

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AJINOMOTO CO., INC.
Petitioner,

v.

ABTIS CO., LTD.
Patent Owner

Patent No. 11,896,675
Issue Date: February 13, 2024

Title: SITE-SPECIFIC ANTIBODY CONJUGATION AND ANTIBODY-DRUG
CONJUGATE AS SPECIFIC EMBODIMENT THEREOF

Inter Partes Review No. IPR2025-0283

**PETITIONER'S OPPOSITION TO PATENT OWNER'S MOTION TO
AMEND**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	DR. ZHOU’S TESTIMONY SHOULD NOT BE GIVEN WEIGHT	1
III.	THE PROPOSED SUBSTITUTE CLAIMS ARE UNPATENTABLE UNDER 35 U.S.C. § 112.....	2
A.	The Proposed Substitute Claims Are Not Enabled and Lack Written Description	2
B.	The Proposed Substitute Claims Are Indefinite.....	5
IV.	PROPOSED SUBSTITUTE CLAIMS 14-16 ARE ANTICIPATED.....	7
V.	PROPOSED SUBSTITUTE CLAIMS 14-16 ARE OBVIOUS	10
A.	Yamada Must Be Considered.....	11
B.	The Shared Limitations of the Proposed Substitute Claims Are Expressly Disclosed in the Art	12
C.	Ground 7 – Claims 14-16 Are Obvious Over Yamada In View of Matsuda	14
D.	Grounds 3 and 5 – Claims 14-16 Are Obvious Over PepTalk Poster or PepTalk Presentation in View of Yamada and Matsuda.....	20
E.	MATSUDA DOES NOT TEACH AWAY FROM USING HETEROATOMS.....	24
F.	THERE IS NOTHING UNEXPECTED OR CRITICAL ABOUT THE CLAIMED STRUCTURES	25
VI.	CONCLUSION.....	25

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Beckman Instruments v. LKB Produkter A&B</i> , 892 F.2d (Fed. Cir. 1989).....	19
<i>Capon v. Eshhar</i> , 418 F.3d 1349 (Fed. Cir. 2005).....	5
<i>Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.</i> , 533 F.3d 1353 (Fed. Cir. 2008).....	18
<i>Gentry Gallery, Inc. v. The Berkline Corp.</i> , 134 F.3d 1473 (Fed. Cir. 1998).....	2
<i>In re Donohue</i> , 766 F.2d 531 (Fed. Cir. 1984).....	19
<i>In re Gurley</i> , 27 F.3d 551 (Fed. Cir. 1994).....	24
<i>Interval Licensing LLC v. AOL, Inc.</i> , 766 F.3d 1364 (Fed. Cir. 2014).....	5, 6
<i>Lockwood v. Am. Airlines, Inc.</i> , 107 F.3d 1565 (Fed. Cir. 1997).....	7
<i>Nautilus, Inc. v. Biosig Instruments, Inc.</i> , 134 S. Ct. 2120 (2014).....	5, 6
<i>Rasmusson v. Smithkline Beecham Corp.</i> , 413 F.3d 1318 (Fed. Cir. 2005).....	7
<i>Realtime Data, LLC v. Iancu</i> , 912 F.3d 1368 (Fed. Cir. 2019).....	13
<i>In re Slayter</i> , 276 F.2d 408 (CCPA 1960)	7

<i>Symbol Techs. Inc. v. Opticon Inc.</i> , 9235 F.2d 1569, 1578 (Fed. Cir. 1991)	19
<i>UCB, Inc. v. Actavis Labs, UT, Inc.</i> , 65 F.4th 679 (Fed. Cir. 2023)	24
<i>United States v. Telectronics, Inc.</i> , 857 F.2d 778 (Fed. Cir. 1988).....	5

