of 0 to 10 (i.e., 11 different options), q is any integer of 0 to 10 (i.e., 11 different options), X is a carbon atom, a nitrogen atom, or a single bond (i.e., 3 different options of various functional groups and much greater than 3 options of individual chemic moieties); wherein when X is a nitrogen atom, R_{1b} is absent; when X is a single bond, R_{1a} and R_{1b} are absent.

88. Taking only those possibilities for L_b , p and q can each be 11 different options (0 to 10), and X can be at least 3 (C, N, or bond H). That alone is 363 possibilities ($11 \times 3 \times 11 = 363$). For R_{1a} and R_{1b} , when X is C, they are both present and can be at least 3 options each at the 2 substituents (e.g., C, N, or bond H) (i.e., at least $3 \times 3 = 9$ options), when x is N R_{1b} is absent and R_{1a} can be at least 3 options each at the 2 substituents (e.g., C, N, or bond H) (i.e., at least $3 \times 3 = 9$ options). In addition, X can also be a single bond. As such, for X along, there are at least 19 options ($9 + 9 + 1$). Altogether, this results in thousands of possibilities ($11 \times 19 \times 11 = 2,299$) for L_b alone.

89. In its most limited reading, C1 can be 21 different bioorthogonal groups as depicted below:

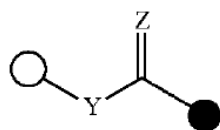


See Ex. 1011, ¶[0593].

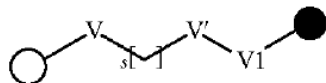
90. As such, C1 in combination with Lb alone lends to more than $(2,299 \times 21 = 48,279)$ options and with variable Rs and ring positions, quickly increases. But that value is not so constrained. Yamada has another section describing C1 with greater variability in paragraph [1696] where it can be the following options: (1)

divalent hydrocarbon group optionally having a substituent (i.e., much greater than 1 option within this group), (2) divalent heterocyclic group optionally having a substituent (i.e., much greater than 1 option for different chemical moieties within this group), (3) -C(=O) , (4) -NRa- substituent (i.e., much greater than 1 option for different chemical moieties within this group), (5) -O- , (6) -S- , (7) -C(=S)- , and a group consisting of a combination of two to eight of these. To keep the combination to its minimum, only 7 options (groups not individual chemical moieties) will be used for the following calculation. Similarly, for “a group of consisting of a combination of two to eight of these,” only a combination of eight of these will used for the following calculation. For a combination of 7 options in a group of 8 alone can be ($7^8 = 7 \times 7 \times 7 \times 7 \times 7 \times 7 \times 7 = 5,764,801$) for C1. Therefore, C1-Lb can be ($2,299 \times 5,764,801 = 13,253,277,499$) over 13 billion possible variables.

91. The number of possibilities for Formula (IV) exceeds 13 billion even without varying groups B, R', or T. B, of course, can be represented by either B-1 or B-2 below:



(B-1)

