

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AJINOMOTO CO., INC.
Petitioner

v.

ABTIS CO., LTD.
Patent Owner

IPR2025-0283
Patent No. 11,896,675

**DECLARATION OF DR. LAWRENCE NATHAN TUMEY
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW**

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

I. INTRODUCTION

1. I have been retained by Foley & Lardner LLP on behalf of Ajinomoto Co., Inc. (“Ajinomoto” or “Petitioner”) as an independent technical expert in the above-captioned proceeding concerning a petition for *inter partes* review of U.S. Patent No. 11,896,675 (“the ’675 Patent”), owned by AbTis Co., Ltd. (“AbTis” or “Patent Owner”). I understand that Ajinomoto filed the petition against all claims of the ’675 Patent, i.e., claims 1-13, which I will refer to as the “Challenged Claims.”

2. This Declaration is based on information currently available to me. I reserve the right to continue my investigation and analysis, which may include a review of documents and information not listed in this Declaration, including any documents and information that may be submitted by AbTis. I also reserve the right to expand or modify my opinions and conclusions as my investigation and study continues, and to supplement my opinions and conclusions in response to any additional information that becomes available to me. I also reserve the right to respond to any argument that AbTis may make in this proceeding.

3. I am being compensated for my time preparing this Declaration at a rate of \$350/hour. My compensation is not contingent on the substance of my opinions and testimony, nor on the outcome of this or any other proceeding. I have no other interest in this proceeding.

II. QUALIFICATIONS

4. My qualifications and professional experience are described in my curriculum vitae, a copy of which is attached to this Declaration as Appendix B. The following is a summary of my qualifications and professional experience.

5. In 1997, I received a Bachelor of Science (B.S.) degree in chemistry from King University. Subsequently, I obtained my Ph.D. in chemistry from Duke University in 2001, where my research focused on the medicinal chemistry of LpxC inhibitors as antibacterial agents.

6. Following graduate school, I spent nearly 15 years in the pharmaceutical and biotechnology industry. From 2002 to 2005, I worked as a Research Scientist at Athersys, where I designed and synthesized compounds that targeted and suppressed the activity of CRTH2 receptors expressed on certain immune cell populations for the treatment of asthma. I was the lead inventor on U.S. Patent No. 7,405,215, which claimed these compounds. I also designed and synthesized compounds that selectively increased the activity of 5HT_{2C} cell surface receptors for the treatment of obesity and related disorders. Additionally, I developed protein kinase inhibitor compounds for the treatment of certain autoimmune and inflammatory diseases, which are claimed in U.S. Patent No. 7,781,591, on which I am a named inventor.

7. From 2005 to 2017, I worked at Pfizer and led multiple drug-discovery programs, including the development of PKC-theta inhibitors for asthma, IRAK4 inhibitors for rheumatoid arthritis and antibody-drug conjugates (ADCs) for the treatment of cancer. In particular, I supervised a team of conjugation and bioanalytical scientists to design and synthesize ADCs for use in oncology applications. The design and synthesis of specific cysteine-engineered ADCs is claimed in U.S. Patent No. 11,364,303, on which I am a named inventor. Moreover, I directly prepared bioconjugates for *in vitro* and *in vivo* evaluation, optimized conjugation conditions in order to minimize aggregation and maximize drug-loading, and developed a variety of bioanalytical methods to assess the purity, identity, and stability of preclinical ADCs in the Pfizer portfolio. My expertise further involved developing and optimizing HIC, SEC, reverse phase, and LCMS methods for protein analysis. I also designed and implemented protein purification strategies to remove aggregate, free drug, and under-loaded species, as well as enhanced purification methods for scaleup campaigns to support exploratory toxicology studies. Finally, I oversaw the development of innovative conjugation solutions in order to optimize ADC drug loading, stability, and efficacy.

8. In 2017, I joined the faculty at Binghamton University. I currently serve as the Assistant Graduate Director and Vice Chair of the pharmaceutical sciences department, and I hold a title of Associate Professor at Binghamton

University's School of Pharmacy and Pharmaceutical Sciences, where I lead a team of research scientists and graduate students specializing in the application of ADCs and related modalities for the treatment of cancer and auto-immune disorders. My laboratory also investigates bioconjugate stability, ADC linker design, and new modalities for targeted drug delivery.

9. I possess over 30 years of expertise and experience that span the areas of organic chemistry, medicinal chemistry, targeted drug delivery, bioconjugate bioanalysis, ADC design, antibody metabolism, and site-specific conjugation chemistry. I further possess considerable expertise in analyzing chemical structures, including evaluating properties such as polarity, hydrophilicity, solubility, and chemical reactivity. I have extensive knowledge of functional groups employed in ADCs and can analyze conjugation sites and interaction of specific moieties, which facilitate designing linkers to improve overall ADC performance. I also have specific experience involving the use of click chemistry in preparing ADCs, and I am a co-author on two peer reviewed papers that utilize click chemistry as a mechanism for conjugating an antibody to a drug-linker (DOI: 10.1002/anie.202001830 and DOI: 10.1021/acs.bioconjchem.9b00246).

10. I have published across the aforementioned fields, with approximately 40 peer-reviewed publications in high-impact academic journals and have received over \$3 million in funding from various national, government, and non-profit

agencies to support my research. I have served as the lead editor for a book titled “Antibody-Drug Conjugates: Methods and Protocols,” published by Springer Publishing (2020). I have also presented my work at various high-profile national and international conferences and symposia related to ADCs.

11. I currently serve on the scientific advisory board of multiple companies, including Araris Biotech and Manhattan Biosolution. I have also served as a technical consultant for numerous pharmaceutical companies, law firms, and financial firms.

III. MATERIALS CONSIDERED

12. The opinions in this Declaration are based on the documents I have reviewed, as well as my education, experience, and professional knowledge and judgment.

13. I have considered the materials referenced throughout this Declaration, including those listed in the table below. Each of these documents is a type of document that an expert in my field would have reasonably relied on when forming their opinion.

Exhibit	Description
1001	U.S. Patent No. 11,896,675
1004	WO 2020/184944
1005	CA 3132959 (Canada National Stage of WO 2020/184944)
1006	Yamada et al., <i>Development of a Novel Chemical Site-Specific Conjugation Platform for ADCs – Ajicap™ Technology</i> , Poster

	Presentation from PEP TALK 2019, THE PROTEIN SCIENCE WEEK, Jan. 14-18, 2019 (“PepTalk Poster”)
1007	Okuzumi, <i>Technology of Site Specific Conjugation for Next Generation ADCs</i> , Luncheon Presentation from PEP TALK 2019, THE PROTEIN SCIENCE WEEK, Jan. 16, 2019 (“PepTalk Presentation”)
1008	WO 2018/199337 (“Yamada”)
1009	U.S. 2020/0190165 (U.S. National Stage of Yamada)
1010	WO 2019/240288 (“Matsuda”)
1011	U.S. 2021/0139541 (U.S. National Stage of Matsuda)
1012	Clarivate Analytics, <i>PepTalk 2019 - CHI's 18th Annual Meeting - The Protein Science Week: Antibody-Drug Conjugates</i> , San Diego, CA, USA, IDDB MEETING REPORT, January 25, 2019 (“PepTalk 2019 Annual Meeting Report”)
1026	Lambert and Berkenblit, <i>Antibody–Drug Conjugates for Cancer Treatment</i> , ANNU. REV. MED., 2018, 69: 191-207.
1027	Birrer et al., <i>Antibody-Drug Conjugate-Based Therapeutics: State of the Science</i> , J. NAT’L CANCER INST., 2019, 111(6): 538-549
1028	Schumacher et al., <i>Current Status: Site-Specific Antibody Drug Conjugates</i> , J. CLIN. IMMUNOL., 2016, 36: S100-S107.
1029	Nejadmoghaddam et al., <i>Antibody-Drug Conjugates: Possibilities and Challenges</i> , AVICENNA J MED BIOTECHNOL., 2019, (1):3-23.
1033	Tam et al., <i>Functional, Biophysical, and Structural Characterization of Human IgG1 and IgG4 Fc Variants with Ablated Immune Functionality</i> , ANTIBODIES, 2017, 6(12): 10.3390/antib6030012.
1034	Lu et al., <i>Beyond binding: antibody effector functions in infectious diseases</i> , NAT. REV. IMMUNOL., 2018, 18(1): 46–61.
1035	Prosecution History for U.S. Patent No. 11,896,675 (“the ‘675 patent”)
1036	Amblard et al., <i>The Cu^I-catalyzed Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes to form 1,2,3-triazoles is the model example of a click reaction</i> , CHEM. REV., 2009, 109(9): 4207-4220.

IV. LEGAL STANDARDS

14. In this section I describe my understanding of certain legal principles that I have relied upon in forming my opinions set forth in this Declaration.

15. I am not an attorney and have not researched patent law. I have been informed of these legal standards by counsel for Ajinomoto and am relying only on Ajinomoto's counsel for my understanding of them. I am not offering any legal opinions in this Declaration.

A. Person of Ordinary Skill in the Art

16. I am informed that patent validity is determined from the perspective of a person of ordinary skill in the pertinent art at the time of the invention ("POSA"). I understand that a POSA is a hypothetical person who is presumed to be aware of all pertinent art and conventional wisdom in the art. I understand the POSA is also a person of ordinary creativity—not an automaton.

17. I am informed that the following factors may be considered in determining the level of ordinary skill in the art: the levels of education and experience of persons working in the field; the types of problems encountered in the field; and the sophistication of the technology.

B. Claim Construction

18. I am informed that a patent may include two types of claims, independent claims and dependent claims. An independent claim stands alone and includes only the limitations it recites. A dependent claim can depend from an independent claim or another dependent claim. I am informed that a dependent

claim includes all the limitations that it recites, in addition to the limitations recited in the claim(s) from which it depends.

19. I understand that patent claim terms can be interpreted, or “construed.” I understand that, in construing a claim, the words of a patent claim are generally given their ordinary and customary meaning, which is the meaning they would have had to a POSA at the time of the invention. I understand that the POSA is considered to read patent claims in view of the entire patent as well as its prosecution history, i.e., the record of proceedings before the Patent Office during the application process. I understand that the patent and its prosecution history are referred to as the “intrinsic evidence.” I am informed that dictionaries, treatises, and other “extrinsic” sources of evidence may assist in determining the ordinary and customary meaning of a claim term, but they cannot override a meaning that is otherwise unambiguous based on the intrinsic evidence. I understand that a claim term may be construed differently from its ordinary and customary meaning only if the term is defined in the patent, or if some aspect of the ordinary and customary meaning, or some subject matter that would ordinarily fall within the scope of the claim, is disclaimed or disavowed in the patent itself or in the prosecution history.

20. Throughout this Declaration, unless explicitly stated otherwise, I have applied the ordinary and customary meaning of each claim term as would have been understood by a POSA at the time of the invention.

21. I have been informed by Ajinomoto's counsel that claim construction is a matter of law for the arbiter of law to decide. I am informed that, in an *inter partes* review, the Patent Trial and Appeal Board interprets claims in the same way as a court would. I also understand that a POSA is considered to interpret claims in the same way in both types of proceedings.

22. I reserve my right to amend or alter my analysis and opinions in view of any claim constructions adopted by the arbiter of law.

C. Priority Date

23. I understand that for a patent to be entitled to priority as of a particular filing date of an earlier application, the earlier application must satisfy the "written description" requirement of 35 U.S.C. § 112 with respect to the patent's claims. I understand that this determination is made on a claim-by-claim basis.

24. I understand that, to satisfy the "written description" requirement, a patent specification must provide a written description of the invention sufficient to convey with reasonable clarity to those skilled in the art that the applicant was in possession of the invention as of the asserted priority date. Although the disclosure need not spell out every detail of the invention, it must do more than merely disclose that which would render the claimed invention obvious and must convey the detailed identity of an invention. Further, I understand that a description of what a material does, rather than what it is, usually does not suffice under the

written description requirement. I understand that to support a negative limitation, the specification must describe alternative features of the patented invention to indicate that the patentees are merely excising the inventions of another, to which they are not entitled. The specification is not required to articulate advantages or disadvantages of each feature to later exclude the alternative feature. When determining whether a negative limitation is supported, the knowledge of ordinary artisans may be used to inform what is actually in the specification, but not to teach limitations that are not in the specification, even if those limitations would be rendered obvious by the disclosure. Thus, negative claim limitations are adequately supported when the specification describes a reason to exclude the relevant limitation or if it is possible for the patentee to support both the inclusion and exclusion of the same material. That is not to say that a patentee may arbitrarily dissect its invention by amending the claims in order to avoid the prior art. Finally, I understand that a description of a species does not always constitute a description of a genus of which it is a part, particularly if the species is not representative of the full variety or scope of the genus.

D. Anticipation

25. I understand that a patent claim is invalid if it is anticipated by a single item of prior art. I understand that the anticipation analysis involves two steps. First, a patent claim is construed to determine its scope. Second, the construed claim is

compared to the prior art reference on an element-by-element basis. If the prior art reference discloses or contains each and every element of the claimed invention, either expressly or inherently, then it anticipates the claim.

26. I understand that anticipation by inherent disclosure is appropriate only when a prior art reference necessarily includes or discloses the unstated claim element. I also understand that the discovery of a new or previously unreported or unappreciated property of a prior art composition, or of a scientific explanation for how a prior art composition operates, does not make the prior art composition patentably new to the entity or person who discovered the new property or mode of operation. I further understand that there is no requirement that a POSA would have recognized the inherent disclosure at the time of the invention.

27. For anticipation by a prior art publication or document, I understand that the reference's description must enable a POSA to practice the claimed invention without undue experimentation.

E. Obviousness

28. I understand that a patent claim is invalid if it would have been "obvious" to a POSA at the time the application was filed. I understand that, unlike anticipation, obviousness does not require that each and every element of a claim be found in a single prior art reference. Rather, obviousness can be found based on a single prior art reference or on a combination of multiple prior art references. I

understand that a claim is invalid for obviousness when the differences between the claim and the prior art are such that the claimed invention would have been obvious to a POSA, considering the following factors:

- the level of ordinary skill in the art at the time the application was filed;
- the scope and content of the prior art; and
- what differences, if any, existed between the claimed invention and the prior art.

29. I understand that there are a variety of rationales that can render a claimed invention obvious based on the prior art, including the following:

- whether the teachings of the prior art references disclose known concepts combined in familiar ways, which, when combined, would yield predictable results;
- whether a person of ordinary skill in the art could implement a predictable variation, and would see the benefit of doing so;
- whether the claimed elements represent one of a limited number of known design choices, and would have a reasonable expectation of success by a person of ordinary skill in the art;
- whether a person of ordinary skill in the art would have recognized a reason to combine known elements in the manner described in the claim;

- whether there is some teaching or suggestion in the prior art to make the modification or combination of elements claimed in the patent; and
- whether the innovation applies a known technique that had been used to improve a similar device or method in a similar way.

30. I understand that a person of ordinary skill in the art has ordinary creativity, and is not an automaton.

31. I understand that in considering obviousness, it is important not to determine obviousness using the benefit of hindsight derived from the patent being considered. I have avoided relying on hindsight in forming my opinions expressed in this Declaration.

32. I understand that certain factors—often called “secondary considerations”—may support or rebut an assertion of obviousness. I understand that such secondary considerations include, among other things, commercial success of the claimed invention, skepticism of those having ordinary skill in the art at the time of the claimed invention, unexpected results of the claimed invention, any long-felt but unsolved need in the art that was satisfied by the claimed invention, the failure of others to make the claimed invention, praise of the claimed invention by those having ordinary skill in the art, and copying of the claimed invention by others in the field. I further understand that, in order for these considerations to carry weight in the analysis, there must be a causal connection or nexus between the secondary

consideration and the claimed invention. I also understand that contemporaneous and independent invention by others is a secondary consideration tending to show obviousness.

F. Provisional Applications and Prior Art

33. I understand that a U.S. patent or patent publication can be considered prior art as of the date of the filing of its provisional application(s) if certain criteria are met. Namely, for a U.S. patent or patent publication to be prior art as of the filing date of the provisional application(s), the provisional application(s) must provide written description support for at least one of the U.S. patent's or patent publication's claims.

V. PERSON OF ORDINARY SKILL IN THE ART

34. I have been asked to provide my opinion on the qualifications that a POSA in the field of the '675 Patent would have had during the 2019-2023 time frame, which includes the different possible priority dates of the '675 Patent.

35. Based on the factors identified above as informing the level of ordinary skill in the art, in my opinion, a POSA in the field of the '675 Patent during the 2019-2023 time frame would have had specialized knowledge in the field of antibody-drug conjugates, which would entail (1) a Ph.D. 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. That person would have familiarity, gained through study, training, and/or experience, with the design and development of antibody-drug conjugates and antibody modifications. People of ordinary skill in the fields of antibodies and ADCs—both academics and industry professionals—routinely attend scientific conferences to share ideas and learn about new developments in the field. Two of the preeminent conferences in this area are the PepTalk conference series and the World ADC conference series, both of which are annual conferences that are widely attended by those with an interest in ADCs.

36. In forming my opinions in this Declaration, I have considered the perspective of the POSA and relied on my understanding of how a POSA would have understood the claims of the '675 Patent in the 2019-2023 time frame, which includes the different possible priority dates for the '675 Patent. During this time frame, I possessed at least the qualifications of the POSA as defined above.

VI. THE '675 PATENT

37. The '675 Patent, titled "Site-Specific Antibody Conjugation and Antibody-Drug Conjugate as Specific Embodiment Thereof," issued from non-provisional U.S. Application No. 18/154,998 ("the '998 Application"), filed January

16, 2023. The '998 Application was a continuation of U.S. Application No. 16,980,503 ("the '503 Application"), filed on September 14, 2020. The '503 Application was a national stage application of PCT Application No. PCT/KR2020/003282, filed on March 9, 2020. The PCT application claimed priority to provisional U.S. Application No. 62/815,557 ("the '557 Provisional"), filed on March 8, 2019. The PCT application was published on September 17, 2020, as International Application No. WO2020/184944 ("the '944 Publication"). The '998 Application also claims priority to the '557 Provisional.

A. Claims

38. The '675 Patent contains 13 claims, of which only claim 1 is independent. A copy of the claims is attached to this Declaration as Appendix A.

39. Independent claim 1 recites:

1. A modified antibody or its fragment comprising 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 comprises a bio-orthogonal click chemistry functional group at terminal end, and

wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.

40. Claim 1 thus recites an antibody (or fragment) that is modified at the lysine residue at position 248 of the heavy chain(s) to include a bio-orthogonal click chemistry functional group and exclude a terminal bio-reactive functional group other than a hydroxyl, carboxyl, thiol, amino, or aldehyde group.

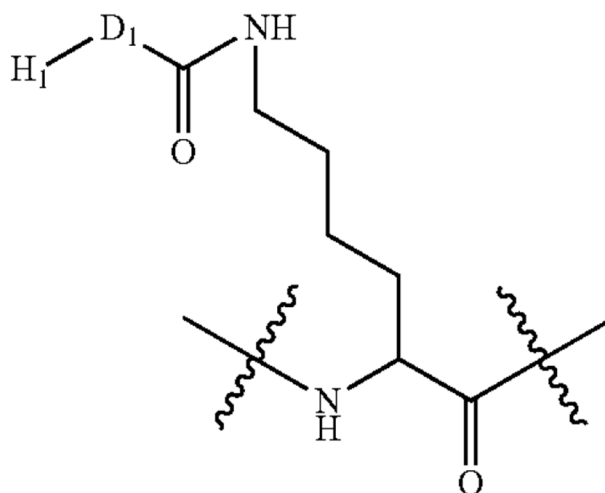
41. I will refer to the final limitation of claim 1, reciting what the “modified lysine residue does not comprise,” as the “Negative Limitation.”

42. Claims 2 and 11 limit the “modified lysine residue” element of claim 1. Claims 3, 5, 6, and 7 depend from claim 2 and further limit the “modified lysine residue.” Claims 4 and 8 limit the “modified heavy chain” element of claim 1. Claims 9 and 10 limit the “bio-orthogonal click chemistry functional group” element of claim 1. Claims 12 and 13 also limit the “bio-orthogonal click chemistry

functional group” but depend from claim 3, and thus incorporate the additional “modified lysine residue” limitations of claims 2 and 3.

43. Claim 2 recites:

2. The modified antibody of claim 1, wherein the modified lysine residue has following structure:



wherein H₁ is a group having the bio-orthogonal click chemistry functional group, and

wherein D₁ is bond, or is selected from C₁₋₄ alkylene,

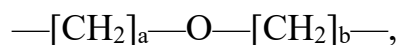
C₂₋₄ alkenylene, C₂₋₄ alkynylene and C₃₋₈ cycloalkylene.

44. Claims 3, 5, 6, and 7 each depend from claim 2 and further limit the D₁ element of claim 2, reciting, respectively:

3. The modified antibody of claim 2, wherein D_1 is bond, or is selected from unsubstituted C_{1-4} alkylene, unsubstituted C_{2-4} alkenylene, unsubstituted C_{2-4} alkynylene and unsubstituted C_{3-8} cycloalkylene.

5. The modified antibody of claim 2, wherein D_1 comprises one or more heteroatoms.

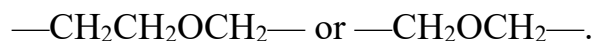
6. The modified antibody of claim 2, wherein D_1 is



wherein each of a and b is independently selected from 0 to 4,
and each of a and b is integer, and

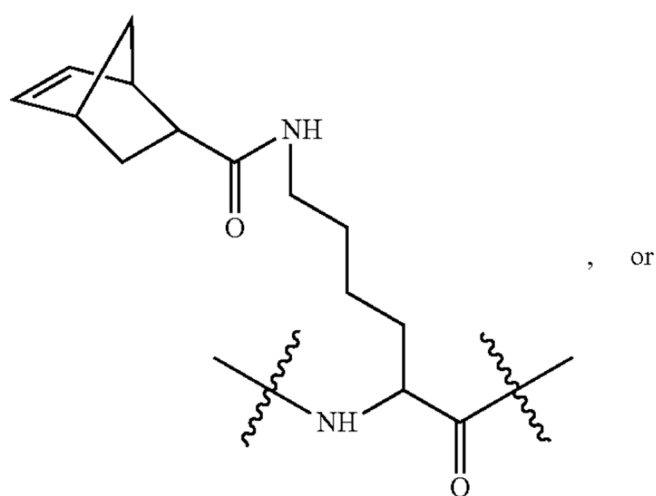
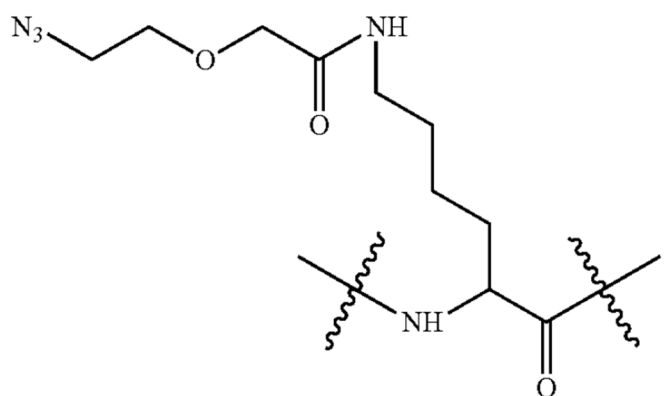
wherein sum of a and b is 0 or more and 4 or less.

7. The modified antibody of claim 2, wherein D_1 is

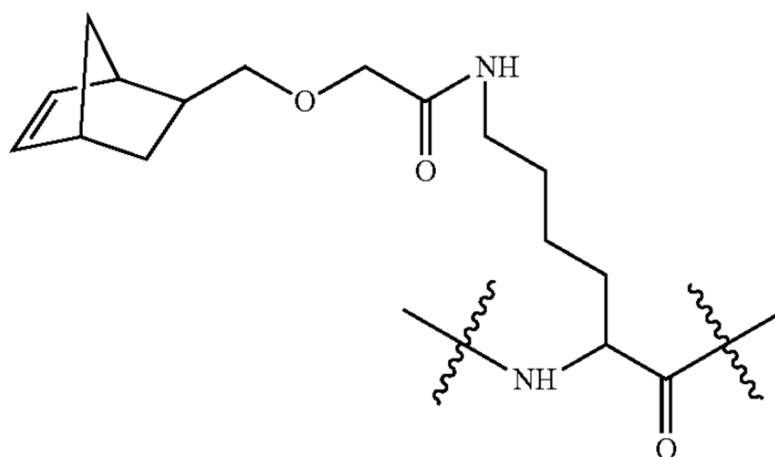


45. Like claim 2, claim 11 depends from independent claim 1 and further limits the “modified lysine residue,” reciting:

11. The modified antibody of claim 1, wherein the modified lysine residue has following structure:

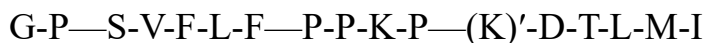


, or



46. Claims 4 and 8 each depend from claim 1 and limit the “modified heavy chain” element of claim 1, reciting, respectively:

4. The modified antibody of claim 1, wherein the modified heavy chain comprises an amino acid sequence having a structure of formula 8-2:



(SEQ ID NO: 21), [formula 8-2]

wherein K' is the modified lysine residue.

8. The modified antibody of claim 1, wherein the modified antibody comprises two modified heavy chains.

47. Claims 9 and 10 depend from independent claim 1 and limit the “bio-orthogonal click chemistry functional group,” reciting, respectively:

9. The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.

10. The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.

48. Claims 12 and 13 recite substantially the same limitations as claims 9 and 10, but these claims depend from claim 3 rather than claim 1:

12. The modified antibody of claim 3, wherein the bio-orthogonal click chemistry group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.

13. The modified antibody of claim 3, wherein the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.

49. The claims of the '675 Patent thus all relate to antibodies modified for use in forming antibody-drug conjugates. More specifically, the claims involve modifying the lysine residue at position 248 of the antibody's heavy chain(s) to include a functional group capable of participating in click-chemistry reactions. These click-chemistry reactions will form the link between the antibody and the drug molecule to form the antibody-drug conjugate. However, the claims do not recite an antibody-drug conjugate or linking a drug or other molecule to the modified antibody. Rather, the claims are limited to the antibody being modified with a click-chemistry functional group at lysine residue 248, along with variations in the structure of the modified lysine residue and the identity of the click-chemistry functional group.

B. Specification

50. The '675 Patent discloses that antibodies have an ability to recognize certain molecules that make them useful for a variety of applications, including detecting the presence of a substance, detecting the route by which a substance moves through the body or its cells, and inducing an immune response to a substance. EX1001, 1:35-42. The '675 Patent discloses that such applications have been facilitated and improved through “antibody labeling,” in which a foreign substance is attached to an antibody. EX1001, 1:43-54.

51. The '675 Patent discloses that antibody labeling was initially performed by randomly attaching the foreign substance to the antibody. The '675 Patent discloses that this random approach resulted in antibodies having a variable number of molecules of the foreign substance attached, resulting in the antibodies having inconsistent effects, which limited the safety and efficacy of antibody-drug conjugates (ADCs). EX1001, 1:55-65. The '675 Patent also discloses that random conjugation could interfere with the antibody's ability to recognize its target by molecules of the foreign substance binding to or near the antibody's antigen-binding domain, which recognizes and binds to the antibody's target. EX1001, 1:66-2:7.

52. The '675 Patent discloses that, due to these limitations, there was a demand for techniques for achieving uniform labeling of antibodies in a site-specific

manner. According to the '675 Patent, relying on existing modification methods was “ineffective in technical and economic aspects.” EX1001, 2:8-20.

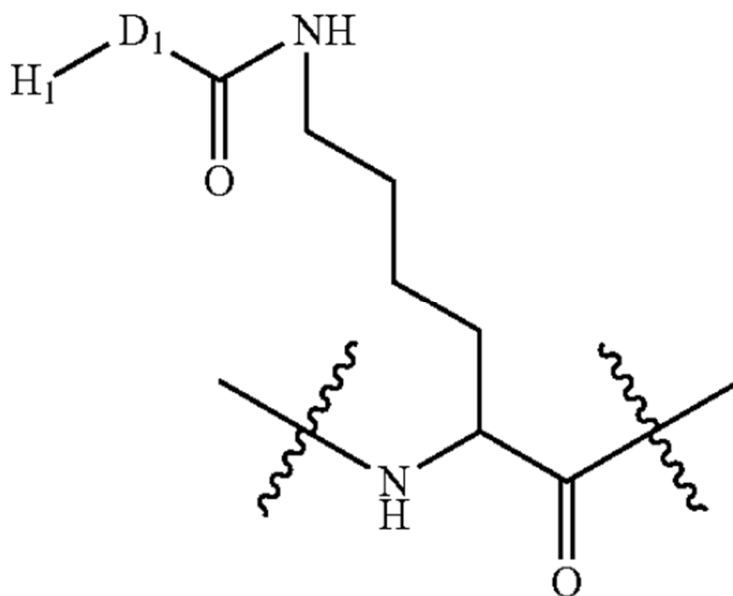
53. The '675 Patent purports to disclose technology for linking a desired number of “chemical functional groups” or “cargo moieties” to an antibody at the lysine residues at positions 246 and/or 248 of the antibody. EX1001, 2:25-62. The '675 Patent discloses that the “chemical functional groups” are click-chemistry functional groups, i.e., functional groups capable of participating in click chemistry reactions, and that “cargo moieties” are linked to the antibody via click chemistry reactions. EX1001, 3:1-12:58. The '675 Patent discloses a “kit” for preparing antibody-drug conjugates based on certain “formulas” consisting of a generalized chemical structure and/or amino acid sequence. EX1001, 3:1-12:58. For example, the '675 Patent discloses a kit for preparing an antibody-drug conjugate where the kit includes an antibody having an amino acid sequence of Formula 8-2, shown below,

[formula 8-2]

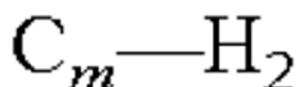
(SEQ ID NO: 21)

G-P-S-V-F-L-F-P-P-K-P- (K) ' -D-T-L-M-I

where K' is a modified lysine 248 having the following general chemical structure,



where D_1 is a covalent bond, C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene, or C_{3-8} cycloalkylene, and H_1 is a first click chemistry functional group; and the kit also includes a compound of Formula 9, shown below,



where C_m is the cargo moiety, and H_2 is a second click chemistry functional group that will pair with the H_1 functional group on the modified lysine residue. EX1001, 11:10-52.

54. The '675 Patent asserts that the disclosed subject matter provides for labeled antibodies having high uniformity without degradation in binding affinity or half-life. EX1001, 14:20-28. However, the '675 Patent asserts that others, including Yamada (WO 2018/199337; EX1008) had already devised methods “to site-

selectively modulate lysine 246 or 248 in an Fc domain using an analogue of Fc-III and use a biorthogonal functional group.” EX1001, 69:48-51. Of note, the ’675 Patent attempts to distinguish Yamada by stating that Yamada “ is similar to the present invention in terms of the form of an agent for transferring a first chemical functional group to an antibody (see section 4 below), but is different from the present invention in that the cross-linker includes two NHS esters.” EX1001, 33:3-9. It is my opinion that Yamada does not require its cross-linkers to always include two NHS esters, and I note that the Negative Limitation of claim 1 of the ’675 Patent does not exclude a cross-linker including two NHS esters.

C. Prosecution History

55. As previously noted, the ’675 Patent was issued based on U.S. Application No. 18/154,998, which was a continuation of U.S. Application No. 16,980,503, which, in turn, claimed priority to PCT Application No. PCT/KR2020/003282.

56. Based on my review of the prosecution history of the ’998 Application, it is my understanding that the Examiner relied on the following reference in making rejections under 35 U.S.C. § 102: WO 2018/199337 (“Yamada”; EX1008). EX1035, 327. The claims were amended to allegedly overcome this rejection. EX1035, 304. In particular, the claim that became independent Claim 1 was amended to include the “Negative Limitation” excluding certain click-chemistry functional groups,

which had originally been recited only in a dependent claim. *Id.* The Examiner subsequently allowed the claims and issued the patent. *Id.*, 90-98.

57. The “Negative Limitation” that was incorporated into the claims recites, “...wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.” I note, however, that Yamada discloses additional terminal bio-reactive functional groups beyond those excluded by the “Negative Limitation,” such as an azide and a norbornene. EX1009, [0151]-[0153] (“[A] a bioorthogonal functional group selected from the group consisting of an azide residue, an aldehyde residue, a thiol residue, an alkyne residue, an alkene residue, a tetrazine residue, a nitron residue, a hydroxyamine residue, a nitrile residue, a hydrazine residue, a ketone residue, a boronic acid residue, a cyanobenzothiazole residue, an allyl residue, a phosphine residue, a maleimide residue, a disulfide residue, a thioester residue, an a-halocarbonyl residue, an isonitrile residue, a sydnone residue, and a selenium residue in a main chain thereof.”).

VII. TECHNOLOGY BACKGROUND

58. I have been asked to review the state of the relevant art as of the 2019-2023 time frame and to provide a background of the relevant technology of the invention.

59. Antibody-drug conjugates (ADCs) are immunoconjugates comprising an antibody tethered to a cytotoxic drug (known as the payload) via a chemical linker, and they are used to selectively target cells or tissues for delivery of therapeutic drugs, such as anti-cancer agents. EX1026, 192; EX1027, 538. They do so by targeting cells or tissues expressing certain antigens, such as tumor-related antigens, with the antibody component of the ADC, and ADCs are thereby able to avoid delivering cytotoxic agents to healthy cells and tissue, leading to fewer side-effects than traditional modes of delivery. EX1027, 538.

60. ADCs were traditionally formed by genetically or chemically modifying an antibody to include a structure suitable for attaching a payload, such as an anti-cancer drug. As of 2019, there were four FDA-approved ADCs, and all employed random conjugation of the cytotoxic drug to either lysine or cysteine residues present in the antibody backbone, which resulted in a heterogeneous mixture of conjugate molecules with different drug-antibody ratios (DARs). *Id.*, 541. At the time, there was an expectation that site-specific conjugation would decrease off-target toxicity and improve the pharmacokinetic properties of the ADC, and thus there was a clear motivation in the art to pursue technologies that allowed site-specific conjugation. *Id.*

61. Random conjugation and other traditional methods of preparing ADCs were notably suboptimal. Random conjugation of the antibody could lead to highly

variable DAR, with different antibodies carrying different numbers of drug molecules, in turn leading to inconsistent therapeutic results, which could result in a number of problems including increased off-target toxicity and altered pharmacokinetics. At the time, there was an expectation that site-specific conjugation would decrease off-target toxicity and improve the pharmacokinetic properties of the antibody, and thus there was a clear motivation in the art to pursue technologies that allowed site-specific conjugation. *Id.*

62. In view of these limitations, and as evidenced by the prior art discussed below, those working in the field of ADCs were motivated to devise means for selectively modifying antibodies at particular sites in order to preserve the antibody's functions and to achieve more consistent DAR values. EX1028, S101-S105. Indeed, it was firmly established before March 2019 that the conjugation site on the antibody component, a well-defined DAR, and homogeneity of the ADC product were important parameters that need to be considered in ADC development, and individuals of ordinary skill in the art had every incentive to develop methodologies that would allow for more predictable and defined ADC production. EX1029, 1, 13-14.

63. One particularly noteworthy approach to site-specific conjugation for ADCs was pioneered by Ajinomoto and called "AJICAP™." The AJICAP™ platform was based on affinity peptide-mediated regioselective functionalization,

which utilizes Fc affinity reagents to target selective lysine residues, onto which payloads could be attached. The technology utilized a peptide, which was conjugated to a linker, that binds to the hinge region of the Fc-domain of human IgG (e.g., IgG 1, 2, or 4). The peptide with the conjugated linker could be directly utilized for site specific conjugation to the IgG at lysine 248, and the resulting ADC displayed an ideal DAR of 2. Prior to March 2019, variants of trastuzumab (Herceptin) and rituximab (Rituxan) had been produced and disclosed by Ajinomoto using this technology to specifically modify the lysine at position 248 of those antibodies. EX1012, 6.

VIII. CLAIM CONSTRUCTION

64. Below I offer my opinions regarding certain terms in the '675 Patent claims.

A. “antibody”

65. All of the '675 Patent claims include the term “antibody.” The '675 Patent explicitly defines “antibody” in the following passage:

According to the present invention, the term “antibody” refers to an immunoglobulin molecule or a fragment thereof. Immunoglobulins are generally well known, and have an ability to specifically bind to a certain antigen. However, because the antibody according to the present invention is a concept that also encompasses a fragment thereof, the antibody does not have to show binding ability to a certain antigen as in case of the Fc fragment. In addition to the naturally occurring immunoglobulins, the

antibody is also intended to encompass all recombinant proteins, fusion proteins, chimeric proteins, human immunoglobulins, non-human animal immunoglobulins, and the like, which have the same or similar structures.

EX1001, 23:40-54.

66. The '675 Patent provides further detail regarding the scope of the term “antibody” in the following passage:

In specific embodiments, the antibody or fragment thereof may be a human antibody. In other specific embodiments, the antibody or fragment thereof may be a non-human animal antibody. In specific embodiments, the antibody or fragment thereof may be immunoglobulin G (IgG). In specific embodiments, the antibody or fragment thereof may be a whole antibody. In other specific embodiments, the antibody or fragment thereof may be a fragment of the antibody. In specific embodiments, the antibody or fragment thereof may be a wild-type antibody. In other specific embodiments, the antibody or fragment thereof may be a manipulated antibody.

EX1001, 52:6-14.

67. Thus, in my opinion, a POSA would have understood the term “antibody” as used in the '675 Patent to encompass any type of immunoglobulin molecule or fragment thereof, including human and non-human immunoglobulin molecules, as well as recombinant proteins, fusion proteins, chimeric proteins, wild-type antibodies, and manipulated antibodies, “and the like, which have the same or similar structures.” I note that the above-cited passages state that “antibody” refers to “an immunoglobulin molecule” (or fragment), and that the antibody “may be”

immunoglobulin G (IgG). A POSA would therefore understand that “antibody” as used in the ’675 Patent claims is not limited to IgG, but rather includes additional isotypes (e.g., IgM, IgA, IgE, and IgD). The term “antibody” is not limited to a particular binding target.

B. “fragment”

68. Unlike the term “antibody,” the term “fragment” is not explicitly defined in the ’675 Patent. However, the ’675 Patent’s definition of “antibody” sheds light on the meaning of “fragment.” For example, the ’675 Patent states that, “because the antibody according to the present invention is a concept that also encompasses a fragment thereof, the antibody does not have to show binding ability to a certain antigen as in case of the Fc fragment.” EX1001, 23:44-48. This statement implies that a “fragment” does not necessarily have the ability to bind to a certain antigen, an Fc fragment being an example. A POSA would therefore understand the term “fragment” as used in the ’675 Patent claims to encompass fragments that have the ability to bind a target antigen and fragments that lack the ability to bind a target antigen. More specifically, a POSA would understand the term “fragment” to encompass all known antibody fragments, including, but not limited to, (i) Fab fragments (monovalent fragments consisting of the V_L , V_H , C_L and C_{H1} domains); (ii) $F(ab')_2$ fragments (bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region); (iii) Fd fragments (comprising the V_H and C_{H1}

domains); (iv) Fv fragments (comprising the V_L and V_H domains of a single arm of an antibody), (v) dAb fragments (comprising a V_H domain); (vi) isolated complementarity determining regions (CDR); (vii) single chain Fv (scFv) constructs; and (viii) Fc fragments.

C. “at 248 position of heavy chain amino acid sequence”

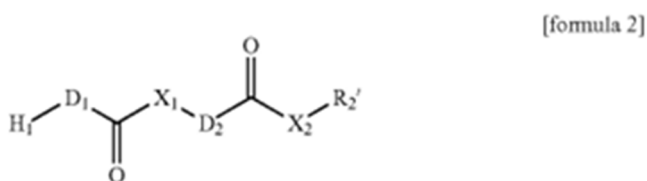
69. The '675 Patent's independent Claim 1 includes the limitation “at 248 position of heavy chain amino acid sequence.” This limitation is not discussed in the prosecution history of the '675 Patent. However, both the patent's specification and the claims themselves make clear that the position number “is determined by an EU numbering system.” EX1001, 27:61-28:2, claim 1. The specification also suggests that this position is commonly “a lysine residue of an Fc domain of the antibody.” EX1001, 6:44-45, 6:54-55, 6:64-65, 7:9-10, 28:1-13; Figures 1, 2, 5, 7.

70. Because EU numbering is a widely accepted system for determining amino acid positions within an antibody, and the “248 position” may be within an Fc domain (e.g., if the antibody is IgG), a POSA would understand how to determine which position within an antibody heavy chain, or a corresponding position for a fragment, is “248 position of heavy chain amino acid sequence.” Accordingly, the phrase “at 248 position of heavy chain amino acid sequence” should be interpreted as an amino acid residue within the heavy chain—possibly within the Fc region—at

position 248 or a corresponding position in the case of a fragment, as determined by the EU numbering system.

D. “terminal”

71. Claim 1 recites, “... wherein the modified lysine residue does not comprise a terminal bio-reactive functional group...”. The term “terminal” is not defined in the specification of the '675 Patent, but it is utilized in claim 1 and col. 3, lines 20-23, which states, “the present application provides the compound wherein H₁ is selected from terminal alkyne, azide, strained alkyne, diene, dienophile, alkene, thiol, and tetrazine.” This statement is made in reference to “Formula 2”:



The H₁ position is located at the very end of the Formula 2, which suggests “terminal” is intended to mean the last or final group at one end of the chemical structure.

72. Accordingly, I believe that the term “terminal” within the context of “the modified lysine residue does not comprise a terminal bio-reactive functional group” should be understood as the group positioned at the end of the modified lysine (e.g., H₁ in Formula 2 and other similar formulas disclosed in the '675 Patent).

IX. PRIORITY DATE ANALYSIS

73. I have been asked to consider whether the '503 Application provides written description support for the claims of the '675 Patent. I understand that, because the '675 Patent issued from the '998 Application, which itself is a continuation of the '503 Application, the '675 Patent and '503 Application share an identical written description. As a result, if the claims of the '675 Patent lack written description support in the specification of the '675 Patent, then they also lack written description support in the identical specification of the '503 Application. I understand that, in that case, the claims of the '675 Patent would not be entitled to claim priority to the September 14, 2020, filing date of the '503 Application, and would instead have a priority date no earlier than the '675 Patent's own filing date of January 16, 2023.

74. In my opinion, the '503 Application does not provide written description support for two limitations in the '675 Patent claims: (1) the "modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end," which I will call the "Modified Lysine Limitation," or (2) the Negative Limitation that excludes certain click chemistry functional groups. Thus, it is my opinion that for either of these reasons, the priority date of the '675 Patent should be no earlier than January 16, 2023.

A. Negative Limitation

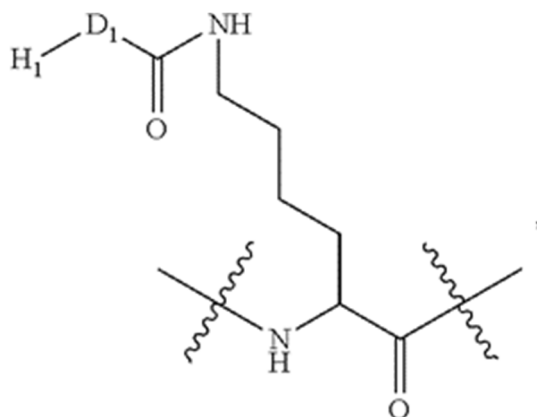
75. The Negative Limitation of Claim 1 of the '675 Patent recites: “wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

76. The '675 Patent does not disclose terminal aldehyde groups as a possible terminal bio-reactive functional group, or as a click chemistry functional group. The only reference to aldehydes in the '675 Patent is in the patent's definition of “alkylene,” where the patent discloses that a “substituted alkylene” may itself be substituted, and such a substituent may include “carbonyls (including ketones, aldehydes, carboxylates, and esters)” EX1001, 18:38-65.

77. In my opinion, because the '675 Patent does not disclose terminal aldehyde groups as a bio-reactive functional group—either to be used or to be avoided—the Negative Limitation is not disclosed in the '675 Patent.

B. Modified Lysine Limitation

78. Claim 2 of the '675 Patent recites that the modified lysine has the structure:



H₁ is defined as “a group having the bio-orthogonal click chemistry functional group” and D₁ is defined as a “bond” or “selected from C₁₋₄ alkylene, C₂₋₄ alkenylene, C₂₋₄ alkynylene and C₃₋₈ cycloalkylene.”

79. The '675 Patent discloses numerous different structural formula for modified lysine, each with various requirements and different variable groups. The modified lysine recited in claim 2 is unique among these, as it requires an amide bond not necessarily present in other examples. The only description in the specification for this structure requires particular adjacent amino acids: GPSVFLFPPKPKDTLMI (corresponding to any one of SEQ ID NOs: 17- 22),¹ which are present in many antibodies. EX1001, 8:1-44; 10:33-11:52; 48:3-50:35; 52:27-54:44. This sequence corresponds to positions 237-253 in the CH2 domain of a human IgG1, IgG2, or IgG4.

¹ Note: SEQ ID NO: 17 is identical to SEQ ID NO: 20, SEQ ID NO: 18 is identical to SEQ ID NO: 21, and SEQ ID NO: 19 is identical to SEQ ID NO: 22.

80. There are many different isotypes of antibodies that have distinct Fc domains (which include the CH2 domain). For example, IgG1, IgG2, and IgG4 variants such as IgG1 σ , IgG2 σ , IgG4 σ 1, and IgG4 σ 2 do not comprise GPSVFLFPPKPKDTLMI (EX1033, 3), nor do other antibody isotypes such as IgA, IgM, IgD, and IgE, which have altogether distinct Fc domains. EX1034, 3. Accordingly, the particular modified lysine structure recited in claim 2 is only disclosed in the context of a particular subclass of antibodies (i.e., human IgG1, IgG2, and IgG4).

X. OVERVIEW OF THE ASSERTED PRIOR ART REFERENCES

81. Before providing a detailed analysis of how the prior art renders the claims of the '675 Patent unpatentable, I provide below a brief summary of the key prior art references.

A. CA 3132959A1 (“the ’959 Publication”; EX1005)

82. The '959 Publication is titled “Site-specific antibody conjugation and antibody-drug conjugate as specific embodiment thereof” and was published on September 17, 2020, from Canadian Patent Application No. 3132959, which was the Canadian national stage entry of International Application No. PCT/KR2020/003282, which was published as WO2020/184944 on September 17, 2020 (EX1004). As previously noted, the '675 Patent was a continuation of the '503 Application that was the U.S. national stage entry of this international application.

Assuming the '675 Patent's earliest priority date is its filing date on January 16, 2023, as discussed in the preceding section, then the '959 Publication is prior art to the '675 Patent.

83. I understand that national stage applications have a disclosure that is identical to the corresponding PCT application, and therefore the disclosure of the '959 Publication and the '675 Patent are expected to be identical.

B. “Development of a Novel Chemical Site-Specific Conjugation Platform for ADCs,” Ajinomoto poster presentation at PepTalk 2019 (“PepTalk Poster”; EX1006)

84. PepTalk Poster is a poster titled “Development of a Novel Chemical Site-Specific Conjugation Platform for ADCs,” which was presented at an annual scientific conference called “PepTalk: The Protein Science Week.” PepTalk conferences are well known and well regarded among individuals working in the antibody and ADC space. I have attended PepTalk conferences in the past and they are largely attended by people of ordinary skill and those interested in antibodies and ADCs. PepTalk Poster lists fifteen individuals as authors or contributors, along with three organizations: Ajinomoto Co., Inc., Kagoshima University, and Ajinomoto Bio-Pharma Services.

85. PepTalk Poster presents Ajinomoto's AJICAP™ technology for preparing antibody-drug conjugates (ADCs) through an improved site-specific

conjugation. PepTalk Poster includes four sections: Introduction, Methods, Results, and Conclusion. The Introduction section provides overviews of ADCs, site-specific conjugation, and existing methods for performing site-specific conjugation. The Methods section provides a summary of Ajinomoto's improved method for site-specific conjugation. The Results section summarizes the results of various studies of the safety and efficacy of Ajinomoto's AJICAP™ technology. The Conclusion section briefly summarizes the benefits of AJICAP™ relative to previous site-specific conjugation technologies.

86. PepTalk Poster was presented at the 2019 PepTalk conference, which was held from January 14-18, 2019, in San Diego, California. PepTalk Poster is prior art to the '675 Patent regardless of whether the '675 Patent has a priority date as of its filing on January 16, 2023 or its earliest claimed priority date of March 8, 2019.

C. “Technology of Site Specific Conjugation for Next Generation ADCs” Slide deck presentation at PepTalk 2019 (“PepTalk Presentation”; EX1007)

87. Like PepTalk Poster, the PepTalk Presentation shows Ajinomoto's AJICAP™ technology for preparing antibody-drug conjugates (ADCs) through an improved site-specific conjugation. PepTalk Presentation includes background on ADC production and improvements made by the AJICAP™ technology. The

PepTalk Presentation also provides a summary of Ajinomoto's improved method for site-specific conjugation, which shows various ways a lysine at position 248 can be modified, and it briefly summarizes the benefits of AJICAP™ relative to previous site-specific conjugation technologies.