Statutes

35 U.S.C. § 112	2, 7
35 U.S.C. § 120	7
35 U.S.C. § 365(c)	7

Regulations

37 C.F.R. § 42.24	1
37 C.F.R. § 42.24(a).....	1
37 C.F.R. § 42.24(b)	1
37 C.F.R. § 42.65(a).....	1

Other Authorities

<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH</i> , IPR2019-01469, Paper 10 at 8 n.9 (PTAB Feb. 13, 2020) (precedential).....	11
<i>Amazon.com, Inc. v. Uniloc Luxembourg S.A.</i> , IPR2017-00948, Paper 34 (January 18, 2019).....	2
<i>Core Survival, Inc., v. S & S Precision, LLC</i> , PGR2015-00022, Paper 8, 8 (PTAB Feb. 19, 2016).....	7
<i>Lectrosonics, Inc. v. Zaxcom, Inc.</i> , IPR2018-01129, 01130, Paper 15 (February 25, 2019; precedential).....	2
<i>Xerox Corp. v. Bytemark, Inc.</i> , IPR2022-00624, Paper 9 (August 24, 2022)	1

CITED EXHIBIT LIST

Ex #	Exhibit Description
1001	U.S. Patent No. 11,896,675 (“the ’675 Patent”)
1002	Declaration of Dr. Lawrence Nathan Tumey
1005	CA 3132959A1 (Canadian 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 PEPTALK 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 PEPTALK 2019, THE PROTEIN SCIENCE WEEK, Jan. 16, 2019 (“PepTalk Presentation”)
1009	U.S. 2020/0190165 (U.S. National Stage of Yamada)
1011	U.S. 2021/0139541 (U.S. National Stage of Matsuda)
1041	Tumey et al., <i>Site Selection: a Case Study in the Identification of Optimal Cysteine Engineered Antibody Drug Conjugates</i> , AAPS JOURNAL, 2017, 19(4):1123-1135.
1042	Tumey et al., <i>Optimization of Tubulysin Antibody–Drug Conjugates: A Case Study in Addressing ADC Metabolism</i> , ACS MEDICINAL CHEMISTRY LETTERS, 2016, 7(11): 977-982.
1043	Graziani et al., <i>PF-06804103, A Site-specific Anti-HER2 Antibody–Drug Conjugate for the Treatment of HER2-expressing Breast, Gastric, and Lung Cancers</i> , MOLECULAR CANCER THERAPEUTICS, 2020, 19, 10, 2068-2078
1044	Sadiki et al., <i>Site-specific conjugation of native antibodies</i> , ANTIBODY THERAPEUTICS, 2020, 3(4):271-284

Ex #	Exhibit Description
1045	Chau et al., <i>Antibody–drug conjugates for cancer</i> , THE LANCET, 2019, 394(10200): 793-804.
1046	Trail et al., <i>Antibody drug conjugates for treatment of breast cancer: Novel targets and diverse approaches in ADC design</i> , PHARMACOLOGY & THERAPEUTICS, 2018, 181: 126-142.
1047	Benjamin et al., <i>Thiolation of Q295: Site-Specific Conjugation of Hydrophobic Payloads without the Need for Genetic Engineering</i> , MOLECULAR PHARMACEUTICS, 2019, 16(6): 2795-2807.
1048	Lyon et al., <i>Reducing hydrophobicity of homogeneous antibody-drug conjugates improves pharmacokinetics and therapeutic index</i> , NATURE BIOTECHNOLOGY, 2015, 33: 733-735.
1049	Staudacher & Brown, <i>Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required?</i> , BRITISH JOURNAL OF CANCER, 2017, 117: 1736-1742.
1050	Pickens et al., <i>Practical Considerations, Challenges, and Limitations of Bioconjugation via Azide–Alkyne Cycloaddition</i> , BIOCONJUGATE CHEMISTRY, 2017, 29(3): 686-701.
1051	Lyon et al., <i>Self-hydrolyzing maleimides improve the stability and pharmacological properties of antibody-drug conjugates</i> , NATURE BIOTECHNOLOGY, 2014, 32: 1059-1062.
1052	Jain et al., <i>Current ADC Linker Chemistry</i> , PHARMACEUTICAL RESEARCH, 2015, 32: 3526-3540.
1053	Knight et al., <i>Synthesis and evaluation of an 18F-laballed norbornene derivative for copper-free click chemistry reaction</i> , ORGANIC & BIOMOLECULAR CHEMISTRY, 2013, 11: 3817-3825.