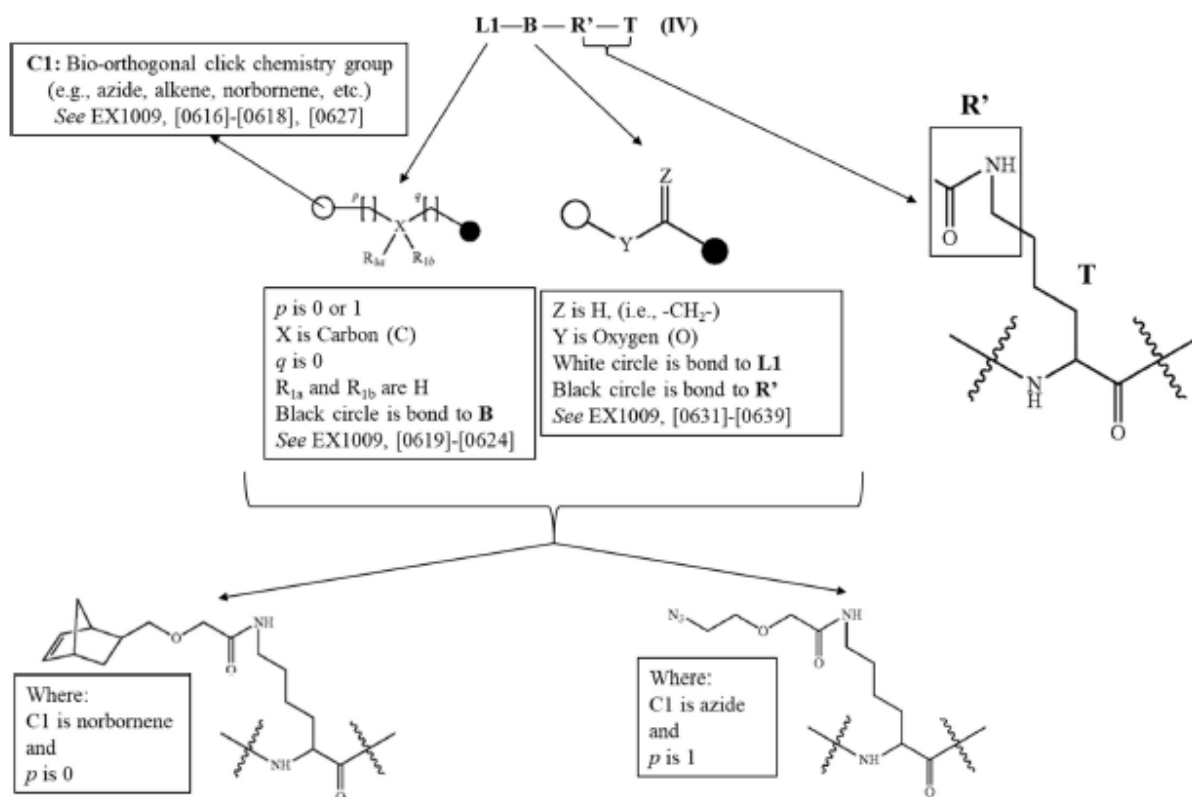


(B-2)

The number of possibilities increases markedly further if varying groups B, R', or T are included in the calculation.

92. More importantly, Dr. Tumey's declaration provides no reason a POSA would be motivated to choose any one variable over any other. In fact, it seems as if the only motivation he suggests begins with the compounds of claim 11, and now proposed claims 14-16, themselves—the epitome of hindsight. His Option 1 and Option 2 diagrams are exactly this—the trace the claimed compounds back to Formula (IV) using Yamada as a massive chemical library to produce them. Ex. 1002 ¶450.