88. PepTalk Presentation was presented on January 16, 2019, at the 2019 PepTalk conference, which was held from January 14-18, 2019, in San Diego, California. PepTalk Presentation is prior art to the '675 Patent regardless of whether the '675 Patent has a priority date as of its filing on January 16, 2023 or its earliest claimed priority date of March 8, 2019.

D. WO 2018/199337 (“Yamada”; EX1008)

89. Yamada published on November 1, 2018, from International Application No. PCT/JP2018/017345, filed on April 27, 2018, which claims priority to Japanese Patent Application No. 2017-090679, filed on April 28, 2017. Accordingly, this reference is prior art to the '675 patent under 35 U.S.C. § 102(a)(1) regardless of whether the '675 patent is accorded its earliest claimed priority date or its filing date. Because the PCT publication was in Japanese, for the purposes of this opinion all citations are made to the U.S. counterpart application, which was filed on October 19, 2019, and published as U.S. 2020/0190165 (EX1009) on June 18, 2020.

90. I understand that U.S. 2020/0190165 is the publication of a U.S. national stage application of Yamada, and I understand that national stage applications have a disclosure that is identical to the corresponding PCT application.

E. WO 2019/240288 (“Matsuda”; EX1010)

91. Matsuda published on December 19, 2019, from International Application No. PCT/JP2019/023779, filed on June 14, 2019, which claims priority to Japanese Patent Application No. 2018-113962, filed on June 14, 2018. Accordingly, this reference is prior art to the '675 patent under 35 U.S.C. § 102(a)(2) regardless of whether the '675 patent is accorded its earliest claimed priority date or its filing date. Because the PCT publication was in Japanese, for the purposes of this opinion all citations are made to the U.S. counterpart application, which was filed on December 11, 2020, and published as U.S. 2021/0139541 (EX1011) on May 13, 2021.

92. I understand that U.S. 2021/0139541 is the publication of a U.S. national stage application of Matsuda, and I understand that national stage applications have a disclosure that is identical to the corresponding PCT application.

XI. OPINIONS RELATING TO INVALIDITY OF THE '675 PATENT

CLAIMS

A. Claims 1-13 of the '675 Patent Are Unpatentable Over the '959 Publication

93. The '959 Publication discloses modified forms of trastuzumab with a lysine at position 248 that was modified to include an azide or a norbornene as a bio-orthogonal click chemistry functional group at its terminal end. EX1005, 222-241, Fig. 43.

1. Independent Claim 1 of the '675 Patent

a. A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group,

94. The '959 Publication discloses “a modified antibody or its fragment comprising bio-orthogonal click chemistry functional group.” In particular, the '959 Publication discloses the antibody trastuzumab, modified with an azide group (EX1005, 54, 225-229) or a norbornene group (*id.*, 54, 223-225, Fig. 43).²

95. For example, the '959 Publication states that “[t]he term ‘click-chemistry functional group’ used in the present invention refers to a functional group that participates in a click-chemistry reaction.” EX1005, 41. The '959 Publication

² It should be noted that in Example 3.2 (starting at the bottom of page 225), the '959 publication inadvertently refers to norbornene several times when the data for this example shows an azide group. This may be a drafting error.

then identifies an azide group as one such click-chemistry functional group, stating, “Exemplary click-chemistry functional groups used in the present invention include a terminal alkyne, an azide, a strained alkyne, a diene, a dienophile, a trans-cyclooctene, an alkene, a thiol, and a tetrazine, but the present invention is not limited thereto.” *Id.* Norbornene is also listed as a click chemistry functional group. *Id.*, 54. The ’959 Publication discloses that a click-chemistry reaction is a bio-orthogonal reaction. In particular, the ’959 Publication states: “The click-chemistry reaction is a biorthogonal reaction, and has an advantage in that the reaction occurs at a very rapid reaction rate and is used to form a strong binding structure.” *Id.*, 147.

96. In describing a “Synthesis Method of Trastuzumab-Azide,” the ’959 Publication states: “To introduce an azide at a certain site of an antibody (trastuzumab, 4 mg/mL), 10 equivalents of Compound IV-SSFI (Dap) was added per one antibody, and reacted at room temperature for 24 hours, and the reaction monitoring and termination were confirmed by HIC-HPLC” (EX1005, 225-226) and similar instructions are given for preparing an “Ab (246/248 Lys)-norbornene” (*id.*, 223).

97. The ’959 Publication discusses the procedure by which the modified trastuzumab-azide structure was confirmed in a section titled “Confirmation of structure of Trastuzumab-Azide.” That section states: “The antibody-azide complex in which an azide linker was bound to an antibody via Compound IV-SSFI (Dap)

was confirmed using mass spectrometry. A molecular weight increase of 249 Da was confirmed when two molecules of an azide compound were bound to trastuzumab.” *Id.*, 229.

98. Figures 56 and 57 of the '959 Publication show mass spectra of trastuzumab and a trastuzumab-azide complex, respectively. *Id.*, 32, 229, Figures 56, 57. The '959 Publication discloses that an azide is a bio-orthogonal click chemistry functional group.

99. The '959 Publication discusses the procedure by which the modified trastuzumab-norbornene structure was confirmed in paragraphs 225 and Figures 44-47. Notably, Figure 43 shows “the structure of the final product” for trastuzumab-norbornene. *Id.*, 225.

100. Thus, by disclosing a modified trastuzumab including an azide group or a norbornene group, the '959 Publication discloses a “a modified antibody or its fragment comprising bio-orthogonal click chemistry functional group.”

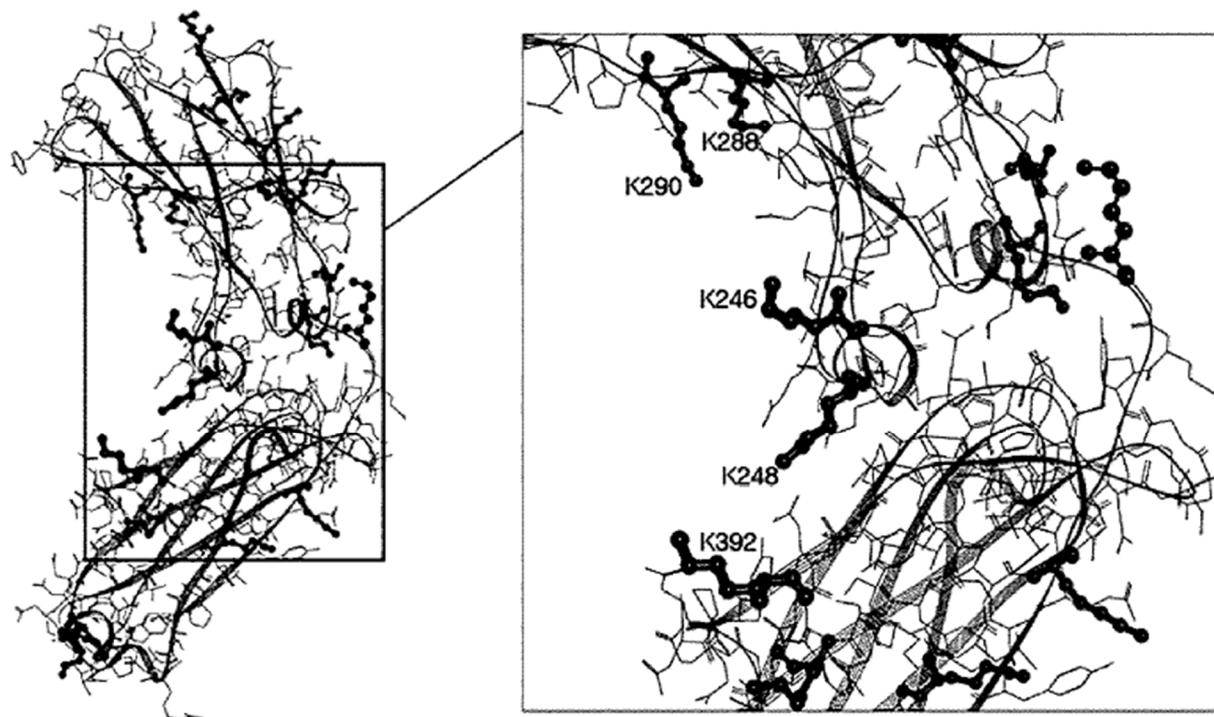
b. wherein the modified antibody comprises one or more modified heavy chain,

101. The '959 Publication discloses “the modified antibody comprises one or more modified heavy chain.”

102. As was known in the art, and disclosed in the '959 Publication, antibodies, such as trastuzumab, have two heavy chains and two light chains. EX1005, 51.

103. The '959 Publication discloses that the trastuzumab modified with an azide is modified at the trastuzumab's lysine residues at positions 246 and 248. EX1005, 225-229. As was known in the art, and disclosed in the '959 Publication, lysine residues 246 and 248 reside in the Fc domain of an IgG antibody such as trastuzumab. *Id.*, 29, 52, 53. For example, Figure 2 of the '959 Publication shows the position of lysine residues, including lysine 248, in an Fc domain. *Id.*, 29, Figure 2.

FIG. 2



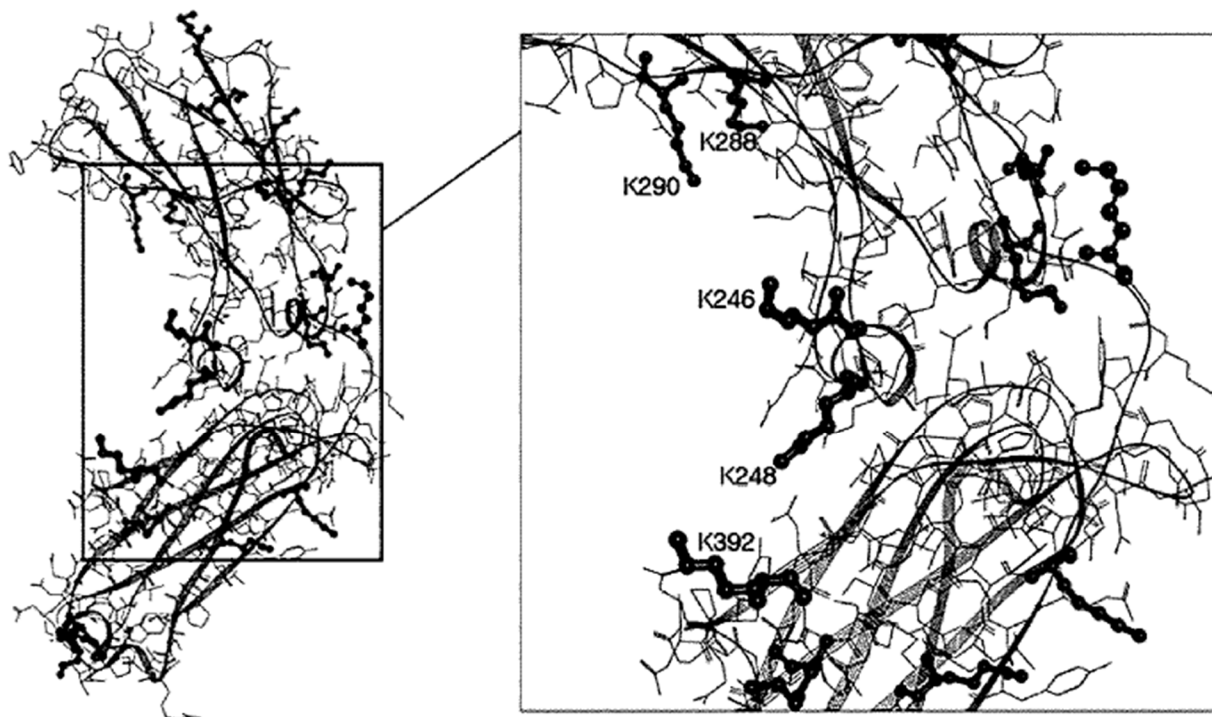
104. Thus, by disclosing a trastuzumab modified with an azide group at lysine residues 246 and 248 in the Fc domain of the heavy chains, the '959 Publication discloses that “the modified antibody comprises one or more modified heavy chain.”

- c. 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*

105. The '959 Publication discloses “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.”

106. As previously discussed, the '959 Publication discloses that the trastuzumab has modified heavy chains, specifically heavy chains with modified lysine residues at positions 246 and 248 of the Fc domains. The '959 Publication shows lysine residues 246 and 248 in Figure 2. EX1005, 29, Figure 2.

FIG. 2



107. The '959 Publication explains that its references to numbers in amino acid sequences are according to the EU numbering system unless stated otherwise. EX1005, 52. Figure 1 depicts the amino acid sequence of the Fc domain from number 237 to number 253, according to EU numbering. *Id.*, 29, 52, Figure 1. As shown in Figure 1, lysine residues, abbreviated “K,” occupy positions 246 and 248.

amino acid sequence :

G—P—S—V—F—L—F—P—P—K—P—K—D—T—L—M—I

**EU numbering
for heavy chain :**

237 239 241 243 245 247 249 251 253
238 240 242 244 246 248 250 252

108. As previously discussed, the '959 Publication discloses trastuzumab modified with an azide group at lysine residues 246 or 248 of the Fc domains of the heavy chains. Namely, the '959 Publication discloses that “two molecules of an azide compound were bound to trastuzumab” (*id.*, 229) and “it was confirmed that the [azide] molecule was bound to a K248 site of the sequence LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF.” (*id.*, 228).

109. The '959 Publication also discloses “the present invention provides technology for specifically transferring a chemical functional group to lysine 248 in the antibody” (EX1005, 3), and that the click chemistry functional group and the antibody may be connected via lysine 246, lysine 248, or both, and further via only one of the two Fc domains or via both Fc domains (*id.*, 87-88).

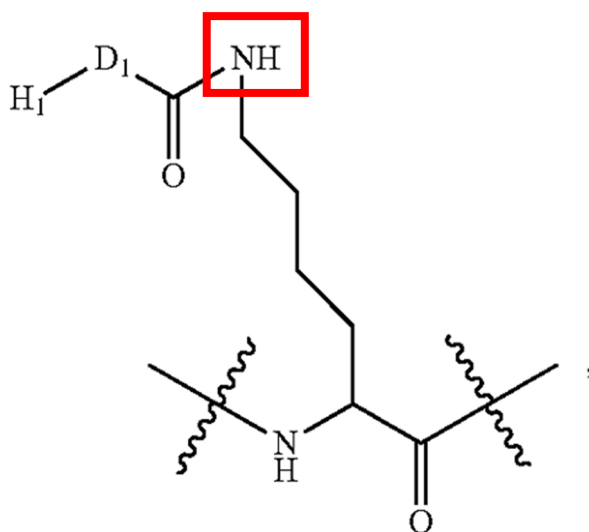
110. The '959 Publication thus discloses that “each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system.”

- d. wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end, and*

111. The '959 Publication discloses “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

112. As previously discussed, the '959 Publication discloses trastuzumab modified with an azide group and trastuzumab modified with a norbornene group at lysine 248. As also previously discussed, an azide group and a norbornene group are bio-orthogonal click chemistry functional groups.

113. The '959 Publication also discloses that this modification is made at the terminal end of the modified lysine residue. For example, the figure below depicts lysine residue 248 modified at its terminal end, represented by “NH,” where the '959 Publication states that H₁ may be an azide (*id.*, 98).



114. Accordingly, the '959 Publication discloses that “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

e. wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.

115. The '959 Publication discloses “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy[l] group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

116. As previously discussed, the '959 Publication discloses trastuzumab modified with an azide group at lysine residues 246 and 248. As was well-understood by persons skilled in the art by 2019 and long before, an azide group is none of a hydroxyl group, carboxyl group, thiol group, amino group, or aldehyde group. There is no indication in the trastuzumab-azide example (*id.*, 225-229) that there were any other terminal bio-reactive functional groups on the modified lysine. Moreover, the '959 Publication reflects this understanding by distinguishing an azide (or azido) group from hydroxyl, carboxyl, thiol, amino, and aldehyde groups. *Id.*, 37. For example, in providing its definition of the term “alkylene,” and specifically a “substituted alkylene,” the '959 Publication identifies example substituents,

including “a hydroxyl group, a carbonyl group (for example, carboxyl . . .), . . . an amino group, . . . an azido group,” and others. *Id.* The ’959 Publication goes on to explain that “a substituted residue on a hydrocarbon chain may itself be substituted,” and identifies substituents including “amino, azido, . . . carbonyls (including . . . aldehydes . . .),” and others. *Id.*, 37-38. Similarly, in identifying “exemplary click-chemistry functional groups used in the present invention,” the ’959 Publication identifies “an azide, . . . a thiol,” and others. *Id.*, 41.

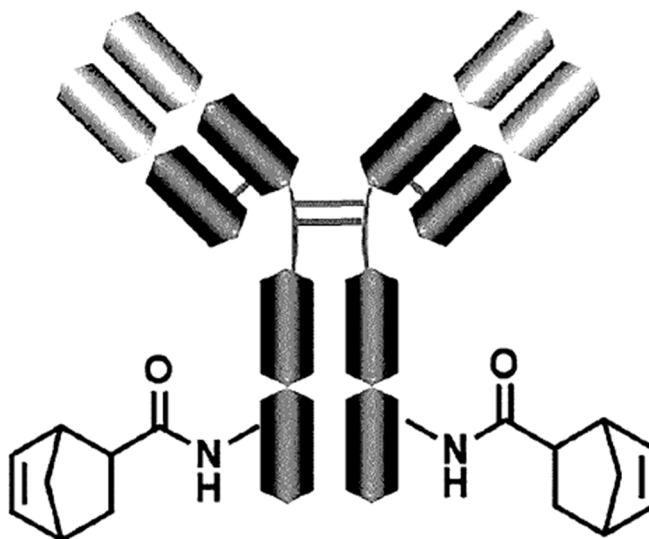
117. Furthermore, the particular trastuzumab-azide species disclosed in the ’959 Publication and discussed in reference to the previous limitations does not include the other bio-reactive functional groups recited in this limitation. The ’959 Publication’s discussion of the synthesized trastuzumab-azide species does not reference any of these functional groups, and persons skilled in the art would have understood that this example involved an azide as the only functional group. This understanding is supported by the headers for these sections of the specification, i.e., “3.2 Synthesis of Antibody-Azide,” “Synthesis Method of Trastuzumab-Azide (4),” and “3.4 Confirmation of Structure of Trastuzumab-Azide,” as well as statements such as “Synthesis of Ab (246/248 Lys)-azide was carried out in a buffer using Compound IV-SSFI (Dap)”; “To introduce an azide at a certain site of an antibody (trastzumab [sic], 4 mg/mL), 10 equivalents of Compound IV-SSFI (Dap) was added per one antibody”; and:

The antibody-azide complex in which an azide linker was bound to an antibody via Compound IV-SSFI (Dap) was confirmed using mass spectrometry. A molecular weight increase of 249 Da was confirmed when two molecules of an azide compound were bound to trastuzumab. The measured mass spectrum of trastuzumab is shown in FIG. 56 , and the mass spectrum of the antibody-azide complex to which two azide molecules were bound is shown in FIG. 57.

See EX1005, 225-226, 229.

118. Thus, by disclosing trastuzumab with lysine residues modified with only an azide group, the '959 Publication discloses that “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

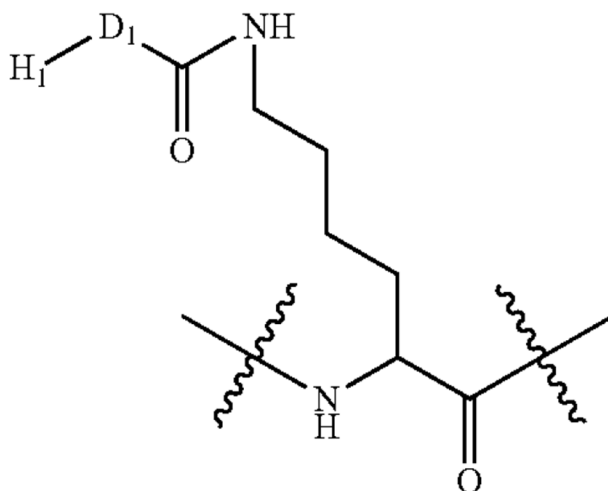
119. Similarly, the trastuzumab-norbornene example (EX1005, 223-225) explicitly provides that Figure 43 is “the structure of the final product.” *Id.*, 225. Figure 43, reproduced below, clearly does not include “a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”



120. The '959 Publication thus discloses the modified antibody of Claim 1.

2. Claim 2 of the '675 Patent

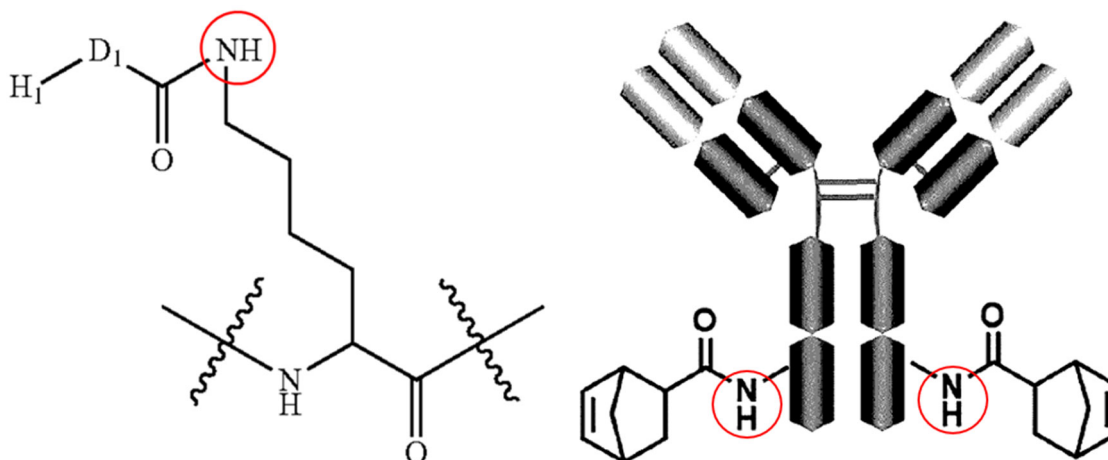
121. Claim 2 recites: "The modified antibody of claim 1, wherein the modified lysine residue has following structure:



wherein H_1 is a group having the bio-orthogonal click chemistry functional group, and wherein D_1 is bond, or is selected from C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene and C_{3-8} cycloalkylene.”

122. The '959 Publication discloses the modified antibody of claim 2.

123. In particular, the trastuzumab-norbornene example (EX1005, 223-225) shows a structure that matches the formula of claim 2. The circled NH of the formula recited in claim 2 corresponds to either of the circled NH groups from Fig. 43 shown below.



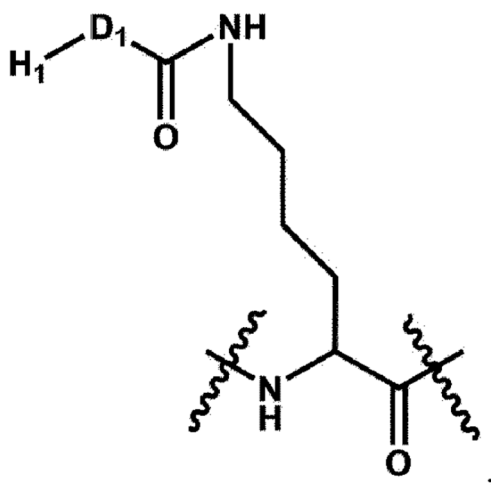
In Fig. 43, D_1 is a bond and H_1 is a norbornene, which is a bio-orthogonal click chemistry functional group.

124. Additionally, as previously discussed, the '959 Publication discloses trastuzumab modified with an azide group at lysine residues 246/248. EX1005, 225-229. As also previously discussed, an azide group is a bio-orthogonal click chemistry functional group, and thus serves as the H_1 of the claimed structure. While

it is difficult to tell from this example precisely what D₁ would be, the most likely connection would be a short alkyl or cycloalkyl, consistent with the requirements of claim 2. If D₁ were a “bond,” the resulting molecule would be an acyl azide, which is highly reactive and useless as a bioconjugate. Thus, the obvious choice for D₁ would be a short alkyl or cycloalkyl.

125. In addition, the '959 Publication discloses the structure recited in Figure 2, for example, at pages 98-99.

126. Page 98 shows an example modified lysine residue with the following general structure:



127. In reference to this structure, the '959 Publication discloses that “H₁ is a first click-chemistry functional group,” and “D₁ is any alkylene, alkenylene, or alkynylene. The antibody or fragment thereof has H₁ connected via lysine 248 in an Fc domain thereof, or a site corresponding to the lysine 248.” EX1005, 98.

128. The '959 Publication goes on to state that, “[i]n specific embodiments, H₁ may include any one selected from an alkyne, an azide, a strained alkyne, a diene, a dienophile, an alkene, a thiol, and a tetrazine,” and “D₁ may include any one selected from a covalent bond, a C₁₋₄ alkylene, a C₂₋₄ alkenylene, a C₂₋₄ alkynylene, and a C₃₋₈ cycloalkylene,” i.e., the same D₁ components recited in Claim 2. *Id.*, 98-99.

129. Thus, the '959 Publication discloses the modified antibody of Claim 1 where the modified lysine has the structure recited in Claim 2.

3. Claim 3 of the '675 Patent

130. Claim 3 recites: “The modified antibody of claim 2, wherein D₁ is bond, or is selected from unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene and unsubstituted C₃₋₈ cycloalkylene.”

131. Because claim 3 includes the option of D₁ being a bond, Figure 43 discloses the limitations of this claim as well.

132. With respect to the rest of claim 3 reciting the D₁ structures are “unsubstituted,” the '959 Publication discloses this limitation of Claim 3. In particular, as previously discussed, the '959 Publication discloses the modified lysine structure recited in Claim 2 where “D₁ may include any one selected from a covalent bond, a C₁₋₄ alkylene, a C₂₋₄ alkenylene, a C₂₋₄ alkynylene, and a C₃₋₈ cycloalkylene.” EX1005, 98-99. In its Definitions section, the '959 Publication

explains that references to terms such as these are intended to encompass both substituted and unsubstituted versions.

133. For example, the '959 Publication states: "When used together with a residue such as an alkylene, an alkenylene, or an alkynylene, the term 'C_{x-y}' is, for example, intended to encompass residues containing x to y carbon atoms in the chain thereof. For example, the term "C_{x-y} alkylene" refers to a substituted or unsubstituted, linear or branched alkylene group that contains x to y carbon atoms in the chain thereof." EX1005, 38.

134. Thus, by disclosing that "D₁ may include any one selected from a covalent bond, a C₁₋₄ alkylene, a C₂₋₄ alkenylene, a C₂₋₄ alkynylene, and a C₃₋₈ cycloalkylene," the '959 Publication also discloses "D₁ is bond, or is selected from unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene and unsubstituted C₃₋₈ cycloalkylene." Accordingly, the '959 Publication discloses the additional limitation of Claim 3.

4. Claim 4 of the '675 Patent

135. Claim 4 recites: "The modified antibody of claim 1, wherein the modified heavy chain comprises an amino acid sequence having a structure of formula 8-2:

G-P—S-V-F-L-F—P-P-K-P—(K)'-D-T-L-M-I (SEQ ID NO: 21),
[formula 8-2]

wherein K' is the modified lysine residue.”

136. The '959 Publication discloses the modified heavy chain comprising an amino acid sequence as recited in Claim 4.

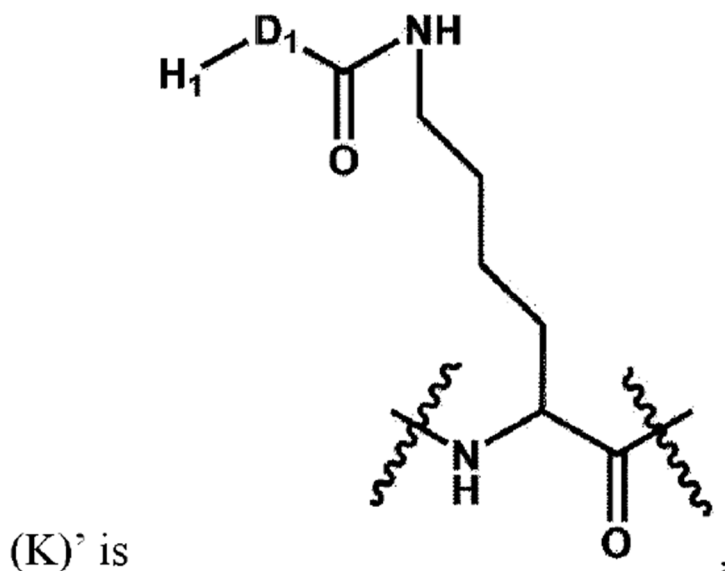
137. For example, the recited formula 8-2 is disclosed on page 98, which states, “The present invention provides an antibody or a fragment thereof, which includes an amino acid sequence of the following Formula 8-2:”

[Formula 8-2]

G—P—S—V—F—L—F—P—P—K—P—(K)'—D—T—L—M—I (SEQ ID NO: 21)

EX1005, 98.

138. The '959 Publication further discloses that K' is the modified lysine residue recited in Claim 2.



Id., 98.

139. Thus, the '959 Publication discloses the modified antibody of Claim 1 where the modified heavy chain includes an amino acid sequence having the structure of Formula 8-2 as recited in Claim 4.

5. Claim 5 of the '675 Patent

140. Claim 5 recites: “The modified antibody of claim 2, wherein D₁ comprises one or more heteroatoms.”

141. The '959 Publication discloses “D₁ comprises one or more heteroatoms.”

142. In particular, as previously discussed, the '959 Publication discloses, in reference to the modified lysine structure recited in Claim 2, that “D₁ may include any one selected from a covalent bond, a C₁₋₄ alkylene, a C₂₋₄ alkenylene, a C₂₋₄ alkynylene, and a C₃₋₈ cycloalkylene.” EX1005, 98-99.

143. The '959 Publication also states that, “when describing a structure of a compound, all the alkylene, the alkenylene, the alkynylene, and the cycloalkylene are intended to include a heteroalkylene, a heteroalkenylene, a heteroalkynylene, and heterocycloalkylene, respectively” EX1005, 55; *see also* 36-37.

144. Thus, in disclosing that D₁ may include any of “C₁₋₄ alkylene, a C₂₋₄ alkenylene, a C₂₋₄ alkynylene, and a C₃₋₈ cycloalkylene,” the '959 Publication also discloses that D₁ may include any of C₁₋₄ heteroalkylene, a C₂₋₄ heteroalkenylene, a C₂₋₄ heteroalkynylene, and a C₃₋₈ heterocycloalkylene.

145. Persons of skill in the art understood that heteroalkylene, heteroalkenylene, heteroalkynylene, and heterocycloalkylene each refer to the corresponding molecule with one or more heteroatoms. The '959 Publication discloses this as well, stating:

The term “hetero” used in the present invention refers to a compound or a group of compounds including at least one heteroatom. The term “heteroatom” refers to an atom other than a carbon or hydrogen atom, and, for example, includes B, Si, N, P, O, S, and Se. Preferably, the heteroatom includes, among others, polyvalent elements such as N, O, and S, or monovalent elements such as F, Cl, Br, and I, but the present invention is not limited thereto.

EX1005, 34.

146. Accordingly, the '959 Publication discloses the modified antibody of Claim 2 where D₁ includes one or more heteroatoms.

6. Claim 6 of the '675 Patent

147. Claim 6 recites: “The modified antibody of claim 2, wherein D₁ is —[CH₂]_a—O—[CH₂]_b—, wherein each of a and b is independently selected from 0 to 4, and each of a and b is integer, and wherein sum of a and b is 0 or more and 4 or less.”

148. Claim 6 thus further limits Claim 2 by requiring that D₁ be —[CH₂]_a—O—[CH₂]_b— where *a* and *b* are each an integer from 0 to 4, whose sum is 0 to 4.

149. The '959 Publication discloses this structure for D₁.

150. In particular, in reference to the modified lysine residue structure recited in Claim 2, the '959 Publication discloses that "D₁ may be —CH₂OCH₂—." EX1005, 99. This D₁ satisfies the structure recited in Claim 6. Specifically, this is the recited structure where *a* and *b* are each 1, which is an integer from 0 to 4, and which sum to 2, which is "0 or more and 4 or less."

151. The '959 Publication thus discloses the modified antibody of Claim 2 where D₁ has the structure recited in Claim 6.

7. Claim 7 of the '675 Patent

152. Claim 7 recites: "The modified antibody of claim 2, wherein D₁ is —CH₂CH₂OCH₂— or —CH₂OCH₂—."

153. The '959 Publication discloses "D₁ is —CH₂CH₂OCH₂— or —CH₂OCH₂—."

154. In particular, as discussed with respect to Claim 6, the '959 Publication discloses, in reference to the modified lysine structure of Claim 2, that "D₁ may be —CH₂OCH₂—." EX1005, 99. This is one of the structures for D₁ recited in Claim 7.

155. Accordingly, the '959 Publication discloses the modified antibody of Claim 2 where D₁ has one of the structures recited in Claim 7.

8. Claim 8 of the '675 Patent

156. Claim 8 recites: "The modified antibody of claim 1, wherein the modified antibody comprises two modified heavy chains."

157. The '959 Publication discloses “the modified antibody comprises two modified heavy chains.”

158. As previously discussed, and as was well-known in the art, antibodies, such as trastuzumab, include two heavy chains. As also previously discussed in connection with Claim 1, the '959 Publication discloses in Example 3.2 a trastuzumab modified with an azide group at lysine residues 246 and/or 248 of the Fc domains of the heavy chains. In discussing the trastuzumab-azide example, the '959 Publication states that “[a] molecular weight increase of 249 Da was confirmed when two molecules of an azide compound were bound to trastuzumab.” EX1005, 229. Moreover, the trastuzumab modified with a norbornene group shown in Figure 43 clearly indicates that both heavy chains are modified.

159. The '959 Publication discloses that the modifications to lysine residue 248 may be made to two Fc domains, i.e., the Fc domain of each of two heavy chains. For example, in discussing Formula 8-2 that includes a modified lysine residue 248 having the structure recited in Claim 2, the '959 Publication states that “the antibody may include the amino acid sequence of Formula 8-2 in both of the two Fc domains thereof.” EX1005, 98-99.

160. The '959 Publication thus discloses the modified antibody of Claim 1 comprising two modified heavy chains.

9. Claim 9 of the '675 Patent

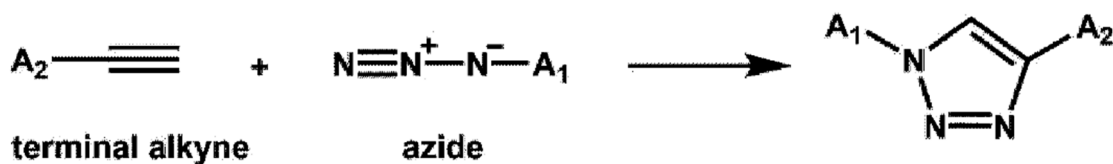
161. Claim 9 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

162. The '959 Publication discloses “the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

163. In particular, as previously discussed in connection with Claim 1, the '959 Publication discloses trastuzumab modified with an azide group. As also previously discussed, an azide group is a bio-orthogonal click chemistry functional group. Persons skilled in the art understood that an azide group is capable of participating in a click-chemistry reaction of Huisgen 1,3-dipolar cycloaddition as well as Diels-Alder reactions.

164. The '959 Publication reflects this understanding and expressly discloses the use of azide groups in Huisgen 1,3-dipolar cycloaddition and Diels-Alder reactions.

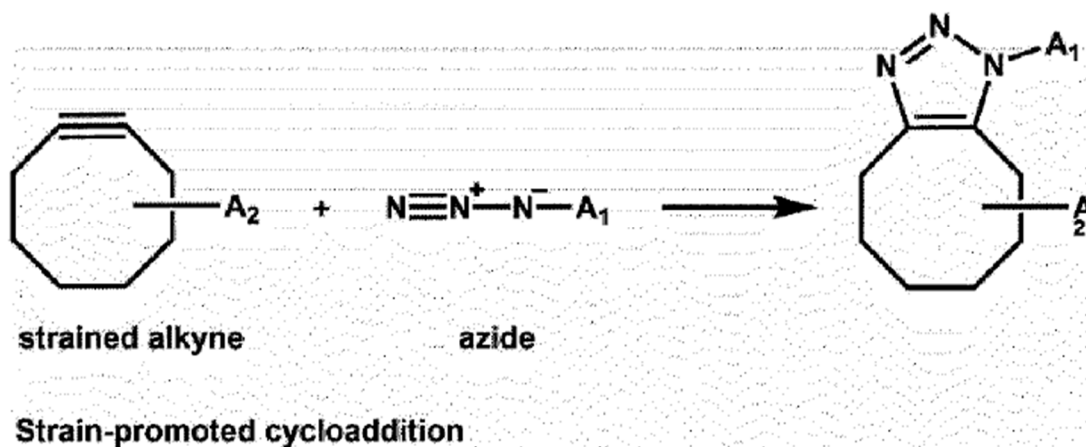
165. The '959 Publication discloses the following “Schematic diagram of Huisgen 1,3-dipolar cycloaddition” between a terminal alkyne and an azide.



1,3-dipolar cycloaddition

EX1005, 39.

166. The '959 Publication also discloses the following “Schematic diagram of strain-promoted cycloaddition” and notes that strain-promoted cycloaddition is an example of a Diels-Alder reaction.



EX1005, 39-40.

167. The '959 Publication thus discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is one capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.

10. Claim 10 of the '675 Patent

168. Claim 10 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

169. The '959 Publication discloses “the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

170. In particular, as previously discussed in connection with Claim 1, the '959 Publication discloses trastuzumab modified with an azide group at lysine 246 and/or 248.

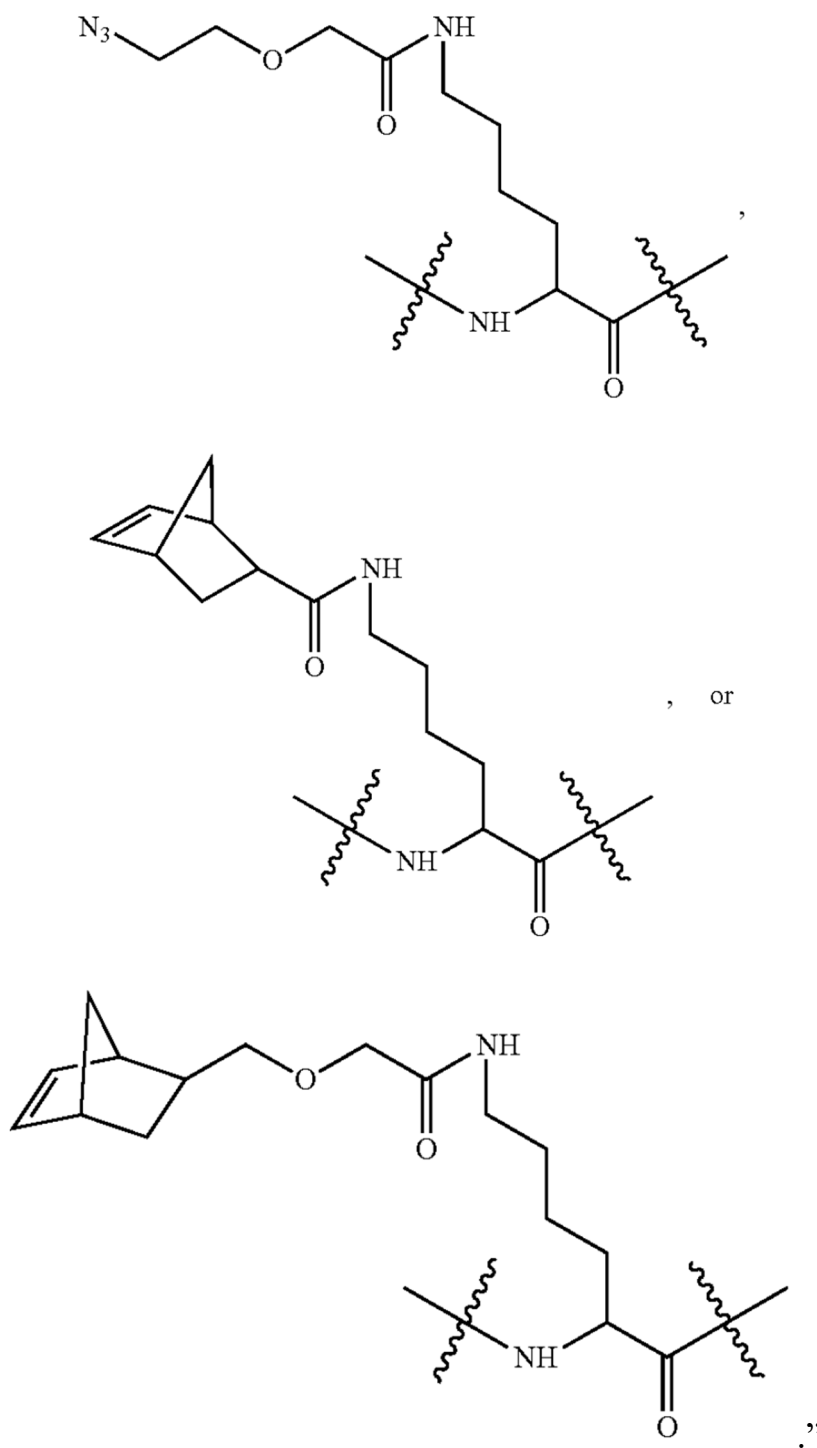
171. The '959 Publication thus discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.

172. In addition, the '959 Publication also discloses trastuzumab modified with norbornene at lysine residues 246 and/or 248. EX1005, 223-225, 226-228.

173. For this additional reason, the '959 Publication discloses the modified antibody of Claim 10.

11. Claim 11 of the '675 Patent

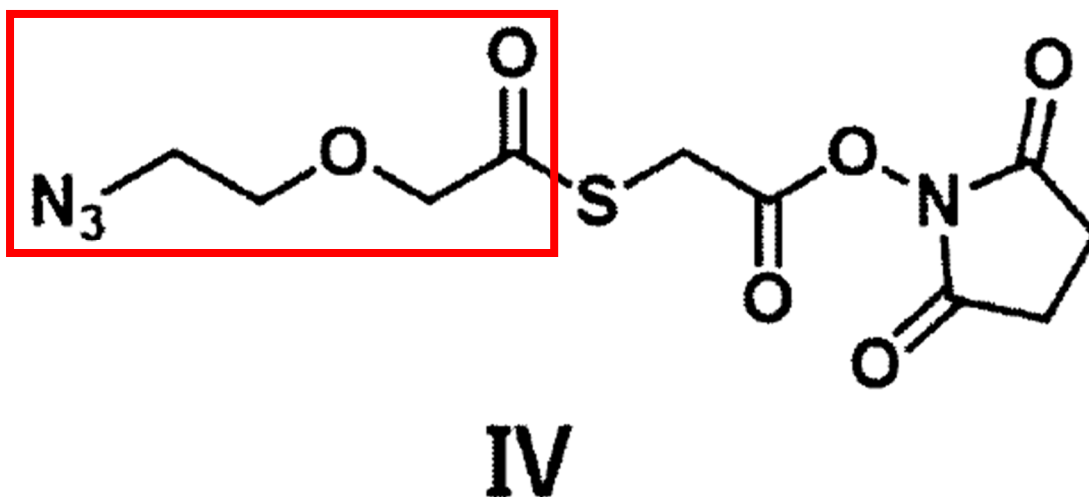
174. Claim 11 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:



175. The '959 Publication discloses the modified lysine residue has one of the three structures shown in Claim 11.

176. In particular, the first structure represents a lysine residue modified with an azide group (N_3) as the click chemistry functional group. As previously discussed in connection with Claim 1, the '959 Publication discloses trastuzumab modified at lysine residues 246 and/or 248 with an azide group. As also previously discussed, the '959 Publication discloses performing this modification by reacting trastuzumab with Compound IV-SSFI (Dap). EX1005, 225-226.

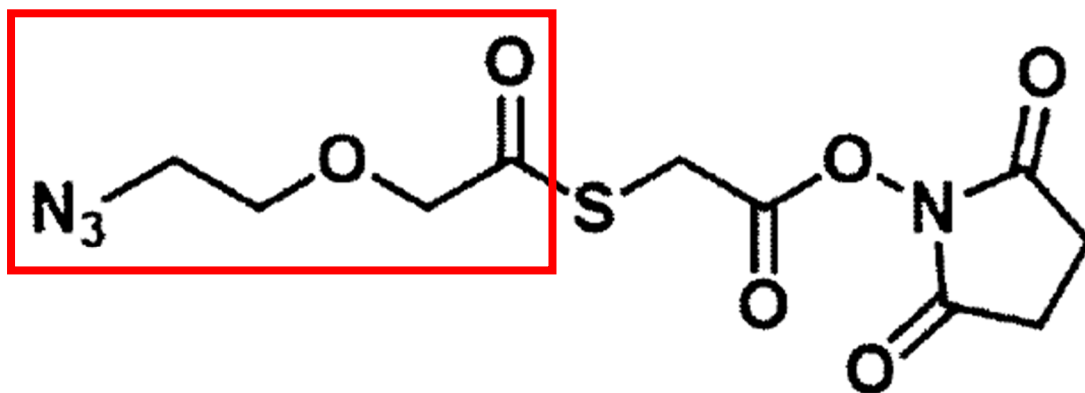
177. The '959 Publication discloses that Compound IV has the following structure:



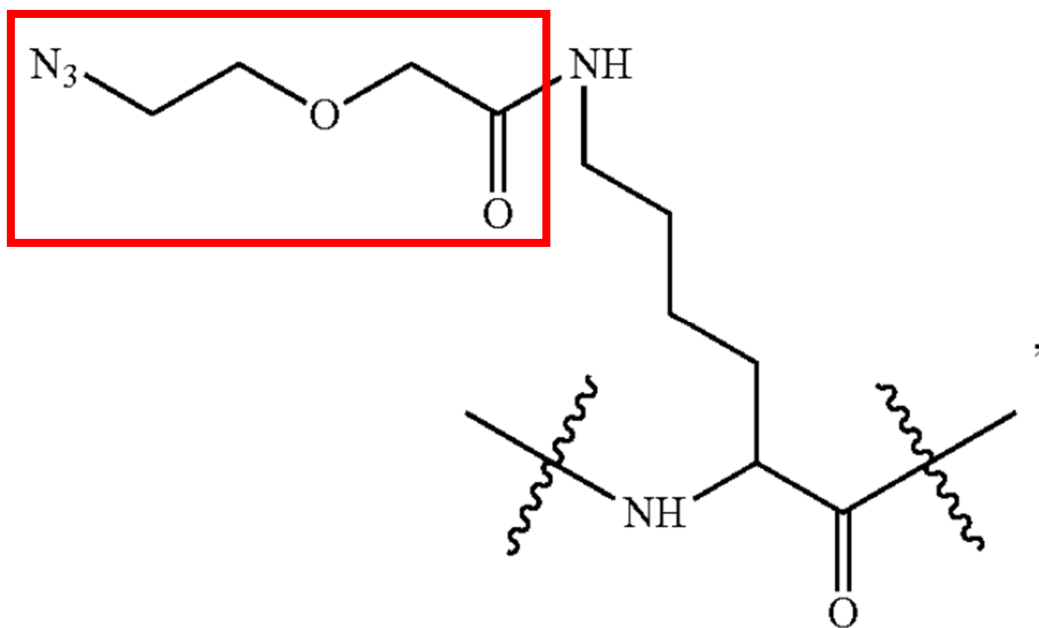
EX1005, Figure 22; see also 171-172.

178. Compound IV is a precursor of the first structure recited in Claim 11. As seen in the figure above, Compound IV includes an azide group (N_3). By reacting trastuzumab with Compound IV-SSFI (Dap), the structure highlighted above is

transferred to and modifies the lysine residues at positions 246 and/or 248 to obtain the first structure recited in Claim 11.

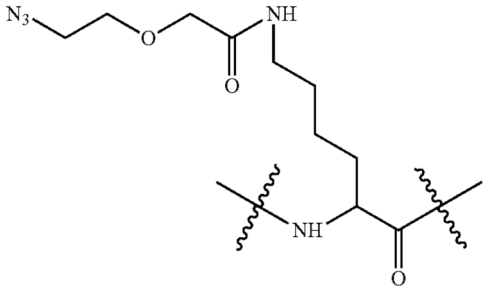
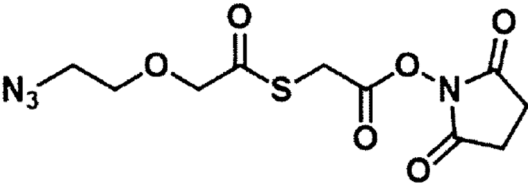
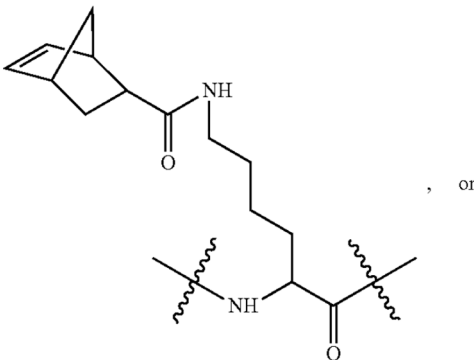
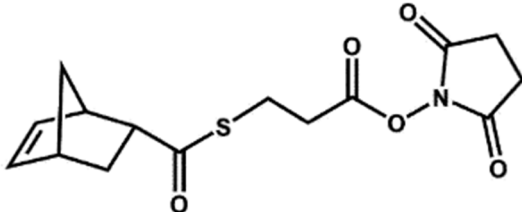
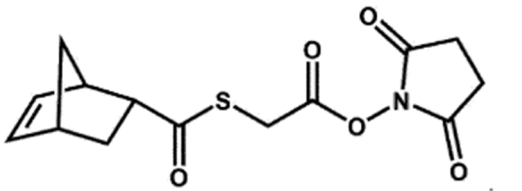
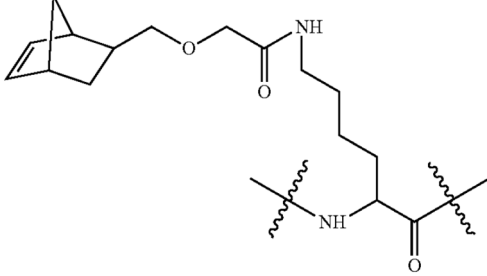
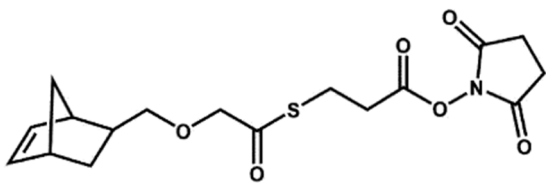


IV



179. Thus, by disclosing the use of Compound IV to modify trastuzumab with an azide group at lysine residues, the '959 Publication discloses that the modified lysine residue has one of the three structures recited in Claim 11.