Ex #	Exhibit Description
1054	Oller-Salvia et al., <i>Rapid and Efficient Generation of Stable Antibody - Drug Conjugates via an Encoded Cyclopropene and an Inverse - Electron - Demand Diels -Alder Reaction</i> , ANGEW CHEM INT ED ENGL., 2018, 57(11): 2831-2834.
1055	Oliveira et al., <i>Inverse electron demand Diels–Alder reactions in chemical biology</i> , CHEMICAL SOCIETY REVIEWS, 2017, 46(16): 4895-4950.
1056	Chalker et al., <i>Methods for converting cysteine to dehydroalanine on peptides and proteins</i> , CHEMICAL SCIENCE, 2011, 2: 1666-1676.
1057	Kirmse et al., <i>Destabilisierte 2-Norbornyl-Kationen</i> , ANGEWANDTE CHEMIE, 1985, 97(1): 51-52.
1058	Mullapudi et al., <i>Resin-Supported Site-Specific Antibody Conjugation Method Leads to Antibody-Drug Conjugates with Retained Efficacy and Improved Stability</i> , BIOCONJUGATE CHEMISTRY, 2025, 36: 1956-1969.
1059	Second Declaration of Dr. Lawrence Nathan Tumey
1060	Deposition Transcript of Dr. Zhaohui Sunny Zhou

I. INTRODUCTION

Petitioner, Ajinomoto Co., Inc. (“Petitioner”), submits its opposition to the Patent Owner’s Motion to Amend (“MTA”), dated October 31, 2025. Patent Owner previously disclaimed all but claim 11 from U.S. Patent No. 11,896,675 (“the ’675 Patent”), and it now moves to cancel claim 11 and separate it into proposed substitute claims 14-16. Patent Owner cites in support of its Motion only two new documents: a Declaration of Dr. Zhaohui Sunny Zhou and the Deposition Transcript of Petitioner’s expert, Dr. Tumey. However, Dr. Zhou’s opinions on the state of the art are conclusory and inconsistent with his own publication. In contrast, Dr. Tumey has maintained that claim 11 of the ’674 Patent is unpatentable, and he provides testimony—that is *actually* substantiated—rebutting Dr. Zhou’s opinions regarding the state of the art and unpatentability of claims 14-16.

In addition, the proposed substitute claims lack enablement and written description support in the ’675 patent specification and priority documents, and are also indefinite. The proposed substitute claims are also anticipated and obvious over the same prior art on which the Board instituted this IPR. For each of these reasons, Patent Owner’s motion should be denied.

II. DR. ZHOU’S TESTIMONY SHOULD NOT BE GIVEN WEIGHT

“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.” 37 C.F.R. § 42.65(a); *Xerox*

Corp. v. Bytemark, Inc., IPR2022-00624, Paper 9 (August 24, 2022). The entirety of Dr. Zhou’s testimony is devoid of any substantiating citation or reference to underlying facts. Instead, Dr. Zhou offers only conclusory opinions that (a) are demonstrably disprovable and inaccurate (EX1059, ¶3-12, 15-16), (b) inconsistent with his own publication (*id.*, ¶13-14) and deposition testimony (EX1060, 85:22-86-3), and (c) generally lack any substantiation. Accordingly, Dr. Zhou’s declaration should be given little or no evidentiary weight.

III. THE PROPOSED SUBSTITUTE CLAIMS ARE UNPATENTABLE UNDER 35 U.S.C. § 112

Under *Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, 01130, Paper 15 (February 25, 2019; precedential), it is Petitioner’s burden to show that any proposed substitute claims are unpatentable by a preponderance of the evidence. To this end, *Amazon.com, Inc. v. Uniloc Luxembourg S.A.*, IPR2017-00948, Paper 34 (January 18, 2019) instructs that the Board may consider issues of unpatentability under Section 112. *Id.*, 5-10.

A. The Proposed Substitute Claims Are Not Enabled and Lack Written Description

In *Gentry Gallery, Inc. v. The Berkline Corp.*, 134 F.3d 1473, 1479 (Fed. Cir. 1998), the Federal Circuit held that a claim may not be broadened beyond the broadest scope described in the specification. Claims 14-16 each recite the phrase “the modified antibody comprises one or more modified heavy chain.” However, the

specifications as filed nowhere describe a “modified antibody” comprising “one or more modified heavy chain.” Indeed, this phrase *only* appears in the granted ‘675 claims, but not in any originally filed claim. Compare EX1001 to 2002, 2003, 1040.