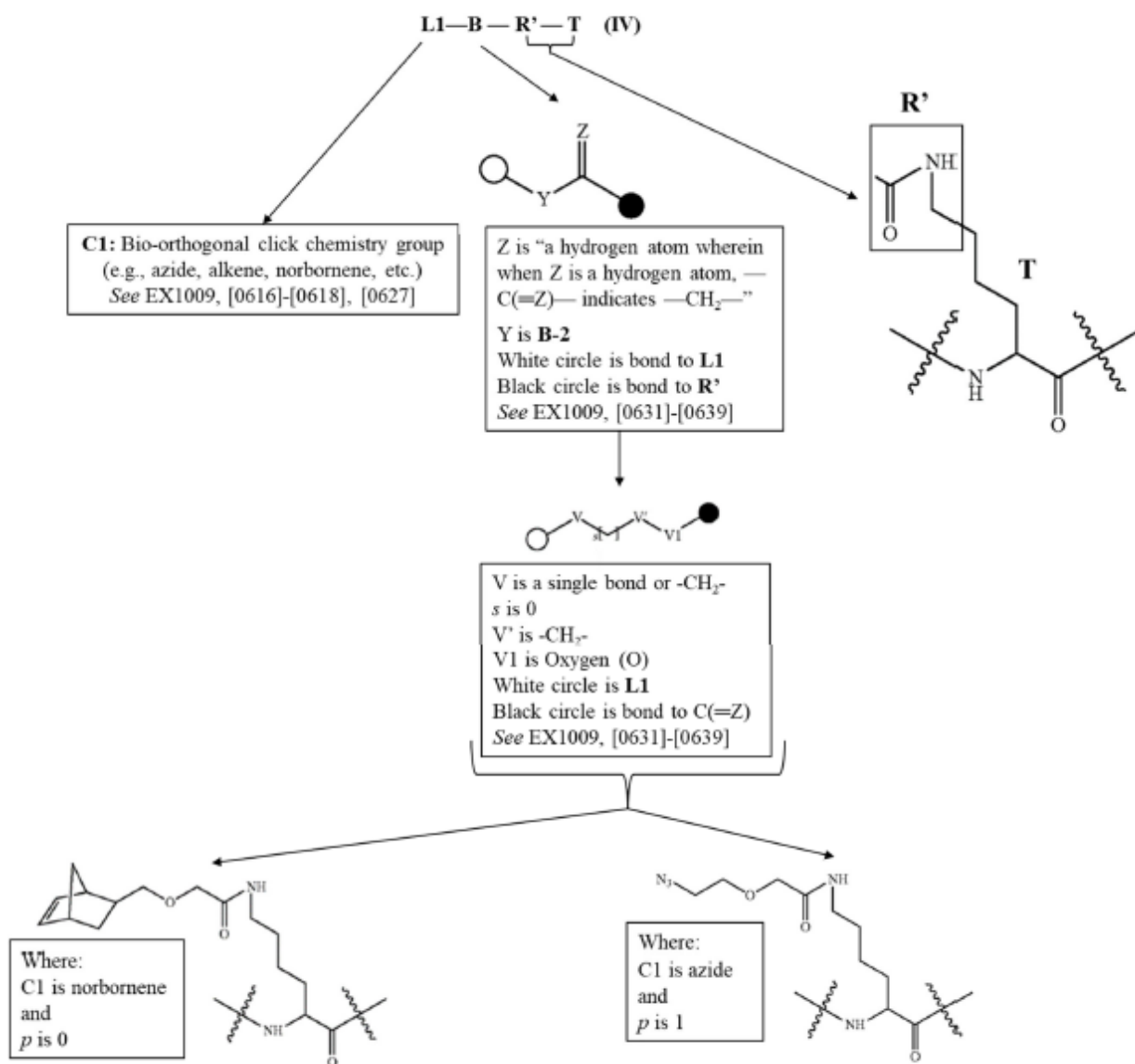
Option 1:



For Option 1, the components of the structures from claim 11 are denoted with their respective positions within Formula (IV):



Option 2:



93. Neither Yamada nor Dr. Tumey provide any reason to make any substituent selection for Formula (IV) other than by starting with the claimed moieties in the '675 Patent.

94. ***Second***, Yamada does not identify any preference for or advantage of directing a POSA to select the ether-containing spacer groups required by substitute claims 14 and 16, or the very short/“no” spacer arrangement of substitute claim 15, nor does it provide a reason to select azide or norbornene over the many other bioorthogonal groups listed. Dr. Tumey does not cite any other prior art teaching them either. Ex. 2006 at 174:16-175:13.

95. Not only does Yamada fail to disclose an ether-containing spacer group, but it also further fails to disclose the position of such a group. Yamada certainly does not disclose placing an ether oxygen at the beta-position in a modified lysine residue.

96. Nothing in Yamada identifies or even suggests the specific subset of structural elements corresponding to the claimed Lys-248 ether-linked or azide- or norbornene-modified lysine residues. Yamada even contains examples of specific compounds. Ex. 1009 at pp. 223-229. Regarding the spacer groups that Yamada does disclose, Dr. Tumey stated that a POSA might alternatively try some of those, including carboxylic acid, amine, and carbonyl groups, because he did not know a reason to choose an ether group over them. Ex. 2006 at 166:8-167:13; 189:3-190:14. None of those specific examples contain an ether spacer group, none contain a norbornene group, and none contain the claimed moieties as a whole. Yamada also does not state a preference for lysine over tyrosine or tryptophan residues. Ex. 1009

¶¶[640]. Yamada does not state a preference for lysine 248 over lysine 246 or lysine 288 to 290. Ex. 1009 ¶¶[598].

97. The sheer numerosity of options, coupled with the absence of any teaching, preference, or motivation toward an ether-oxygen spacer (or no spacer) or norbornene handle, would have dissuaded a POSA from attempting such a modification of the PepTalk References. Nor would a POSA have had a reasonable expectation of success that any given combination drawn from Yamada’s vast genus would yield a viable site-specific conjugate compatible with the AJICAP platform.

iv. Dr. Tumey’s Analysis of *Yamada* Formula (IV) Is Scientifically Flawed

98. I disagree with Dr. Tumey’s analysis and conclusions regarding Yamada’s Formula (IV). Dr. Tumey’s analysis improperly combines isolated definitional passages from multiple sections of the reference to assemble a structure that Yamada itself never teaches or suggests, and involves a scientifically infeasible reconstruction.