180. In addition, the '959 Publication discloses precursors of the second and third structures recited in Claim 11 in Formulas 2-1, 2-2, and 2-3. These formulae, and Compound IV, are shown next to the corresponding structures of Claim 11 in the table below. EX1005, 5, Figure 22; see also 171-172.

Claim 11	'959 Publication
	 IV
 , or	[formula 2-2]  [formula 2-3] 
	[formula 2-1] 

181. Synthesis of the third structure of claim 11 is shown in Experimental Example 1 of the '959 publication (EX1005, 165-174), and the modified antibody disclosed in Figure 43 has a lysine with the middle structure recited in claim 11.

182. For these additional reasons, the '959 Publication discloses the modified lysine residue having a structure as recited in Claim 11.

12. Claim 12 of the '675 Patent

183. Claim 12 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

184. The '959 Publication discloses “the bio-orthogonal click chemistry group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

185. In particular, as previously discussed in connection with Claim 1, the '959 Publication discloses trastuzumab modified at lysine residues 246 and/or 248 with an azide group as the bio-orthogonal click chemistry functional group.

186. As previously discussed in connection with Claim 2 and Claim 3, the '959 Publication discloses the modified lysine residue structure recited in Claim 2, where D1 is a covalent bond, unsubstituted C₁₋₄ alkylene, unsubstituted C₂-

₄ alkenylene, unsubstituted C₂₋₄ alkynylene or unsubstituted C₃₋₈ cycloalkylene, as required by Claim 3.

187. As previously discussed in connection with Claim 9, an azide group is a group capable of participating in a Huisgen 1,3-dipolar cycloaddition.

188. The '959 Publication thus discloses the modified antibody of Claim 12.

13. Claim 13 of the '675 Patent

189. Claim 13 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.”

190. The '959 Publication discloses “the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.”

191. As previously discussed, the '959 Publication discloses the modified antibody of Claim 3, where the modified antibody is trastuzumab modified at lysine residues 246 and/or 248 with an azide group as the click chemistry functional group. The '959 Publication thus discloses the modified antibody of Claim 13.

192. As also discussed in connection with Claim 10, the '959 Publication also discloses trastuzumab modified at lysine residues 246 and/or 248 with

norbornene as the click chemistry functional group. For this additional reason, the '959 Publication discloses the modified antibody of Claim 13.

B. Claims 1-13 of the '675 Patent Are Unpatentable Over PepTalk Poster (EX1006)

193. 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.

1. Independent Claim 1 of the '675 Patent

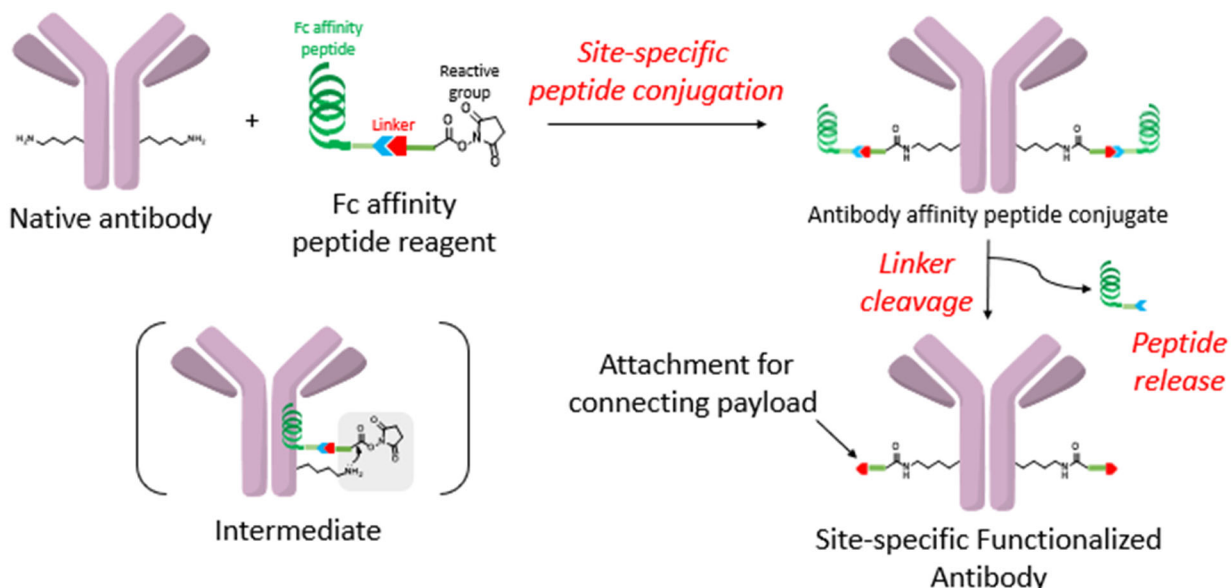
a. A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group,

194. PepTalk Poster discloses the limitation “a modified antibody or its fragment comprising bio-orthogonal click chemistry functional group.”

195. PepTalk Poster discloses a method for modifying antibodies to include a bio-orthogonal functional group that can be used to attach a payload, such as an anti-cancer drug.

196. PepTalk Poster depicts a generalized process for modifying an antibody to include a bio-orthogonal functional group in the following figure:

1. Concept of AJICAP

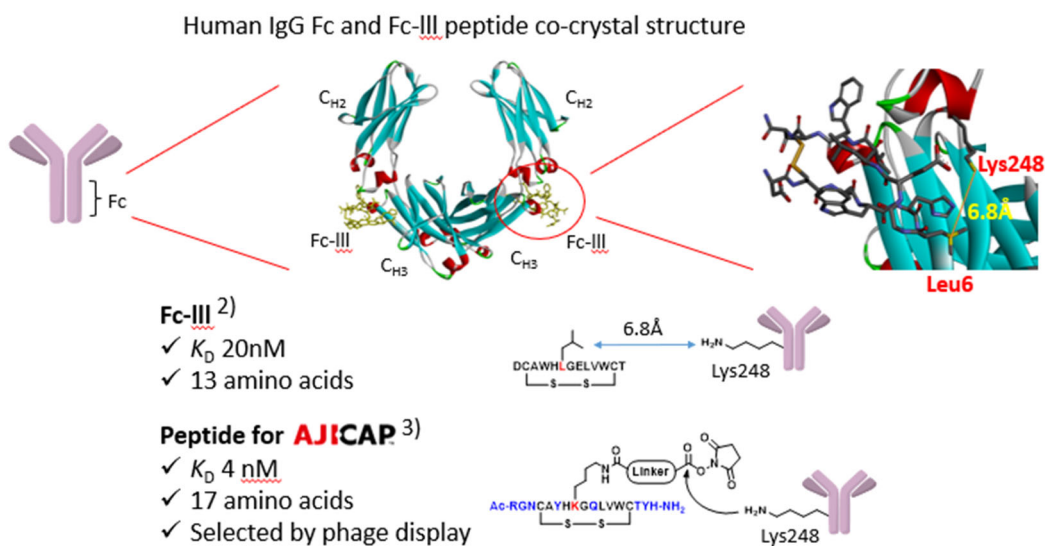


EX1006.

197. This figure shows an antibody being modified through steps of “site-specific peptide conjugation” and “linked cleavage” to include an “attachment for connecting payload.” The “attachment for connecting payload” includes a bio-orthogonal click chemistry functional group.

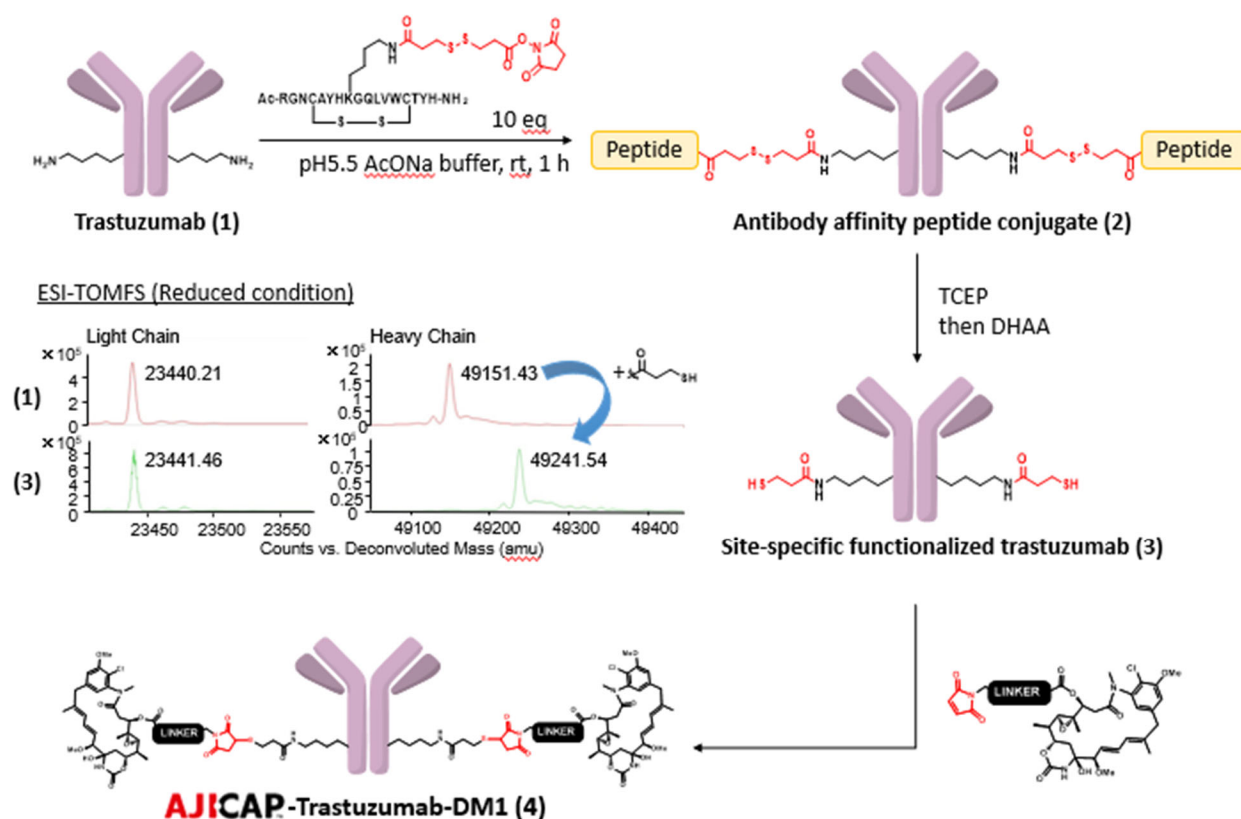
198. PepTalk Poster also depicts in Panel 2 (reproduced below) that the site-specific modification shown in Panel 1, above, and Panel 3, below, occurs on the lysine residue at position 248.

2. Determine Target Lysine Residue



199. PepTalk Poster depicts, in the following figure, an example of this process in which the antibody trastuzumab is modified to include a bio-orthogonal click chemistry functional group.

3. Synthesis of Site-Specific ADC by AJICAP[®]



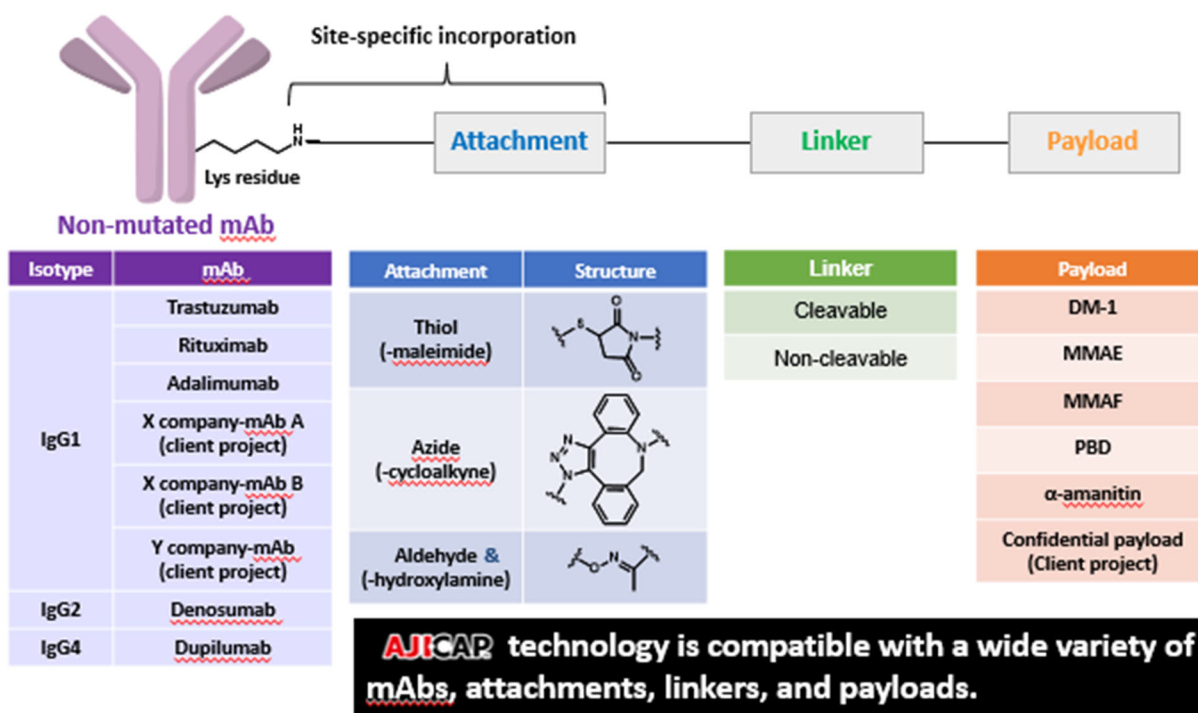
200. In this figure, the antibody trastuzumab is first modified to include a peptide conjugate that contains a precursor to a bio-orthogonal functional group. Through a subsequent reaction, the peptide conjugate is cleaved and removed, leaving, in this example, a thiol group bound to the amino acid residue of the antibody.

201. Persons having ordinary skill in the art understood that the thiol group shown in Step (3) is an example of a bio-orthogonal click chemistry functional group. PepTalk Poster also discusses, in its Introduction section, that existing technologies for performing site-specific conjugation aim to incorporate a

“biorthogonal functional group” by methods such as genetic modification of the antibody.

202. PepTalk Poster also discloses, in the following figure, that the AJICAP™ technology is compatible with a variety of antibodies, click-chemistry functional groups, and payloads.

1. Capability of **AJICAP**



203. In the “Attachment” column shown in this figure, PepTalk Poster discloses three examples of click-chemistry reactions that can be used with AJICAP™ technology: thiol (-maleimide), azide (-cycloalkyne), and aldehyde (-hydroxylamine). A POSA would have understood that each of these three examples represents a pair of click-chemistry functional groups that participate in a click-

chemistry reaction. A POSA would also have understood that click-chemistry reactions are bio-orthogonal reactions, such that the functional groups that participate in a click-chemistry reaction are bio-orthogonal click-chemistry functional groups.

204. Finally, a POSA would also have understood that the orientation of the click chemistry functional groups is reversible. In other words, to the extent that PepTalk Poster's teaching of the attachment "Thiol-maleimide" is interpreted as: [antibody]-[thiol] conjugated to [maleimide]-[drug]; a POSA would understand that the arrangement [antibody]-[maleimide] conjugated to [thiol]-[drug] would be expected to be functionally equivalent.

205. PepTalk Poster thus discloses a modified antibody comprising a bio-orthogonal click chemistry functional group.

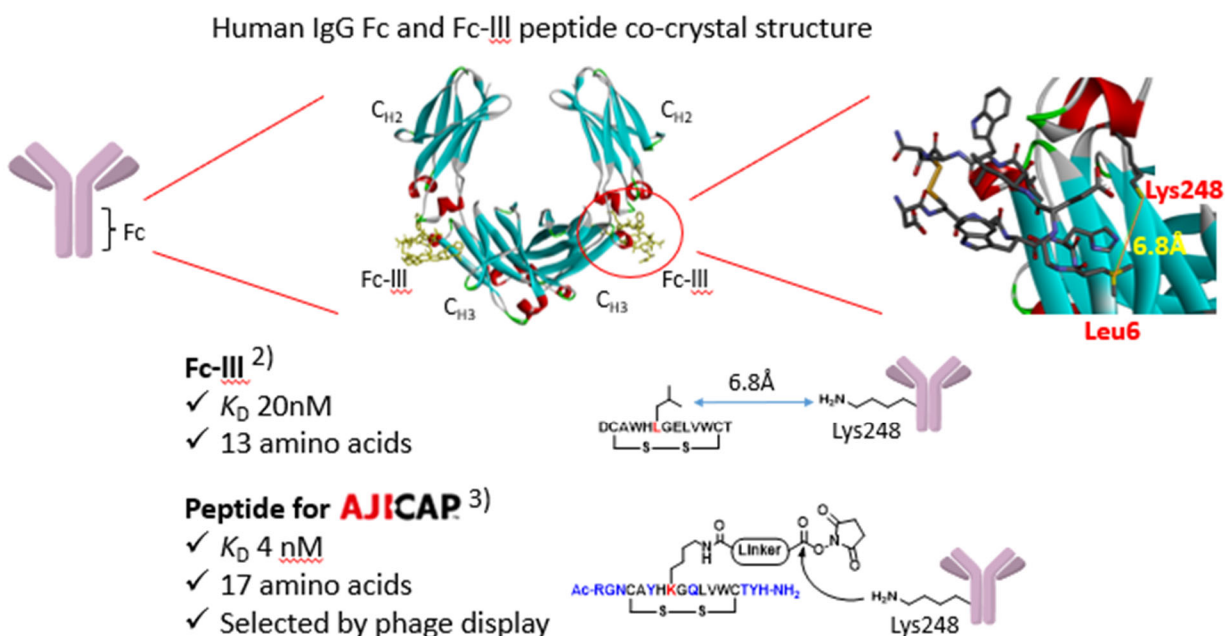
b. wherein the modified antibody comprises one or more modified heavy chain,

206. PepTalk Poster discloses the limitation "the modified antibody comprises one or more modified heavy chain."

207. It was well known in the art that antibodies, including trastuzumab and the other antibodies referenced in PepTalk Poster, have two heavy chains and two light chains.

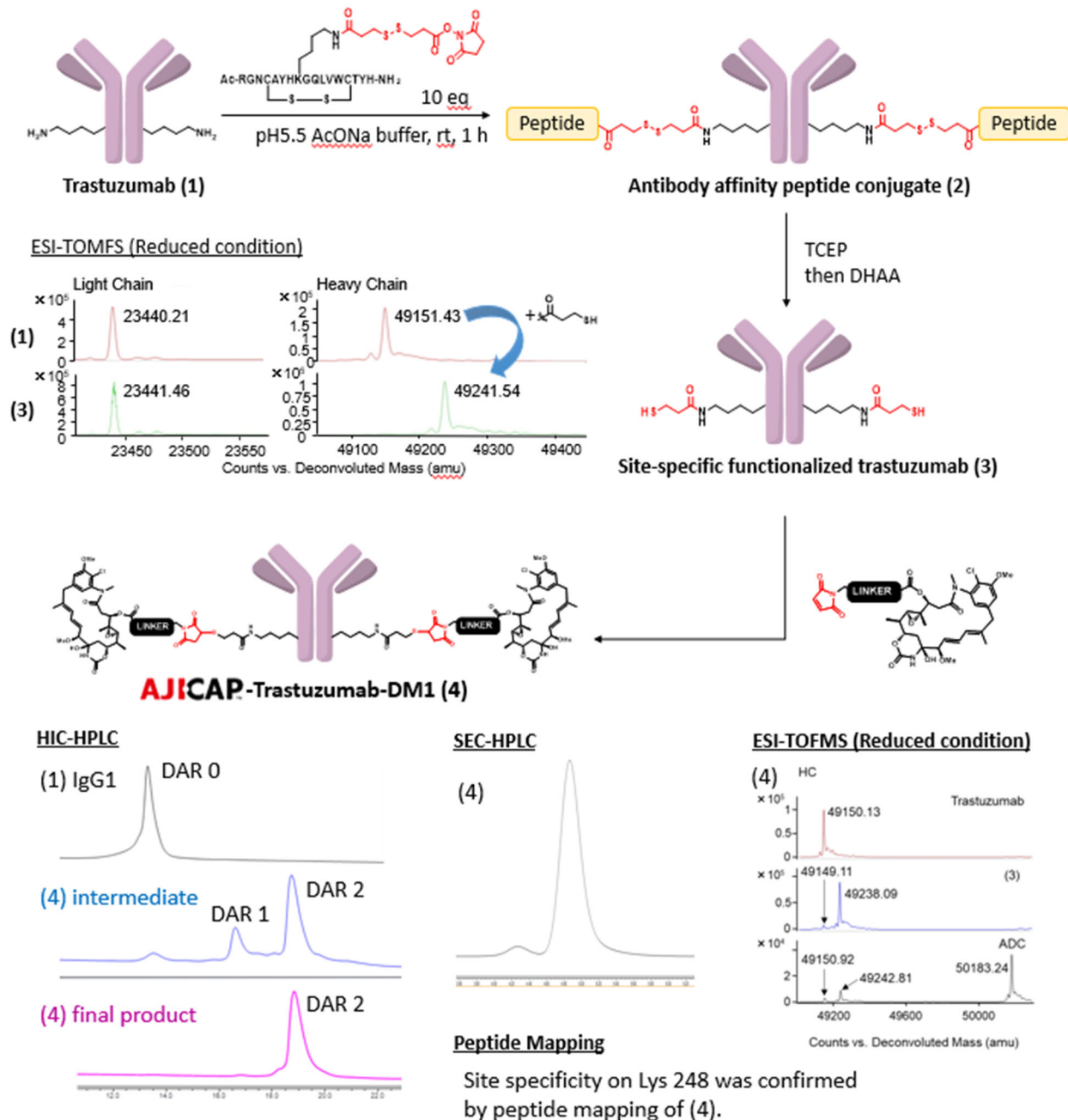
208. PepTalk Poster discloses modifying antibodies, including trastuzumab, at lysine residue 248 of the antibody's Fc domains. For example, in the figure below, PepTalk Poster discloses modifying lysine 248.

2. Determine Target Lysine Residue



209. Furthermore, in the figure below, PepTalk Poster discloses modifying lysine 248 in the Fc domains of both heavy chains.

3. Synthesis of Site-Specific ADC by **AJICAP**



210. The POSA understood that the Fc domains reside in the heavy chains of the antibody.

211. Thus, by disclosing antibodies modified to include bio-orthogonal click chemistry functional groups at lysine residue 248, PepTalk Poster discloses that the modified heavy chain comprises one or more modified heavy chains.

c. 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

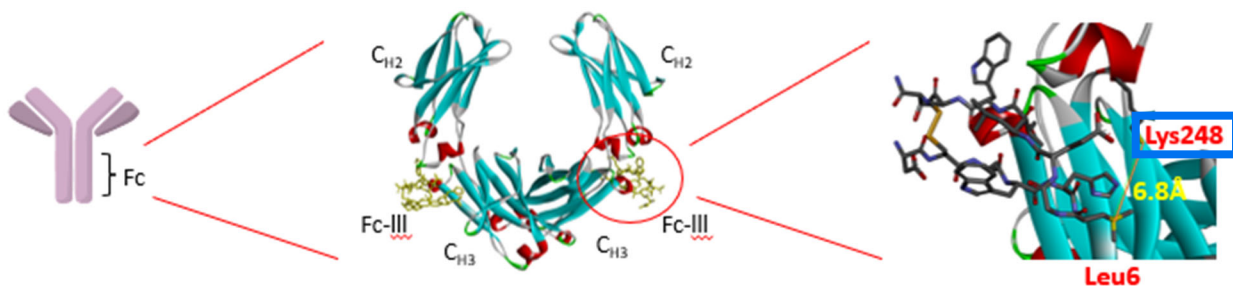
212. PepTalk Poster discloses the limitation “each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system.”

213. As previously discussed, the PepTalk Poster discloses modifying an antibody to include a bio-orthogonal click chemistry functional group at lysine residue 248 of the Fc domains of the antibody’s heavy chains. PepTalk Poster discloses this generally and by reference to a specific example of trastuzumab.

214. PepTalk Poster’s disclosures of modifying lysine residues 248 of the heavy chain are shown in the following figures.

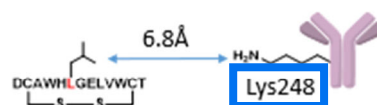
2. Determine Target Lysine Residue

Human IgG Fc and Fc-III peptide co-crystal structure



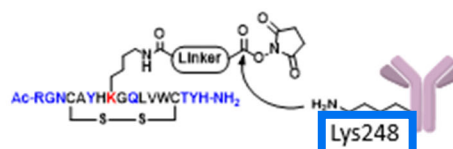
Fc-III²⁾

- ✓ K_D 20nM
- ✓ 13 amino acids

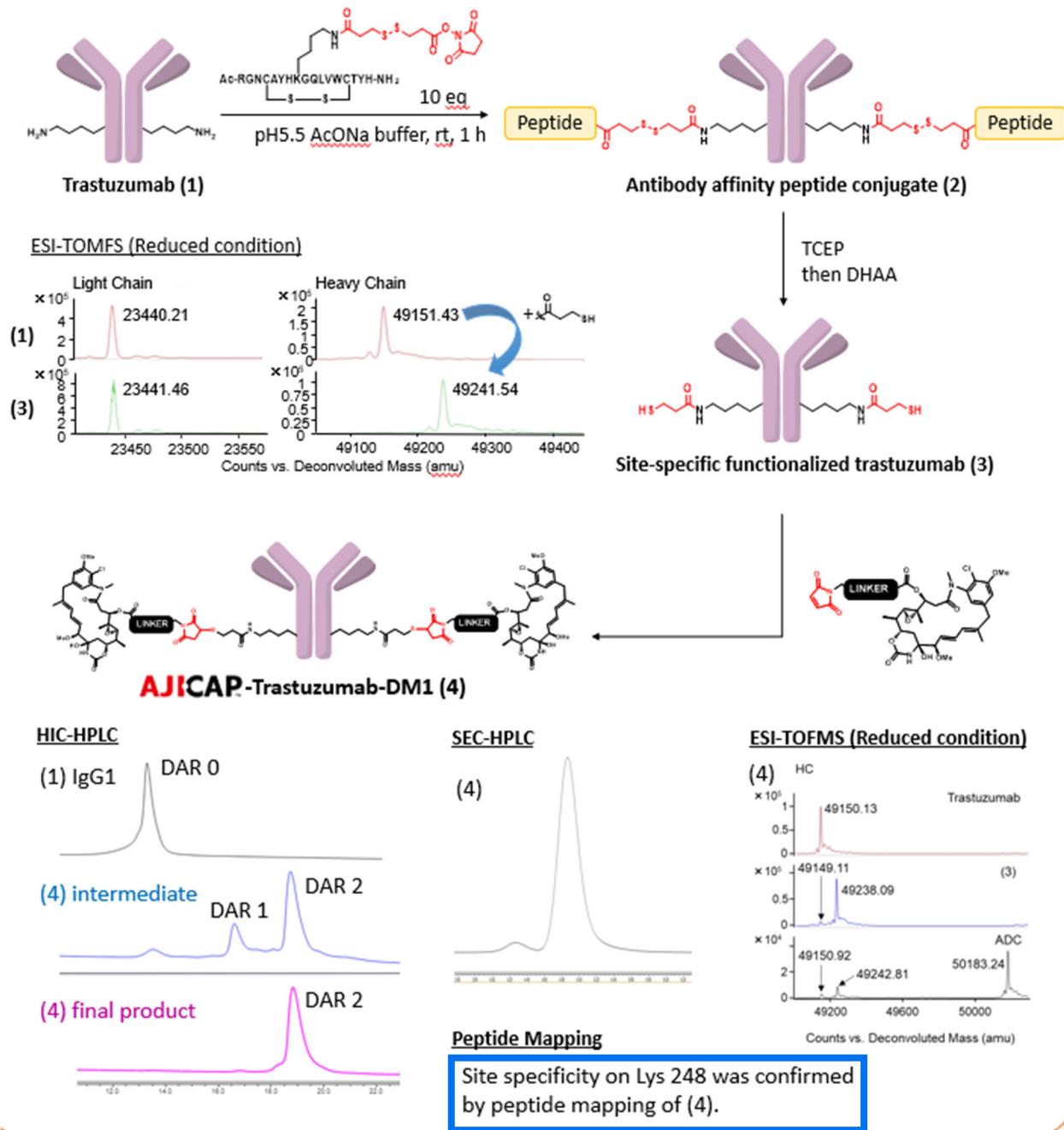


Peptide for AJICAP³⁾

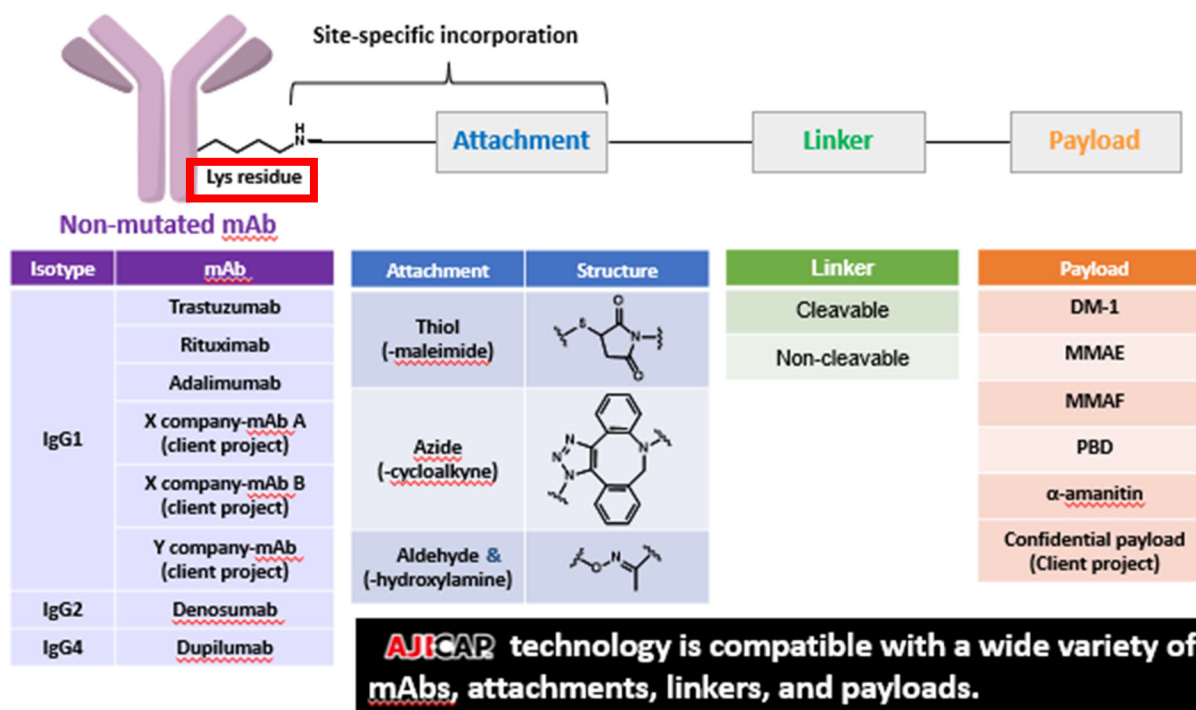
- ✓ K_D 4 nM
- ✓ 17 amino acids
- ✓ Selected by phage display



3. Synthesis of Site-Specific ADC by AJICAP



1. Capability of AJICAP™



215. The POSA understood that the position 248 discussed in PepTalk Poster refers to the EU numbering system for antibody amino acid sequences.

216. PepTalk Poster thus discloses that each of the modified heavy chains comprise a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system.

d. wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end, and

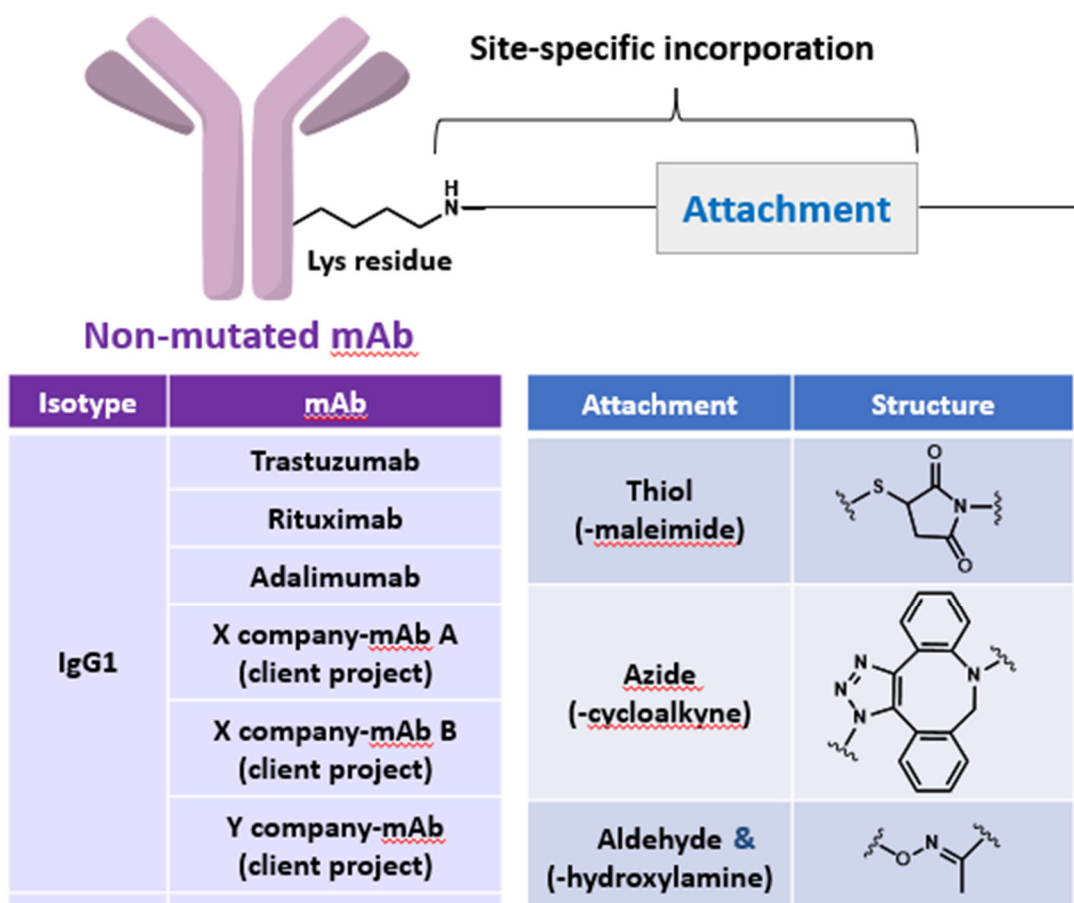
217. PepTalk Poster discloses the limitation “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

218. As previously discussed, the PepTalk Poster discloses modifying an antibody with a bio-orthogonal click chemistry functional group at lysine residue position 248. PepTalk Poster discloses making such modifications using thiol, azide, and aldehyde functional groups as examples. PepTalk Poster also discloses that these modifications are made at the terminal end of the modified lysine residue. For example, the figure below depicts lysine residue 248 modified with a thiol group at the lysine's terminal end, represented by "NH."



Site-specific functionalized trastuzumab (3)

219. Similarly, PepTalk Poster discloses modifying antibodies at the terminal end of lysine residue 248 with any of a thiol group, azide group, or aldehyde group in the following figure.

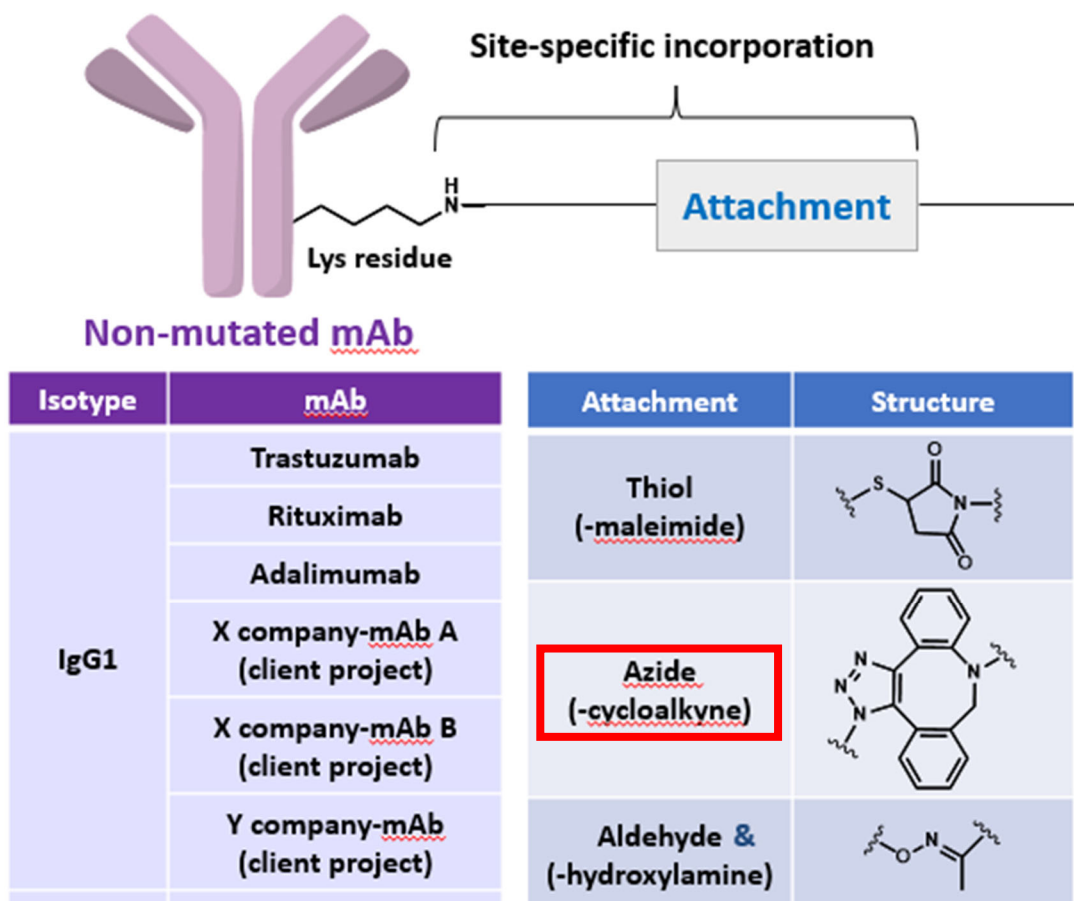


220. Accordingly, PepTalk Poster discloses that “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

- e. wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.*

221. PepTalk Poster discloses the limitation “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy[l] group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

222. As previously discussed, PepTalk Poster discloses modifying an antibody at lysine residue 248 to include an azide group as the click chemistry functional group. PepTalk Poster discloses using an azide group as the functional group in the following figure.



223. PepTalk Poster further discloses the use of an azide group as the bio-orthogonal click chemistry functional group in the following figures.

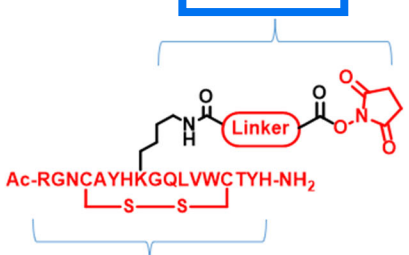
1. Features of **AJICAP**⁴⁾

Ajinomoto Co. has developed an innovative direct chemical site-selective conjugation method used towards intact native antibodies.
Our novel technology provides significant advantages for next generation ADCs:

1. **Straightforward CMC**
 - **Direct modification of intact antibody**
 - **No genetic modification required**
2. **Enhancement of Therapeutic Window compared to stochastic ADCs**
 - **Site specific, controlled DAR 2**
3. **Wide drug-linker compatibility: reactive group compatibility includes thiol, alkyne, azide, etc**
4. **High productivity, short conjugation reaction times, ease to manufacture**

2. A glance at second generation **AJICAP**™ technology

Flexible introduction of thiol, azide group



Ac-RGNCA YHKGQLVWCTYH-NH₂

Using other peptides to modify other sites in Fc region.

- ✓ Shorter reaction process
- ✓ No red/ox chemistry
- ✓ Lower aggregation propensity
- ✓ Introduction of azide group to mAb
- ✓ Expansion of conjugation sites (LysXXX, LysYYY, etc.) through peptide SAR
- ✓ Stability enhancement of peptide reagent

224. As was well-understood by persons skilled in the art by 2019 and long before, an azide group is none of a hydroxyl group, carboxyl group, thiol group, amino group, or aldehyde group.

225. Thus, by disclosing antibodies with lysine residue 248 modified with an azide group as the bio-orthogonal click chemistry functional group, PepTalk Poster discloses that “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

226. PepTalk Poster thus discloses the modified antibody of Claim 1.

2. Claim 4 of the '675 Patent

227. Claim 4 recites: “The modified antibody of claim 1, wherein the modified heavy chain comprises an amino acid sequence having a structure of formula 8-2:

G-P—S-V-F-L-F—P-P-K-P—(K')-D-T-L-M-I (SEQ ID NO: 21),
[formula 8-2]

wherein K' is the modified lysine residue.”

228. PepTalk Poster discloses the modified heavy chain comprising an amino acid sequence as recited in Claim 4.

229. In particular, as previously discussed, PepTalk Poster discloses modifying trastuzumab, a human IgG1, at lysine residue 248 to include a bio-orthogonal click chemistry functional group. EX1006. The modified lysine residue referred to as K' in Claim 4 is lysine residue 248. The lysine residue at position 248, by definition, resides in the amino acid sequence recited in Claim 4.

230. Indeed, the '675 Patent itself shows this amino acid sequence, with a lysine residue (K) at position 248 (EX1001, 14:35-37, Figure 1).

amino acid sequence :

G—P—S—V—F—L—F—P—P—K—P—K—D—T—L—M—I

**EU numbering
for heavy chain :**

237 239 241 243 245 247 249 251 253
238 240 242 244 246 248 250 252

231. This amino acid sequence was not invented in the '675 Patent. Rather, it is an amino acid sequence that occurs naturally in the Fc domain of heavy chains in IgG1 antibodies, such as trastuzumab, including having a lysine residue at the position designated 248 under EU numbering conventions. Specifically, the sequence is part of a human IgG1, 2, or 4 CH2 domain with a modification (i.e., K') at position 248.

232. Thus, by disclosing the modified antibody of Claim 1, where the modified lysine residue is lysine residue 248 in the Fc domain of the heavy chain, PepTalk Poster inherently discloses that the modified heavy chain has the amino acid sequence recited in Claim 4. PepTalk Poster thus discloses the modified antibody of Claim 4.

3. Claim 8 of the '675 Patent

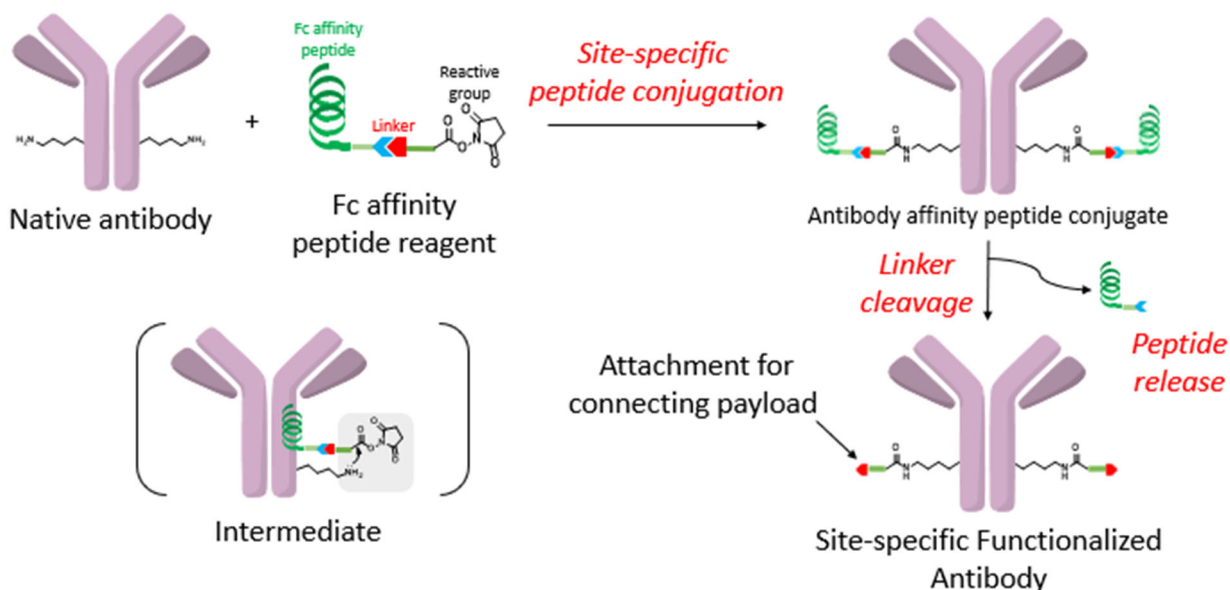
233. Claim 8 recites: “The modified antibody of claim 1, wherein the modified antibody comprises two modified heavy chains.”

234. PepTalk Poster discloses “the modified antibody comprises two modified heavy chains.”

235. As previously discussed, and as was well-known in the art, antibodies, such as trastuzumab, include two heavy chains. As also previously discussed in connection with Claim 1, PepTalk Poster discloses an antibody modified to include an azide group at lysine residue 248 of the Fc domains of the heavy chains.

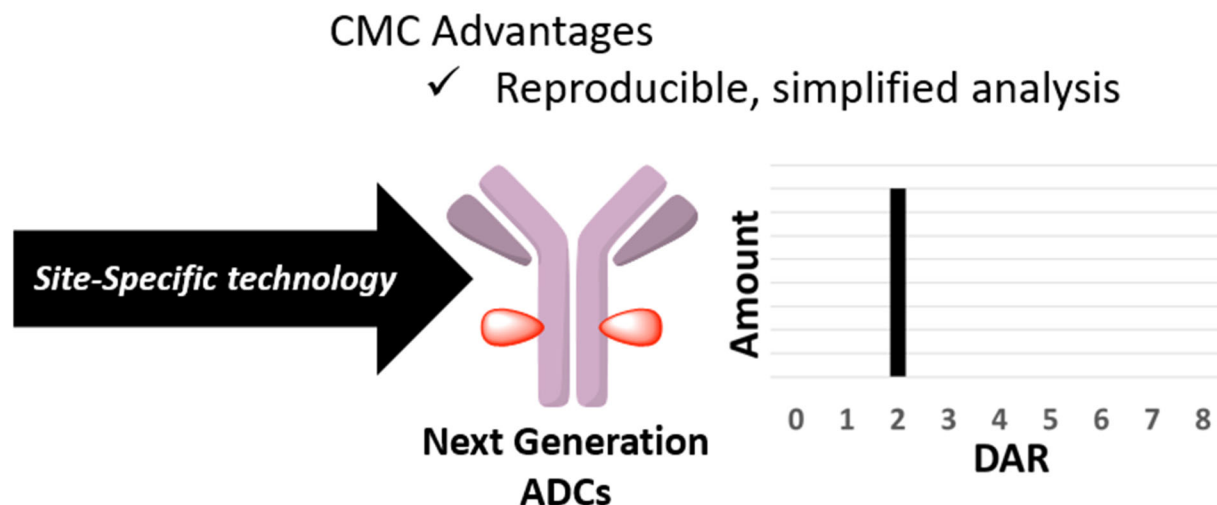
236. PepTalk Poster further discloses that its modified antibodies are modified at lysine residue 248 in the Fc domains of both heavy chains. This is shown, for example, in the figure below.