While the specification describes “an antibody or a fragment thereof comprising one or more amino acid sequences selected from formula 8-1, formula 8-2, and formula 8-3” (EX2003, [0059]), this is not the same scope of modified antibody that is presented in claims 14-16. Rather, a “modified antibody” that “comprises one or more modified heavy chain[s]” as in claims 14-16 may encompass amino acids adjacent to the modified Lys 248 that are different from those shown in each of formulas 8-1, 8-2, and 8-3. Thus, the scope of proposed substitute claims 14-16 is broader than what is described in the specification.

Further, the Summary of Invention section, which contains the broadest description of the invention, only describes antibodies with 2 modified lysines at position 248, 2 modified lysines at position 246, or 4 modified lysines, with 2 at 246 and 2 at 248. EX2003, [0008]-[0011]. In other words, the specification only describes antibodies with two modified heavy chains, but—by virtue of reciting “one or more modified heavy chain”—claims 14-16 necessarily encompass antibodies with exactly/only one modified heavy chain and antibodies with three or more

modified heavy chains.¹ The specification fails to provide any disclosure indicating position of an antibody having exactly/only one modified heavy chain or an antibody with three or more modified heavy chains, and it likewise fails to disclose a process for making or using either such antibody. EX1059, ¶17-21.

Instead, the specification provides only a single example of each claimed modification, and in each instance the sole modified antibody (trastuzumab) has two modified heavy chains. EX2003, [1272]-[1329]; EX1059, ¶18-19. It would require a tremendous amount of work to develop a process that *always* resulted in exactly one modified heavy chain, if it were possible at all, and the specification provides no examples, direction or guidance with respect to modifying antibodies and “similar structures” that have more than two heavy chains (e.g., IgM). EX1059, ¶20-21. Even Dr. Zhou asserts, “a POSA could not predict with confidence whether a modification that succeeded for one antibody would also succeed for another.” EX2004, ¶40.

¹ The '675 Patent defines “antibody” as “an immunoglobulin molecule or a fragment thereof” including “naturally occurring immunoglobulins” and “all recombinant proteins, fusion proteins, chimeric proteins, human immunoglobulins, non-human animal immunoglobulins, and the like, which have the same or similar structures” and therefore the claims extend to antibodies and “similar structures” that have more than two heavy chains (e.g., IgM). EX1001, 40:52-57.

The hallmark of sufficient written description is showing possession of the full scope of the claims (*Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005)) and enablement requires sufficient direction to make and use the claims without “undue experimentation” (*United States v. Teletronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)). Neither requirement is satisfied here given the scope of a “modified antibody” that “comprises one or more modified heavy chain[s]” in the proposed substitute claims. Accordingly, claims 14-16 are not supported by the specification of the ’675 Patent or the specifications of any of the preceding applications in the priority chain. *See, e.g.*, EX1004, 2002, and 2003.

B. The Proposed Substitute Claims Are Indefinite

“[A] patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention” (*Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014)),² and “[t]he claims, when read in light of the specification and the prosecution history, must provide objective boundaries for those of skill in the art” (*Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1371 (Fed. Cir. 2014)). The ability to give “some

² On January 6, 2021, the USPTO issued a Memorandum providing binding agency guidance that the Board shall follow *Nautilus* in post-grant proceedings.

meaning” to a phrase cannot save an otherwise indefinite term. *Nautilus*, 134 S. Ct. at 2129-30. Instead, a claim is indefinite where “the claim language ‘might mean several different things.’” *Interval Licensing*, 766 F.3d at 1371.

The proposed substitute claims do not meet the *Nautilus* standard because claims 14-16 all contain the following language: “A modified antibody comprising a bio-orthogonal click chemistry functional group ... wherein the modified lysine has following structure:” The claims each reference and require “a bio-orthogonal click chemistry group”, but this group is never referenced again. Instead, the rest of the claim refers only to the structure and location of the “modified lysine.” Thus, a POSA could interpret these claims in at least two ways:

- i) wherein the later-referenced “modified lysine” is the same as the earlier referenced “bio-orthogonal click chemistry group”; or
- ii) wherein the “modified lysine” represents a separate structure containing a bio-orthogonal click chemistry group in addition to the other “bio-orthogonal click chemistry functional group” referenced earlier in the claim.