99. Although Yamada lists numerous independent variables for L1, B, R’, and T, each is presented as part of a separate generalized definition, not as an integrated embodiment. The citation to paragraphs [0616]-[0624] (Ex. 1002, ¶ 273, 368, 447) identifies many *optional* (not interchangeable) substituents—including “azide” and “norbornene”—within an extensive genus of monovalent groups, but

Yamada never shows, exemplifies, or prefers those groups in combination with the specific B or R' fragments that would connect to a lysine residue. A POSA would have understood that these lists of alternatives are independent options, not interchangeable components meant to be stitched together haphazardly.

100. Further, the cross-reference to paragraph [1571] of Yamada (Ex. 1002, ¶ 274) merely permits reuse of general definitions; it does not instruct the reader to combine every possible variable with every other.

101. Accordingly, Dr. Tumey's reconstruction of Yamada's Formula (IV) is untenable.

102. 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.

103. Specifically, Yamada depicts L₁ as formed by cleavage of a cleavable linker "L" between Formula (II) and Formula (IV). Under Dr. Tumey's mapping,

azide or norbornene would need to be produced as a result of cleavage of another “L” group to serve as L₁. However, Dr. Tumey does not identify any precursor “L” group that would cleave to form azide or norbornene as “L₁”, which undermines the asserted feasibility of Dr. Tumey’s scheme to form the claimed compounds. When questioned about whether his proposed Options 1 and 2 work, Dr. Tumey admitted that he “do[es] not have a synthetic scheme to make the compounds of Claim 11.” Ex. 2006, 205:5-14. If Dr. Tumey is confused by Yamada’s disclosure, a POSA would be as well.

104. Even assuming a POSA viewed Formula (IV) as an invitation to choose among alternatives, the number of permutations across L₁, B, R’, and chain lengths is extremely large. Again, the specific subset yielding an ether-linked D₁ spacer joined to a click chemistry-reactive group at Lys-248 is one of many thousands of theoretical combinations; in my opinion, the references provide no reasoned path to the claimed selections.

105. Accordingly, Yamada’s disclosure describes an entirely different chemical architecture: the cleavage of L eliminates the very fragment Dr. Tumey asserts is retained, and the only linkage exemplified for lysine modification is an amide bond without specified spacers, not the ether-spacer or direct attachment (no spacer) claimed here. A POSA would therefore understand that Dr. Tumey’s interpretations of Yamada’s conjugation pathway presented in his Options 1 and 2

cannot generate, teach, or render obvious the azide- or norbornene-modified Lys-248 structures recited in the proposed substitute claims.

v. The Combination of the PepTalk Poster or the PepTalk Presentation and Yamada and Matsuda Fails to Render Obvious the Proposed Substitute Claims

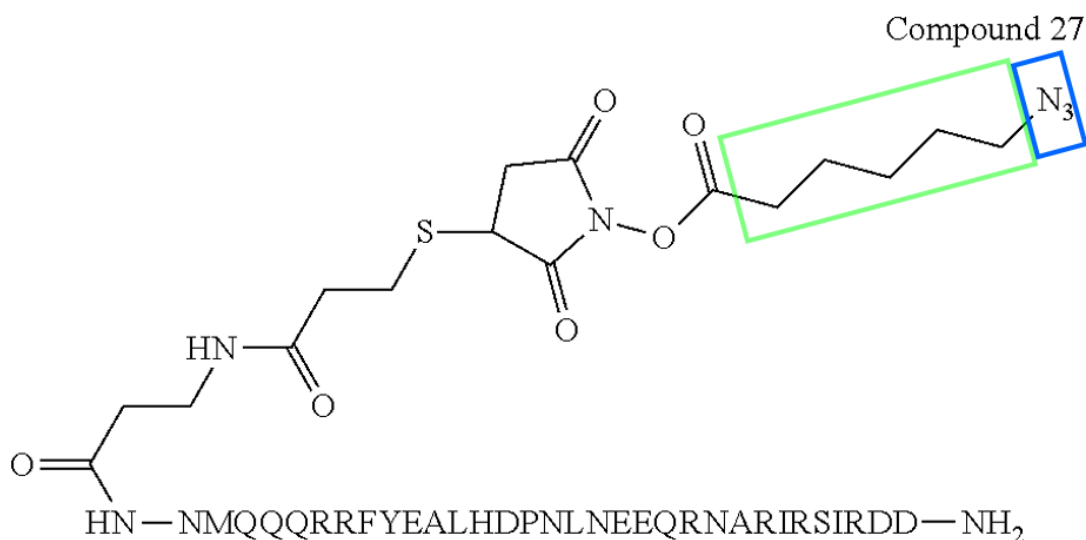
- a. Matsuda alone or in combination with the cited art fails to render obvious the Proposed Substitute Claims