1. Concept of AJICAP



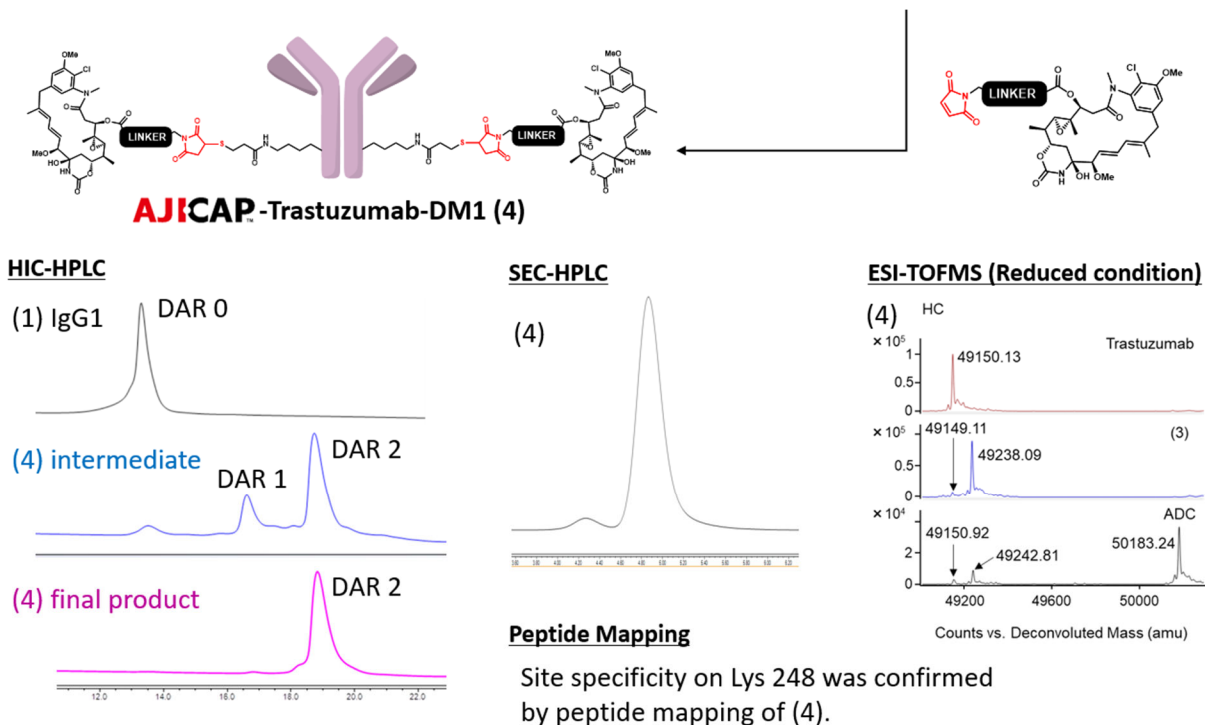
237. As seen in this figure, the initial “site-specific peptide conjugation” occurs in both heavy chains, and, following cleavage of the “linked,” the antibody has a lysine residue 248 modified with the “attachment” (i.e., click-chemistry functional group) on both heavy chains.

238. PepTalk Poster further discloses modifying two heavy chains in teaching the advantages of its approach to site-specification conjugation. Namely, PepTalk Poster teaches that its approach produces a consistent drug-antibody ratio (“DAR”) of 2, where the value 2 represents two drug molecules bound to a single antibody. PepTalk Poster illustrates the DAR value of 2 in the following figure, which show that the two drug molecules are bound at the two heavy chains via the modified lysine residue 248.



239. PepTalk Poster further discloses that Ajinomoto’s AJICAP™ technology allows for “Site specific, controlled DAR 2.”

240. PepTalk Poster further discloses that the modified antibodies have two modified heavy chains, providing for a DAR value of 2, by way of its example using a thiol group as the bio-orthogonal click chemistry functional group, as shown in the figure below.



241. Thus, by disclosing a modified antibody with lysine residues 248 modified to include an azide group, PepTalk Poster discloses the modified antibody of Claim 1 where the modified antibody includes two modified heavy chains.

4. Claim 9 of the '675 Patent

242. Claim 9 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a

click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

243. PepTalk Poster discloses “the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

244. In particular, as previously discussed in connection with Claim 1, the '959 Publication discloses a modified antibody with lysine residues 248 modified with an azide group. As also previously discussed, an azide group is a bio-orthogonal click chemistry functional group. Persons skilled in the art understood that an azide group is capable of participating in a click-chemistry reaction of Huisgen 1,3-dipolar cycloaddition. EX1036.

245. This understanding is also evidenced by the '959 Publication, which expressly discloses the use of azide groups in Huisgen 1,3-dipolar cycloaddition. EX1005, 39.

246. Thus, by disclosing a modified antibody with lysine residues 248 modified with an azide group, PepTalk Poster discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is one capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.

5. Claim 10 of the '675 Patent

247. Claim 10 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

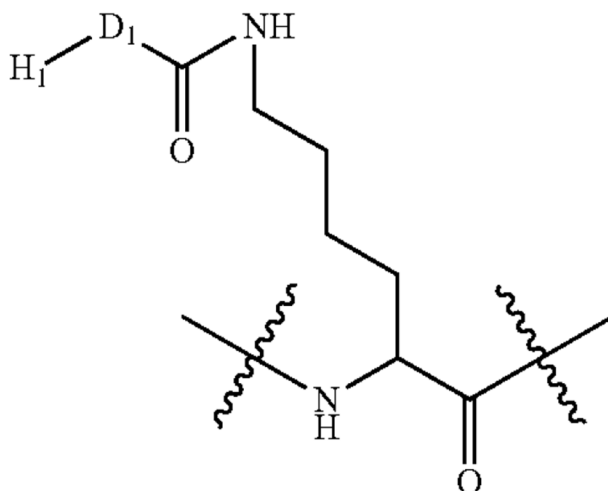
248. PepTalk Poster discloses “the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

249. In particular, as previously discussed in connection with Claim 1, the PepTalk Poster discloses a modified antibody with lysine residues 248 modified with an azide group.

250. PepTalk Poster thus discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group. It is also worth noting that a POSA would equate these four click chemistry functional groups. In other words, it is my experience and my understanding of the art that if an azide “works,” then a POSA would immediately assume that a tetrazine, DBCO, and norbornene would also work. Indeed, if any one of these (or other well-known bio-orthogonal click chemistry groups) works, then a POSA would reasonably expect that other bio-orthogonal click chemistry groups could be substitute in its place and function in essentially the same way.

6. Claim 2 of the '675 Patent

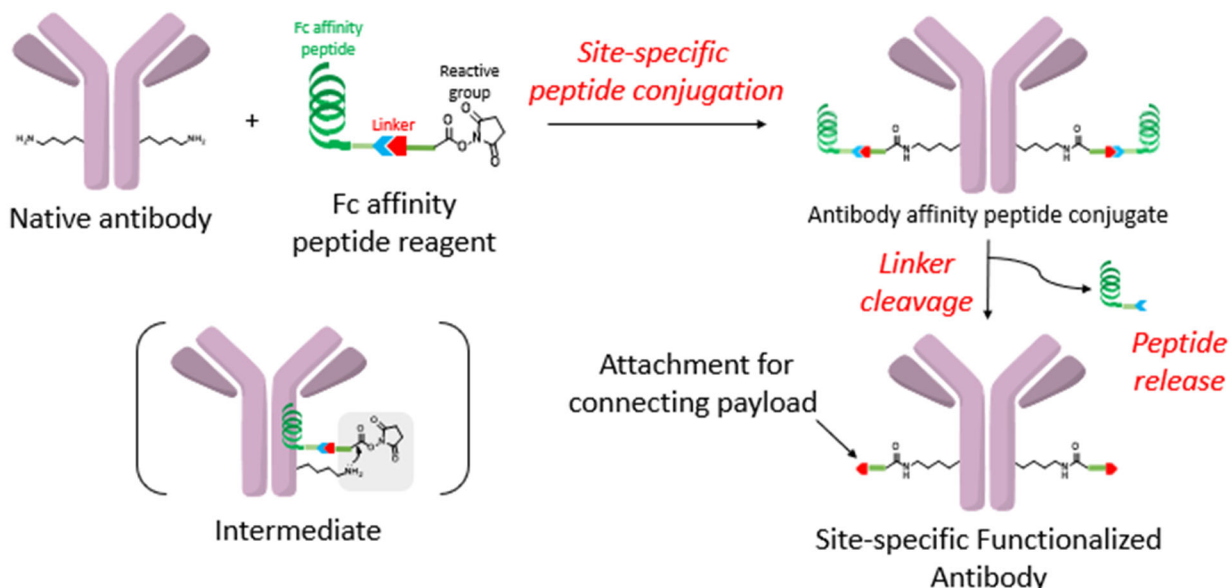
251. Claim 2 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:



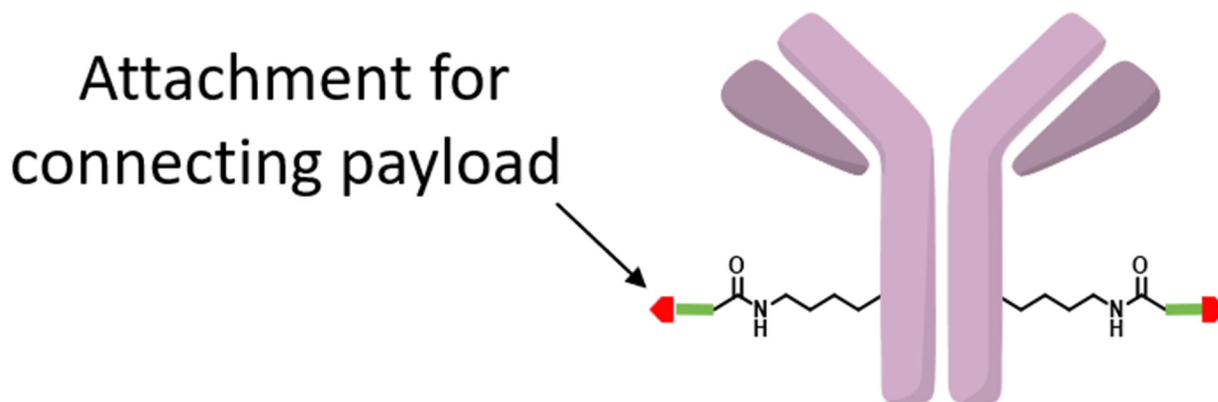
wherein H_1 is a group having the bio-orthogonal click chemistry functional group, and wherein D_1 is bond, or is selected from C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene and C_{3-8} cycloalkylene.”

252. As previously discussed, PepTalk Poster discloses an antibody modified to include an azide group at lysine residue 248. In particular, PepTalk Poster discloses using an “Fc affinity peptide reagent” containing a “linker” to modify lysine 248 to include an “attachment” to which drug molecules or other payloads can connect. This is depicted in the following figure.

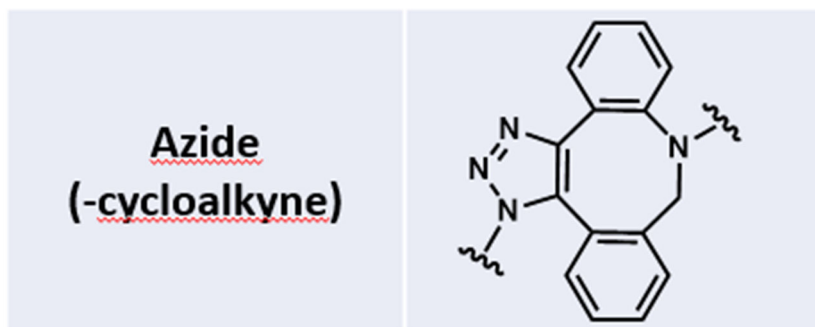
1. Concept of AJICAP



The “linker” represented in this figure is a pair of click-chemistry functional groups in their bound state. This figure depicts this linker being cleaved, leaving one of the click chemistry functional groups bound to the lysine residue, as seen more clearly in the figure below.

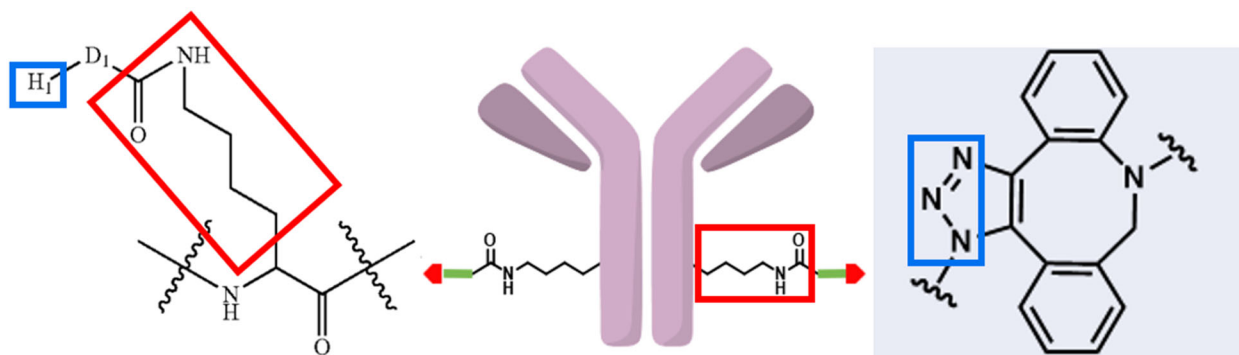


253. PepTalk Poster discloses that this attachment may be an azide group, shown with its click-chemistry partner, a cycloalkyne, in the figure below.



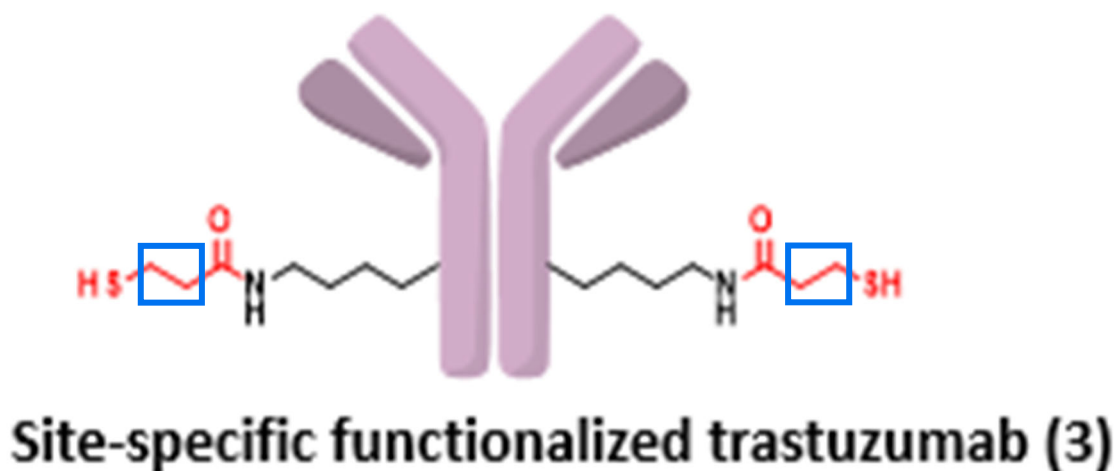
254. An antibody modified with an azide group in the manner taught by PepTalk Poster can have the structure recited in Claim 2.

255. In particular, as shown below, PepTalk Poster teaches that the antibody as modified to include the attachment includes the structure highlighted by the red rectangle below, i.e., the structure other than D₁ and H₁. By disclosing an azide group as a suitable bio-orthogonal click chemistry functional group, PepTalk Poster discloses an azide group as H₁ in the structure of Claim 2, as indicated by the blue rectangle.



256. The POSA would understand that, when an azide group is used as H₁, the D₁ component would most likely be an alkyl or cycloalkyl.

257. This understanding is evidenced by PepTalk Poster's example that includes a thiol group as the click-chemistry functional group. As shown in the figure below, PepTalk Poster discloses an example of trastuzumab where lysine residue 248 is modified to have the structure recited in Claim 2, where the click-chemistry functional group, H₁, is a thiol group (-SH), and D₁ is an unsubstituted C₂ alkylene, indicated by the blue squares below.

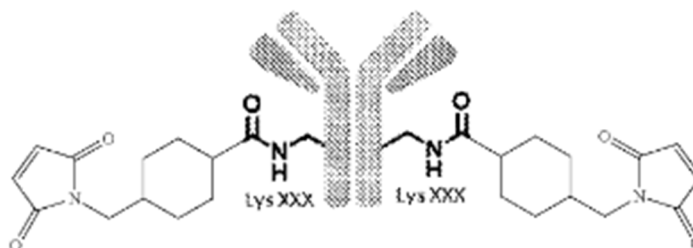


A POSA would need only to substitute the thiol group for an azide, which is also disclosed in PepTalk Poster, to arrive at the structure of Claim 2.

258. Thus, PepTalk Poster discloses the modified antibody of Claim 1 and all of the components of the modified lysine has the structure recited in Claim 2.

259. Additionally, Matsuda (EX1010) discloses Example 3-4 of Matsuda (reproduced below) includes an unsubstituted C₆ cycloalkylene, consistent with the requirement of D₁ for claim 2. A POSA would understand that the H1 of Matsuda's

Example 3-4 could be readily substituted with, for example, an azide, as disclosed in PepTalk Poster, and the skilled person would expect the modified lysine to function effectively the same.



Example 3-4 of Matsuda (EX1011, p. 90)

260. Matsuda also discloses Example 5-2-1, which has an azide in the H₁ position and an unsubstituted C₅ alkylene (*id.*, p. 92), which is only one more carbon than claim 2 allows. A POSA would understand that this C₅ alkylene could be slightly longer or shorter and still function effectively the same. Thus, all of the elements of claim 2 are disclosed in PepTalk Poster and Matsuda, and a POSA could readily combine these disclosures to predictably arrive at claim 2 with a reasonable expectation of success.

7. Claim 3 of the '675 Patent

261. Claim 3 recites: “The modified antibody of claim 2, wherein D₁ is bond, or is selected from unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene and unsubstituted C₃₋₈ cycloalkylene.”

262. Claim 3 thus limits Claim 2 by requiring that the options for D₁ recited in Claim 2 are “unsubstituted.” PepTalk Poster discloses this limitation.

263. The term “unsubstituted” in this context means that each carbon atom in the alkylene, alkenylene, alkynylene, or cycloalkylene is bound to the maximum number of hydrogen atoms possible given the carbon atom’s bonds to adjacent carbon atoms. This is in contrast to a “substituted” alkylene, alkenylene, alkynylene, or cycloalkylene, in which one of the carbon atoms has some other chemical species substituted for a hydrogen atom.

264. As previously discussed, PepTalk Poster discloses the modified antibody of Claim 1 and it discloses all of the components of the modified lysine residue has the structure recited in Claim 2, including the D₁ of an unsubstituted C₁₋₄ alkylene. A POSA would understand that, where D₁ is a C₁₋₄ alkylene, C₂₋₄ alkenylene, C₂₋₄ alkynylene or C₃₋₈ cycloalkylene, these molecules could be unsubstituted, with each carbon atom having the maximum number of hydrogen atoms. Indeed, the D₁ component would most likely be an alkyl or cycloalkyl.

265. Thus, by disclosing the modified antibody of Claim 1 having the structure recited in Claim 2, including the possible D₁ components, PepTalk Poster also discloses the structure of Claim 2 where D₁ is a bond, or an unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene or unsubstituted C₃₋₈ cycloalkylene, as required by Claim 3. PepTalk Poster thus

discloses the additional limitation of Claim 3. Specifically, A POSA would need only to substitute the thiol group in the PepTalk Poster example discussed under Claim 2 with an azide, as also disclosed in PepTalk Poster, to arrive at the structure of Claim 3.

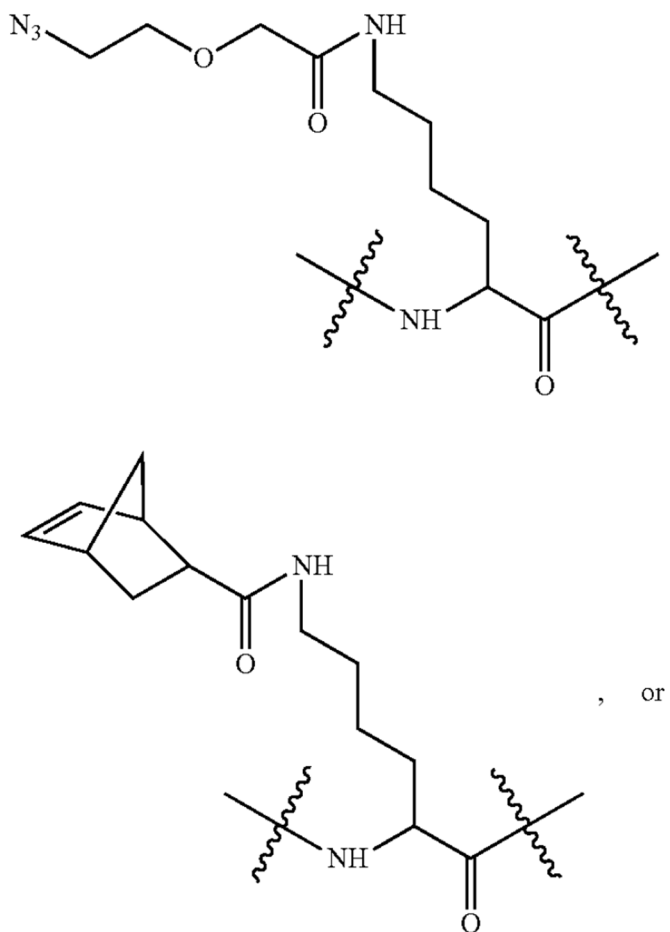
8. Claims 5-7 and 11 of the '675 Patent

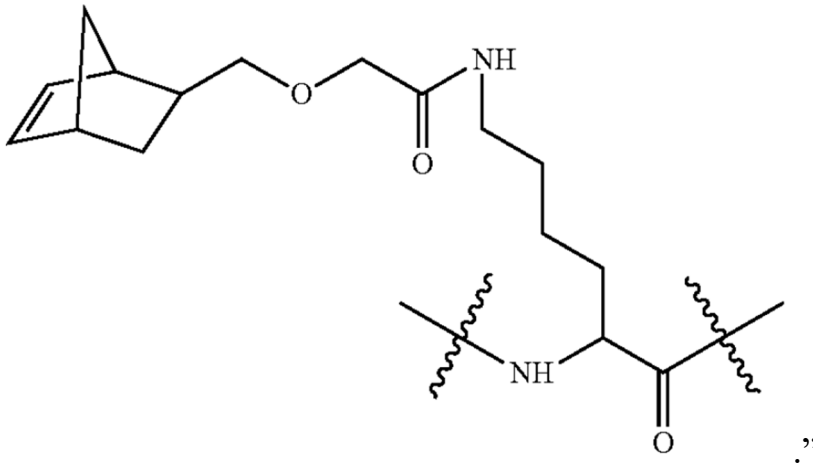
266. Claim 5 recites: “The modified antibody of claim 2, wherein D₁ comprises one or more heteroatoms.”

267. As previously discussed, PepTalk Poster discloses the modified antibody of Claim 2, where D₁ may include any one selected from a covalent bond, a C₁₋₄ alkylene (i.e., the modified trastuzumab shown in Panel 3 of the Methods section), and the D₁ component would most likely be an alkyl or cycloalkyl when using an azide as the bio-orthogonal click chemistry group.

268. A POSA would understand that any of the recited alkylene, alkenylene, alkynylene, and cycloalkylene recited in claim 2 of the '674 Patent could be unsubstituted (i.e., having the maximum number of hydrogen atoms allowed given the carbon atom's bonds with adjacent carbon atoms) or that any of these hydrocarbons could be substituted (i.e., another chemical species in place of a hydrogen atom). Heteroatoms would be understood to be among the possible substituents. Moreover, structures including one or more heteroatoms are disclosed in Yamada, as explained below.

269. Claim 6 recites: “The modified antibody of claim 2, wherein D₁ is —[CH₂]_a—O—[CH₂]_b—, wherein each of a and b is independently selected from 0 to 4, and each of a and b is integer, and wherein sum of a and b is 0 or more and 4 or less.” Claim 7 recites: “The modified antibody of claim 2, wherein D₁ is —CH₂CH₂OCH₂— or —CH₂OCH₂—.” Claim 11 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:





270. I am discussing claims 5-7 and 11 together because the first and third structures recited in claim 11 include all of the limitations of claims 5-7. Thus, by showing that the first and third structures recited in claim 11 were previously disclosed, it would be apparent that the broader limitations of claims 5-7 had also been previously disclosed.

271. PepTalk Poster discloses a modified antibody with lysine residues 248 modified with an azide group, and Yamada likewise discloses antibodies modified at lysine 248 (EX1009, [0222], [1037], [1109], [1114], etc.) with an azide (*id.*, [0151], [0153], [1037], Figure 18) or a norbornene (*id.*, [0151], [0153]).

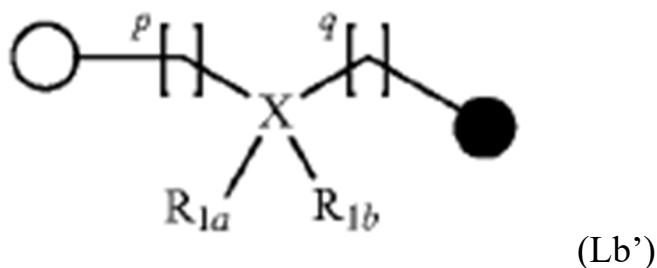
272. Yamada discloses an antibody regioselectively modified with a bio-orthogonal functional group represented by (Formula (IV)):

L1-B-R'-T (IV)

in which “L1 is (i’) a monovalent group comprising a bioorthogonal functional group or (ii’) a monovalent group comprising no bioorthogonal functional group; B is (a)

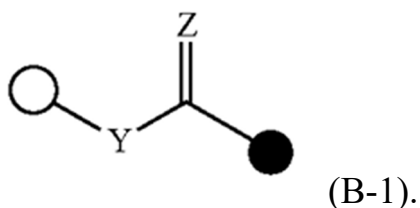
a divalent group comprising a bioorthogonal functional group or (b) a divalent group comprising no bioorthogonal functional group; R' is a portion formed by a reaction between a soluble protein and a reactive group; and T is a soluble protein.” EX1009, [0584]-[0588]. It is my understanding that in the context of Yamada, the term “monovalent group” refers to a group that has a single covalent bond to another group, and the term “divalent group” means a group that has two covalent bonds connecting it to two other groups.

273. Paragraphs [0616]-[0624] further define L1 with specific groups. In particular, these paragraphs explain that L1 can either be C1, can be a bio-orthogonal functional group (e.g., azide, norbornene, etc.; *see* EX1009, [0626]-[0627]) or it can have a structure of C1-Lb, wherein LB is:

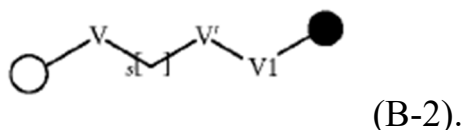


in which the White Circle indicates a bond to C1, which (as noted above) can be a bio-orthogonal click chemistry group (e.g., azide, norbornene, etc.); *p* and *q* are integers from 0-10; X can be a carbon (C) a nitrogen (N), or a single bond; and R_{1a} and R_{1b} can be present as a substituent or absent. The black circle indicates the bond to B

274. Paragraphs [0631]-[0639] further define B with specific groups. In particular, these paragraphs explain that B is defined as having a structure of:



Within (B-1), the White Circle is the connection to L1; the Black Circle is the connection to R'; Z can be "an oxygen atom, a sulfur atom, or a hydrogen atom wherein when Z is a hydrogen atom, -C(=Z)- indicates -CH₂-"; and Y can be -NH-, -O-, -CH₂-, or B-2:



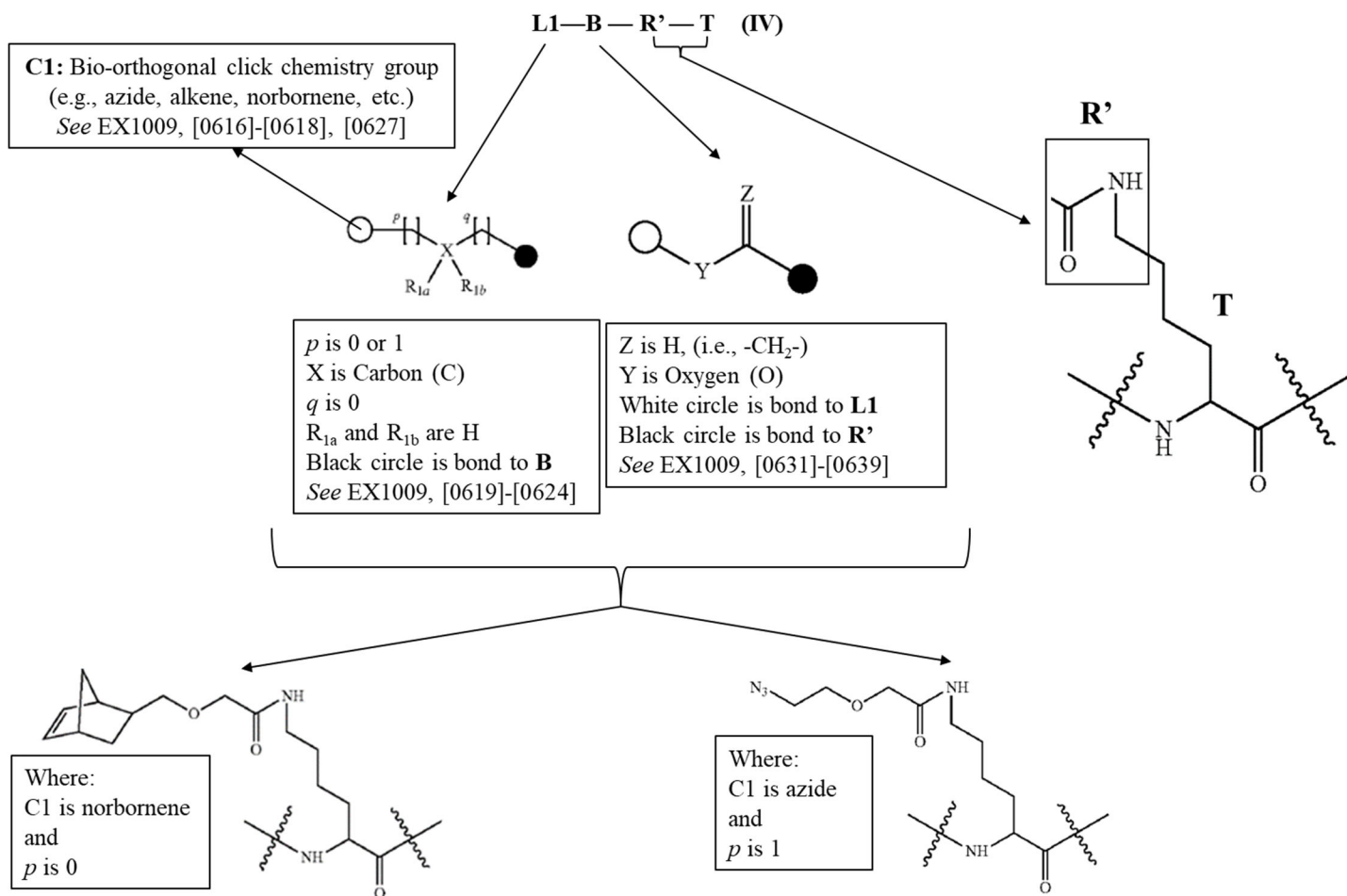
When Y is B-2, paragraphs [0634]-[0636] explain that V and V' can each independently be -NH-, -O-, -CH₂-, or a single bond; V1 is "a divalent group comprising a bioorthogonal functional group"; and s is any integer from 0 to 10. I note that paragraph [1571] indicates that with respect to B-2 (this paragraph references "partial structural formulae ... (B-1) to (B-4)...") that this "technical element" is described various ways throughout the application. Specifically, paragraph [1571] states, "these matters can be quoted as appropriate in the inventions described below without any special reference" and "the technical

elements of a specific invention described in the inventions described below can be quoted as appropriate as the technical elements of the present invention and other inventions.” I understand this to mean that the various disclosures of formula B-2 throughout the publication can be substituted for one another. Accordingly, where paragraph [1470] describes the same Formula (B-2) in a similar context, and paragraphs [1472] and [1480] indicate “V1 is (a) a divalent group comprising a bioorthogonal functional group or (b) a divalent group comprising no bioorthogonal functional group,” a POSA would understand that the bio-orthogonal functional group within V1 is optional. As such, V1 could be, for example, an oxygen (-O-) which fits Yamada’s description of “a divalent group.” *See e.g.*, [1465]. Note that the white and black circles in B-2 are simply included to show the orientation of the fragment in relation to the structure of B-1.

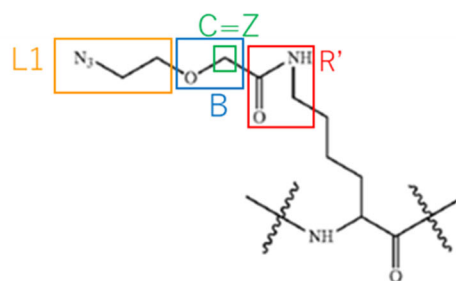
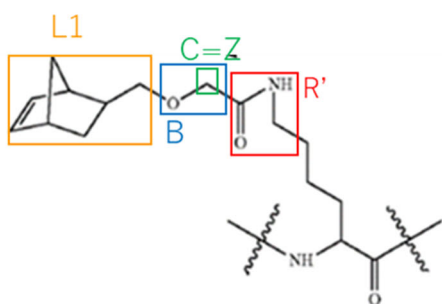
275. As noted above, R’ is defined as “a portion formed by a reaction between a soluble protein and a reactive group.” Yamada describes “[e]xamples of a linking portion formed by a reaction between the reactive group specific to a side chain of a lysine residue and the amino group (NH₂) present in the side chain of the lysine residue include an amide residue...” EX1009, [1510]. Thus, the amide portion of the partial structure from claim 2 of the ’675 Patent should be considered as R’. Accordingly, there are two ways in which Formula (IV) can be completed to arrive at the first and third structures of claim 11.

276. Specifically, a POSA could envisage that first and third structures recited in claim 11 by selecting the components of Formula (IV) as shown in the flow diagrams below:

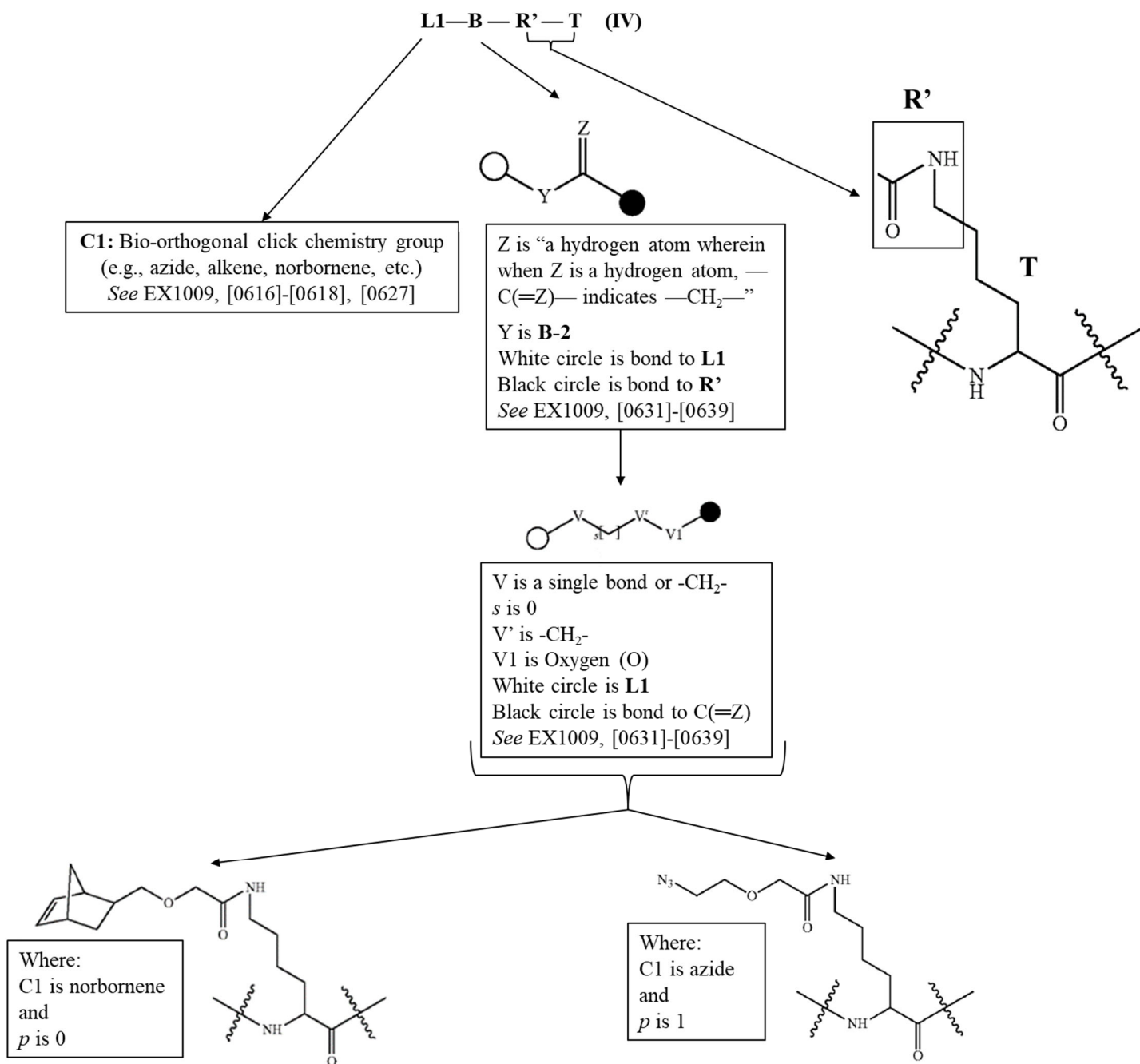
Option 1:



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



Option 2:



For Option 2, the components of the structures from claim 11 are denoted with their respective positions within Formula (IV):

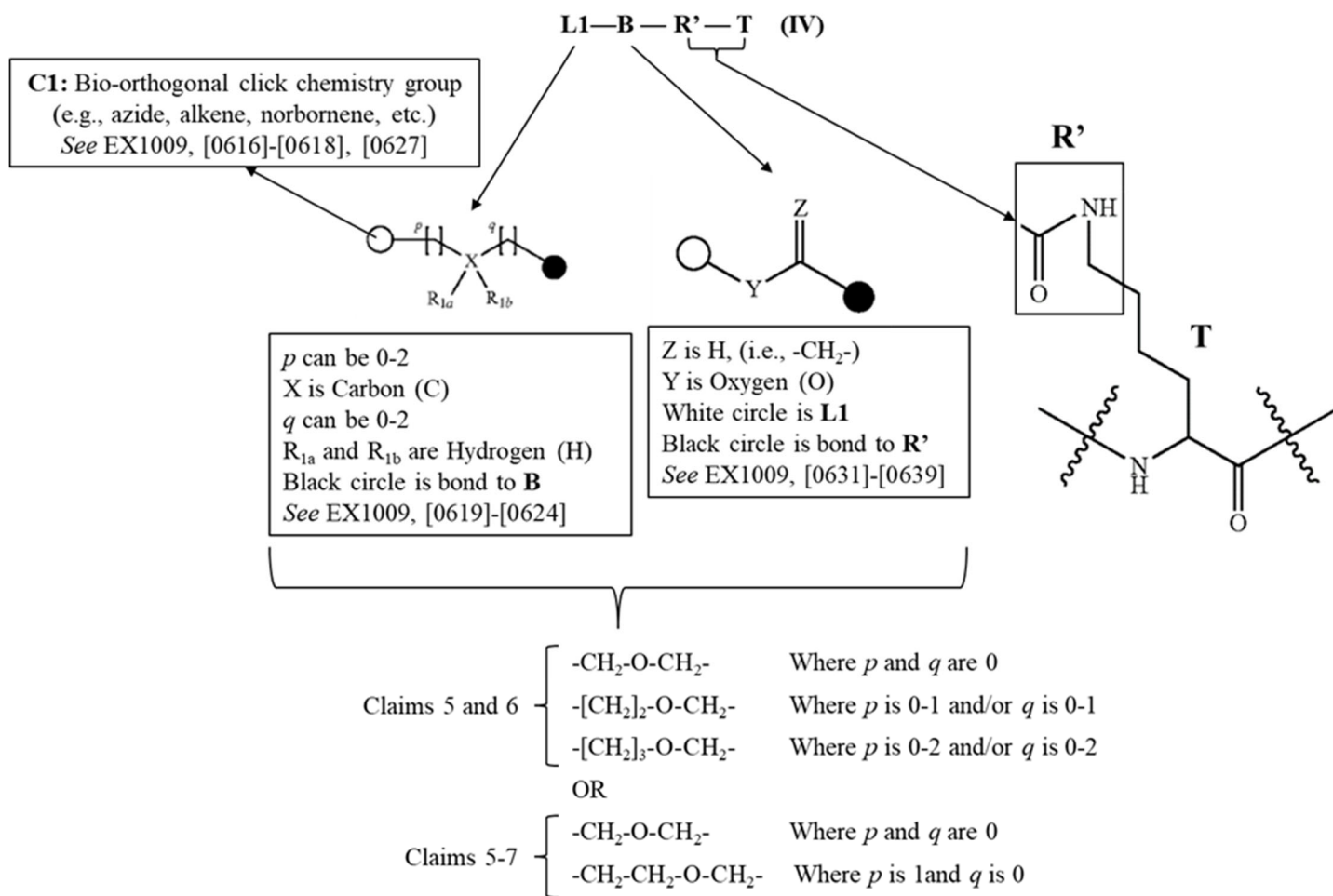


277. Thus, the first and third structures recites in claim 11 of the '675 Patent are disclosed in Yamada and could be predictably constructed based on Yamada's disclosure. As such, the limitations of claims 5-7 are also disclosed, as each of these structures includes a heteroatom (i.e., oxygen) within the segment corresponding to D1 (i.e., the limitations of claim 5) and the specific D1 structures recited in claims 6 and 7 (i.e., $\text{—CH}_2\text{CH}_2\text{OCH}_2\text{—}$ or $\text{—CH}_2\text{OCH}_2\text{—}$) correspond to the azide-containing structure on the right and the norbornene-containing structure on the left, respectively.

278. In addition to these particular compounds, Yamada also makes very clear that the segment of its modified structures corresponding to D1 fall within the scope of claims 5-76.

279. Both L1 and B of Formula (IV) contain multiple options for inclusion of a heteroatom. Specifically, when L1 includes Lb, it may comprise "a carbon atom, a nitrogen atom, or a single bond" as the X component (EX1009, [0622]), and in formula (B-1), the Y component could be —NH— or —O— or CH_2 (*id.*, [0633]). Each of these allows for various constructions that would fall within the scope of claims 5

and 6. For example, inserting -O- as the Y component and a carbon atom as the X component can yield a number of combinations that satisfy both claims 5 and 6. Indeed, positions p and q could be varied in numerous ways and still remain within the scope of these claims. Claim 7 would also be covered with this arrangement as summarized in the flow chart below.



280. Accordingly, all of the components of claims 5-7 and 11 of the '675 Patent are taught and suggested in PepTalk Poster and Yamada, and a POSA would

reasonably expect to be able to combine these components to arrive at the claims based on simple substitutions.

9. Claim 12 of the '675 Patent

281. Claim 12 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

282. PepTalk Poster discloses this limitation. In particular, PepTalk Poster discloses a modified antibody with lysine residues 248 modified with an azide group. As previously discussed in connection with Claim 9, an azide group is a group capable of participating in a Huisgen 1,3-dipolar cycloaddition. *See* paragraphs 242-246 (Section XI(B)(4), above).

283. As previously discussed in connection with Claim 2 and Claim 3, PepTalk Poster and Matsuda disclose modified lysine structures that correspond to and/or comprise all of the elements of the structures recited in Claims 2 and 3. *See* paragraphs 251-261 (Sections XI(B)(6)-(7), above).

284. Thus, PepTalk Poster and Matsuda disclose all of the elements of the modified antibody of Claim 12, and a POSA could readily combine these disclosures to predictably arrive at claim 12 with a reasonable expectation of success.

10. Claim 13 of the '675 Patent

285. Claim 13 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.”

286. PepTalk Poster discloses both an azide group and a dibenzocyclooctyne group as bio-orthogonal functional groups. EX1006. Yamada likewise discloses antibodies modified at lysine 248 (EX1009, [0222], [1037], [1109], [1114], etc.) with an azide (*id.*, [0151], [0153], [1037], Figure 18) or a norbornene (*id.*, [0151], [0153]), as does Matsuda (EX1011, [0046]-[0047], [0592]-[0593]).

287. As previously discussed in connection with Claim 2 and Claim 3, PepTalk Poster and Matsuda disclose modified lysine structures that correspond to and/or comprise all of the elements of the structures recited in Claims 2 and 3. *See* paragraphs 251-261 (Sections XI(B)(6)-(7), above).

288. Thus, PepTalk Poster and Matsuda disclose all of the elements of the modified antibody of Claim 13, and a POSA could readily combine these disclosures to predictably arrive at claim 13 with a reasonable expectation of success.

C. Claims 1-13 of the '675 Patent Are Unpatentable Over PepTalk Presentation

289. PepTalk Presentation, like 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.

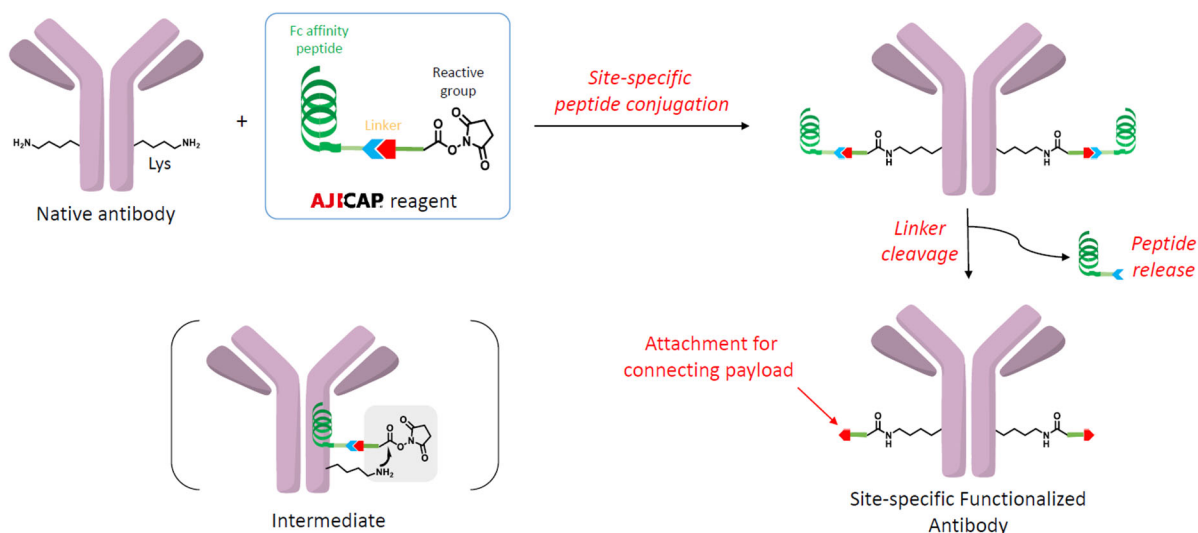
1. Independent Claim 1 of the '675 Patent

a. A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group,

290. PepTalk Presentation discloses the limitation, “a modified antibody or its fragment comprising bio-orthogonal click chemistry functional group.”

291. Specifically, PepTalk Presentation discloses a method for modifying antibodies to include a bio-orthogonal functional group that can be used to attach a payload, such as an anti-cancer drug. PepTalk Presentation depicts a generalized process for modifying an antibody to include a bio-orthogonal functional group in the following figure:

Strategy of AJICAP™

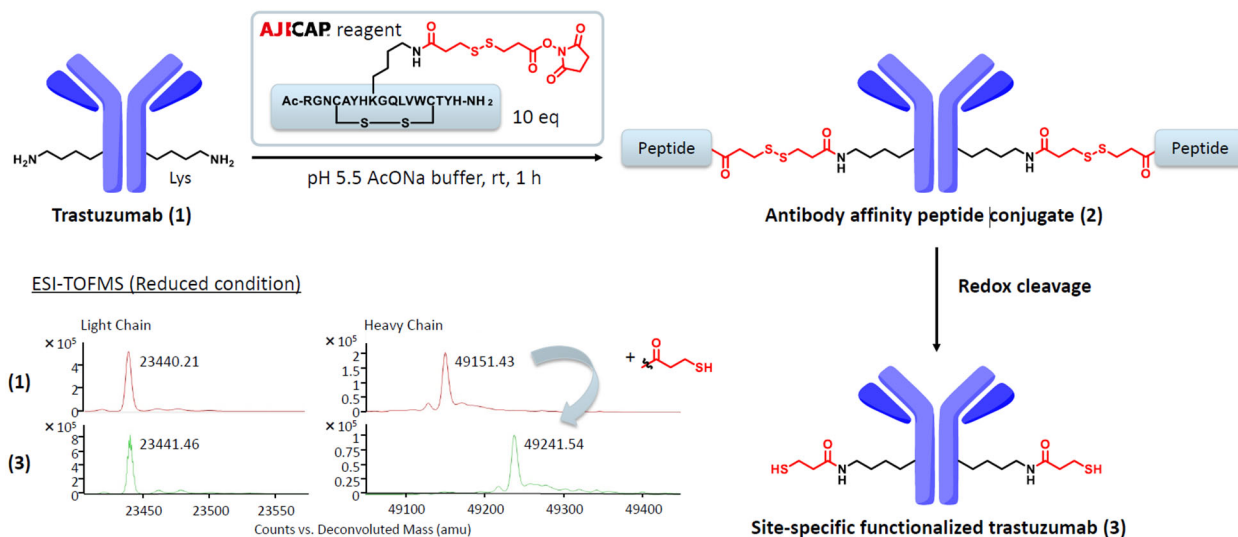


EX1007, 15.