106. Dr. Tumey says that Matsuda discloses various features of disclaimed original independent claim 1. However, Dr. Tumey failed to acknowledge that Matsuda expressly *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.

107. Matsuda teaches away from the beta (β)-heteroatom ether linkers required by claims 14 and 16. Matsuda discloses beta (β)-heteroatom (e.g., ether-containing) chain substituents (e.g., compounds 26 and 60) and reports that the antibody modification reactions “had not progressed” despite extended incubation (*see, e.g.*, Ex. 1011, ¶¶[1014], [1023], [1150]-[1152]). By contrast, conjugation proceeded when using analogs lacking the beta (β)-heteroatom (compounds 27-29) (*see, e.g., id.* at ¶[1152]). A POSA would understand this as discouraging beta (β)-heteroatom (ether) spacers because the beta (β)-oxygen at the specified position confers special stereoelectronic effects on the acylation reaction and suppresses

conjugation reactivity toward lysine residues. In my opinion, that is a clear teaching away from the ether-linked D₁ spacers of claims 14 and 16, and it contradicts Dr. Tumey's proposed modification path.

108. Specifically, and put in chemical terms, the beta (β)-heteroatom exerts stereoelectronic effects that prevent the acylation reaction with the epsilon (i.e., side chain) amine of lysine. This mechanistic consequence directly explains the experimental failure reported in Matsuda. Thus, Matsuda identifies the beta (β)-heteroatom as the structural feature responsible for unsuccessful antibody modification and expressly favors linkers that do not contain such heteroatoms. *See, e.g.,* Ex. 1011, ¶¶[1014], [1023], [1150]-[1152]. Accordingly, it is my opinion that Matsuda unambiguously teaches away from the beta (β)-heteroatom-containing (e.g., ether-linked) D₁ spacers of proposed substitute claims 14 and 16. A POSA would have understood Matsuda as discouraging the inclusion of an ether oxygen in the beta (β)-position because its stereoelectronic effects significantly reduces the rate of acylation by the lysine epsilon (ε)-amine. This is far from motivating a POSA to combine Matsuda with the other cited art, such as Yamada, to achieve the claimed ether-linked azide- or norbornene-modified Lys-248 conjugates. Rather, Matsuda would have led a POSA in the opposite direction toward non-heteroatom hydrocarbon linkers. Indeed, this was achieved and reported in Matsuda (e.g., Ex. 1011, ¶¶1018 (compound 27), [1080]).



Ex. 1011, ¶¶1018 (compound 27) (terminal bioorthogonal group is shown in blue; spacer is shown in green and only contains an alkyl chain (methylene groups) not any heteroatom).

109. Put plainly, Dr. Tumey's proposed combination is self-contradictory: Yamada provides only schematic, generic Formula (IV) with no direction to select an ether-linked spacer, while Matsuda explicitly reports that ether-linked (β -heteroatom) spacers do not work as intended.

110. At base, the record shows no disclosure or reasoned motivation in the cited references to arrive at the azide- and norbornene-modified Lys-248 residues with the particular spacer architectures recited in the proposed substitute claims; Matsuda affirmatively discourages the ether-linked variants; and Dr. Tumey's mappings depend on post hoc assembly from large, undirected lists.

VII. RESERVATION OF RIGHTS

111. I reserve the right to amend or supplement this declaration as this case proceeds and any additional information comes to light.

112. I declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true. I also declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001. I declare under the penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: October 31, 2025



Dr. Zhaohui Sunny Zhou