292. This figure shows an antibody being modified through steps of “site-specific peptide conjugation” and “linked cleavage” to include an “attachment for connecting payload.” The “attachment for connecting payload” includes a bio-orthogonal functional group.

293. PepTalk Presentation depicts, in the following figure, an example of this process in which the antibody trastuzumab is modified to include a bio-orthogonal functional group.

Site-Specific Functionalization of Trastuzumab at Lys248

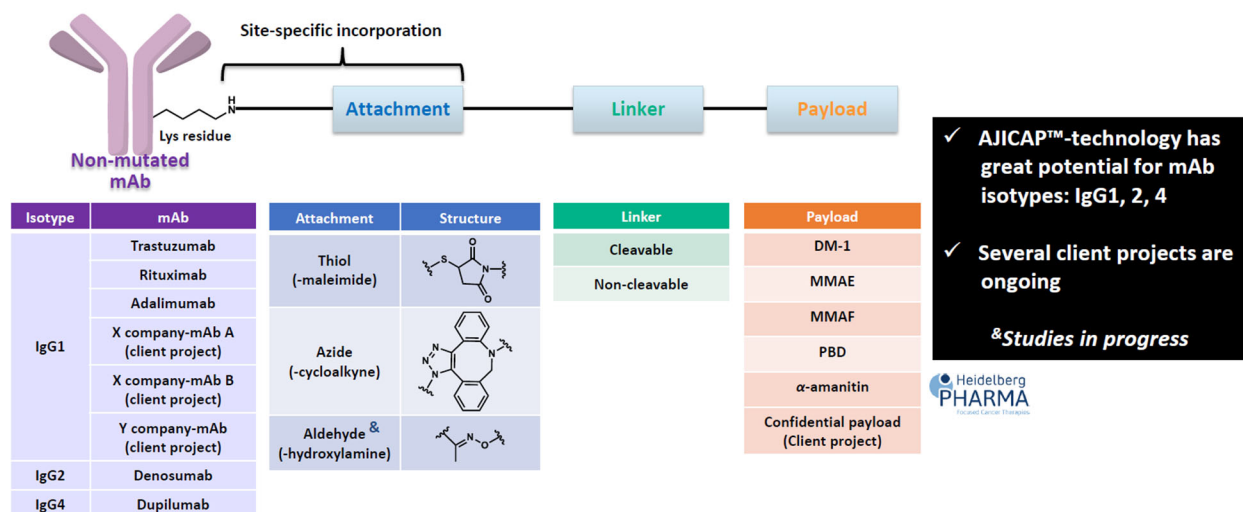


EX1007, 16.

294. In this figure, the antibody trastuzumab (a human IgG1) is first modified to include a peptide conjugate that contains a precursor to a bio-orthogonal functional group. Through a subsequent reaction, the peptide conjugate is cleaved and removed, leaving, in this example, a thiol group bound to the amino acid residue of the antibody. Persons having ordinary skill in the art understood that the thiol group shown in Step (3) is an example of a bio-orthogonal click chemistry functional group.

295. PepTalk Presentation also discloses, in the following figure, that the AJICAP™ technology is compatible with a variety of antibodies, click-chemistry functional groups, and payloads.

Compatibility with Various mAbs, Payloads and Linkers



EX1007, 20.

296. In the “Attachment” table shown in this figure, PepTalk Presentation discloses three examples of click-chemistry reactions that can be used with AJICAP™ technology: thiol (-maleimide), azide (-cycloalkyne), and aldehyde (-hydroxylamine). I note that the -cycloalkyne reacted with the azide is an example of a dibenzocycloalkyne or “DBCA”). A POSA would have understood that each of these three examples represents a pair of click-chemistry functional groups that participate in a click-chemistry reaction. A POSA would also have understood that click-chemistry reactions are bio-orthogonal reactions, such that the functional groups that participate in a click-chemistry reaction are bio-orthogonal click-chemistry functional groups.

297. Finally, a POSA would also have understood that the orientation of the click chemistry functional groups is reversible. In other words, to the extent that PepTalk Presentation's teaching of the attachment "Thiol-maleimide" is interpreted as: [antibody]-[thiol] conjugated to [maleimide]-[drug]; a POSA would understand that the arrangement [antibody]-[maleimide] conjugated to [thiol]-[drug] would be expected to be functionally equivalent.

298. PepTalk Presentation thus discloses a modified antibody comprising a bio-orthogonal click chemistry functional group.

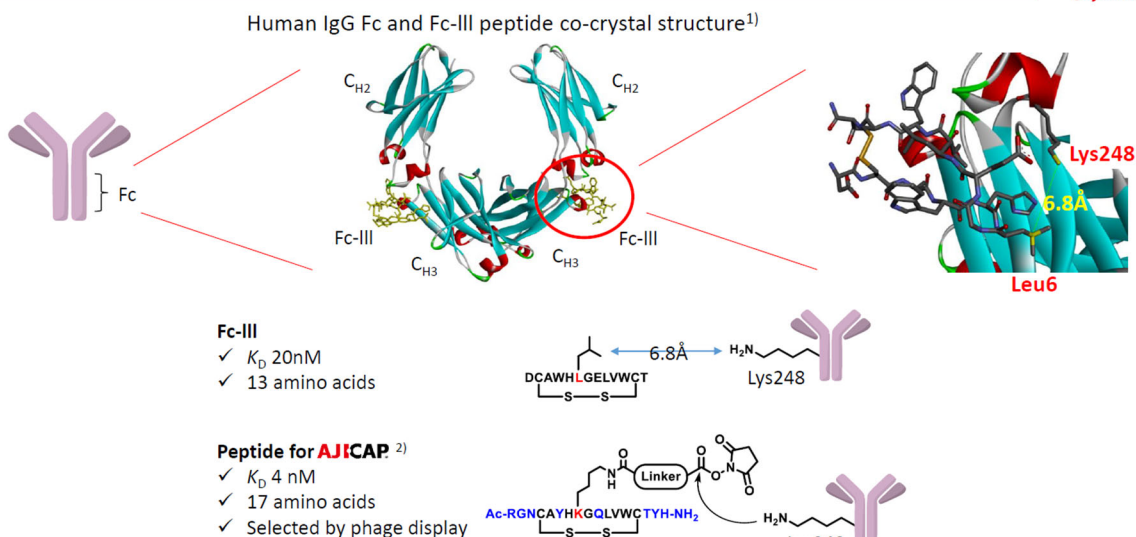
b. wherein the modified antibody comprises one or more modified heavy chain,

299. PepTalk Presentation discloses the limitation "the modified antibody comprises one or more modified heavy chain."

300. It was well known in the art that antibodies, including trastuzumab and the other antibodies referenced in PepTalk Presentation, have two heavy chains and two light chains.

301. PepTalk Presentation discloses modifying antibodies, including trastuzumab, at lysine residue 248 of the antibody's Fc domains. For example, in the figure below, PepTalk Presentation discloses modifying lysine 248.

Background of Affinity Peptide and Reaction Concept of AJICAP™



2019/2/9

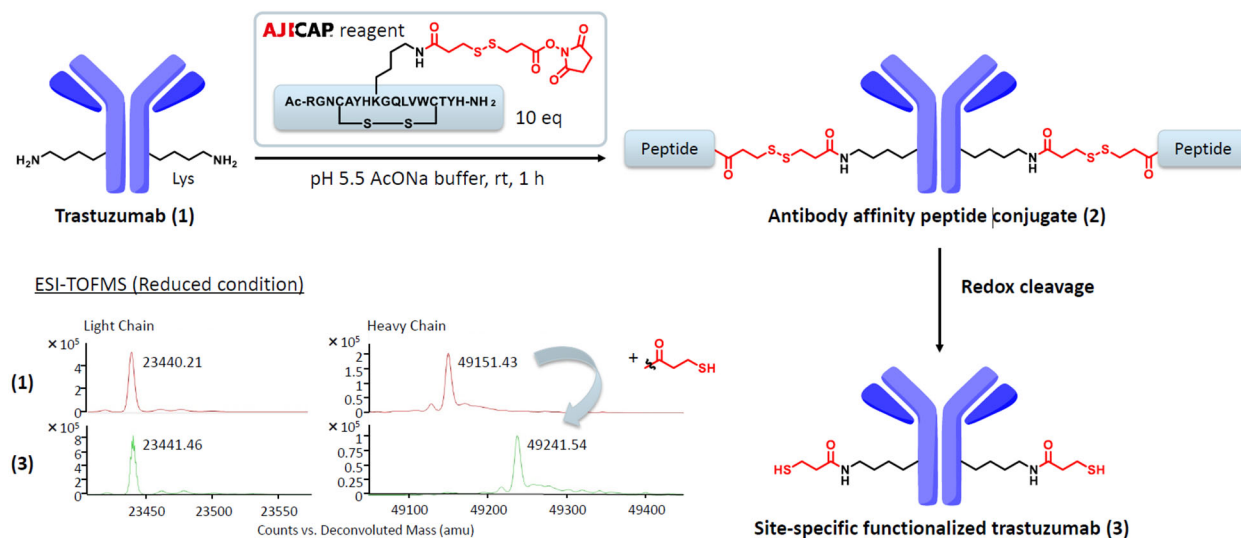
PepTalk 2019 / Ajinomoto Co., Inc

Ref.
1) DeLano, W. L.; Ultsch, M. H.; de Vos, A. M.; Wells, J. A. *Science*, **2000**, 287, 1279-1283.
2) WO2016/186206 14

EX1007, 14.

302. Furthermore, in the figure below, PepTalk Presentation discloses modifying lysine 248 in the Fc domains of both heavy chains. *Id.*, 16

Site-Specific Functionalization of Trastuzumab at Lys248



303. Thus, a POSA understood that the Fc domains reside in the heavy chains of the antibody, and by disclosing antibodies modified to include bio-orthogonal click chemistry functional groups at lysine residue 248, PepTalk Presentation discloses that the modified heavy chain comprises one or more modified heavy chains.

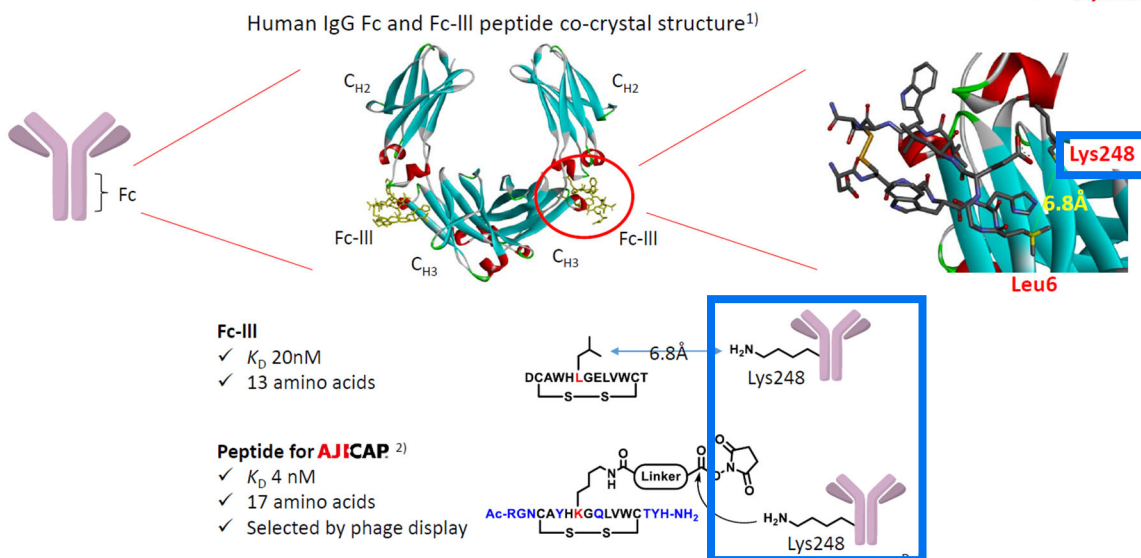
c. wherein each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and

304. PepTalk Presentation discloses the limitation “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.”

305. As previously discussed, the PepTalk Presentation discloses modifying an antibody to include a bio-orthogonal click chemistry functional group at lysine residue 248 of the Fc domains of the antibody’s heavy chains. PepTalk Presentation discloses this generally and by reference to a specific example of trastuzumab.

306. PepTalk Presentation’s disclosures of modifying lysine residues 248 of the heavy chain are shown in the following figures. *See* EX1007, 14, 16-18, 20.

Background of Affinity Peptide and Reaction Concept of AJICAP™

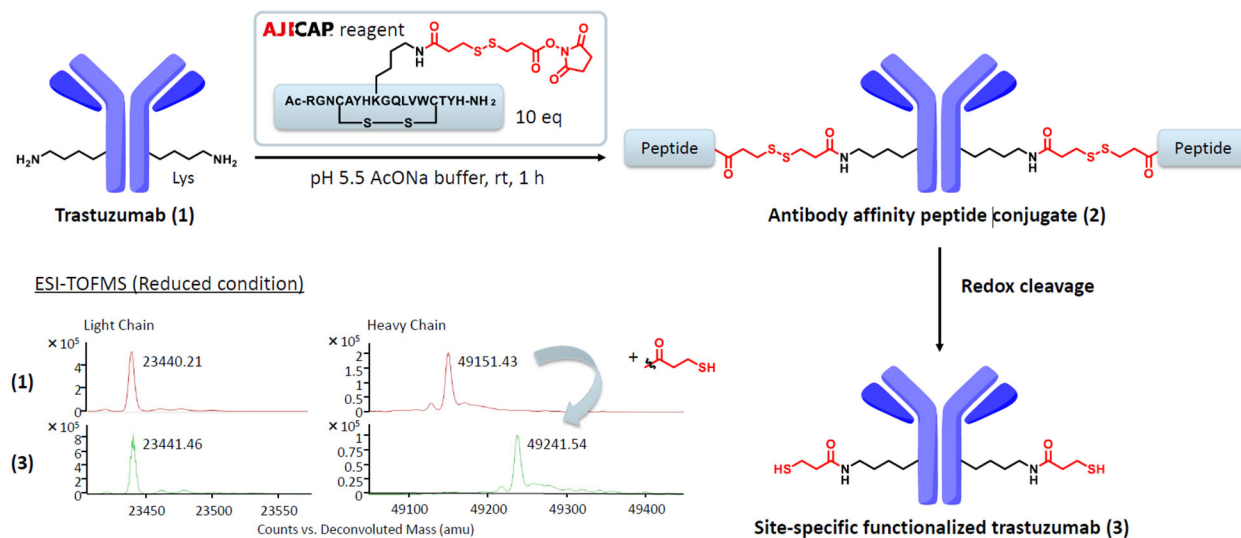


2019/2/9

PepTalk 2019 / Ajinomoto Co., Inc

1) DeLano, W. L.; Ultsch, M. H.; de Vos, A. M.; Wells, J. A. *Science*, **2000**, 287, 1279-1283.
2) WO2016/186206 14

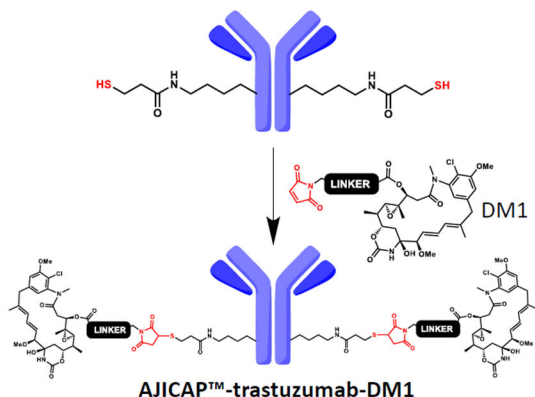
Site-Specific Functionalization of Trastuzumab at Lys248



Analysis of AJICAP™-ADC

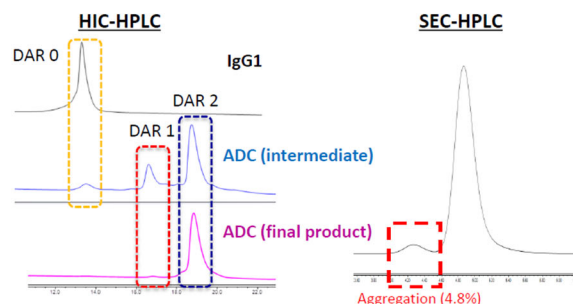


We began testing the AJICAP™ technology by using commercially available trastuzumab and a DM1-maleimide drug-linker.

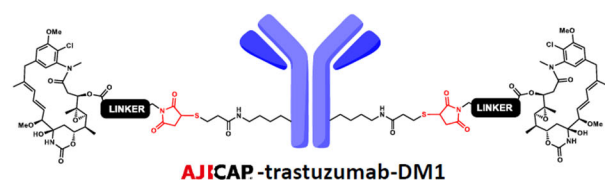


Target parameters

ADC	Trastuzumab-DM1
DAR	1.6~2.0 (Q-TOF, HIC)
Aggregation	< 10% (SEC)
Conjugated site	Confirmed by peptide mapping



Analysis of AJICAP™-ADC



Peptide mapping

LC: 100% coverage

1	YGRKP	RAAPRLIIYS	ASFLT	SGVPS	RPSGS	RSSTD	FTTIT	35
34	SSLOP	EDFAT	YYCQ	HTTTP	PTFGQ	GTVE	TKRIV	115
76	FTFPF	SDFGL	KISGA	SVVCL	LRRFY	PRIRK	VQKIV	150
116	SRHSQ	ESVTE	QDSND	STTSL	STTIT	LSRIAD	YKIKIV	185
156	VTRQG	LSSPV	TKSEH	RIGEC	C-termin			214

HC: 93% coverage

1	YGRKP	RAAPRLIIYS	ASFLT	SGVPS	RPSGS	RSSTD	FTTIT	35
34	SSLOP	EDFAT	YYCQ	HTTTP	PTFGQ	GTVE	TKRIV	115
76	FTFPF	SDFGL	KISGA	SVVCL	LRRFY	PRIRK	VQKIV	150
116	SRHSQ	ESVTE	QDSND	STTSL	STTIT	LSRIAD	YKIKIV	185
156	VTRQG	LSSPV	TKSEH	RIGEC	C-termin			214

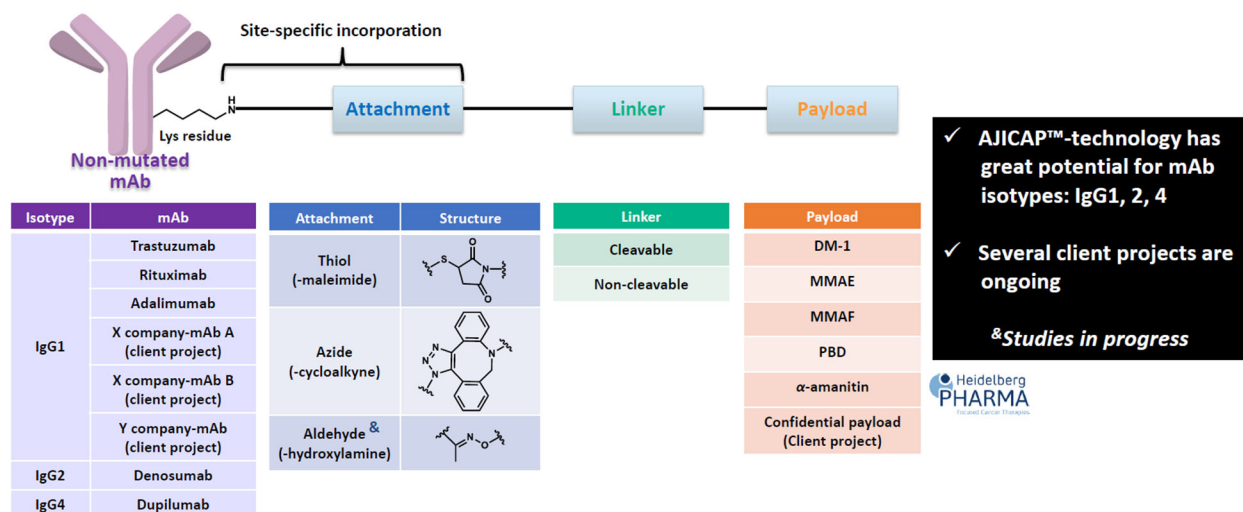
Q-TOFMS



THTCPPCAPELLGGPSVFLFPPKP²⁴⁸KDTLMISR

Linker-DM1 at 4687.3 Da. This mass was found and indicates that ONLY K248 was substituted.

Compatibility with Various mAbs, Payloads and Linkers



307. The POSA understood that the position 248 discussed in PepTalk Presentation refers to the EU numbering system for antibody amino acid sequences.

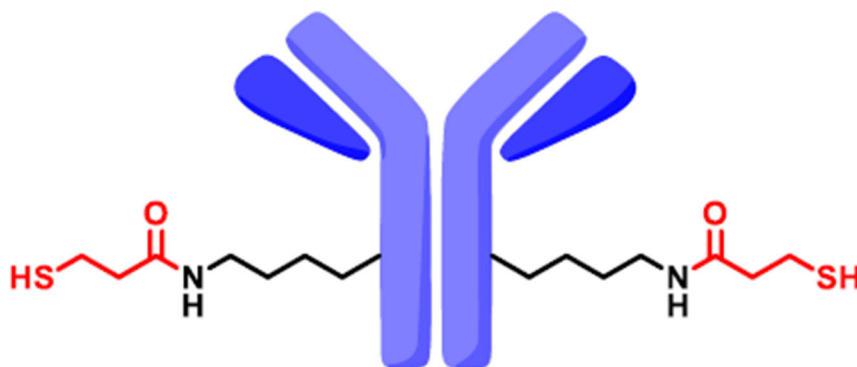
308. PepTalk Presentation thus discloses that each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system.

d. wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end, and

309. PepTalk Presentation discloses the limitation “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

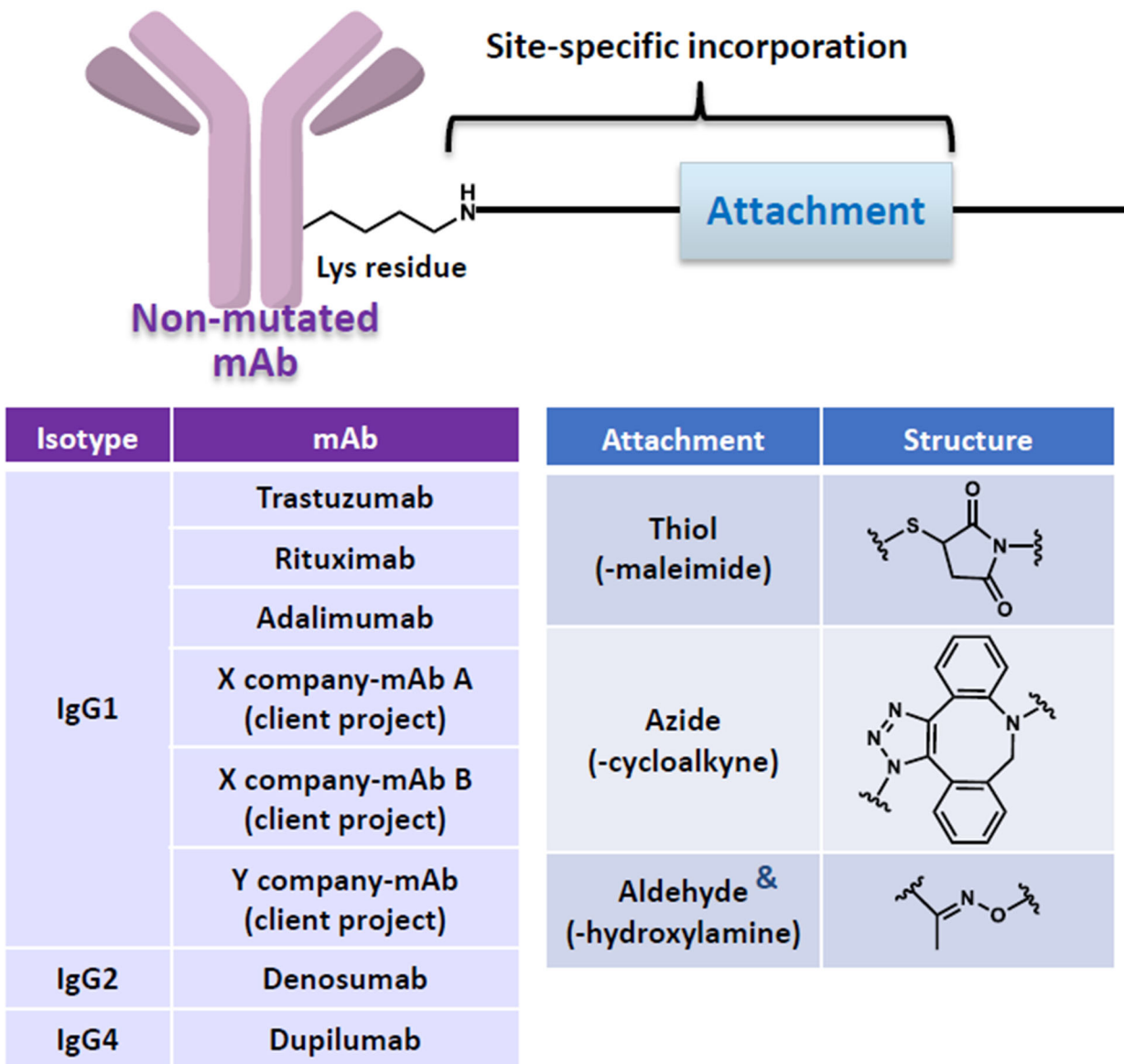
310. As previously discussed, PepTalk Presentation discloses modifying an antibody with a bio-orthogonal click chemistry functional group at lysine residue

position 248. PepTalk Presentation discloses making such modifications using thiol, azide, and aldehyde functional groups as examples. PepTalk Presentation also discloses that these modifications are made at the terminal end of the modified lysine residue. For example, the figure below depicts lysine residue 248 modified with a thiol group at the lysine's terminal end, represented by "NH." EX1007, 16.



Site-specific functionalized trastuzumab (3)

311. Similarly, PepTalk Presentation discloses modifying antibodies at the terminal end of lysine residue 248 with any of a thiol group, azide group, or aldehyde group in the following figure. EX1007, 20.

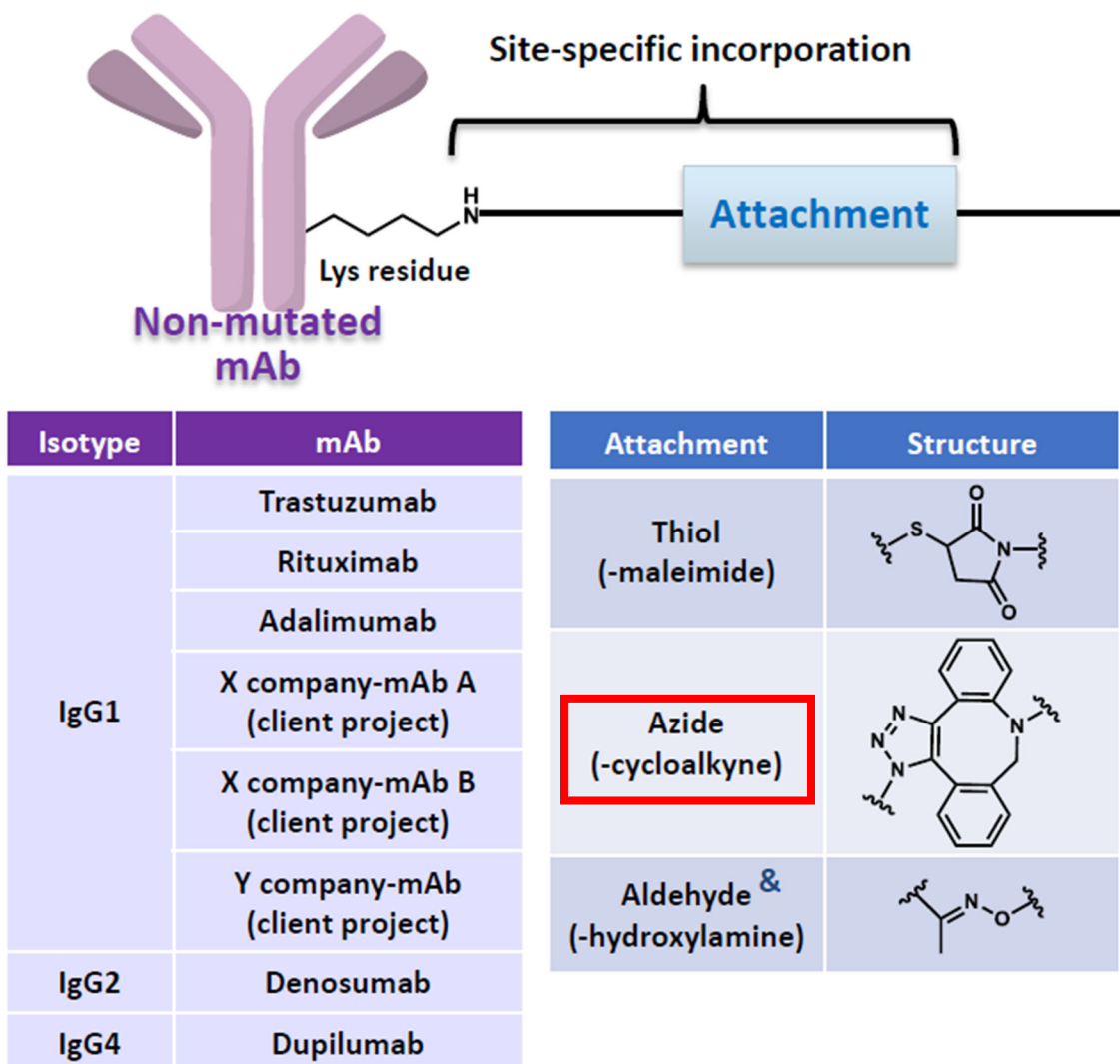


312. Accordingly, PepTalk Presentation discloses that “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

- e. *wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.*

313. PepTalk Presentation discloses the limitation “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

314. As previously discussed, PepTalk Presentation discloses modifying an antibody at lysine residue 248 to include an azide group as the click chemistry functional group. PepTalk Presentation discloses using an azide group as the functional group in the following figure. EX1007, 20.



315. PepTalk Presentation further discloses the use of an azide group as the bio-orthogonal click chemistry functional group in the following figure. EX107, 13.

Summary of Advantage of AJICAP™



AJICAP™

Ajinomoto Co. has developed an innovative direct chemical site-selective conjugation method for use with intact native antibodies.

Our novel technology provides significant advantages for next generation ADCs:

1. **Straightforward CMC**
 - Direct modification of intact antibody
 - No genetic modification required
2. **Enhancement of Therapeutic Window compared to stochastic ADCs**
 - Site specific, controlled DAR 2
3. **Wide drug-linker compatibility: reactive group compatibility includes thiol, alkyne, azide etc**
4. **High yields, short conjugation reaction times, ease to manufacture**

316. As was well-understood by persons skilled in the art by 2019 and long before, an azide group is none of a hydroxyl group, carboxyl group, thiol group, amino group, or aldehyde group.

317. Thus, by disclosing antibodies with lysine residue 248 modified with an azide group as the bio-orthogonal click chemistry functional group, PepTalk Presentation discloses that “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

318. Additionally, as noted above, a POSA would also have understood that the orientation of the click chemistry functional groups is reversible. Thus, PepTalk Presentation’s teaching of the attachment “Thiol-maleimide” on slide 20 would be

understood as disclosure of a maleimide as a bio-orthogonal click chemistry group, and the -cycloalkyne counterpart of the azide disclosed in slide 20 would be understood as disclosure of DBCA as a bio-orthogonal click chemistry group.

319. PepTalk Presentation thus discloses the modified antibody of Claim 1.

2. Claim 4 of the '675 Patent

320. Claim 4 recites: “The modified antibody of claim 1, wherein the modified heavy chain comprises an amino acid sequence having a structure of formula 8-2:

G-P—S-V-F-L-F—P-P-K-P—(K)'-D-T-L-M-I (SEQ ID NO: 21),
[formula 8-2]

wherein K' is the modified lysine residue.”

321. PepTalk Presentation discloses the modified heavy chain comprising an amino acid sequence as recited in Claim 4.

322. In particular, as previously discussed, PepTalk Presentation discloses an antibody modified at lysine residue 248 to include a bio-orthogonal click chemistry functional group. The modified lysine residue referred to as K' in Claim 4 is lysine residue 248. The lysine residue at position 248, by definition, resides in the amino acid sequence recited in Claim 4.

323. Indeed, the '675 Patent itself shows this amino acid sequence, with a lysine residue (K) at position 248.

amino acid sequence :

G—P—S—V—F—L—F—P—P—K—P—K—D—T—L—M—I

**EU numbering
for heavy chain :**

237 239 241 243 245 247 249 251 253
238 240 242 244 246 248 250 252

EX1001, Figure 1; 14:35-37.

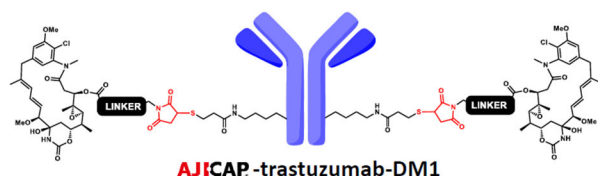
324. This amino acid sequence was not invented in the '675 Patent. Rather, it is an amino acid sequence that occurs naturally in the Fc domain of heavy chains in certain antibodies, such as trastuzumab, including having a lysine residue at the position designated 248 under EU numbering conventions.

325. Thus, by disclosing the modified antibody of Claim 1, where the modified lysine residue is lysine residue 248 in the Fc domain of the heavy chain, PepTalk Presentation inherently discloses that the modified heavy chain has the amino acid sequence recited in Claim 4.

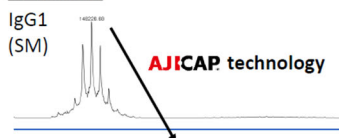
326. PepTalk Presentation also expressly discloses that the modified heavy chain has the amino acid sequence recited in Claim 4, depicting that sequence in the following figure relating to analysis of a trastuzumab modified at lysine 248.



Analysis of AJICAP™-ADC



Q-TOFMS



Peptide mapping

LC: 100% coverage

1	N-term	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V N T A V A W	35
36		Y Q Q K P G K I A P K I L L I Y S A S F L Y S G V P S R I F S G S R S G T D F T L T I	75
76		S S L Q P E D F A T Y Y C Q Q H Y T T P P T F G Q G T K V E I K I R I V A A P S V	115
116		F I F P P S D E Q L K I S G T A S V V C L L N N F Y P R I E A K I V Q W K I V D N A L Q	155
156		S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K I V Y A C E	195
196		V T H Q G L S S P V T K S F N R I G E C	214
		C-term	

HC: 93% coverage

1	N-term	E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N I K I D T Y I H	35
36		W V R I Q A P G K I G L E W V A R I I Y P T N G Y T R I Y A D S V K I G R I F T I S A D T S	75
76		K I N T A Y L Q M N S L R A E D T A V Y Y C S R I W G G D G F Y A M D Y W G Q G T L	115
116		V T V S S A S T K I G P S V F P L A P S S K I S T S G G T A A L G C L V K I D Y F P E	155
156		P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S	195
196		L G T Q T Y I C N V N H K P S N T K I V D K I K I V E P K I S C D K I T H T C P P C P A P	235
236		E L L G G P S V F L F P P K P K I D T L M I S R T P E V T C V V V D V S H E D P E	275
276		V K I F N W Y V D G V E V H N A K I T K P R I E E Q Y N S T Y R I V V S V L T V L H Q D	315
316		W L N G K I E Y K I C K I V S N K I A L P A P I E K I T I S K I A K I G Q P R I E P Q V Y T L P	355
356		P S R I E E M T K I N Q V S L T C L V K I G F Y P S D I A V E W E S N G Q P E N N Y K I	395
396		T T P P V L D S D G S F F L Y S K I L T V D K I S R I W Q Q G N V F S C S V M H E A L	435
436		H N H Y T Q K I S L S L S P G	449
		C-term	

THTCPPCPAPPELLGGPSVFLFPPKP²⁴⁸KDTLMISR

Linker-DM1 at 4687.3 Da. This mass was found and indicates that **ONLY K248** was substituted.

EX1007, 18.

327. In the following excerpt of this figure, the amino acid sequence recited in Claim 4 is highlighted in yellow, and “HC” refers to “heavy chain.”

Peptide mapping

LC: 100% coverage

1	N-term	D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V N T A V A W	35
36		Y Q Q K P G K I A P K I L L I Y S A S F L Y S G V P S R I F S G S R S G T D F T L T I	75
76		S S L Q P E D F A T Y Y C Q Q H Y T T P P T F G Q G T K V E I K I R I V A A P S V	115
116		F I F P P S D E Q L K I S G T A S V V C L L N N F Y P R I E A K I V Q W K I V D N A L Q	155
156		S G N S Q E S V T E Q D S K D S T Y S L S S T L T L S K A D Y E K H K I V Y A C E	195
196		V T H Q G L S S P V T K S F N R I G E C	214
		C-term	

HC: 93% coverage

1	N-term	E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N I K I D T Y I H	35
36		W V R I Q A P G K I G L E W V A R I I Y P T N G Y T R I Y A D S V K I G R I F T I S A D T S	75
76		K I N T A Y L Q M N S L R A E D T A V Y Y C S R I W G G D G F Y A M D Y W G Q G T L	115
116		V T V S S A S T K I G P S V F P L A P S S K I S T S G G T A A L G C L V K I D Y F P E	155
156		P V T V S W N S G A L T S G V H T F P A V L Q S S G L Y S L S S V V T V P S S S	195
196		L G T Q T Y I C N V N H K P S N T K I V D K I K I V E P K I S C D K I T H T C P P C P A P	235
236		E L L G G P S V F L F P P K P K I D T L M I S R T P E V T C V V V D V S H E D P E	275
276		V K I F N W Y V D G V E V H N A K I T K P R I E E Q Y N S T Y R I V V S V L T V L H Q D	315
316		W L N G K I E Y K I C K I V S N K I A L P A P I E K I T I S K I A K I G Q P R I E P Q V Y T L P	355
356		P S R I E E M T K I N Q V S L T C L V K I G F Y P S D I A V E W E S N G Q P E N N Y K I	395
396		T T P P V L D S D G S F F L Y S K I L T V D K I S R I W Q Q G N V F S C S V M H E A L	435
436		H N H Y T Q K I S L S L S P G	449
		C-term	

THTCPPCPAPPELLGGPSVFLFPPKP²⁴⁸KDTLMISR

Linker-DM1 at 4687.3 Da. This mass was found and indicates that **ONLY K248** was substituted.

EX1007, 18.

328. PepTalk Presentation thus discloses the modified antibody of Claim 4.

3. Claim 8 of the '675 Patent

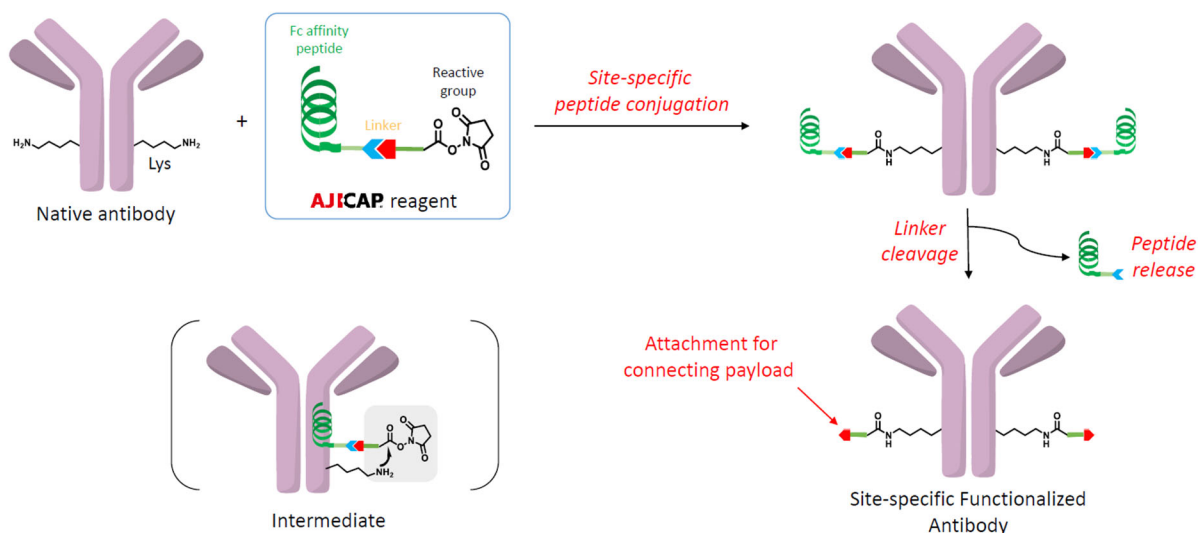
329. Claim 8 recites: “The modified antibody of claim 1, wherein the modified antibody comprises two modified heavy chains.”

330. PepTalk Presentation discloses “the modified antibody comprises two modified heavy chains.”

331. As previously discussed, and as was well-known in the art, antibodies, such as trastuzumab, include two heavy chains. As also previously discussed in connection with Claim 1, PepTalk Presentation discloses an antibody modified to include an azide group at lysine residue 248 of the Fc domains of the heavy chains.

332. PepTalk Presentation further discloses that its modified antibodies are modified at lysine residue 248 in the Fc domains of both heavy chains. This is shown, for example, in the figure below.

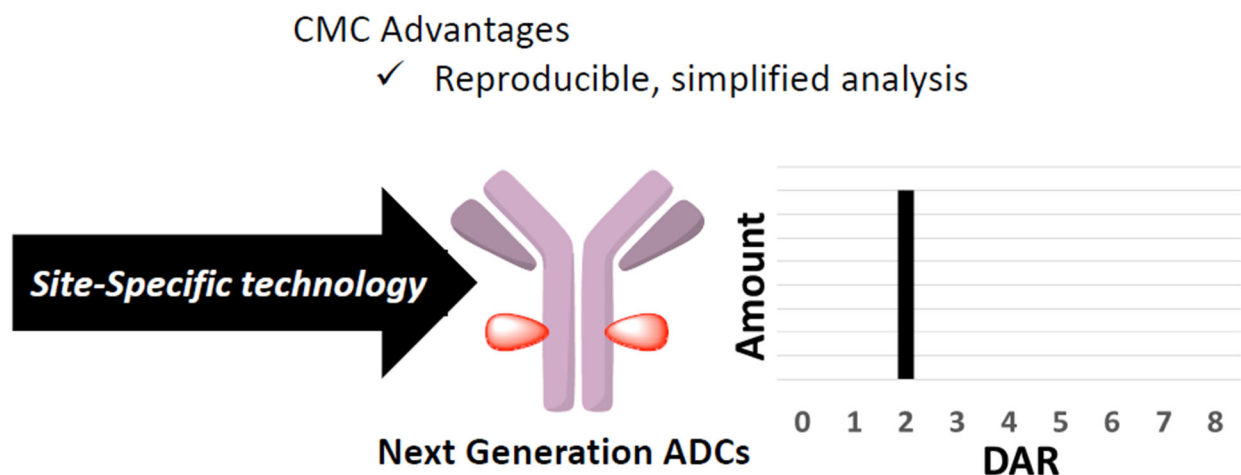
Strategy of AJICAP™



EX1007, 15.

333. As seen in this figure, the initial “site-specific peptide conjugation” occurs in both heavy chains, and, following cleavage of the “linker,” the antibody has a lysine residue 248 modified with the “attachment” (i.e., click-chemistry functional group) on both heavy chains.

334. PepTalk Presentation further discloses modifying two heavy chains in teaching the advantages of its approach to site-specification conjugation. Namely, PepTalk Presentation teaches that its approach produces a consistent drug-antibody ratio (“DAR”) of 2, where the value 2 represents two drug molecules bound to a single antibody. PepTalk Presentation illustrates the DAR value of 2 in the following figure, which show that the two drug molecules are bound at the two heavy chains via the modified lysine residue 248.



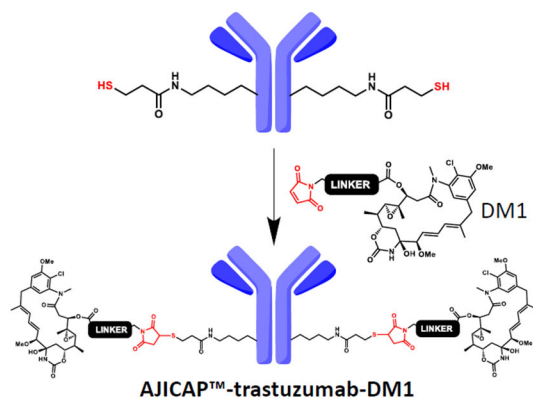
EX1007, 11.

335. PepTalk Presentation further discloses that Ajinomoto's AJICAP™ technology allows for “Site specific, controlled DAR 2.” *Id.* 13. PepTalk Presentation further discloses that the modified antibodies have two modified heavy chains, providing for a DAR value of 2, by way of its example using a thiol group as the bio-orthogonal click chemistry functional group, as shown in the figure below. *Id.* 17.

Analysis of AJICAP™-ADC

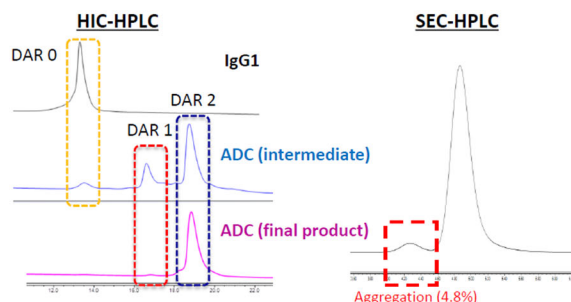


We began testing the AJICAP™ technology by using commercially available trastuzumab and a DM1-maleimide drug-linker.



Target parameters

ADC	Trastuzumab-DM1
DAR	1.6~2.0 (Q-TOF, HIC)
Aggregation	< 10% (SEC)
Conjugated site	Confirmed by peptide mapping



336. Thus, by disclosing a modified antibody with lysine residues 248 modified to include an azide group, PepTalk Presentation discloses the modified antibody of Claim 1 where the modified antibody includes two modified heavy chains.

4. Claim 9 of the '675 Patent

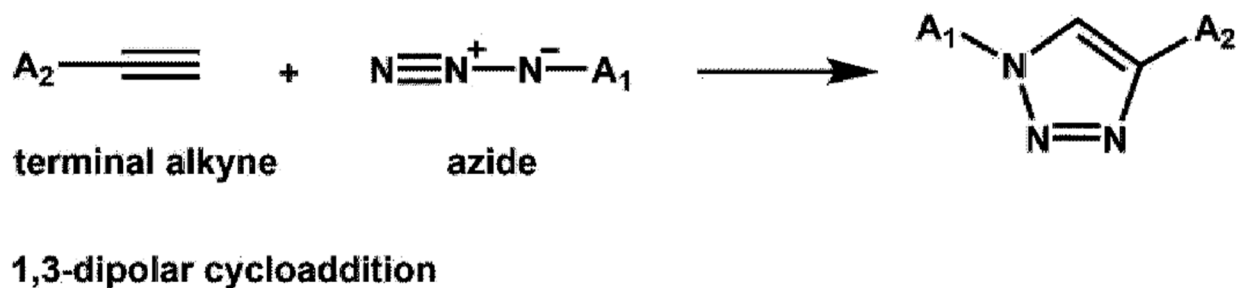
337. Claim 9 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

338. PepTalk Presentation discloses “the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

339. In particular, as previously discussed in connection with Claim 1, the PepTalk Presentation discloses a modified antibody with lysine residues 248 modified with an azide group. As also previously discussed, an azide group is a bio-orthogonal click chemistry functional group. Persons skilled in the art understood that an azide group is capable of participating in a click-chemistry reaction of Huisgen 1,3-dipolar cycloaddition.

340. This understanding is evidenced by the '959 Publication, which expressly discloses the use of azide groups in Huisgen 1,3-dipolar cycloaddition. EX1036.

341. The '959 Publication discloses the following “Schematic diagram of Huisgen 1,3-dipolar cycloaddition” between a terminal alkyne and an azide.



EX1005, 39.

5. Claim 10 of the '675 Patent

342. Claim 10 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

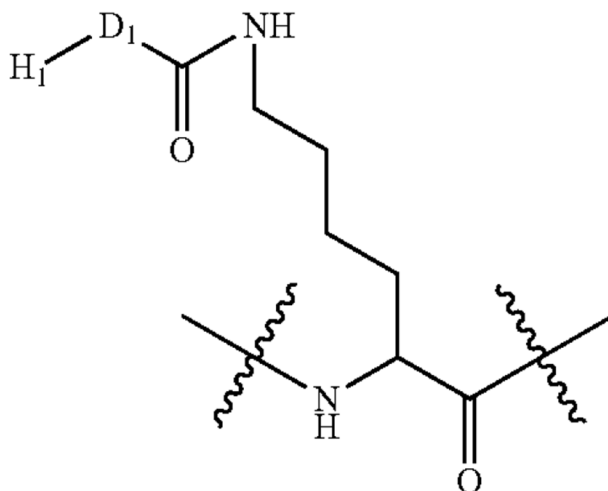
343. PepTalk Presentation discloses “the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.” It is worth noting that a POSA would equate these four click chemistry functional groups. In other words, it is my experience and my understanding of the art that if an azide “works,” then a POSA would immediately assume that a tetrazine, DBCO, and norbornene would also work. Indeed, if any one of these (or other well-known bio-orthogonal click chemistry groups) works, then a POSA would reasonably expect that other bio-orthogonal click chemistry groups could be substitute in its place and function in essentially the same way.

344. In particular, as previously discussed in connection with Claim 1, PepTalk Presentation discloses a modified antibody with lysine residues 248 modified with an azide group (or a DCBA).

345. PepTalk Presentation thus discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.

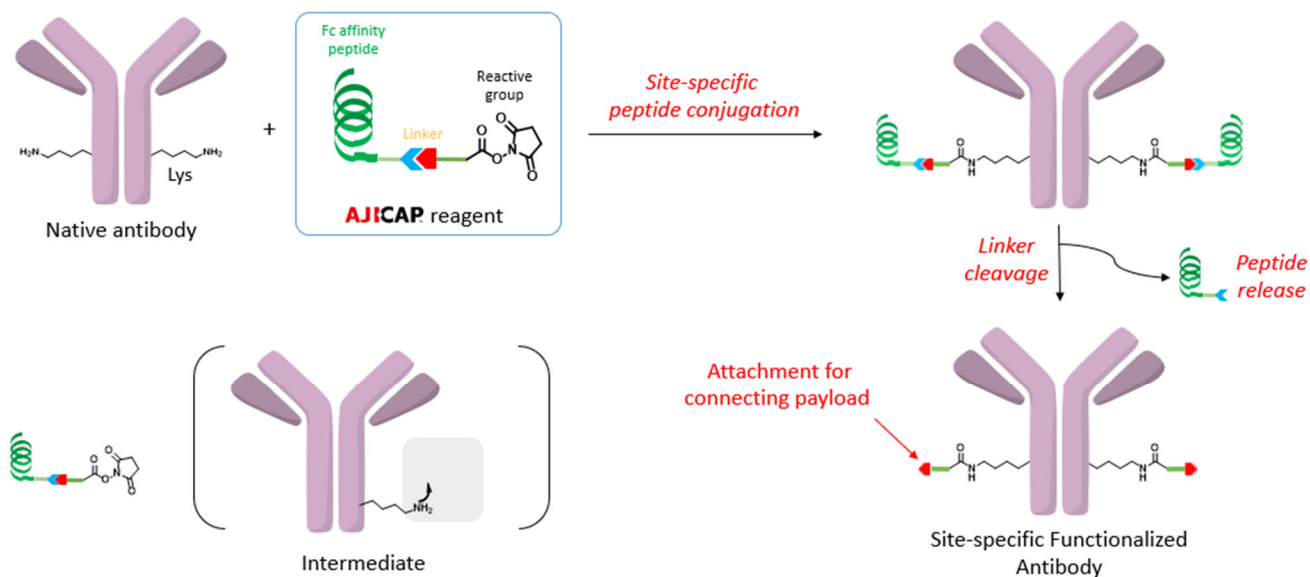
6. Claim 2 of the '675 Patent

346. Claim 2 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:

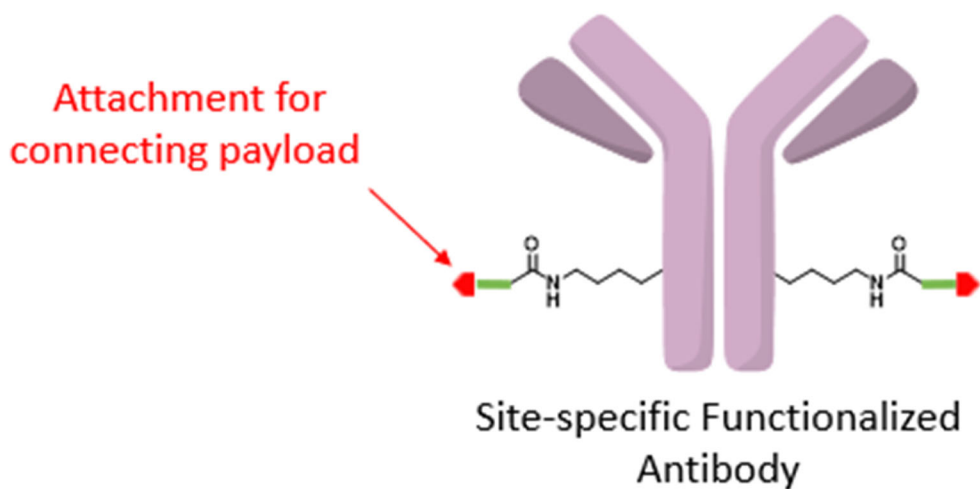


wherein H_1 is a group having the bio-orthogonal click chemistry functional group, and wherein D_1 is bond, or is selected from C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene and C_{3-8} cycloalkylene.”

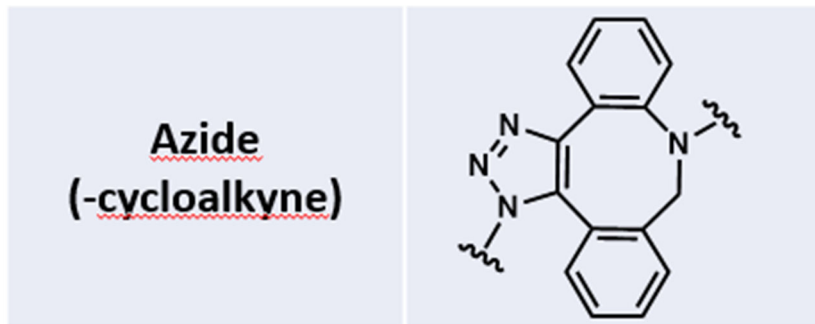
347. As previously discussed, PepTalk Presentation discloses an antibody modified to include an azide group at lysine residue 248. EX1007, 15-16, 18, 20. In particular, PepTalk Presentation discloses using an “Fc affinity peptide reagent” containing a “linker” to modify lysine 248 to include an “attachment” to which drug molecules or other payloads can connect. This is depicted in the following figure.



EX1007, 15. The “linker” represented in this figure is a pair of click-chemistry functional groups in their bound state. This figure depicts this linker being cleaved, leaving one of the click chemistry functional groups bound to the lysine residue, as seen more clearly in the figure below.



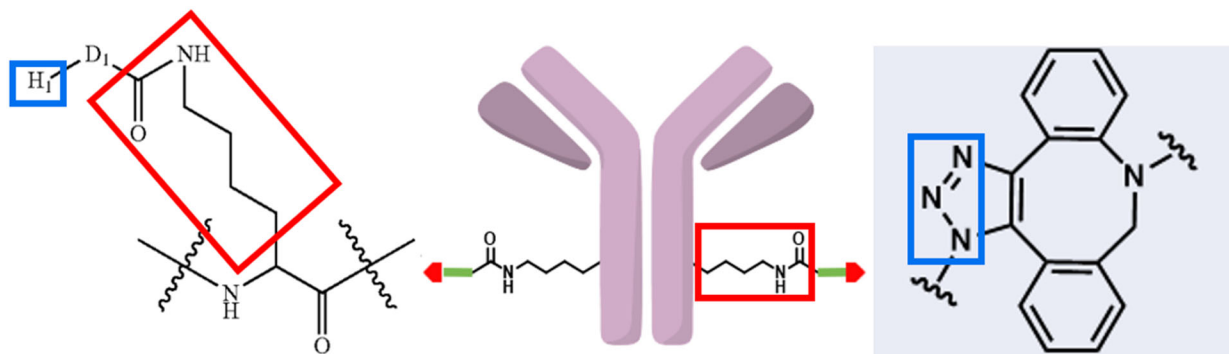
348. PepTalk Presentation discloses that this attachment may be an azide group, shown with its click-chemistry partner, a cycloalkyne, in the figure below.



EX1007, 20.

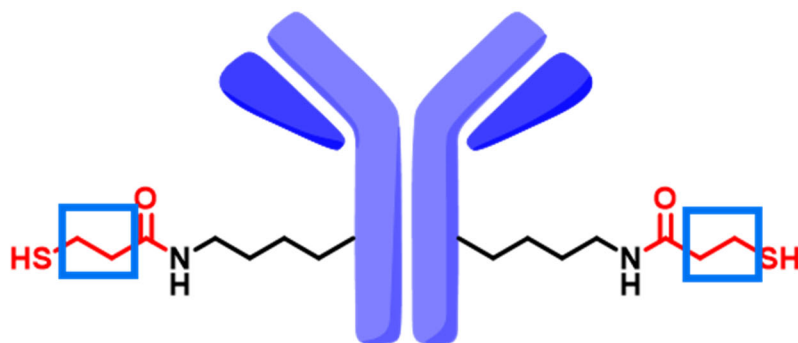
349. An antibody modified with an azide group in the manner taught by PepTalk Presentation can have the structure recited in Claim 2.

350. In particular, as shown below, PepTalk Presentation teaches that the antibody as modified to include the attachment includes the structure highlighted by the red rectangle below, i.e., the structure other than D₁ and H₁. By disclosing an azide group as a suitable bio-orthogonal click chemistry functional group, PepTalk Presentation discloses an azide group as H₁ in the structure of Claim 2, as indicated by the blue rectangle.



351. The POSA would understand that, when an azide group is used as H₁, the D₁ component would most likely be an alkyl or cycloalkyl.

352. This understanding is evidenced by PepTalk Presentation's example that includes a thiol group as the click-chemistry functional group. As shown in the figure below, PepTalk Presentation discloses an example of trastuzumab where lysine residue 248 is modified to have the structure recited in Claim 2, where the click-chemistry functional group, H₁, is a thiol group (-SH), and D₁ is an unsubstituted C₂ alkylene, indicated by the blue squares below.

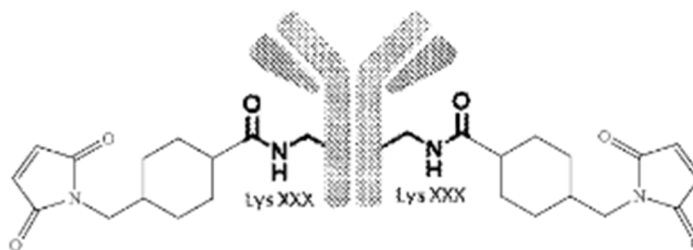


Site-specific functionalized trastuzumab (3)

EX1007, 16. A POSA would need only to substitute the thiol group for an azide, as disclosed on Slide 20 of PepTalk Presentation, to arrive at the structure of Claim 2.

353. Thus, PepTalk Presentation discloses the modified antibody of Claim 1 and all of the components of the modified lysine has the structure recited in Claim 2.

354. Additionally, Matsuda (EX1010) discloses Example 3-4 of Matsuda (reproduced below) includes an unsubstituted C₆ cycloalkylene, consistent with the requirement of D₁ for claim 2. A POSA would understand that the H₁ of Matsuda's Example 3-4 could be readily substituted with, for example, an azide, as disclosed in PepTalk Presentation, and the skilled person would expect the modified lysine to function effectively the same.



Example 3-4 of Matsuda (EX1011, p. 90)

355. Matsuda also discloses Example 5-2-1, which has an azide in the H₁ position and an unsubstituted C₅ alkylene (*id.*, p. 92), which is only one more carbon than claim 2 allows. A POSA would understand that this C₅ alkylene could be slightly longer or shorter and still function effectively the same. Thus, all of the elements of claim 2 are disclosed in PepTalk Presentation and Matsuda, and a POSA could readily combine these disclosures to predictably arrive at claim 2 with a reasonable expectation of success.

7. Claim 3 of the '675 Patent

356. Claim 3 recites: “The modified antibody of claim 2, wherein D₁ is bond, or is selected from unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene and unsubstituted C₃₋₈ cycloalkylene.”

357. Claim 3 thus limits Claim 2 by requiring that the options for D₁ recited in Claim 2 are “unsubstituted.” PepTalk Presentation discloses this limitation.

358. The term “unsubstituted” in this context means that each carbon atom in the alkylene, alkenylene, alkynylene, or cycloalkylene is bound to the maximum number of hydrogen atoms possible given the carbon atom's bonds to adjacent carbon atoms. This is in contrast to a “substituted” alkylene, alkenylene, alkynylene, or cycloalkylene, in which one of the carbon atoms has some other chemical species substituted for a hydrogen atom.

359. As previously discussed, PepTalk Presentation discloses the modified antibody of Claim 1 and it discloses all of the components of the modified lysine residue has the structure recited in Claim 2, including the D₁ of an unsubstituted C₁₋₄ alkylene. A POSA would understand that, where D₁ is a C₁₋₄ alkylene, C₂₋₄ alkenylene, C₂₋₄ alkynylene or C₃₋₈ cycloalkylene, these molecules could be unsubstituted, with each carbon atom having the maximum number of hydrogen atoms. Indeed, the D₁ component would most likely be an alkyl or cycloalkyl.

360. Thus, by disclosing the modified antibody of Claim 1 having the structure recited in Claim 2, including the possible D₁ components, PepTalk Presentation also discloses the structure of Claim 2 where D₁ is a bond, or an unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene or unsubstituted C₃₋₈ cycloalkylene, as required by Claim 3. PepTalk Presentation thus discloses the additional limitation of Claim 3. Specifically, A POSA would need only to substitute the thiol group on the modified antibody of Slide 16 with an azide, as disclosed on Slide 20 of PepTalk Presentation, to arrive at the structure of Claim 3.

8. Claims 5-7 and 11 of the '675 Patent

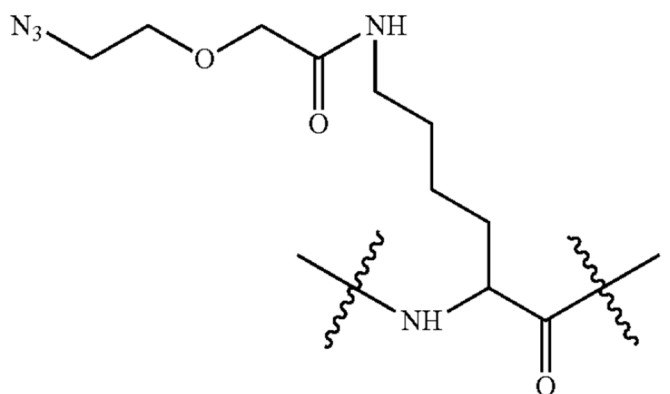
361. Claim 5 recites: “The modified antibody of claim 2, wherein D₁ comprises one or more heteroatoms.”

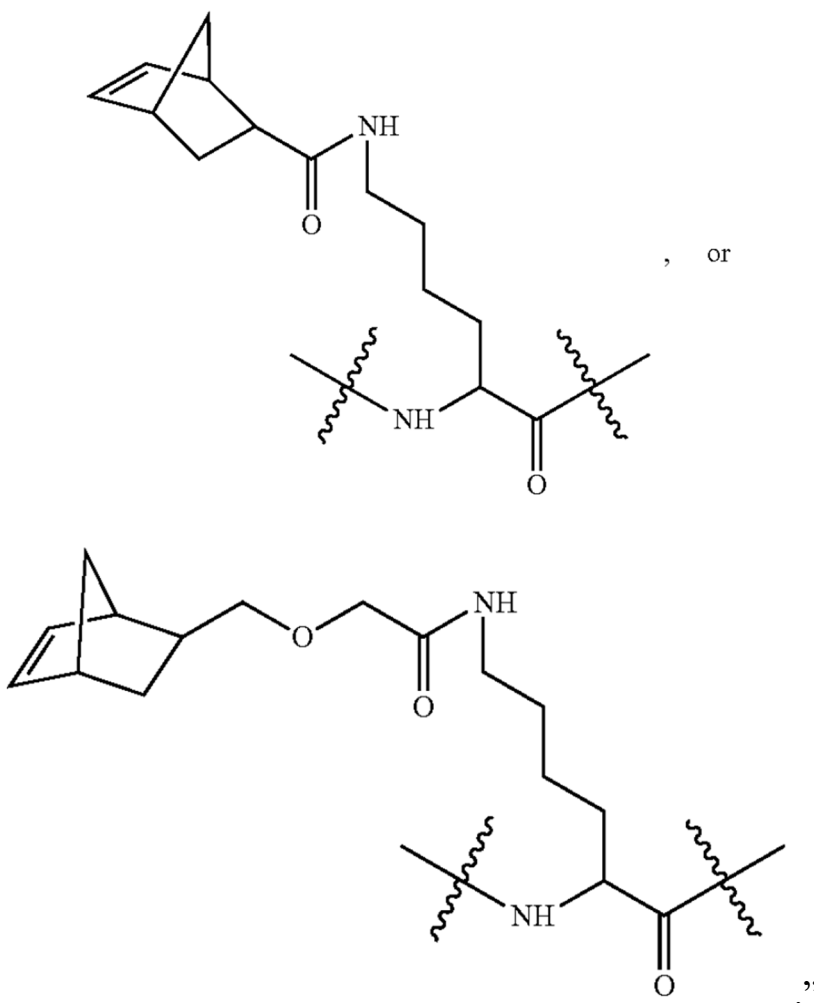
362. As previously discussed, PepTalk Presentation discloses the modified antibody of Claim 2, where D₁ may include any one selected from a covalent bond, a C₁₋₄ alkylene (i.e., the modified trastuzumab shown in Panel 3 of the Methods section), and the D₁ component would most likely be an alkyl or cycloalkyl when using an azide as the bio-orthogonal click chemistry group.

363. A POSA would understand that any of the recited alkylene, alkenylene, alkynylene, and cycloalkylene recited in claim 2 of the '674 Patent could be unsubstituted (i.e., having the maximum number of hydrogen atoms allowed given

the carbon atom's bonds with adjacent carbon atoms) or that any of these hydrocarbons could be substituted (i.e., another chemical species in place of a hydrogen atom). Heteroatoms would be understood to be among the possible substituents. Moreover, structures including one or more heteroatoms are disclosed in Yamada, as explained below.

364. Claim 6 recites: “The modified antibody of claim 2, wherein D₁ is —[CH₂]_a—O—[CH₂]_b—, wherein each of a and b is independently selected from 0 to 4, and each of a and b is integer, and wherein sum of a and b is 0 or more and 4 or less.” Claim 7 recites: “The modified antibody of claim 2, wherein D₁ is —CH₂CH₂OCH₂— or —CH₂OCH₂—.” Claim 11 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:





365. I am discussing claims 5-7 and 11 together because the first and third structures recited in claim 11 include all of the limitations of claims 5-7. Thus, by showing that the first and third structures recited in claim 11 were previously disclosed, it would be apparent that the broader limitations of claims 5-7 had also been previously disclosed.

366. PepTalk Presentation discloses a modified antibody with lysine residues 248 modified with an azide group (EX1007, 15-16, 18, 20), and Yamada likewise discloses antibodies modified at lysine 248 (EX1009, [0222], [1037],

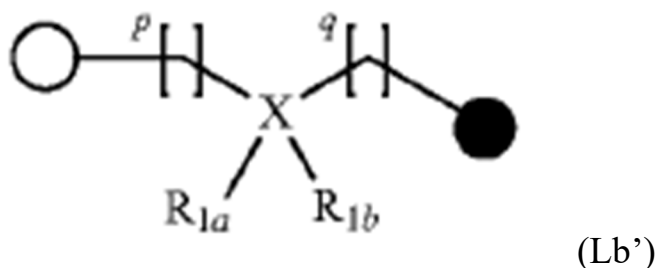
[1109], [1114], etc.) with an azide (*id.*, [0151], [0153], [1037], Figure 18) or a norbornene (*id.*, [0151], [0153]).

367. Yamada discloses an antibody regioselectively modified with a bio-orthogonal functional group represented by (Formula (IV)):

L1-B-R'-T (IV)

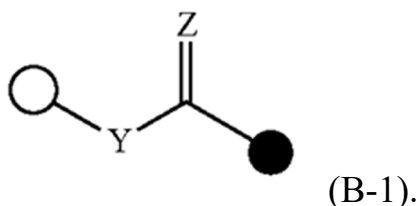
in which “L1 is (i') a monovalent group comprising a bioorthogonal functional group or (ii') a monovalent group comprising no bioorthogonal functional group; B is (a) a divalent group comprising a bioorthogonal functional group or (b) a divalent group comprising no bioorthogonal functional group; R' is a portion formed by a reaction between a soluble protein and a reactive group; and T is a soluble protein.” EX1009, [0584]-[0588]. It is my understanding that in the context of Yamada, the term “monovalent group” refers to a group that has a single covalent bond to another group, and the term “divalent group” means a group that has two covalent bonds connecting it to two other groups.

368. Paragraphs [0616]-[0624] further define L1 with specific groups. In particular, these paragraphs explain that L1 can either be C1, can be a bio-orthogonal functional group (e.g., azide, norbornene, etc.; *see* EX1009, [0626]-[0627]) or it can have a structure of C1-Lb, wherein LB is:

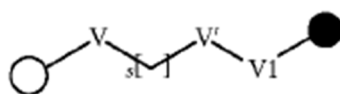


in which the White Circle indicates a bond to C1, which (as noted above) can be a bio-orthogonal click chemistry group (e.g., azide, norbornene, etc.); p and q are integers from 0-10; X can be a carbon (C) a nitrogen (N), or a single bond; and R_{1a} and R_{1b} can be present as a substituent or absent. The black circle indicates the bond to B

369. Paragraphs [0631]-[0639] further define B with specific groups. In particular, these paragraphs explain that B is defined as having a structure of:



Within (B-1), the White Circle is the connection to L1; the Black Circle is the connection to R'; Z can be "an oxygen atom, a sulfur atom, or a hydrogen atom wherein when Z is a hydrogen atom, -C(=Z)- indicates -CH₂-"; and Y can be -NH-, -O-, -CH₂-, or B-2:



(B-2).

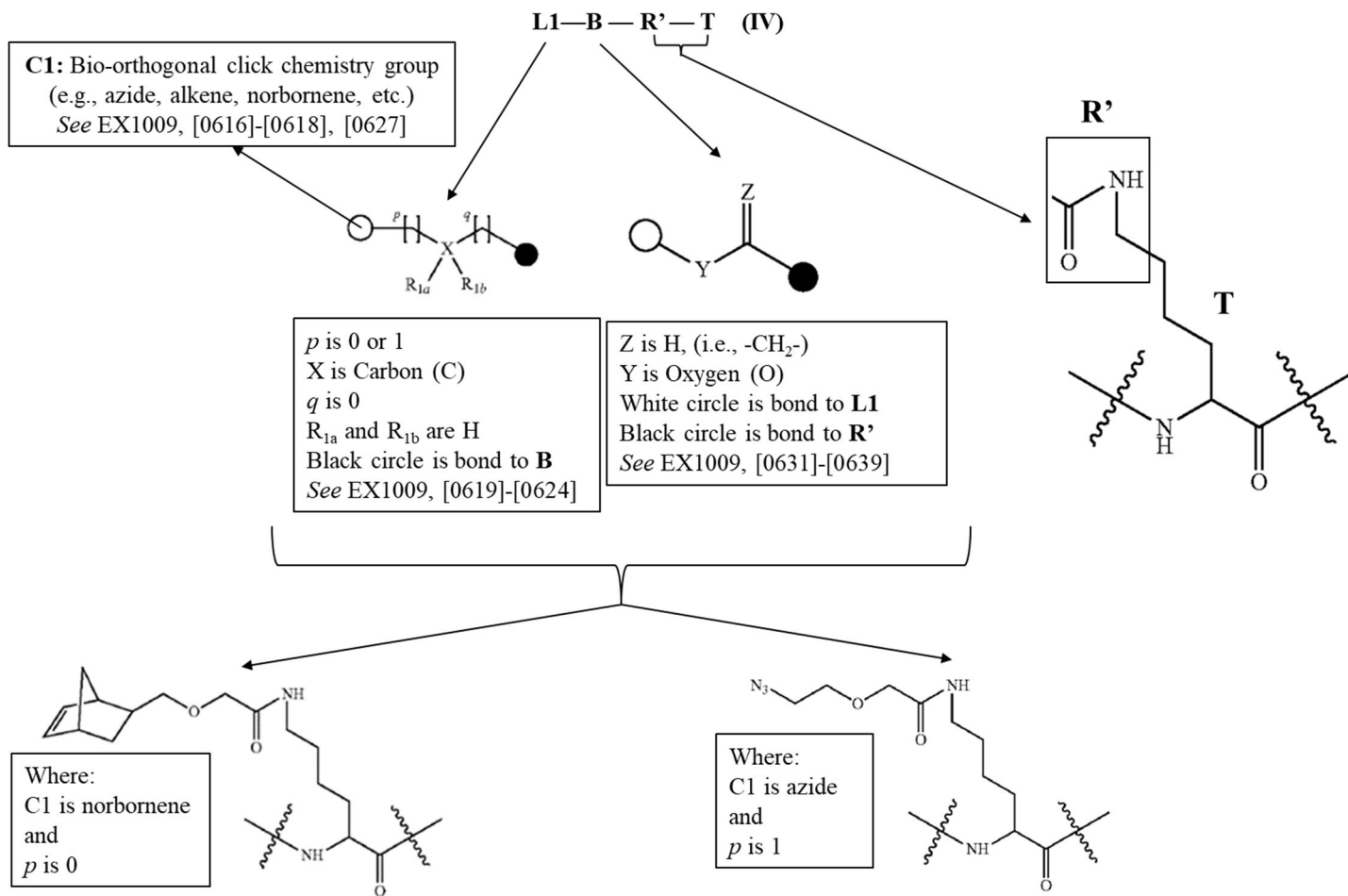
When Y is B-2, paragraphs [0634]-[0636] explain that V and V' can each independently be -NH-, -O-, -CH₂-, or a single bond; V1 is “a divalent group comprising a bioorthogonal functional group” ; and s is any integer from 0 to 10. I note that paragraph [1571] indicates that with respect to B-2 (this paragraph references “partial structural formulae ... (B-1) to (B-4)...”) that this “technical element” is described various ways throughout the application. Specifically, paragraph [1571] states, “these matters can be quoted as appropriate in the inventions described below without any special reference” and “the technical elements of a specific invention described in the inventions described below can be quoted as appropriate as the technical elements of the present invention and other inventions.” I understand this to mean that the various disclosures of formula B-2 throughout the publication can be substituted for one another. Accordingly, where paragraph [1470] describes the same Formula (B-2) in a similar context, and paragraphs [1472] and [1480] indicate “V1 is (a) a divalent group comprising a bioorthogonal functional group or (b) a divalent group comprising no bioorthogonal functional group,” a POSA would understand that the bio-orthogonal functional group within V1 is optional. As such, V1 could be, for

example, an oxygen (-O-) which fits Yamada's description of "a divalent group." *See e.g.*, [1465]. Note that the white and black circles in B-2 are simply included to show the orientation of the fragment in relation to the structure of B-1.

370. As noted above, R' is defined as "a portion formed by a reaction between a soluble protein and a reactive group." Yamada describes "[e]xamples of a linking portion formed by a reaction between the reactive group specific to a side chain of a lysine residue and the amino group (NH₂) present in the side chain of the lysine residue include an amide residue..." EX1009, [1510]. Thus, the amide portion of the partial structure from claim 2 of the '675 Patent should be considered as R'. Accordingly, there are two ways in which Formula (IV) can be completed to arrive at the first and third structures of claim 11.

371. Specifically, a POSA could readily envisage that first and third structures recited in claim 11 by selecting the components of Formula (IV) as shown in the flow diagrams below:

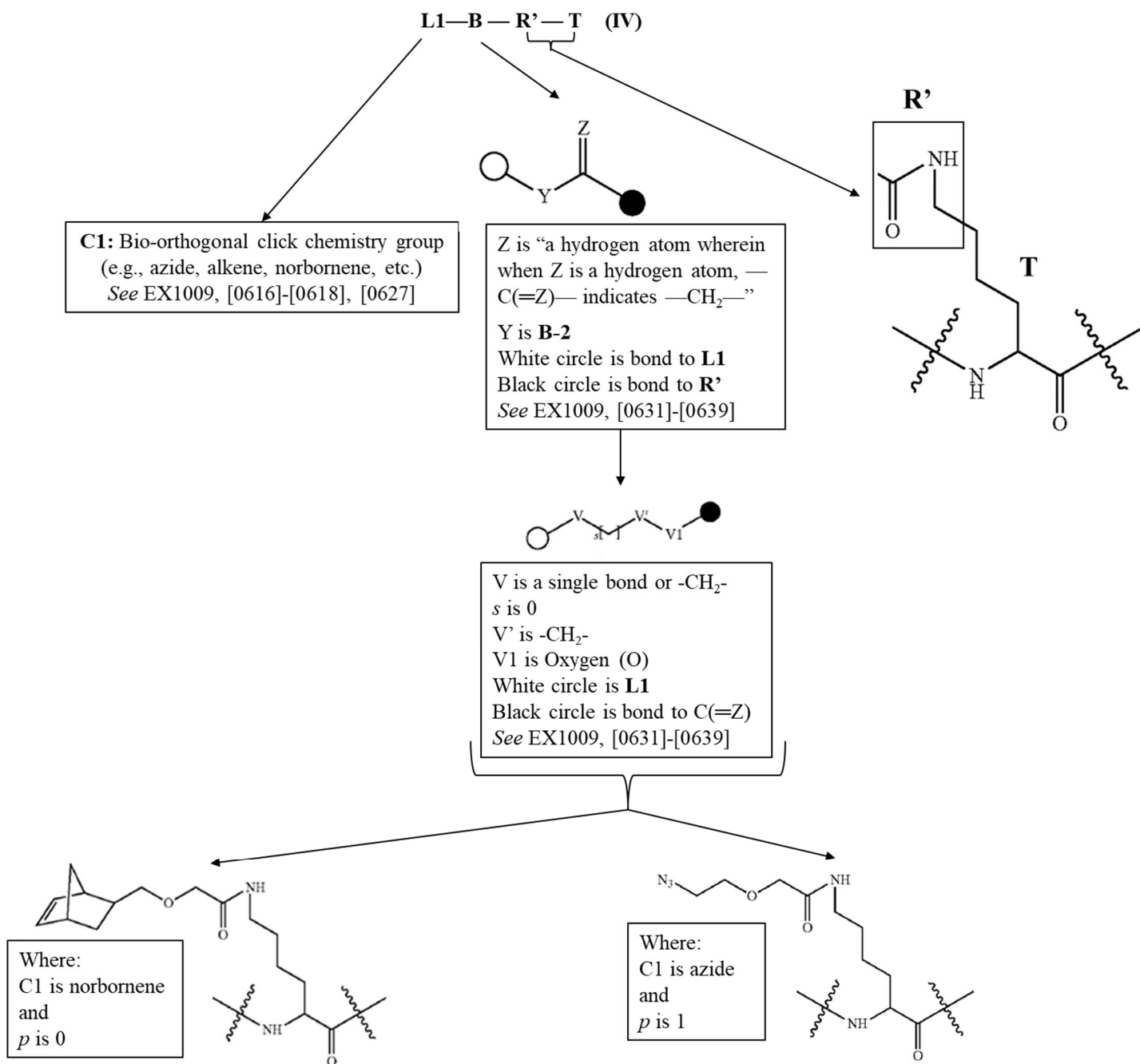
Option 1:



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



Option 2:



For Option 2, the components of the structures from claim 11 are denoted with their respective positions within Formula (IV):

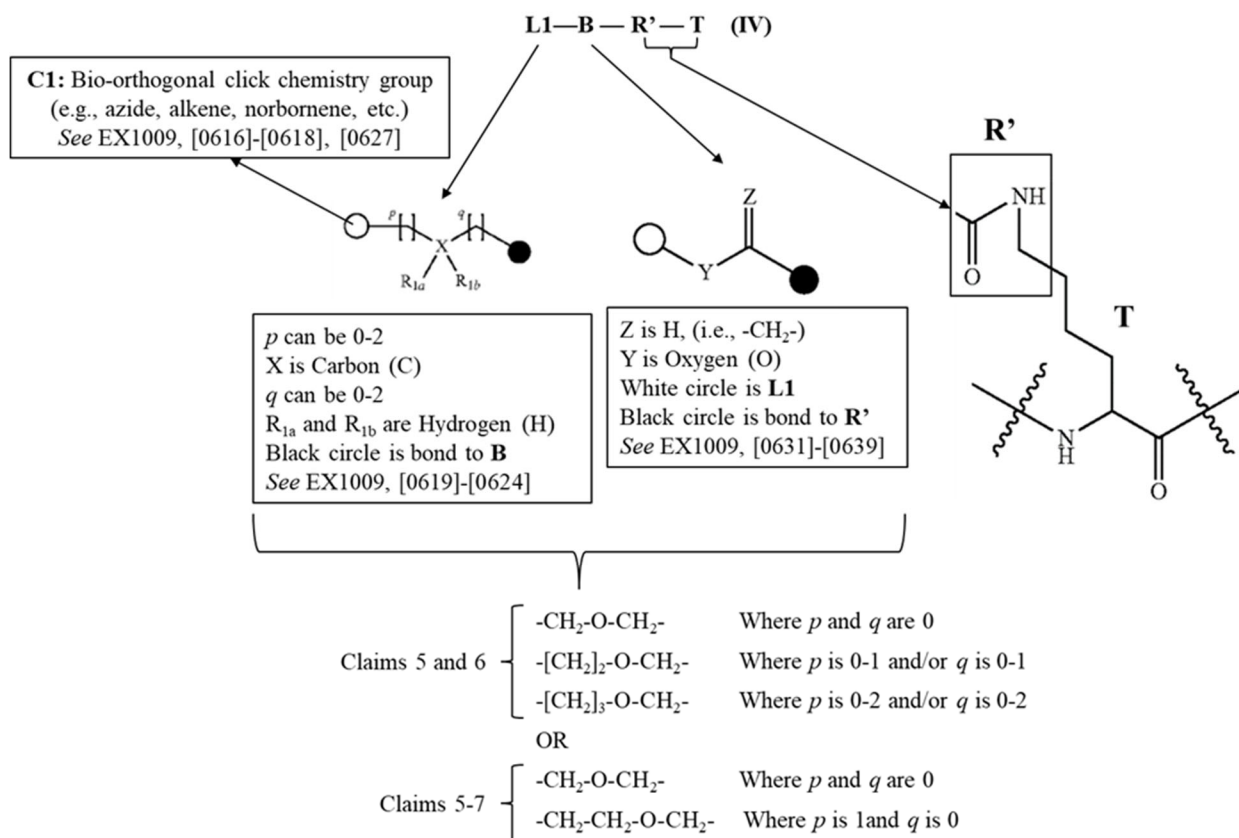


372. Thus, the first and third structures recites in claim 11 of the '675 Patent are disclosed in Yamada and could be predictably constructed based on Yamada's disclosure. As such, the limitations of claims 5-7 are also disclosed, as each of these structures includes a heteroatom (i.e., oxygen) within the segment corresponding to D1 (i.e., the limitations of claim 5) and the specific D1 structures recited in claims 6 and 7 (i.e., $\text{—CH}_2\text{CH}_2\text{OCH}_2\text{—}$ or $\text{—CH}_2\text{OCH}_2\text{—}$) correspond to the azide-containing structure on the right and the norbornene-containing structure on the left, respectively.

373. In addition to these particular compounds, Yamada also makes very clear that the segment of its modified structures corresponding to D1 fall within the scope of claims 5-7.

374. Both L1 and B of Formula (IV) contain multiple options for inclusion of a heteroatom. Specifically, when L1 includes Lb, it may comprise "a carbon atom, a nitrogen atom, or a single bond" as the X component (EX1009, [0622]), and in formula (B-1), the Y component could be —NH— or —O— or CH_2 (*id.*, [0633]). Each of these allows for various constructions that would fall within the scope of claims 5

and 6. For example, inserting -O- as the Y component and a carbon atom as the X component can yield a number of combinations that satisfy both claims 5 and 6. Indeed, positions p and q could be varied in numerous ways and still remain within the scope of these claims. Claim 7 would also be covered with this arrangement as summarized in the flow chart below.



375. Accordingly, all of the components of claims 5-7 and 11 of the '675 Patent are taught and suggested in PepTalk Presentation and Yamada, and a POSA would reasonably expect to be able to combine these components to arrive at the claims based on simple substitutions.

9. Claim 12 of the '675 Patent

376. PepTalk Presentation discloses this limitation. In particular, PepTalk Presentation discloses a modified antibody with lysine residues 248 modified with an azide group. EX1002, 15-16, 18, 20. As previously discussed in connection with Claim 9, an azide group is a group capable of participating in a Huisgen 1,3-dipolar cycloaddition. *See* paragraphs 242-246 (Section XI(C)(4), above).

377. As previously discussed in connection with Claim 2 and Claim 3, PepTalk Presentation and Matsuda disclose modified lysine structures that correspond to and/or comprise all of the elements of the structures recited in Claims 2 and 3. *See* paragraphs 251-261 (Sections XI(C)(6)-(7), above).

378. Thus, PepTalk Presentation and Matsuda disclose all of the elements of the modified antibody of Claim 12, and a POSA could readily combine these disclosures to predictably arrive at claim 12 with a reasonable expectation of success.

10. Claim 13 of the '675 Patent

379. Claim 13 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.”

380. PepTalk Presentation discloses both an azide group and a dibenzocyclooctyne group as bio-orthogonal functional groups. EX1007, 15-16, 18, 20. Yamada likewise discloses antibodies modified at lysine 248 (EX1009, [0222], [1037], [1109], [1114], etc.) with an azide (*id.*, [0151], [0153], [1037], Figure 18) or a norbornene (*id.*, [0151], [0153]), as does Matsuda (EX1011, [0046]-[0047], [0592]-[0593]).

381. As previously discussed in connection with Claim 2 and Claim 3, PepTalk Presentation and Matsuda disclose modified lysine structures that correspond to and/or comprise all of the elements of the structures recited in Claims 2 and 3. *See* paragraphs 251-261 (Sections XI(C)(6)-(7), above).

382. Thus, PepTalk Presentation and Matsuda disclose all of the elements of the modified antibody of Claim 13, and a POSA could readily combine these disclosures to predictably arrive at claim 13 with a reasonable expectation of success.

D. Claims 1-13 of the '675 Patent Are Unpatentable in View of Yamada (EX1008) and Matsuda (EX1009)

383. The combination of Yamada (EX1008) and Matsuda (EX1009) render Claims 1-13 of the '675 Patent unpatentable. More specifically, Yamada itself discloses the modified antibody of claims 1, 4, 8, and 10. The modified antibodies of dependent Claims 2-13 would have been obvious to a POSA based on the

combination of Yamada and Matsuda for the reasons discussed below; namely, because all of the elements of Claims 2-13 are explicitly disclosed or suggested in Yamada, Matsuda, or both, and a POSA could combine the disclosed elements with a reasonable expectation of success.

1. Independent Claim 1 of the '675 Patent

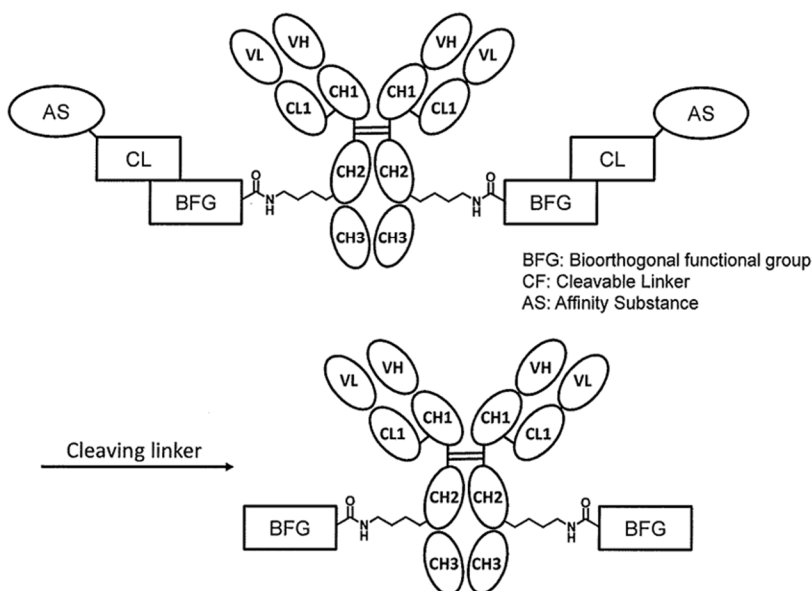
a. A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group,

384. Yamada discloses the limitation “a modified antibody or its fragment comprising bio-orthogonal click chemistry functional group.”

385. In particular, Yamada discloses “(1) A soluble protein regioselectively having a bioorthogonal functional group(s), or a salt thereof” EX1009, [0581]. Yamada discloses that the soluble protein is an antibody. For example, Yamada discloses “(3) The soluble protein or salt thereof according to (1) or (2), wherein the soluble protein is a monoclonal antibody.” *Id.*, [0592].

386. Yamada illustrates regioselective modification of a soluble protein such as an antibody in Figure 1-2, shown below.

FIG. 1-2

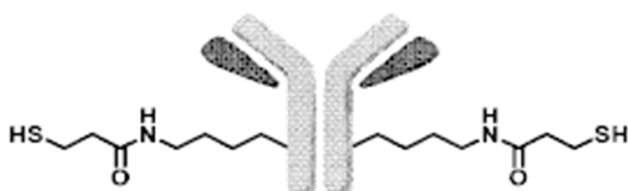


EX1009, [1019].

387. Regarding Figure 1-2, Yamada states: “FIG. 1-2 is a schematic diagram (No. 2) of the concept of regioselective modification of a soluble protein (e.g., an antibody) with the compound of the present invention. Cleavage of a cleavable portion in a linker (L) produces a soluble protein (e.g., an antibody) regiospecifically modified with bioorthogonal functional groups.” *Id.* As shown in the legend of Figure 1-2, the bio-orthogonal functional group is indicated by “BFG” and is shown attached to a lysine residue of each of the CH2 domains of the antibody.

388. A POSA would understand that a bio-orthogonal functional group attached via “cleavable linker” in Figure 1-2 is a click chemistry functional group at least because (a) Yamada discloses in paragraphs [0151]-[0153] various click

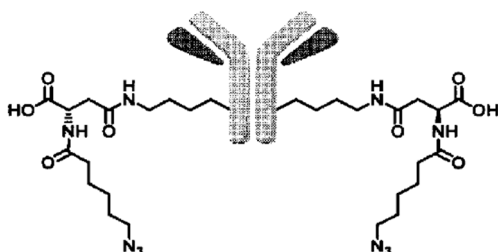
chemistry functional groups (e.g., azide, norbornene, etc.) as examples of a “bioorthogonal function group,” and (b) Yamada further discloses, in Table 3, examples of resulting antibodies regioselectively modified with a bio-orthogonal functional group. As just some examples, Yamada discloses the following modified antibodies including bio-orthogonal functional groups, which all include click chemistry functional groups:



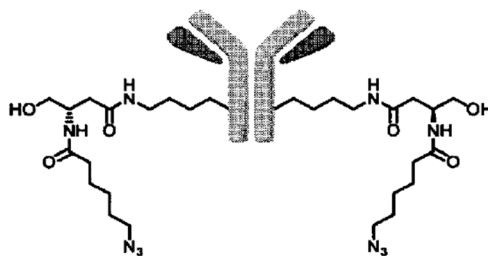
(prepared with the compound of Example 2-2);



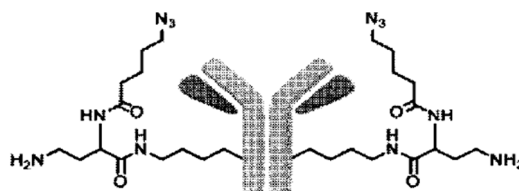
(prepared with the compound of Example 2-3);



(prepared with the compound of Example 11-1);



(prepared with the compound of Example 11-2); and



(prepared with the compound of Example 57)

EX1005, p. 147-148.

389. Yamada thus discloses “a modified antibody or its fragment comprising bio-orthogonal click chemistry functional group.”

b. wherein the modified antibody comprises one or more modified heavy chain,

390. Yamada discloses the limitation “the modified antibody comprises one or more modified heavy chain.”

391. In particular, Yamada discloses “(15) The soluble protein or salt thereof according to any one of (1), (3) to (14), wherein the soluble protein is an antibody comprising a plurality of heavy chains, and the bioorthogonal functional groups are present in positions of the one or more specific amino acid residues in a plurality of

heavy chains such that the antibody has a plurality of bioorthogonal functional groups.” EX1009, [0606]-[0608].

392. As noted regarding the previous limitation, in Yamada’s embodiment (3), the soluble protein is a monoclonal antibody. The above-cited embodiment (15) specifies that the antibody of embodiment (3) has a plurality of heavy chains with bio-orthogonal functional groups. As also noted regarding the previous limitation, Yamada discloses several examples of modified antibodies in Table 3, where each example antibody has two modified heavy chains. EX1005, p. 147-148.

393. Yamada therefore discloses that “the modified antibody comprises one or more modified heavy chain.”

c. 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

394. Yamada discloses “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.”

395. In particular, Yamada discloses: “(9) The soluble protein or salt thereof according to (8), wherein the target region is (a) a region consisting of amino acid residues at positions 246 to 248 in an human IgG Fc region, (b) a region consisting of amino acid residues at positions 288 to 290 in the human IgG Fc region, or (c) a

region consisting of an amino acid residue at position 317 in the human IgG Fc region.” EX1005, [0598].

396. Thus, in embodiment (9), Yamada discloses that the target region may consist of amino acid residues at positions 246 or 248 in an Fc region of human IgG. The POSA understood that human IgG is the antibody Immunoglobulin G. The “target region” referenced in embodiment (9) refers back to embodiment (1), in which “the soluble protein comprises one or more specific amino acid residues in a target region,” and “the bioorthogonal functional group(s) binds to the one or more specific amino acid residues in the target region” EX1005, [0581]-[0583]. Although embodiment (9) only expressly refers to embodiment (8), embodiment (9) includes the features of embodiment (1), including the target region and bioorthogonal functional groups. That is because each embodiment in Yamada’s embodiments (1)-(9) builds off of the preceding embodiment. For example, embodiment (9) is “[t]he soluble protein or salt thereof according to embodiment (8),” and embodiment (8) is “[t]he soluble protein or salt thereof according to any one of (1) to (7),” and (7) is “[t]he soluble protein or salt thereof according to any one of (1) to (6),” etc., back to embodiment (3), which is “[t]he soluble protein or salt thereof according to (1) or (2),” where (1) and (2) are each a standalone embodiment. *Id.*, [0581]-[0598].

397. Embodiment (9) therefore includes an antibody, such as human IgG, with bioorthogonal functional groups bound at a target region of amino acid residue position 248 in the Fc region.

398. The POSA understood that amino acid residue position 248 in the Fc region was a lysine residue. The POSA also understood that position 248 is determined by an EU numbering system.

399. In addition, as discussed regarding the preceding limitation, Yamada discloses in embodiment (15) an antibody having a plurality of heavy chains modified with bioorthogonal functional groups. EX1005, [0606]-[0608]. Yamada also discloses that embodiment (15) is “[t]he soluble protein or salt thereof according to any one of (1), (3) to (14)” *Id.*, [0606]. Embodiment (15) thus includes embodiment (9), but where each of the plurality of heavy chains has a lysine residue 248 modified with a bioorthogonal functional group.

400. Yamada further discloses modification of lysine 248 in disclosing:

More specifically, in the present invention, in view of, while maintaining the function of a protein such as an antibody (that is, while maintaining native folding without denaturing the protein), modifying amino acid residues present at specific positions in the protein, **preferred is regioselective modification of amino acid residues exposed to the surface of the protein.** In human IgG such as human IgG1, for example, **exposed lysine residues** and exposed tyrosine residues are present at the following positions (refer to

<http://www.imgt.org/IMGTScientificChart/Numbering/HuIGHGnber.html> by EU numbering).

(1) Exposed Lysine Residues:

CH2 domain (position 246, **position 248**, position 274, position 288, position 290, position 317, position 320, position 322, and position 338) **CH3 domain** (position 360, position 414, and position 439).

EX1005, [1108]-[1109].

401. In this passage, Yamada discloses that position 248, “by EU numbering,” contains a lysine residue, and that lysine residues exposed to the surface of the antibody, such as lysine 248, are preferred for modification.

402. In addition, Yamada discloses modification of lysine residue 248 in antibodies trastuzumab and IgG1 Fc in Example 8. EX1005, [1945]-[1971]. For example, Yamada discloses:

An MS spectrum of the peptide fragment of LLGGPSVFLFPPKPKD (SEQ ID NO: 6), which is a peptide consisting of 16 amino acid residues comprising a modified site to a lysine residue by Glu-C Protease digestion of trastuzumab (a thiol-introduced portion subjected to carboxymethylation with iodoacetic acid (+146.004 Da)) (measured value: m/z 929.49573; theoretical value: 929.49527; and divalent) was observed (FIG. 11); and from a CID spectrum, a product ion of m/z 505.22 (theoretical value: 505.20) corresponding to divalent y3 indicating **modification of a lysine residue at position 248 in EU numbering of the heavy chain was determined** (FIG. 12).

Id., [1969].

403. Yamada also provides motivation for those skilled in the art to prepare an antibody regioselectively modified with a bio-orthogonal functional group at the lysine residue at position 248. In particular, Yamada discloses that the development of antibody drug conjugates (ADCs) has the problem of nonuniformity. For example, to prepare an ADC, a small molecule drug is randomly reacted with about 70 to 80 lysine residues in an antibody, resulting in an ADC having a drug to antibody ratio (DAR) ranging from 0-8. A mixture of ADCs is thereby produced, where the ADCs in the mixture can have a different number of drugs conjugated to the antibody. The DAR of an ADC can influence its stability, solubility, antigen binding, clearance, and biodistribution, resulting in different DAR species having distinct pharmacokinetics behaviors. A POSA would therefore be motivated to regioselectively modify an antibody in order to prepare ADCs with a known and consistent DAR so that the pharmacokinetic properties of the ADC can be consistent.

404. Yamada thus discloses that “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.”

d. wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end, and

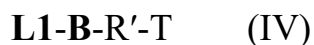
405. Yamada discloses “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

406. As previously discussed, Yamada discloses an antibody modified at lysine residues at position 248 to include bioorthogonal functional groups.

407. Yamada further discloses that the bioorthogonal functional groups are bioorthogonal click chemistry functional groups, for example, in relation to embodiments (2), (28), and (30).

408. Regarding (2), Yamada discloses:

(2) A soluble protein regioselectively having a bioorthogonal functional group(s) represented by the following Formula (IV):



wherein

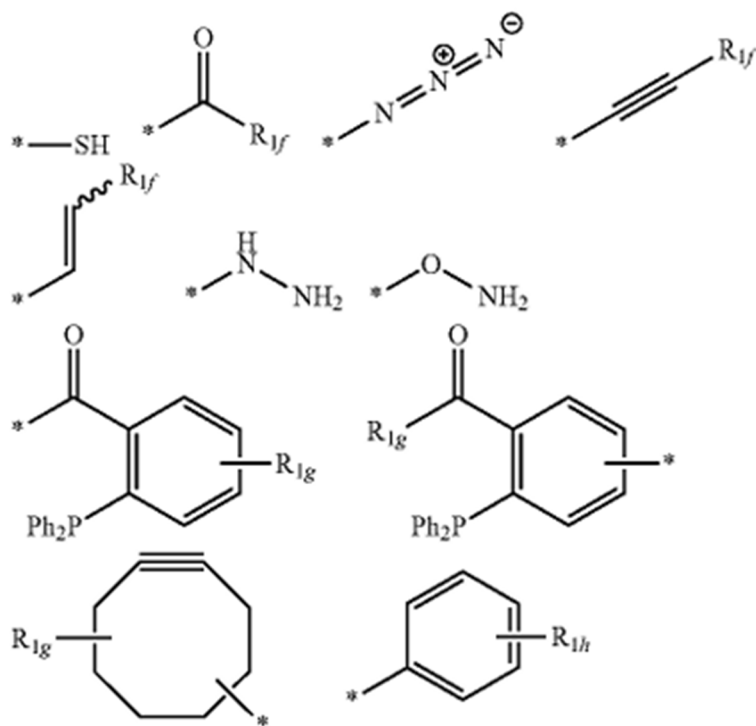
L1 is (i') a monovalent group comprising a bioorthogonal functional group or (ii') a monovalent group comprising no bioorthogonal functional group; **B is (a) a divalent group comprising a bioorthogonal functional group** or (b) a divalent group comprising no bioorthogonal functional group; **R'** is a portion formed by a reaction between a soluble protein and a reactive group; and **T** is a soluble protein

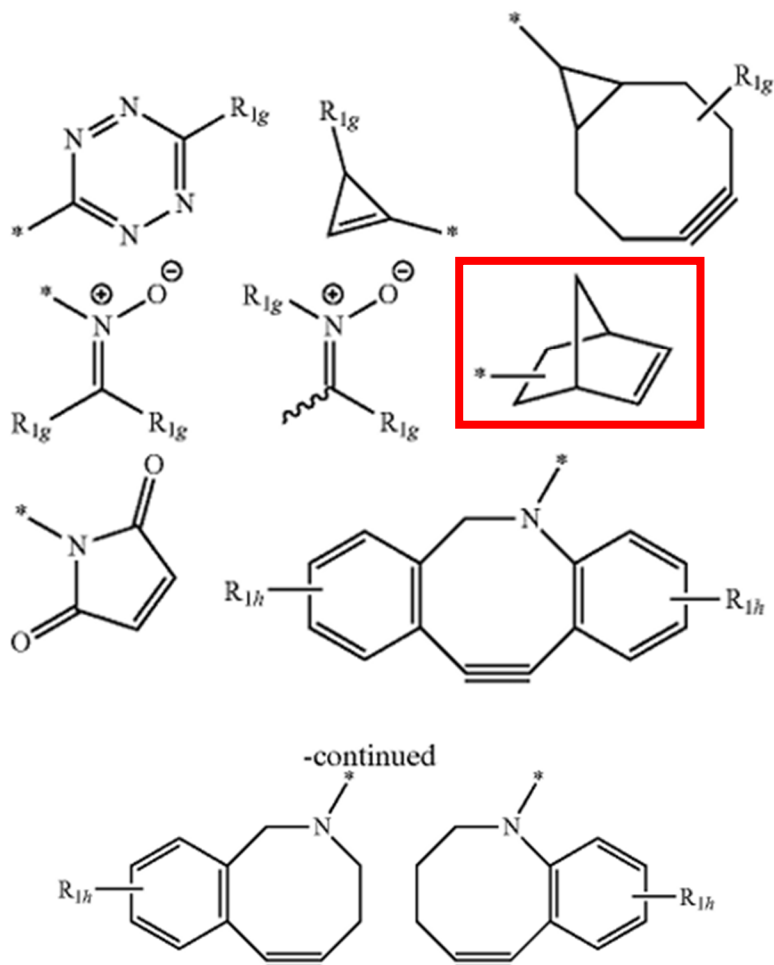
EX1005, [0584]-[0588].

409. Yamada discloses that the bioorthogonal functional groups may be any of a number of known click chemistry functional groups. For example, in relation to embodiment (28), “[t]he compound or salt thereof according to any one of (1) to (27),” Yamada discloses that the divalent group comprising a bioorthogonal functional group may be any of “an azide residue, an aldehyde residue, a thiol

residue, an alkyne residue, an alkene residue, a tetrazine residue, a nitron residue, a hydroxyamine residue, a nitrile residue, a hydrazine residue, a ketone residue, a boronic acid residue, a cyanobenzothiazole residue, an allyl residue, a phosphine residue, a maleimide residue, a disulfide residue, a thioester residue, an a-halocarbonyl residue, an isonitrile residue, a sydnone residue, and a selenium residue in a main chain thereof.” EX1005, [0151].

410. Yamada further discloses the structures of suitable bioorthogonal functional groups. For example, in relation to embodiment (30), “[t]he compound or salt thereof according to any one of (1) to (29),” Yamada discloses that the bioorthogonal functional group is any one of the following:





EX1005, [0153] (norbornene is highlighted with a box).

411. The POSA understood that this set of bioorthogonal functional groups includes several click chemistry functional groups. As just one example, the bioorthogonal functional groups depicted above include norbornene, highlighted in red), which the '675 Patent itself discloses as a bioorthogonal click chemistry functional group. EX1001, 151:50-153:32.

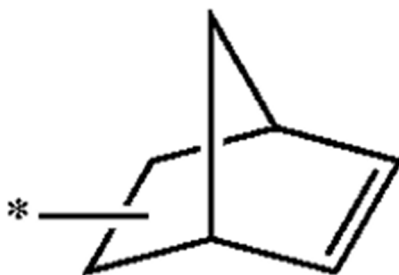
412. Accordingly, Yamada discloses that “the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end.”

- e. wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.*

413. Yamada discloses the limitation “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy[l] group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

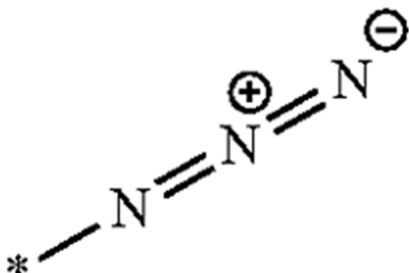
414. As previously discussed, Yamada discloses an antibody modified to include a bioorthogonal click chemistry functional group at lysine residue 248.

415. As discussed regarding the previous limitation, Yamada discloses a wide variety of bioorthogonal functional groups, including bioorthogonal click chemistry functional groups. As previously noted, in connection with embodiment (30), Yamada discloses norbornene as one such bioorthogonal click chemistry functional group. The depiction of norbornene in Yamada is shown below.



EX1005, [0153].

416. As another example, Yamada discloses an azide group as a bioorthogonal functional group, as shown below.



Id.

417. The POSA understood that an azide group is a bio-orthogonal click chemistry functional group. Indeed, the '675 Patent itself discloses the use of an azide as a bioorthogonal click chemistry functional group. EX1001, 153:33-53.

418. Neither norbornene nor an azide group are among the functional groups excluded by Claim 1.

419. Yamada thus discloses that “the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.”

420. Yamada thus discloses the modified antibody of Claim 1.

f. Yamada can be combined with Matsuda to render Claim 1 Obvious

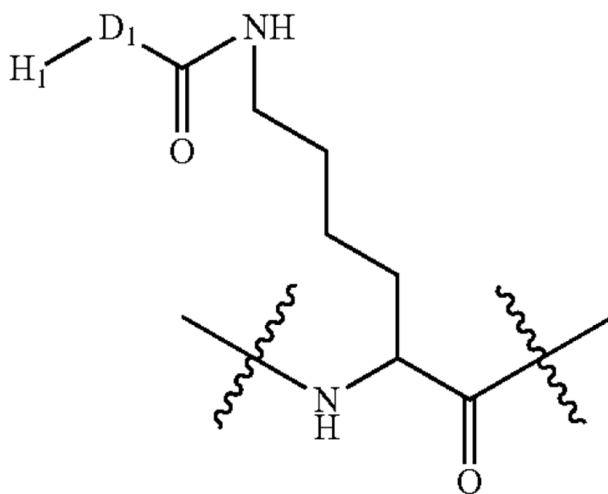
421. Yamada provides motivation for a POSA to prepare an antibody regioselectively modified with a bio-orthogonal functional group at the lysine residue at position 248. Yamada discloses that the development of antibody drug conjugates (ADCs) has the problem of nonuniformity. EX1005, [0004]. For example, to prepare an ADC, a small molecule drug is randomly reacted with about 70 to 80 lysine residues in an antibody, resulting in an ADC having a drug to antibody ratio (DAR) ranging from 0-8. Thus, a mixture of ADCs is produced, where the ADCs in the mixture can have a different number of drugs conjugated to the antibody. *Id.* The DAR of an ADC can influence its stability, solubility, antigen binding, clearance and biodistribution, resulting in different DAR species having distinct pharmacokinetics behaviors. *Id.*, EX1027, 541. Thus, a person of ordinary skill would be motivated to regioselectively modify an antibody in order to prepare ADCs with a known and consistent DAR so that the pharmacokinetic properties of the ADC can be consistent.

422. Matsuda provides further motivation for a POSA to regioselectively modify an antibody at the lysine residue at position 248 with a bio-orthogonal functional group and a terminal bio-reactive functional group that is not a hydroxy group, carboxyl group, thiol group, amino group, and aldehyde group. Specifically,

Matsuda discloses lysine 248 as one of only five preferred positions (EX1011, [0329], [0431]). Matsuda also demonstrates that antibodies can be regioselectively modified with a terminal azide as a bio-orthogonal functional group (Example 5-2-1) and a terminal azide as a terminal bio-reactive functional group (Example 5-2-2). EX1011, [1018]-[1029],[1289]-[1290], and [1296]-[1298]. The modified antibodies prepared in Examples 5-2-1 and 5-2-2 of Matsuda are shown below:

2. Claim 2 of the '675 Patent

423. Claim 2 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:



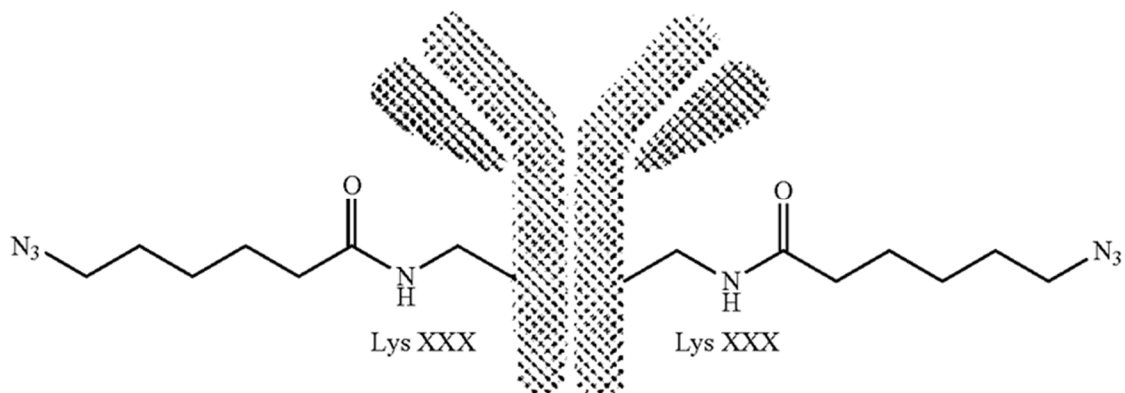
wherein H₁ is a group having the bio-orthogonal click chemistry functional group, and wherein D₁ is bond, or is selected from C₁₋₄ alkylene, C₂₋₄ alkenylene, C₂₋₄ alkynylene and C₃₋₈ cycloalkylene.”

424. As previously discussed regarding claim 1, Yamada discloses an antibody modified at lysine residue 248 to include a bio-orthogonal click chemistry functional group, including a terminal azide group.

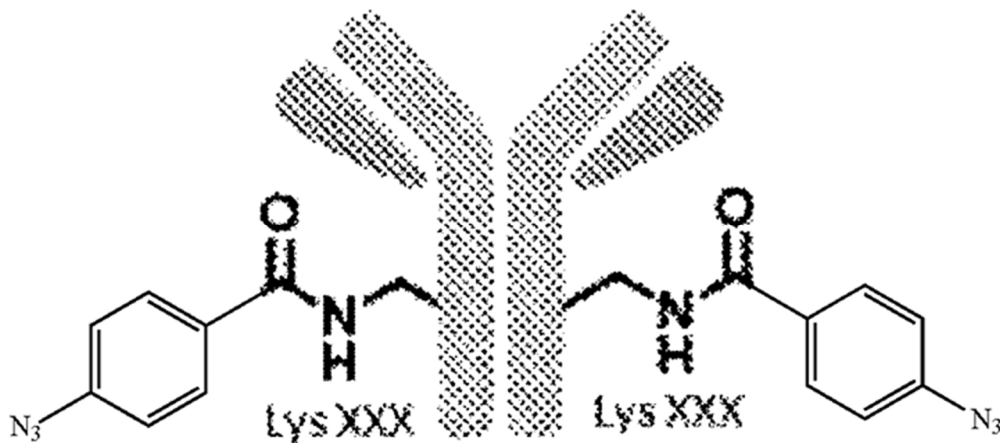
425. Matsuda also discloses an antibody modified at lysine residue 248 to include a bio-orthogonal click chemistry functional group, including a terminal azide and a terminal maleimide.

426. In particular, Matsuda discloses Examples 5-2-1 and 5-2-2, shown below, where the bio-orthogonal click chemistry functional group is a terminal azide.

5-2-1



5-2-2



EX1011, Table 3, p. 92.

427. The unsubstituted cycloalkyl of Example 5-2-2 satisfies all of the limitations of claim 2, and Example 5-2-1 has an unsubstituted C₅ alkylene as D₁, which is only one more carbon than claim 2 allows. A POSA would understand that this C₅ alkylene could be slightly longer or shorter and still function effectively the same. The specification of the '675 patent does not indicate any criticality with respect to the recited upper limit of C₄. To the contrary, the '675 Patent discloses at col. 48, lines 14-30 the same formula as recited in claim 2 and indicates that “D₁ is *any alkylene*, alkenylene, or alkynylene” and col. 30, lines 26-27 teach, “D₁ may include any one selected from a C₁₋₇ alkylene...” EX1001, 28:45-57; 29:56-30-2; 30:53-65; 38:43-58; 40:1-17; 41:6-21; 42:48-62; 43:37-53; 49:15-31; 50:16-32; 52:38-54; 53:30-46; 54:25-40.

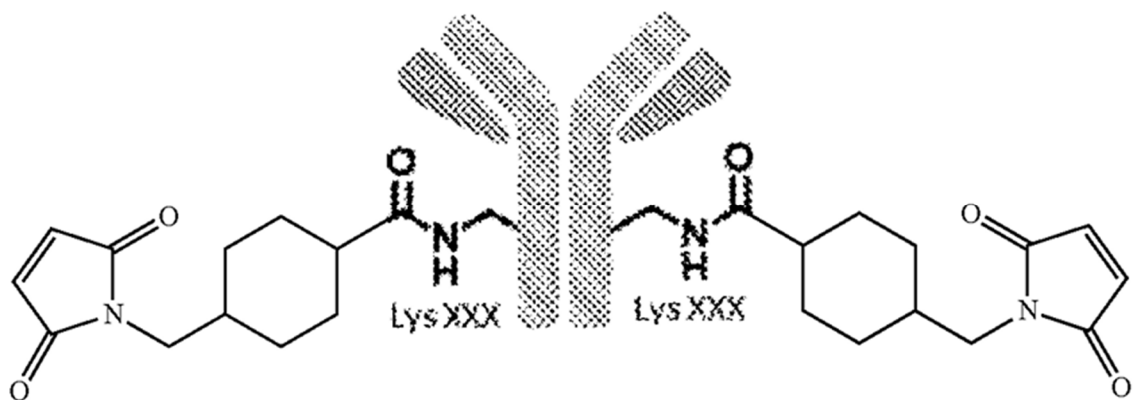
428. Although the particular lysine residue in these examples is not identified, Matsuda discloses modification of lysine residue 248 is preferable. For example, Matsuda discloses “(26) The antibody or salt thereof according to any of (23) to (25), wherein the antibody is a human IgG regioselectively having a bioorthogonal functional group or bioorthogonal functional groups in a region consisting of **amino acid residues at positions 246 to 248** or 288 to 290 in a human IgG Fc region.” EX1011, [0146].

429. Matsuda further discloses that, among lysine residues, lysine 248 is a preferred lysine residue for modification: “When human IgG such as human IgG1 is

modified with a lysine residue, among the positions of (1), **lysine residues present at certain positions** (e.g., position 246, **position 248**, position 288, position 290, and position 317) in the CH2 domain, which can be efficiently modified in the present invention, **may be more preferably modified.**" EX1011, [0329]

430. Similarly, Matsuda discloses that “The target region may be more specifically the following residues following Eu numbering in human IgG Fc: (1) a **Lys248 residue** (hereinafter, also referred to simply as “Lys248” in the present specification and corresponding to the 18th residue in a human IgG CH2 region (SEQ ID NO: 1)) or a Lys246 residue (hereinafter, also referred to simply as “Lys246” in the present specification and corresponding to the 16th residue in the human IgG CH2 region (SEQ ID NO: 1))” EX1011, [0330]-[0331].

431. Matsuda further discloses an example with a D₁, namely a C₆ cycloalkylene, and an H₁, namely a maleimide, in Example 3-4, shown below.



EX1011, p. 90. This structure satisfies all of the limitations of claim 2.

432. With respect to the structure recited in claim 2, the terminal azide disclosed in both Yamada and Matsuda constitutes an H₁, a group having the bio-orthogonal click chemistry functional group, as does the terminal maleimide disclosed in Matsuda.

433. I note also that Matsuda's Example 5-2-1 discloses a C₅ alkylene, which is only one more carbon than the C₁-C₄ alkylene recited in Claim 2. The specification of the '675 patent does not indicate any criticality with respect to the recited upper limit of C₄. To the contrary, the '675 Patent discloses at col. 48, lines 14-30 the same formula as recited in claim 2 and indicates that "D₁ is *any alkylene*, alkenylene, or alkynylene" and col. 30, lines 26-27 teach, "D₁ may include any one selected from a C₁₋₇ alkylene..." EX1001, 28:45-57; 29:56-30-2; 30:53-65; 38:43-58; 40:1-17; 41:6-21; 42:48-62; 43:37-53; 49:15-31; 50:16-32; 52:38-54; 53:30-46; 54:25-40.

434. Yamada and Matsuda thus both disclose modified antibodies with terminal azide modifications at lysine 248, which satisfy H₁, and Matsuda further discloses a suitable D₁ in the form of a C₆ cycloalkylene. It would have been obvious to a POSA to combine the teachings of Yamada and Matsuda to prepare a modified antibody with a terminal azide modification at lysine 248 that includes a C₆ cycloalkylene in the position represented by D₁ in Claim 2.

3. Claim 3 of the '675 Patent

435. Claim 3 recites: “The modified antibody of claim 2, wherein D₁ is bond, or is selected from unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene and unsubstituted C₃₋₈ cycloalkylene.”

436. Claim 3 thus limits Claim 2 by requiring that the options for D₁ recited in Claim 2 are “unsubstituted.” Matsuda and Yamada both disclose this further limitation. In particular, the C₆ cycloalkylenes in Examples 3-4 and 5-2-2 of Matsuda and C₅ alkylene in Example 5-2-1 discussed above with respect to Claim 2 are all unsubstituted (i.e., there are no heteroatoms, only carbons/hydrogens).

437. Thus, the combination of Yamada and Matsuda teach all of the limitations of Claim 3 for the same reasons as Claim 2.

4. Claim 4 of the '675 Patent

438. Claim 4 recites: “The modified antibody of claim 1, wherein the modified heavy chain comprises an amino acid sequence having a structure of formula 8-2:

G-P—S-V-F-L-F—P-P-K-P—(K)'-D-T-L-M-I (SEQ ID NO: 21),
[formula 8-2]

wherein K' is the modified lysine residue.”

439. As previously discussed, Yamada teaches the modification of the lysine residue at position 248. Yamada further teaches a peptide fragment of trastuzumab

having a lysine residue (position 246) modified with an azide or a thiol as the bio-orthogonal functional group. In particular, Yamada discloses the peptide fragment of THTCPPCPAPELLGGPSVFLFPPKPKDTLMISR (SEQ ID NO: 40), “comprising a modified site to a lysine residue by trypsin digestion of trastuzumab (an azide-introduced portion (+254.102 Da)) . . . indicating modification of a lysine residue at position 246 in EU numbering of the heavy chain was determined (FIG. 26).” EX1005, [2080]. Similarly, Yamada discloses the same peptide fragment, “comprising a modified site to a lysin residue by trypsin digestion of trastuzumab (a thiol-introduced portion subjected to carbamidomethylation with iodoacetamide (+145.019 Da))” EX1005, [2557].

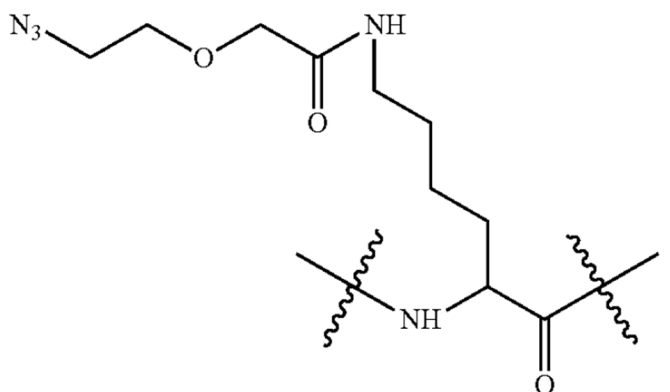
440. In addition, Matsuda teaches the same peptide fragment of trastuzumab modified with an azide group at lysine residues 246 or 248. In particular, Matsuda discloses “an MS spectrum of the peptide fragment of THTCPPCPAPELLGGPSVFLFPPKPKDTLMISR (SEQ ID NO: 11), which is a peptide consisting of 33 amino acid residues comprising a modified site to a lysine residue by trypsin digestion of azidobenzoic acid-modified trastuzumab (aminebenzoic acid-introduced compound (+119.037 Da)) . . . indicating modification of a lysine residue at position 246 or 248 in EU numbering of the heavy chain was determined (FIG. 50).” EX1011, [1312].

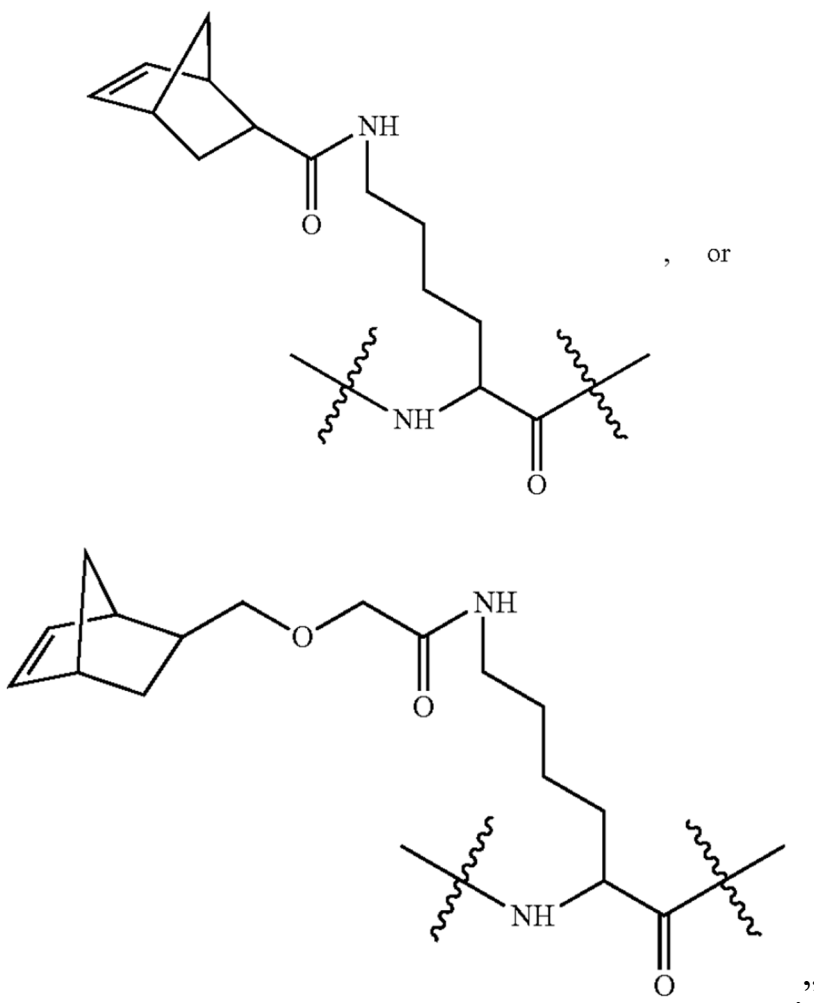
441. Yamada and Matsuda thus both disclose the amino acid sequence recited in Claim 4 with azide modification of a lysine residue, and Matsuda expressly discloses that the lysine residue may be at position 248. Claim 4 is therefore obvious over the combination of Yamada and Matsuda.

5. Claims 5-7 and 11 of the '675 Patent

442. Claim 5 recites: “The modified antibody of claim 2, wherein D₁ comprises one or more heteroatoms.”

443. Claim 6 recites: “The modified antibody of claim 2, wherein D₁ is —[CH₂]_a—O—[CH₂]_b—, wherein each of a and b is independently selected from 0 to 4, and each of a and b is integer, and wherein sum of a and b is 0 or more and 4 or less.” Claim 7 recites: “The modified antibody of claim 2, wherein D₁ is —CH₂CH₂OCH₂— or —CH₂OCH₂—.” Claim 11 recites: “The modified antibody of claim 1, wherein the modified lysine residue has following structure:





444. I am discussing claims 5-7 and 11 together because the first and third structures recited in claim 11 include all of the limitations of claims 5-7. Thus, by showing that the first and third structures recited in claim 11 were previously disclosed, it would be apparent that the broader limitations of claims 5-7 had also been previously disclosed.

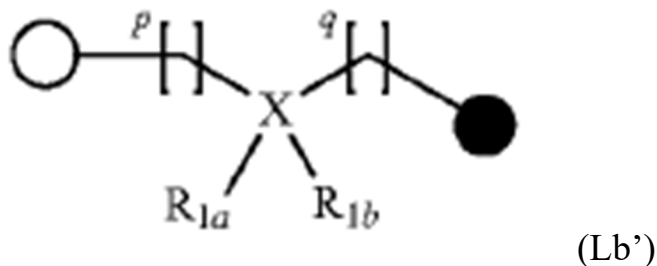
445. Yamada likewise discloses antibodies modified at lysine 248 (EX1009, [0222], [1037], [1109], [1114], etc.) with an azide (*id.*, [0151], [0153], [1037], Figure 18) or a norbornene (*id.*, [0151], [0153]).

446. Yamada discloses an antibody regioselectively modified with a bio-orthogonal functional group represented by (Formula (IV)):

L1-B-R'-T (IV)

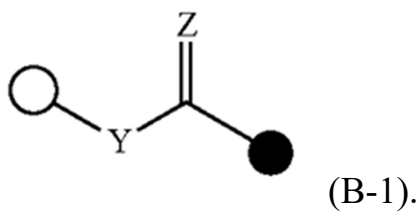
in which “L1 is (i') a monovalent group comprising a bioorthogonal functional group or (ii') a monovalent group comprising no bioorthogonal functional group; B is (a) a divalent group comprising a bioorthogonal functional group or (b) a divalent group comprising no bioorthogonal functional group; R' is a portion formed by a reaction between a soluble protein and a reactive group; and T is a soluble protein.” EX1009, [0584]-[0588]. It is my understanding that in the context of Yamada, the term “monovalent group” refers to a group that has a single covalent bond to another group, and the term “divalent group” means a group that has two covalent bonds connecting it to two other groups.

447. Paragraphs [0616]-[0624] further define L1 with specific groups. In particular, these paragraphs explain that L1 can either be C1, can be a bio-orthogonal functional group (e.g., azide, norbornene, etc.; *see* EX1009, [0626]-[0627]) or it can have a structure of C1-Lb, wherein LB is:

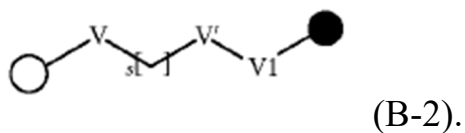


in which the White Circle indicates a bond to C1, which (as noted above) can be a bio-orthogonal click chemistry group (e.g., azide, norbornene, etc.); p and q are integers from 0-10; X can be a carbon (C) a nitrogen (N), or a single bond; and R_{1a} and R_{1b} can be present as a substituent or absent. The black circle indicates the bond to B

448. Paragraphs [0631]-[0639] further define B with specific groups. In particular, these paragraphs explain that B is defined as having a structure of:



Within (B-1), the White Circle is the connection to L1; the Black Circle is the connection to R'; Z can be "an oxygen atom, a sulfur atom, or a hydrogen atom wherein when Z is a hydrogen atom, -C(=Z)- indicates -CH₂-"; and Y can be -NH-, -O-, -CH₂-, or B-2:



When Y is B-2, paragraphs [0634]-[0636] explain that V and V' can each independently be -NH-, -O-, -CH₂-, or a single bond; V1 is "a divalent group comprising a bioorthogonal functional group"; and s is any integer from 0 to 10. I

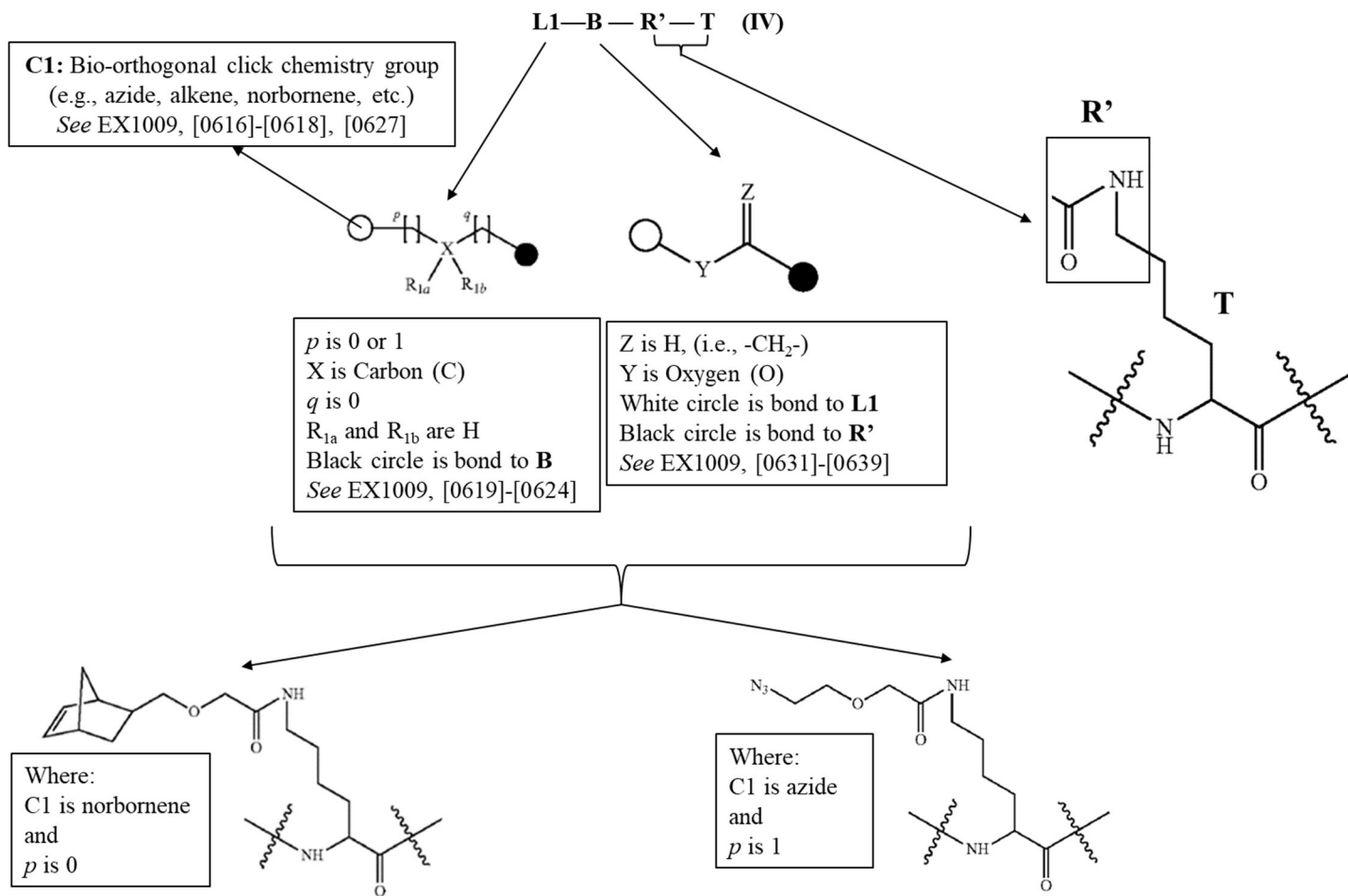
note that paragraph [1571] indicates that with respect to B-2 (this paragraph references “partial structural formulae ... (B-1) to (B-4)...”) that this “technical element” is described various ways throughout the application. Specifically, paragraph [1571] states, “these matters can be quoted as appropriate in the inventions described below without any special reference” and “the technical elements of a specific invention described in the inventions described below can be quoted as appropriate as the technical elements of the present invention and other inventions.” I understand this to mean that the various disclosures of formula B-2 throughout the publication can be substituted for one another. Accordingly, where paragraph [1470] describes the same Formula (B-2) in a similar context, and paragraphs [1472] and [1480] indicate “V1 is (a) a divalent group comprising a bioorthogonal functional group or (b) a divalent group comprising no bioorthogonal functional group,” a POSA would understand that the bio-orthogonal functional group within V1 is optional. As such, V1 could be, for example, an oxygen (-O-) which fits Yamada’s description of “a divalent group.” *See e.g.*, [1465]. Note that the white and black circles in B-2 are simply included to show the orientation of the fragment in relation to the structure of B-1.

449. As noted above, R’ is defined as “a portion formed by a reaction between a soluble protein and a reactive group.” Yamada describes “[e]xamples of a linking portion formed by a reaction between the reactive group specific to a side

chain of a lysine residue and the amino group (NH₂) present in the side chain of the lysine residue include an amide residue...” EX1009, [1510]. Thus, the amide portion of the partial structure from claim 2 of the '675 Patent should be considered as R'. Accordingly, there are two ways in which Formula (IV) can be completed to arrive at the first and third structures of claim 11.

450. Specifically, a POSA could readily envisage that first and third structures recited in claim 11 by selecting the components of Formula (IV) as shown in the flow diagrams below:

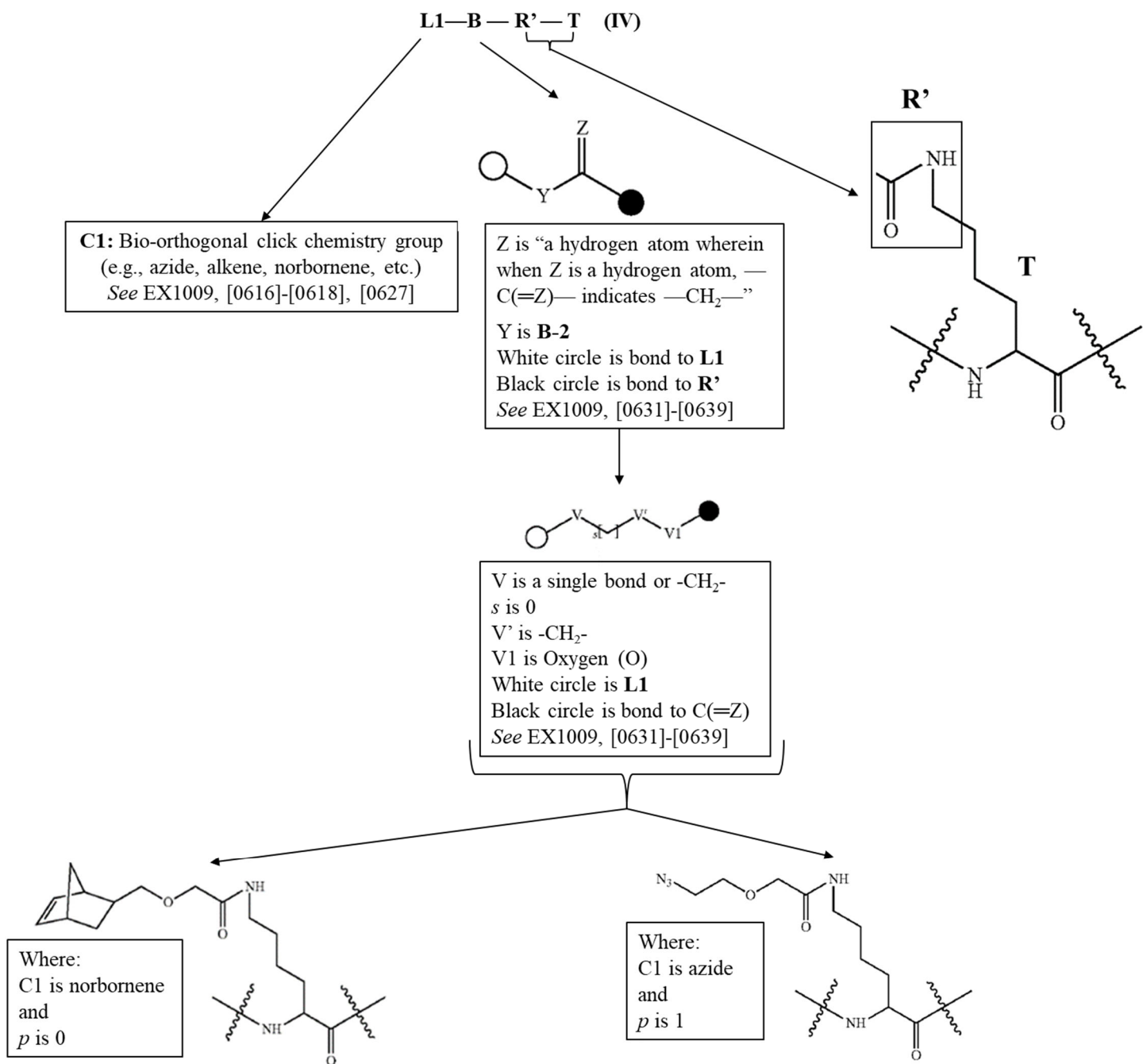
Option 1:



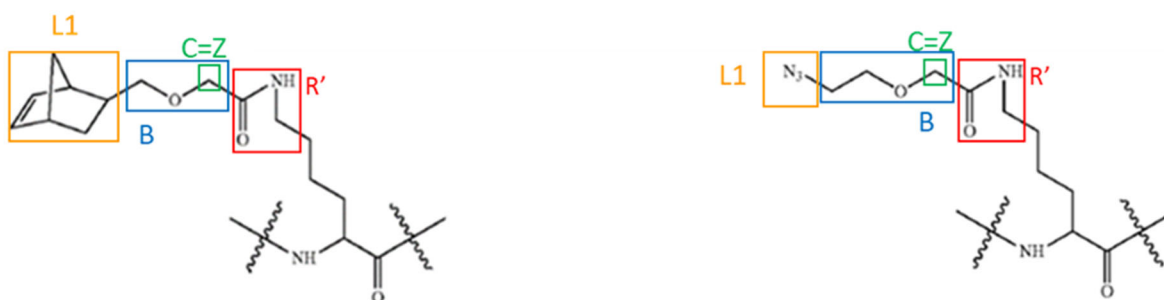
For Option 1, the components of the structures from claim 11 are denoted with their respective positions within Formula (IV):



Option 2:



For Option 2, the components of the structures from claim 11 are denoted with their respective positions within Formula (IV):

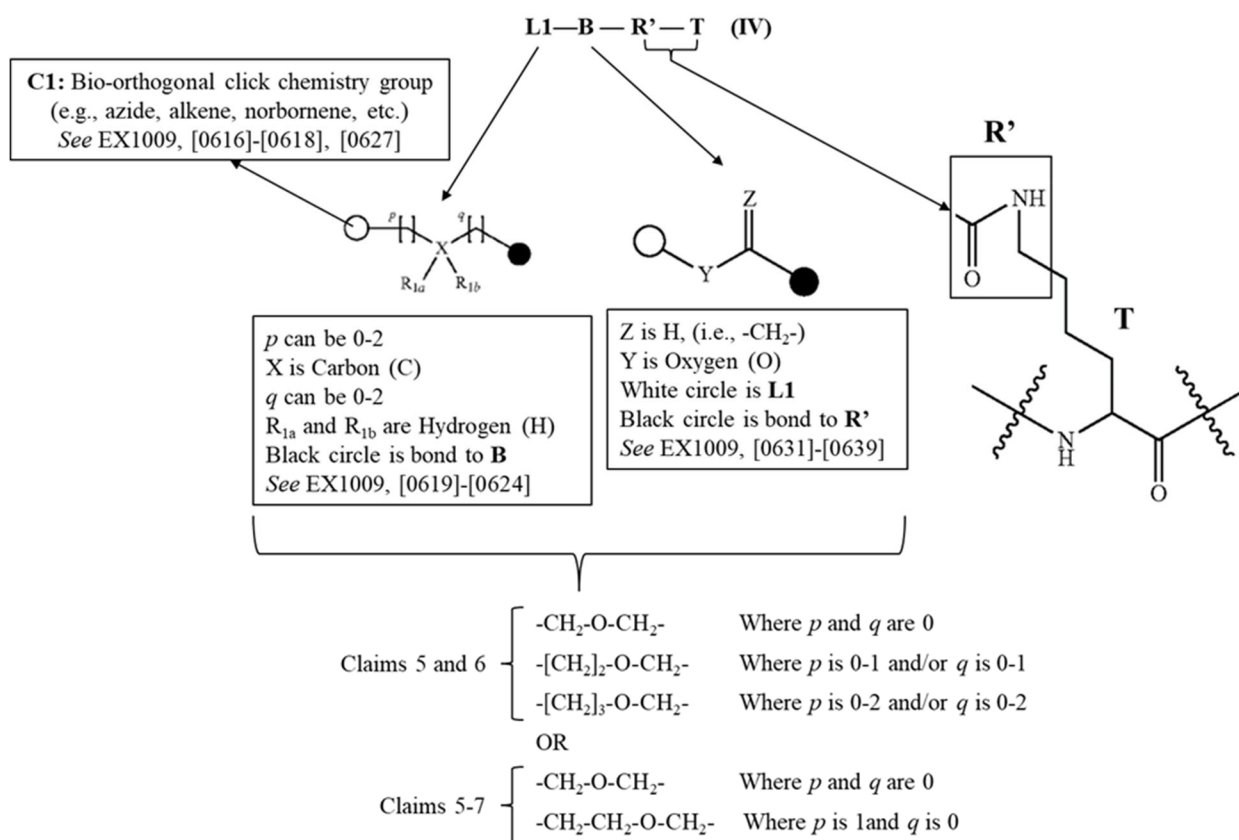


451. Thus, the first and third structures recites in claim 11 of the '675 Patent are disclosed in Yamada and could be predictably constructed based on Yamada's disclosure. As such, the limitations of claims 5-7 are also disclosed, as each of these structures includes a heteroatom (i.e., oxygen) within the segment corresponding to D1 (i.e., the limitations of claim 5) and the specific D1 structures recited in claims 6 and 7 (i.e., $\text{—CH}_2\text{CH}_2\text{OCH}_2\text{—}$ or $\text{—CH}_2\text{OCH}_2\text{—}$) correspond to the azide-containing structure on the right and the norbornene-containing structure on the left, respectively.

452. In addition to these particular compounds, Yamada also makes very clear that the segment of its modified structures corresponding to D1 fall within the scope of claims 5-76.

453. Both L1 and B of Formula (IV) contain multiple options for inclusion of a heteroatom. Specifically, when L1 includes Lb, it may comprise "a carbon atom, a nitrogen atom, or a single bond" as the X component (EX1009, [0622]), and in formula (B-1), the Y component could be —NH— or —O— or CH_2 (*id.*, [0633]). Each of these allows for various constructions that would fall within the scope of claims 5

and 6. For example, inserting -O- as the Y component and a carbon atom as the X component can yield a number of combinations that satisfy both claims 5 and 6. Indeed, positions p and q could be varied in numerous ways and still remain within the scope of these claims. Claim 7 would also be covered with this arrangement as summarized in the flow chart below.



454. Accordingly, all of the components of claims 5-7 and 11 of the '675 Patent are taught and suggested in Yamada, and a POSA would reasonably expect to be able to combine these components to arrive at the claims based on simple substitutions.

6. Claim 8 of the '675 Patent

455. Claim 8 recites: “The modified antibody of claim 1, wherein the modified antibody comprises two modified heavy chains.”

456. Yamada discloses “the modified antibody comprises two modified heavy chains.” *See* EX1009, Figure 1-2, [0607]. As previously discussed in connection with Claim 1, Yamada discloses “(15) The soluble protein or salt thereof according to any one of (1), (3) to (14), wherein the soluble protein is an antibody comprising a plurality of heavy chains, and the bioorthogonal functional groups are present in positions of the one or more specific amino acid residues in a plurality of heavy chains such that the antibody has a plurality of bioorthogonal functional groups.” EX1005, [0606]-[0608]. Yamada thus expressly discloses the modified antibody having two (or more) heavy chains modified with bio-orthogonal functional groups.

457. Matsuda’s Example 3-4, 5-2-1, and 5-2-2 (EX1011, p. 90, 92) likewise show antibodies in which both heavy chains are modified.

458. Yamada and Matsuda thus discloses modified antibodies meeting all of the limitations of Claim 8.

7. Claim 9 of the '675 Patent

459. Claim 9 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a

click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

460. Yamada discloses the limitation “the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

461. In particular, as previously discussed, Yamada discloses a modified antibody with a terminal azide modification of lysine 248. EX1009, [0151]-[0153]. Matsuda similarly discloses antibodies with a terminal azide modification of lysine 248. EX1011, p. 92. As also previously discussed, an azide group is a bio-orthogonal click chemistry functional group, and POSAs understood that an azide group participates with a terminal alkyne in a click-chemistry reaction of Huisgen 1,3-dipolar cycloaddition. EX1036.

462. Yamada thus discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is one capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.

8. Claim 10 of the '675 Patent

463. Claim 10 recites: “The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

464. Yamada discloses the limitation “the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.”

465. In particular, as previously discussed, Yamada discloses a modified antibody where lysine residue 248 is modified to include an azide group as the bio-orthogonal functional group. *See e.g.*, [0151]-[0153]. Indeed, Yamada also discloses norbornene and DCBA. *Id.* Matsuda similarly discloses antibodies with a terminal azide modification and a maleimide modification of lysine 248. EX1011, p. 90, 92. Yamada and Matsuda thus expressly discloses the modified antibody of Claim 1 where the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.

9. Claim 12 of the '675 Patent

466. Claim 12 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.”

467. As previously discussed in connection with Claim 2 and Claim 3, the modified lysine residue structure recited in Claim 2, where D₁ is a covalent bond, unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂-

4 alkynylene or unsubstituted C₃₋₈ cycloalkylene, as required by Claim 3, would have been obvious to a POSA based on the combination of Yamada and Matsuda.

468. As previously discussed, Yamada discloses a modified antibody with a terminal azide modification of lysine 248. EX1009, [0151]-[0153]. Matsuda similarly discloses antibodies with a terminal azide modification of lysine 248. EX1011, p. 92. As previously discussed in connection with Claim 9, an azide group is a group capable of participating in a Huisgen 1,3-dipolar cycloaddition.

469. It is my opinion that the modified antibody of Claim 12 is therefore obvious over the combination of Yamada and Matsuda.

10. Claim 13 of the '675 Patent

470. Claim 13 recites: “The modified antibody of claim 3, wherein the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.”

471. As previously discussed in connection with Claim 2 and Claim 3, the modified lysine residue structure recited in Claim 2, where D1 is a covalent bond, unsubstituted C₁₋₄ alkylene, unsubstituted C₂₋₄ alkenylene, unsubstituted C₂₋₄ alkynylene or unsubstituted C₃₋₈ cycloalkylene, as required by Claim 3, would have been obvious to a POSA based on the combination of Yamada and Matsuda.

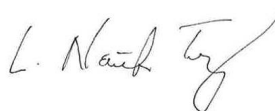
472. As previously discussed, Yamada discloses a modified antibody where lysine residue 248 is modified to include an azide group as the bio-orthogonal functional group. *See e.g.*, [0151]-[0153]. Indeed, Yamada also discloses norbornene and DCBA. *Id.* Matsuda similarly discloses antibodies with a terminal azide modification and a maleimide modification of lysine 248. EX1011, p. 90, 92. Yamada and Matsuda thus expressly discloses that the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group. Thus, all of the elements of claim 13 are disclosed in Yamada and Matsuda, and a POSA could readily combine these disclosures to predictably arrive at claim 13 with a reasonable expectation of success.

XIII. CONCLUSION

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

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

Executed on Dec. 23rd, 2024



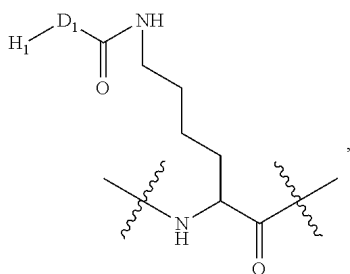
Lawrence Nathan Tumey

Appendix A

Challenged Claims

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

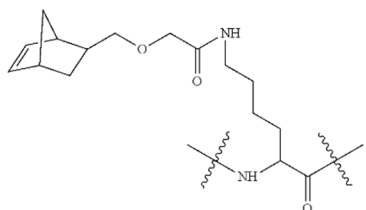
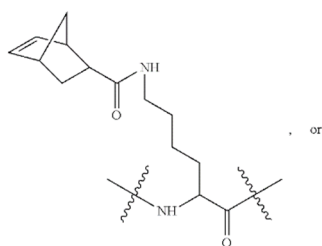
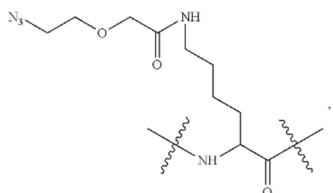
1. A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group,
wherein the modified antibody comprises one or more modified heavy chain,
wherein each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and
wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end, and
wherein the modified lysine residue does not comprise a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group.
2. The modified antibody of claim 1, wherein the modified lysine residue has following structure:



wherein H_1 is a group having the bio-orthogonal click chemistry functional group, and
wherein D_1 is bond, or is selected from C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene and C_{3-8} cycloalkylene.

3. The modified antibody of claim 2, wherein D_1 is bond, or is selected from unsubstituted C_{1-4} alkylene, unsubstituted C_{2-4} alkenylene, unsubstituted C_{2-4} alkynylene and unsubstituted C_{3-8} cycloalkylene.
4. The modified antibody of claim 1, wherein the modified heavy chain comprises an amino acid sequence having a structure of formula 8-2:
G-P—S-V-F-L-F—P-P-K-P—(K)'-D-T-L-M-I (SEQ ID NO: 21),
[formula 8-2]
wherein K' is the modified lysine residue.
5. The modified antibody of claim 2, wherein D_1 comprises one or more heteroatoms.
6. The modified antibody of claim 2, wherein D_1 is $—[CH_2]_a—O—[CH_2]_b—$, wherein each of a and b is independently selected from 0 to 4, and each of a and b is integer, and wherein sum of a and b is 0 or more and 4 or less.
7. The modified antibody of claim 2, wherein D_1 is $—CH_2CH_2OCH_2—$ or $—CH_2OCH_2—$.
8. The modified antibody of claim 1, wherein the modified antibody comprises two modified heavy chains.
9. The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.

10. The modified antibody of claim 1, wherein the bio-orthogonal click chemistry functional group is selected from azide group, tetrazine group, dibenzocyclooctyne group, and norbornene group.
11. The modified antibody of claim 1, wherein the modified lysine residue has following structure:



12. The modified antibody of claim 3, wherein the bio-orthogonal click chemistry group is a group capable of participating in a click chemistry reaction selected from Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction.
13. The modified antibody of claim 3, wherein the bio-orthogonal click chemistry functional group is selected from the group consisting of an azide

group, a tetrazine group, a dibenzocyclooctyne group, and a norbornene group.

Appendix B

Curriculum Vitae

CURRICULUM VITAE

L. NATHAN TUMEY, PH.D.

Associate Professor
Binghamton University
School of Pharmacy and Pharmaceutical Sciences
P.O. Box 6000, Binghamton NY 13902
Email: ntumey@binghamton.edu
Website: www.Tumeylab.com
Phone: 607-777-5844

EDUCATION

Duke University, Durham, NC.

Ph.D., Organic chemistry, December 2001.

- Dissertation research with Professor Michael Pirrung.
- Certificate in Biological Chemistry (program emphasis)
- Dissertation title: "Medicinal chemistry and high throughput synthesis of inhibitors of lipid A biosynthesis."

King College, Bristol, TN.

B.S., *Summa cum laude*, May 1997. Double major, Chemistry and Biology. Minor, Computer Science.

PROFESSIONAL EXPERIENCE

2022-present	Associate Professor , Binghamton University School of Pharmacy and Pharmaceutical Sciences, Binghamton, NY -Vice Chair, Dept. of Pharmaceutical Sciences (2024-present) -Assistant Graduate Director (2022-present) -Courtesy appointment in Chemistry Dept. (2021-present) -Courtesy appointment in Biomedical Engineering (2018-present)
2017-2022	Assistant Professor , Binghamton University School of Pharmacy and Pharmaceutical Sciences, Binghamton, NY
2010-2017	Associate Research Fellow , Pfizer, Groton, CT
2005-2010	Principal Research Scientist , Wyeth Research, Pearl River, NY
2002-2005	Senior Scientist , Athersys Inc., Cleveland, OH
2000-2001	Organic Chemistry Instructor , Kaplan MCAT prep class, Durham, NC
1997-2001	Graduate Assistant , Mentor: Dr. Michael Pirrung, Duke University Department of Chemical Sciences, Durham NC

CONSULTING, ADVISORY, AND LEADERSHIP EXPERIENCE

Expert Witness and Legal Consulting:

Quinn Emmanuel LLP (2021-present)

Latham and Watkins LLP (2021-present)

Professional consulting work:

Heidelberg Pharma (2022-present)

OnCusp Therapeutics (2022-present)

Ardeagen (2021-present)

Bighat Biosciences (2021-2022)

Iksuda Therapeutics (2021-2022)

Synthesis Inc (2019-present)

Loxo Oncology / Eli Lilly (2020-present)

Takeda Pharmaceuticals (2017-2021)

ImmuNext Biopharma (2018-2019)

Cue Biopharma (2018-2019)

Vertex Pharmaceuticals (2019)

Angiex Pharmaceuticals (2018-2020)

GIMV NV (2019)

Pontifax (2019-2020)

Scientific advisory board member,

Araris Biotech AG (2019-present)

Manhattan Biosolutions (2022-present)

Awards/Scientific leadership roles:

2024-2027, standing member NIH Drug and Biologic Therapeutic Delivery (DBTD) review panel. (07/01/2024 - 06/30/2027)

2023, NIH review panel, Drug and Biologic Therapeutic Delivery (DBTD), Oct. 17-18 2023; Feb. 1-2, 2024.

2023, Outstanding Academic Investigator Award, World ADC Awards, Oct. 18, 2023.

2023, Provost's Award for Excellence in Undergraduate Research Mentoring

2022, chair, "Next Generation Payloads" symposium at ADC World Summit.

2022, NIH grant review panel, Gene and Drug Delivery (GDD), ad hoc member. (Oct 25-26, 2022)

2020, NIH grant review panel, Synthetic and Biological Chemistry A (SBCA), ad hoc member. (October 13-14, 2020)

2014-2017, Bioconjugation Network Leadership Team (Pfizer, Inc)

2014, Co-chair, Bioconjugation Summit (Pfizer, Inc)

2015, Chair, Bioconjugation Summit (Pfizer, Inc)

2014-2017, Bioconjugation Network Leadership Team (Pfizer, Inc)

RESEARCH INTERESTS

Targeted drug delivery; Antibody-drug conjugates (ADCs); Auto-immune disease; Oncology medicinal chemistry; Small molecule drug discovery; Immuno-oncology; Drug metabolism/DMPK; Bioanalytical chemistry; Mass spectroscopy.

PRIVATE SECTOR (PHARMACEUTICAL) WORK EXPERIENCE

Associate Research Fellow, Pfizer, Groton, CT (March 2010-January 2017)

Oncology Medicinal Chemistry, ADC bioconjugation.

- Led a small team of synthetic and bioanalytical scientists that design and synthesize antibody-drug conjugates for use in oncology applications. Prepared bioconjugates for *in vitro* and *in vivo* evaluation.
- Optimized conjugation conditions in order to result in conjugates with minimal aggregation and maximal drug-loading. Developed a variety of bioanalytical methods to assess the purity, identity, and stability of preclinical antibody-drug-conjugates in the Pfizer portfolio. Coordinated across sites and departments to harmonize analytical methods and analytical requirements in order to facilitate technology transfer and data analysis.
- Developed patenting strategies to protect key inventions while simultaneously building the visibility of the team through aggressive external publication and presentation strategies.
- Implemented the use of site-specific conjugation techniques to solve metabolic, synthetic, analytical, and stability issues. Worked with biochemists, biologists, and DMPK scientists to better understand the impact of conjugation site on efficacy and PK.
- Served as the chemistry team leader on multiple ADC programs. Worked with key members of the team to decide on ADCs for advancement into PK, efficacy, and toxicology studies.
- Worked with a small team of scientists and IT specialists to establish an informatics system to track ADCs across Pfizer.
- Mentored three direct reports (2 PhD and 1 MS) and a summer intern (BS).

Principal Research Scientist, Wyeth Research, Pearl River, NY (2005-2010)

Chemistry team leader (2008-2009), IRAK4 kinase program (inflammation)

Chemistry team member (2005-2008), PKC θ (inflammation)

- Coordinated efforts of multiple medicinal chemists across two sites ensuring that each individual had an adequate understanding of the project and had appropriate molecular targets/goals. Directly supervised the synthetic chemistry efforts of three chemists and led an outsourced team of five chemists.
- Responsible for managing and prioritizing all secondary assay requests including DMPK studies, *in vivo* efficacy studies, pharmaceutical properties screening, and selectivity screening.
- Worked with team members to identify strategies to address issues with kinase selectivity, DNA binding, pgp efflux, permeability, *in vitro* metabolism, and drug physical properties. Collaborated with scientists from enzymology, analytical chemistry, DMPK, and pharmaceutical profiling in order to study these issues.
- Represented the project to the management team. Responsible for maintaining project timelines and ensuring the meeting of key deliverables.
- Responsible for establishing and maintaining an intellectual property (IP) position around each lead series. Worked with company attorneys and research librarians in order to evaluate related prior art.

Senior Scientist, Athersys Inc., Cleveland, OH (2002-2005)

- Designed two novel series of CRTH2 antagonists based on literature precedent and competitor's compounds. Synthesized numerous analogs and libraries in order to establish key SAR. Lead inventor on two patent applications claiming these series.
- Designed and synthesized selective agonists of 5HT2C for use in obesity and related disorders resulting in multiple patent applications. Established SAR that led to agonists with excellent selectivity (>100x) over 5HT2A/2B and exhibited good oral bioavailability.
- Responsible for hit-to-lead evaluation, lead-optimization, and molecular design/synthesis.
- Directly supervised two associate chemists.

GRANT FUNDING (active) –

Heidelberg Pharma 12/2022-12/2024

“Optimization of TLR7 Agonist ADCs for the treatment of Cancer”

Total direct costs: \$285,075 (+\$162,493 indirect)

Role: PI

NIH R01 GM144450-01 02/2022-12/2025

“Legumain to the rescue: A new ADC linker strategy to address the limitations of cathepsin cleavage”

Total direct costs: \$800,000 (+\$412,224 indirect)

Role: PI (collaboration with Tracy Brooks)

NIH R01 GM140026-01A1 08/2021-08/2025

“Exploiting the Hydrophobic Glycosyl Pocket of IgG1 for Imaging and Drug Delivery Applications”

Total direct costs: \$800,000 (+\$434,112 indirect)

Role: PI (collaboration with Tracy Brooks and Fake Lu)

NIH R15 CA249793-01, NIH/NCI 07/2020-07/2023

“Synthesis and optimization of antibody:DNAi conjugates targeting the MYC G4”

Total direct costs: \$300,000 (+\$171,000 indirect)

Role: Co-I (PI is Tracy Brooks)

GRANT FUNDING (completed)

NIH R03 AI156696-01A1 06/2021-06/2023

“Molecular whack-a-mole: Targeting transmembrane-TNFα for the delivery of anti-inflammatory drugs.”

Total direct costs: \$100,000. (+\$57,000 indirect)

Role: PI (sole investigator)

NIH R15 AI149755-01 01/2020-01/2023

“Cell-specific blockage of TLR activation: A new strategy for addressing inflammatory disorders.”

Total direct costs: \$300,000 (+\$150,480 indirect)

Role: PI (sole investigator)

Binghamton University XCEED Technology Accelerator (ED19HDQ0200038)

09/2021-12/2021

“Development of TLR-activating ADC technology”

Total direct costs: \$24,000.

Role: PI

Synthis Inc., Award 90784

04/2021-07/2021

“Analysis of cell lysate” (testing agreement)

Total direct costs: \$13,816 (+\$3,454 indirect)

Role: PI (sole investigator)

Takeda Pharmaceuticals, Award 83181

11/2018-04/2020

“The identification of lysosomal-selective proteolytically cleavable linkers”

Total direct costs: \$162,217 (+\$95,251 indirect)

Role: PI (sole investigator)

Binghamton University Translational Areas of Excellence.

06/2018-06/2019

“Understanding Antibody-Drug Conjugate (ADC) Internalization Via Stimulated Raman Scattering (SRS) Imaging of Alkyne-Tags in Live Cancer Cells”.

Total direct costs: \$10,000

Role: Co-I (collaboration with Fake Lu / BME)

ORIGINAL ARTICLES, REVIEWS, AND BOOK CHAPTERS

***Indicates corresponding author**

BOOK CHAPTERS

“ADC Linker Strategies for the Release of Alcohol-Containing Payloads”, Miller, Jared T., **Tumey, L. Nathan***, Chemical Linkers in Antibody-Drug Conjugates (ADCs); Royal Society of Chemistry; **2021**, pg 232-262.

“The design and development of antibody-drug conjugates (ADCs) for the treatment of cancer”, **Tumey, L. Nathan***, Burger’s Medicinal Chemistry, Drug Discovery and Development; Wiley Publishing, **2021**.
<https://doi.org/10.1002/0471266949.bmc283>

“An overview of the current ADC discovery landscape”, **Tumey, L. Nathan***, Methods in Molecular Biology, Springer Publishing, **2019**, 1-22.

“Detection and Removal of Small-Molecule and Endotoxin Contaminants in ADC Preparations”, Casavant, Jeffery*; Ratnayake, Anokha S.; Puthenveetil, Sujiet; **Tumey, L. Nathan**, Methods in Molecular Biology, Springer Publishing, **2019**, 291-299.

“Next generation payloads for ADCs” (book chapter), **L. Nathan Tumey***, Springer Publishing, “Innovations for Next-Generation Antibody-Drug Conjugates”, **2018**.

PEER REVIEWED PUBLICATIONS

2024

“A comparison of the activity, lysosomal stability, and efficacy of legumain-cleavable and cathepsin cleavable ADC linkers”, Meghan E. Gray, Karina M. Zielinski, Fanny Xu, Kayla K. Elder, Steven J. McKay, Victor T. Ojo, Samantha R. Benjamin, Aiman A. Yaseen, Tracy A. Brooks, L. Nathan Tumey*, *Xenobiotica*, **2024**, in press. doi: 10.1080/00498254.2024.235205

2023

“ValCitGlyPro-Dexamethasone Antibody Conjugates Selectively Suppress the Activation of Human Monocytes”, Justin M Howe, Siteng Fang, Kelsey A. Watts, Fanny Xu, Samantha R Benjamin and **L. Nathan Tumey***, *RSC Medicinal Chemistry*, **2023**, 14, p2348.
<https://pubs.rsc.org/en/content/articlelanding/2023/md/d3md00336a>

“Synthesis and Optimization of 1-Substituted Imidazo[4,5-c]quinoline TLR7 Agonists”, Emma G. DeYoung, Justin M. Howe, Siteng Fang, Mullapudi Mohan Reddy, Jillian P. Handel, Jared T. Gillen Miller, Daniel R. Wheeler, and **L. Nathan Tumey***, *ACS Med. Chem. Lett.*, **2023**, 14, 10, 1358-68.
<https://doi.org/10.1021/acsmchemlett.3c00260>

“Visualizing drug-induced lipid accumulation in lysosomes of live cancer cells with stimulated Raman imaging”, Yuhao Yuan, Emmanuel O. Olawode, **L. Nathan Tumey**, and Fake Lu; *Biomedical Optics Express*, **2023**, 14(6), pp. 2551-2564;
<https://doi.org/10.1364/BOE.487527>

2022

“Evaluation of an ester-linked immunosuppressive payload: A case study in understanding the stability and cleavability of ester-containing ADC linkers”, Courtney P. Jackson, Siteng Fang, Samantha R. Benjamin, Tchilabalo Alayi, Yetrib Hathout, Sarah M. Gillen, Jillian P. Handel, Brittany M. Brems, Justin M. Howe, **L. Nathan Tumey***; *Bioorganic and Medicinal Chemistry Letters*, 75, **2022**. DOI: 10.1016/j.bmcl.2022.128953

“Design and Characterization of Immune-Stimulating Imidazo[4,5-c]quinoline Antibody-Drug Conjugates”, Siteng Fang, Brittany M Brems, Emmanuel O Olawode, Jared T Miller, Tracy A Brooks, **L Nathan Tumey***; *Molecular Pharmaceutics*, 2022, 19, 9, 3228–3241.
<https://doi.org/10.1021/acs.molpharmaceut.2c00392>

“Indoloquinoline-Mediated Targeted Downregulation of KRAS through Selective Stabilization of the Mid-Promoter G-Quadruplex Structure”, AM Psaras, RK Carty, JT Miller, LN Tumey, TA Brooks; *Genes* **2022**, 13 (8), 1440

2021

“Enzyme-Agnostic Lysosomal Screen Identifies New Legumain-Cleavable ADC Linkers”, Jared T Miller, Caitlin N Vitro, Siteng Fang, Samantha R Benjamin, **L Nathan Tumey***; *Bioconjugate Chemistry*, **2021**, 32, 4, 842-858. DOI: <https://doi.org/10.1021/acs.bioconjchem.1c00124>

“Development of Highly Optimized Antibody–Drug Conjugates against CD33 and CD123 for Acute Myeloid Leukemia”, Yoon-Chi Han, Jennifer Kahler, Nicole Piché-Nicholas, Wenying Hu, Stephane Thibault, Fan Jiang, Mauricio Leal, Madan Katragadda, Andreas Maderna, Russell Dushin, Nadira Prashad, Manoj B

Charati, Tracey Clark, **L Nathan Tumey**, Xingzhi Tan, Andreas Giannakou, Edward Rosfjord, Hans-Peter Gerber, Lioudmila Tchistiakova, Frank Loganzo, Christopher J O'Donnell, Puja Sapra, Clinical Cancer Research, **2021**, 27(2), 622-631. DOI: 10.1158/1078-0432.CCR-20-2149

“Chemical and Physical Stability of an Admixture Containing Cefepime and Vancomycin in Lactated Ringer Solution”, Pegah Shakeraneh, Risako Robinson, Wesley D Kufel, L Nathan Tumey, Samantha R Benjamin, Christopher D Miller, William Darko, Luke A Probst, Robert W Seabury; Hospital Pharmacy; 2021; <https://doi.org/10.1177/0018578719901278>.

2020

“PF-06804103, A Site-specific Anti-HER2 Antibody–Drug Conjugate for the Treatment of HER2-expressing Breast, Gastric, and Lung Cancers”; Edmund I Graziani, Matthew Sung, Dangshe Ma, Bitha Narayanan, Kimberly Marquette, Sujiet Puthenveetil, **L Nathan Tumey**, Jack Bikker, Jeffrey Casavant, Eric M Bennett, Manoj B Charati, Jonathon Golas, Christine Hosselet, Cynthia M Rohde, George Hu, Magali Guffroy, Hadi Falahatpisheh, Martin Finkelstein, Tracey Clark, Frank Barletta, Lioudmila Tchistiakova, Judy Lucas, Edward Rosfjord, Frank Loganzo, Christopher J O'Donnell, Hans-Peter Gerber, Puja Sapra; Molecular Cancer Therapeutics, **2020**, 19, 10, 2068-2078. DOI: 10.1158/1535-7163.MCT-20-0237

“Expanding the Versatility of Microbial Transglutaminase Using α -Effect Nucleophiles as Noncanonical Substrates.” Tak Ian Chio; Breanna R. Demestichas; Brittany M. Brems; Susan L. Bane*; **L. Nathan Tumey***, Angew. Chemie, 59, 13814–13820 **2020**. (co-corresponding authors) DOI: 10.1002/anie.202001830

2019

“Case report: Albendazole associated psychosis”, Doughty, Bennett; **Tumey, L. Nathan**; Williams, Karen; Mental Health Clinician, November 2019, 9, 6, 397-400. DOI: 10.9740/mhc.2019.11.397

“Thiolation of Q295: Site-specific conjugation of hydrophobic payloads without the need for genetic engineering”, Benjamin, Samantha R.; Jackson, Courtney P.; Fang, Siteng; Carlson, Dane P.; Guo, Zhongyuan; **Tumey, L. Nathan***, Molecular Pharmaceutics, 2019, 16,6, 2795-2807. DOI: 10.1021/acs.molpharmaceut.9b00323

“Site-Specific Bioconjugation and Multi-Bioorthogonal Labeling via Rapid Formation of a Boron–Nitrogen Heterocycle”, Choi, Tak Ian; Gu, Han; Mukherjee, Kamalika; Tumey, **L. Nathan Tumey***; Bane, Susan L. * (co-corresponding authors), Bioconjugate Chemistry, 2019, 30, 5, 1554-1564. DOI: 10.1021/acs.bioconjchem.9b00246

“Natural Product Bis-Intercalator Depsipeptides as a New Class of Payloads for Antibody-Drug Conjugates”, Ratnayake, Anokha S.*; Chang, Li-ping; **Tumey, L. Nathan**; Loganzo, Frank; Chemler, Joseph A.; Wagenaar, Melissa; Musto, Sylvia; Li, Fengping; Janso, Jeffrey E.; Ballard, T. Eric; Rago, Brian; Steele, Greg L.; Ding, WeiDong; Feng, Xidong; Hosselet, Christine; Buklan, Vlad; Lucas, Judy; Koehn, Frank E.; O'Donnell, Christopher J.; Graziani, Edmund I., Bioconjugate Chemistry, 2019, 30(1), 200-209. DOI:10.1021/acs.bioconjchem.8b00843

“Novel PIKK inhibitor antibody-drug conjugates: Synthesis and anti-tumor activity”, Zhou, Dahui*; Casavant, Jeffrey; Graziani, Edmund I.; He, Haiyin; Janso, Jeffrey; Loganzo, Frank; Musto, Sylvia; **Tumey, Nathan**; O'Donnell, Christopher J.; Dushin, Russell, *Bioorganic & Medicinal Chemistry Letters*, 2019, 29(7), 943-957. DOI:10.1016/j.bmcl.2019.01.009

2017

“Thinking Small and Dreaming Big: Medicinal Chemistry Strategies for Designing Optimal ADCs”, **L. Nathan Tumey***, *Medicinal Chemistry Reviews*, Chapter 19, 2017, 52, 363-379.

“Site selection: A case study in the identification of optimal cysteine engineered ADCs.”, **L. Nathan Tumey***, Fengping Li, Brian Rago, Xiaogang Han, Frank Loganzo, Sylvia Musto, Edmund I. Graziani, Sujiet Puthenveetil, Jeffrey Casavant, Kimberly Marquette, Tracey Clark, Jack Bikker, Eric M. Bennett, Frank Barletta, Nicole Piche-Nicholas, Amy Tam, Christopher J. O'Donnell, Hans Peter Gerber, and Lioudmila Tchistiakova; *AAPS Journal*, 2017, 19(4), 1123-1135.

“Quantitative Conjugated Payload Measurement Using Enzymatic Release of Antibody-Drug Conjugate with Cleavable Linker.”, Brian Rago, **L. Nathan Tumey**, Cong Wei, Frank Barletta, Tracey Clark, Steve Hansel, and Xiaogang Han*; *Bioconjugate Chemistry*, 2017, 28(2), 620-626.

“ADME Considerations for the Development of Biopharmaceutical Conjugates Using Cleavable Linkers”, **L. Nathan Tumey*** and Sean Han, *Current Topics in Medicinal Chemistry*, 2017, 17(32), 3444-3462.

“Multivalent peptidic linker enables identification of preferred sites of conjugation for a potent thialanstatin antibody drug conjugate”, Puthenveetil, Sujiet*; He, Haiyin; Loganzo, Frank; Musto, Sylvia; Teske, Jesse; Green, Michael; Tan, Xingzhi; Hosselet, Christine; Lucas, Judy; **Tumey, L. Nathan**; Sapra, Puja; Subramanyam, Chakrapani; O'Donnell, Christopher J.; Graziani, Edmund I, 2017, *PLoS One*, 12(5), e0178452/1-e0178452/16. DOI:10.1371/journal.pone.0178452

2016

“Optimization of Tubulysin Antibody-Drug-Conjugates: A Case Study in Addressing ADC Metabolism”, **L. Nathan Tumey***, Carolyn A. Leverett, Beth Vetelino, Fengping Li, Brian Rago, Xiaogang Han, Frank Loganzo, Sylvia Musto, Guoyun Bai, Sai Chetan K. Sukuru, Edmund I. Graziani, Sujiet Puthenveetil, Jeffrey Casavant, Anokha Ratnayake, Kimberly Marquette, Sarah Hudson, Venkata Ramana Doppala-pudi, Joseph Stock†, Lioudmilla Tchistiakov, Andrew J. Bessire, Tracey Clark, Judy Lucas, Christine Hosselet, Christopher J. O'Donnell, and Chakrapani Subramanyam; *ACS Medicinal Chemistry Letters*, 2016, 7(11), 977-982. **[Selected as cover article for November 2016 edition]**

“Calculated conjugated payload from immunoassay and LC-MS intact protein analysis measurements of antibody-drug conjugate”, Brian Rago, Tracey Clark, Lindsay King, Jenny Zhang, **L. Nathan Tumey**, Fengping Li, Frank Barletta, Cong Wei, Mauricio Leal, Steve Hansel*, & Xiaogang Han; *Bioanalysis*, 2016, 8(21), 2205-2217.

“Natural Product Splicing Inhibitors: A New Class of Antibody-Drug Conjugate (ADC) Payloads”, Puthenveetil, Sujiet*; Loganzo, Frank; He, Haiyin; Dirico, Ken; Green, Michael; Teske, Jesse; Musto, Sylvia; Clark, Tracey; Rago, Brian; Koehn, Frank; Veneziale, Robert; Falahaptisheh, Hadi; Han, Xiaogang; Barletta, Frank; Lucas, Judy; Subramanyam, Chakrapani; O'Donnell, Christopher J.; **Tumey, L. Nathan**; Sapra, Puja; Gerber, Hans Peter; Ma, Dangshe; Graziani, Edmund I; *Bioconjugate Chemistry*, 2016, 27(8), 1880-1888.

“Where Did the Linker-Payload Go? A Quantitative Investigation on the Destination of the Released Linker-Payload from an Antibody-Drug Conjugate with a Maleimide Linker in Plasma”, Wei, Cong*; Zhang, Guodong; Clark, Tracey; Barletta, Frank; **Tumey, L. Nathan**; Rago, Brian; Hansel, Steven; Han, Xiaogang; *Analytical Chemistry*, 2016, 88(9), 4979.

“Development of Solid-Phase Site-Specific Conjugation and Its Application toward Generation of Dual Labeled Antibody and Fab Drug Conjugates”, Puthenveetil, Sujiet*; Musto, Sylvia; Loganzo, Frank; **Tumey, L. Nathan**; O'Donnell, Christopher J.; Graziani, Edmund; *Bioconjugate Chemistry*, **2016**, 27(4) 1030.

2015

“In vivo biotransformations of antibody-drug conjugates”, **Tumey, L. Nathan**; Rago, Brian; Han, Xiaogang*; *Bioanalysis*, 2015, 7(13), 1649.

2014

“Mild method for succinimide hydrolysis on ADCs: Impact on ADC potency, stability, exposure, and efficacy”, **L. Nathan Tumey***, Manoj Charati, Tao He, Eric Sousa, Dangshe Ma, Xiaogang Han, Tracey Clark, Jeff Casavant, Frank Loganzo, Frank Barletta, Judy Lucas, and Edmund I. Graziani; *Bioconjugate Chemistry*, 2014, 25(10), p1871-1880.

“Identification and optimization of indolo[2,3-c]quinoline inhibitors of IRAK4” **Tumey, L. Nathan***; Boschelli, Diane H.; Bhagirath, Niala; Shim, Jaechul; Murphy, Elizabeth A.; Goodwin, Deborah; Bennett, Eric M.; Wang, Mengmeng; Lin, Lih-Ling; Press, Barry; Shen, Marina; Frisbie, Richard K.; Morgan, Paul; Mohan, Shashi; Shin, Julia; Rao, Vikram R., *Bioorganic and Medicinal Chemistry Letters*, 2014, 24, 2066-2072.

2013

“Recent advances in antibody-drug conjugates” Graziani, Edmund I.*; **Tumey, L. Nathan**, *RSC Drug Discovery Series*, 2013, 36 (Biotherapeutics), 145-175.

2012

“CRTH2 antagonists” **Tumey, L. Nathan*** *RSC Drug Discovery Series*, 2012, 26 (Anti-Inflammatory Drug Discovery), 104-134.

2009

“5-Vinyl-3-pyridinecarbonitrile inhibitors of PKC θ : Optimization of enzymatic and functional activity.”, **Tumey, L. Nathan***; Bhagirath, Niala; Brennan, Agnes; Brooijmans, Natasja; Lee, Julie; Yang, Xiaoke; Boschelli, Diane H., *Bioorg. Med. Chem*, 2009, 17, 7933-7948.

“First generation 5-vinyl-3-pyridinecarbonitrile PKC-theta inhibitors”, Niu, Chuansheng; Boschelli, Diane H.; **Tumey, L. Nathan**; Bhagirath, Niala; Subrath, Joan; Shim, Jaechul; Wang, Yan; Wu, Biqu; Eid, Clark; Lee, Julie; Yang, Xiaoke; Brennan, Agnes; Chaudhary, Divya, *Bioorg. Med. Chem. Lett.*, 2009, 19(20), 5829-5832.

2008

“2-Alkenylthieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKC-theta”, **Tumey, L. Nathan***; Boschelli, Diane H.; Lee, Julie; Chaudhary, Divya. *Bioorg. Med. Chem. Lett.*, 2008, 18(15), 4420-4423.

“A facile, scalable preparation of 4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carbonitriles”, **Tumey, L. Nathan**; Bhagirath, Niala; Wu, Biqu; Boschelli, Diane H., *Tetrahedron Lett.*, 2008, 49(48), 6850-6852.

2005

“Isosteric ramatroban analogs: selective and potent CRTH-2 antagonists.”, Robarge, Michael J.; Bom, David C.; **Tumey, L. Nathan**; Varga, Norbert; Gleason, Elizabeth; Silver, Daniel; Song, Jianping; Murphy, Steven M.; Eckema, George; Doucette, Chris; Hanniford, Doug; Palmer, Marc; Pawlowski, Gary; Danzig, Joel; Loftus, Margaret; Hunady, Karen; Sherf, Bruce A; Mays, Robert W; Stricker-Krongrad, Alain; Brunden, Kurt R; Harrington, John J; Bennani, Youssef L, *Bioorg. Med. Chem. Lett.* 2005, 15(6), 1749-1753.

“The identification and optimization of a N-hydroxy urea series of flap endonuclease 1 inhibitors”, **Tumey, L. N.***; Bom, D.; Huck, B.; Gleason, E.; Wang, J.; Silver, D.; Brunden, K.; Boozer, S.; Rundlett, S.; Sherf, B.; Murphy, S.; Dent, T.; Leventhal, C.; Bailey, A; Harrington, J; Bennani, Y. L.”, *Bioorg. Med. Chem. Lett.* 2005, 15(2), 277-81.

2004

“The identification and optimization of 2,4-diketobutyric acids as flap endonuclease 1 inhibitors”, **Tumey, L.N.***; Huck, B.; Gleason, E.; Wang, J.; Silver, D.; Brunden, K.; Boozer, S.; Rundlett, S.; Sherf, B.; Murphy, S.; Bailey, A.; Dent, T.; Leventhal, C.; Harrington, J.; Bennani, Y.L., *Bioorg. Med. Chem. Lett.*, 2004, 14(19), 4915-8.

2003

“High-Throughput Catch-and-Release Synthesis of Oxazoline Hydroxamates. Structure-Activity Relationships in Novel Inhibitors of *Escherichia coli* LpxC: In Vitro Enzyme Inhibition and Antibacterial Properties”, Pirrung, M. C.; **Tumey, L. N.**; McClerren, A. L.; Raetz, C. R. H., *J. Am. Chem. Soc.*, 2003, 125 (6), 1575-1586.

2002

“Inhibition of the antibacterial target UDP-(3-O-acyl)-N-acetylglucosamine deacetylase (LpxC): isoxazoline zinc amidase inhibitors bearing diverse metal binding groups”, Pirrung, M.C.; **Tumey, L.N.**; Raetz, C.R.; Jackman, J.E.; Snehalatha, K.; McClerren, A.L.; Fierke, C.A.; Gantt, S.L.; Rusche, K.M., *J. Med. Chem.*, 2002, 45(19), 4359-70.

“19F-Encoded Combinatorial Libraries: Discovery of Selective Metal Binding and Catalytic Peptoids”, Michael C Pirrung; Kaapjoo Park; L Nathan Tumey, *J. Comb. Chem.*, **2002**, 4, 4, 329-344.

2000

“Antibacterial agents that target lipid A biosynthesis in gram-negative bacteria. Inhibition of diverse UDP-3-O-(r-3-hydroxymyristoyl)-n-acetylglucosamine deacetylases by substrate analogs containing zinc binding motifs.”, Jackman JE; Fierke CA; Tumey LN; Pirrung M; Uchiyama T; Tahir SH; Hindsgaul O; Raetz CR., *J. Biol. Chem.*, **2000**, 275(15), 11002-9.

“Oxazoline Synthesis from Hydroxyamides by Resin Capture and Ring-Forming Release”, Michael C. Pirrung; L. Nathan Tumey, *J. Comb. Chem.*, **2000**, 2, 6, 675-680.

EDITORIAL / PEER REVIEW / REFEREE EXPERIENCE

Book Editor:

Springer, Method in Molecular Biology, “Antibody-Drug Conjugates: Methods and Protocols”. Publishing date: Fall 2019. Served as lead editor for this 26-chapter volume. Authored two of the chapters.

Referee service: (typically ~10 per year)

ACS Medchem Letters,
Bioconjugate Chemistry
Protein Engineering, Design, and Selection
Molecular Cancer Therapeutics
Analytical Chemistry
Pharmaceutical Medicine
ACS Omega
Currents in Pharmacy Teaching and Learning (CPTL)
Angewandte Chemie

External examiner, PhD thesis Committee (outside of Binghamton University)

S. R. Shindi, external examiner (thesis committee) – PhD pharmaceutical sciences, 2022, University of Kwazulu-Natal (Nigeria)

PROFESSIONAL AFFILIATIONS

American Chemical Society (1995-present)
American Association of Pharmaceutical Sciences (2017-present)
American Associate of Colleges of Pharmacy (2017-2019)
Society for the Immunotherapy of Cancer (SITC) (2022-present)

TEACHING EXPERIENCE

- PHRM501** “Foundations of Pharmacology”. Delivered ~15 hours of lectures plus one group “case study” and multiple review sessions. Content: Medicinal chemistry, drug design, drug metabolism.
Delivered: Fall 2017, Fall 2018, Fall 2019, Fall 2020, Fall 2021
- PHRM515** “Pharmaceutics II: Dosage Forms and Drug Delivery”. Delivered 9 hours of lectures plus 3h of review sessions. Content: Parenteral drug delivery, dispersed systems.
Delivered: Spring 2018
- PHRM522** “Integrated Pharmacotherapy IV: Endocrine, Renal and Reproductive Health”. Delivered ~7 hours of lectures plus various review sessions. Content: Medicinal chemistry of diabetic drugs, glucocorticoids, mineralocorticoids, diuretics, birth control, PBH, and erectile dysfunction.
Delivered: Fall 2018, Fall 2019 [*co-coordinator*], Fall 2020
- PHRM524** “Integrated Pharmacotherapy VI: Infections Diseases”. Delivered ~15 hours of lecture and active learning activities. Content: Medicinal chemistry and pharmacology of antiviral agents, antifungal agents, and antibacterial agents.
Delivered: Spring 2019, spring 2020, spring 2021
- PHRM523** “Integrated pharmacotherapy V: Neurology, Psychiatry, Anesthesiology”. Delivered ~2 hours of lectures. Content: Medicinal chemistry of drugs for multiple sclerosis and Alzheimer’s disease.
Delivered: Spring 2019
- PHRM542** “Integrated Pharmacotherapy VIII: Hematology / Oncology / Autoimmune Diseases” Delivered ~13 hours of lectures plus various review sessions. Content: Medicinal chemistry of immunomodulating agents and chemotherapeutic agents.
Delivered: Fall 2019, Fall 2020, Fall 2021
- PHRM580E** “Drug discovery and development”. *Course designer / coordinator*. Content: Delivered ~15h of lectures and active learning. Coordinated all guest lectures, exams, and projects. Instructor of record.
Delivered: Fall 2020
- UNIV101S** “Science, Faith, and Ethics”. [Class delivered for Harpur College] Delivered ~15 hours of lectures and class activities. Content: Philosophy of science, ethical theories, and history of science and faith. *Course designer / coordinator*.
Delivered: Fall 2019
- BME442/542** “Nanotechnology and Drug Delivery” [Class in Watson], delivered ~5h of lectures each year on pharmacokinetics and pharmacodynamics. *Guest lecturer*.
Delivered: Fall 2020, Fall 2021

MENTORSHIP OF STUDENTS AND POSTDOCTORAL FELLOWS [@BINGHAMTON]

Year	Name	Program of study	Outcome / current position
2017-2019	Courtney Jackson	-Undergraduate independent study -Completed honors thesis -Pharmacy School Summer Intern Program (full time)	PharmD candidate, UNC Chapel Hill
2017-2020	Tak Ian Choi	PhD student (co-mentor)	Postdoctoral fellow, U. Penn.
2018	Zhongyuan	Postdoctoral Fellow	Postdoctoral fellow,

	"Lenny" Guo		Harvard School of Public Health
2018-2019	Dane Carlson	MS Student (BME)	R&D associate, Regeneron Pharmaceuticals
2018-2020	Emanuel Oladwode	Postdoctoral Fellow	Assistant Professor of Pharmaceutical Sciences
2018-2020	Kelsey Watts	Undergraduate independent study	Scientific writer, Regeneron Pharmaceuticals
2018-2021	Jared Miller	-Undergraduate independent study -Completed honors thesis -Summer researcher (full time)	PhD candidate at Scripps Research Institute
2018-present	Siteng Fang	PhD Student, BME	Current student
2019-2021	Caitlin Vitro	-Undergraduate independent study -Completed honors thesis -Summer researcher (full time)	PhD candidate at UNC Chapel Hill
2019-2021	Brittany Bremms	-Undergraduate independent study -Completed Honors thesis -Summer researcher (full time)	PhD candidate at Northeastern University
2019-2021	James "JP" Maher	PharmD student researcher	PharmD graduate
2019	Sarah Gillen	NSF REU student	Engineer at MedTronic
2019	Jared Frick	Undergraduate independent study	Medical Student at Albany College of Medicine
2020-2021	Rhea Johns	MS Student (BME)	PhD candidate, Virginia Tech
2020-2022	Katherine J Leong	-Undergraduate independent study -Pharmacy School Summer Intern Program (full time)	Researcher at New York Blood Center
2020-present	Samantha Benjamin	PhD Student, Chemistry	Current student
2021-2022	Daniel Wheeler	-Undergraduate independent study -Summer researcher (full time)	Current student

		-Summer Scholars and Artists Program (2021)	
2021-2022	Caleb Manheim	Undergraduate independent study	MS student at Binghamton University
2021-present	Emma DeYoung	-Undergraduate independent study -Summer researcher (full time)	Current student
2020-2022	Justin M Howe	-Undergraduate independent study -Summer researcher (full time) -Summer Scholars and Artists Program (2020)	Medical student at Virginia Tech Carilion School of Medicine
2021	Sophia Cook	NSF REU student	Student at Rowan University
2021-2022	Jillian P. Handel	-Undergraduate independent study	MS Student at Binghamton University (PharmSci)
2022	Karina Zielenski	-Undergraduate independent study	Current student
2022	Steven McKay	-Undergraduate independent study	PhD student at Binghamton University
2022	Victor Ojo	-PhD candidate	Current student
2022	Megan Grey	-PharmD student (research track)	Current student
2022	Nicholas Bianchi	-Undergraduate independent study	Current student
2023	Lina Wu	-Undergraduate independent study	Current student
2023	Mohan Mullapudi	Postdoctoral Fellow	Current fellow
2023	Mohammad Asikur Rahman	Postdoctoral Fellow	Current fellow

Graduate Student Committee Service, not listed above:

- **Julien Avelino Viel**, external examiner (thesis committee) – PhD Chemistry, 2021
- **Laura Zielewicz**, external examiner (thesis committee) – PhD Chemistry, 2021
- **Soujanya Karantha**, external examiner (thesis committee) – PhD Biomedical Engineering, 2021
- **Victor Wamboa**, external examiner (thesis committee) – PhD Chemistry, 2020
- **Yuhao Yuan**, thesis committee member, Biomedical Engineering. (completed comprehensive exam and prospectus. Expected graduation ~2022)

- **Stephanie Zhang**, thesis committee member, Biomedical Engineering. (completed comprehensive exam and prospectus. Expected graduation ~2022)
- **Yundi Chen**, MS/PhD defense committee, Biomedical Engineering, 2020-2022.
- **Saptarshi Ghosh**, external examiner (thesis committee) – PhD Chemistry, 2020
- **S. R. Shindi**, external examiner (thesis committee) – PhD pharmaceutical sciences, 2022, University of Kwazulu-Natal (Nigeria)

Faculty mentorship, not listed above:

- Tony Davis, 2020-present. (SOPPS faculty mentorship committee member)
- Tracy Brooks, 2022-present. (SOPPS faculty mentorship committee member)

MANAGERIAL EXPERIENCE (direct reports, full time)

Fanny Xu (2021-present) – Research technician, Binghamton University
 Jared Miller (2020-2021) – Research technician, Binghamton University
 Samantha Benjamin (2017-2020) – Research technician, Binghamton University
 Jeff Casavant (2013-2017) – Associate Scientist, Pfizer Inc.
 Anokha Ratneyake, PhD (2015-2017) – Senior Scientist, Pfizer Inc.
 Sujiet Puthenveetil, PhD (2013-2017) – Senior Scientist, Pfizer Inc.
 Niala Bhagirath (2006-2010) - Assistant Research Scientist, Wyeth Pharmaceuticals
 Joan Subrath (2008-2010) - Assistant Research Scientist, Wyeth Pharmaceuticals
 Elizabeth Gleason (2002-2006) – Research Associate, Athersys Inc.

INVITED SEMINARS / ORAL PRESENTATIONS

- | | |
|------|---|
| 2024 | “Optimizing the Efficacy and PK of Immune Stimulating Antibody Conjugates”, Protein Engineering Summit (PEGS), May 17, 2024, Boston MA. |
| 2024 | “ADC Training Workshop”, Protein Engineering Summit (PEGS), May 14-15, 2024, Boston MA. |
| 2024 | “Next-generation topoisomerase ADC technology”, DAVA oncology 2024 Antibody Drug Conjugates and Bispecifics Think Tank, March 15-17 2024, Victoria BC. |
| 2024 | “The promise and the risk of TLR7 stimulating ADCs”, DAVA oncology 2024 Antibody Drug Conjugates and Bispecifics Think Tank, March 15-17 2024, Victoria BC. |
| 2024 | “ADC technology: How did we get here and where are we going?”, Lotte Biopharma, Syracuse NY, March 6 th , 2024. |
| 2024 | “Precision Therapeutics: Using Chemistry to Supercharge Antibodies”, Feb. 6 th , 2024, Houghton University, Caneadea NY. |
| 2023 | Bristol-Myers Squibb invited presentation, July 17, 2023. “Lessons in ADC design: Conjugation, Linkers, and Payloads” |

- 2023 Hanson-Wade Linker and Conjugation Summit, August 22nd 2023. “Delving Into Site-Specific Conjugations to Create Homogenous ADCs” – Workshop leader.
- 2023 Hanson-Wade Linker and Conjugation Summit, August 23rd 2023. “Looking Beyond Cathepsins: Understanding & Optimizing Legumain-Cleavable ADC Linkers”
- 2023 PEGS, May 15-19, Boston MA. “Dual-function antibody conjugates: Combining multiple modes of action to maximize ADC efficacy”
- 2022 Northeast Regional ADC Meeting (NERM), October 4 2022. Rochester, NY; “Design, synthesis, and evaluation of anti-inflammatory antibody-drug-conjugates (ADCs) that target monocytes and macrophages”
- 2022 ADC World Summit, San Diego, CA, September 6, 2022 “New Strategies for the Design of TRL7 Agonist ADCs”
- 2021 ADC World Summit, October 14-15 2021, “Design & Optimization of TLR-activating ADCs for Use in Cancer & Infectious Diseases”
- 2021 Loxo Oncology, invited lecture, February 12 2021, “Challenges and opportunities in the design of antibody-drug conjugates”
- 2021 Bighat Biosciences, ADC workshop leader. April 16, April 29, May 13. Led a 4.5 hour training workshop on antibody-drug-conjugate design.
- 2021 PEGS 2021 Protein Engineering and Cell Therapy Summit, May 13, 2021. “Alternatives to ValCitPABC: New Cleavable Linker and Self-Immolation Strategies for ADCs”
- 2020 Takeda Pharmaceutical Company, invited lecture, October 19, 2020. “New proteolytic linker strategies for ADCs”
- 2020 European Antibody Congress, Oct. 22 2020. “New proteolytic linker strategies for ADCs”
- 2019 Wells College, Nov. 8, 2019. “Macromolecular Medicinal Chemistry: Strategies for Optimizing Antibody-Drug-Conjugates”
- 2018 Binghamton University, Department of Chemistry, March 9, 2018. “Macromolecular Medicinal Chemistry.”
- 2018 Takeda Pharmaceutical Company, invited lecturer, May 22nd, 2018. “Macromolecular Medicinal Chemistry.”
- 2018 “Bioanalysis on a Budget”, L. Nathan Tumey, ADC World Summit, San Diego, CA, November 2018.

- 2017 University of Buffalo, School of Pharmacy, Sept. 14, 2017. “Dreaming Big and Thinking Small: Medicinal Chemistry Strategies for the Optimization of Antibody Drug Conjugates.”
- 2017 Binghamton University, Biomedical Engineering, Sept. 26, 2017. “Dreaming Big and Thinking Small: Medicinal Chemistry Strategies for the Optimization of Antibody Drug Conjugates.”
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