Thus, the claim “might mean several different things” and is therefore indefinite. *Interval Licensing*, 766 F.3d at 1371. The Board should not make a “post hoc” effort to “ascribe some meaning to a patent’s claims.” *Nautilus*, 134 S. Ct. at 2129-30.

IV. PROPOSED SUBSTITUTE CLAIMS 14-16 ARE ANTICIPATED

Ground 1 of the Petition asserts that claim 11 of the '675 Patent is anticipated by the '959 Publication because neither the '675 Patent nor any of the applications to which it claims priority provide the requisite support for priority entitlement. *See* Petition, 13-19, 22. For at least the reasons discussed in Section III, the '675 Patent and the applications to which it claims priority (e.g., EX1004, 2002 & 2003) do not enable or provide sufficient written description for claims 14-16, and thus, the claims are only entitled to priority as of the filing date of the '998 application. The '959 Publication remains prior art. *See* 35 U.S.C. §§ 120 and 365(c); *Core Survival, Inc., v. S & S Precision, LLC*, PGR2015-00022, Paper 8, 8 (PTAB Feb. 19, 2016); *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565,1571 (Fed. Cir. 1997).

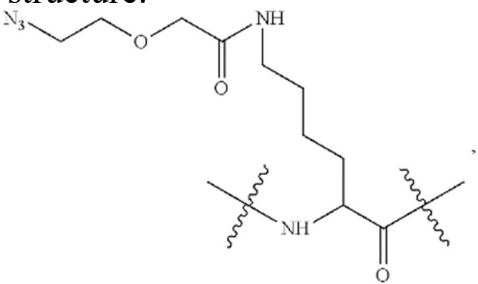
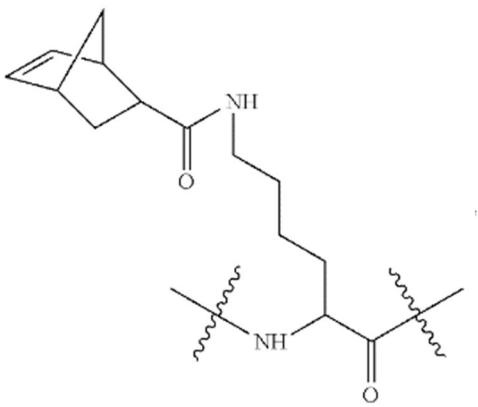
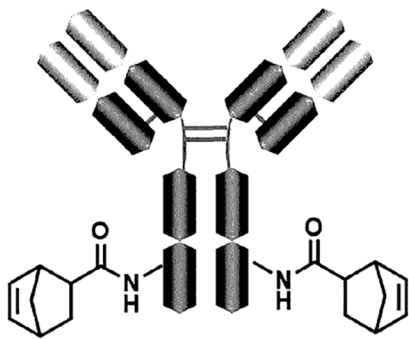
Although a prior art reference needs to be enabled, the enablement standard for prior art is a lower threshold than that of § 112 (*Rasmusson v. Smithkline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005)), and a species will always anticipate a more broadly claimed genus (*In re Slayter*, 276 F.2d 408, 411 (CCPA 1960)). The '959 Publication discloses trastuzumab with a modified lysine at position 248 with the same structures recited in claims 14-16.

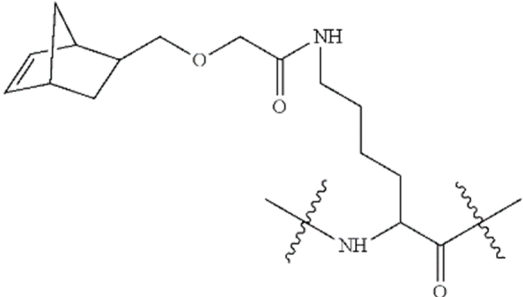
While Dr. Zhou alleges that “Dr. Tumey agrees that the proposed substitute claims are supported by the original patent because he shows that support in contending that claim 11 is anticipated by the '959 Publication” (EX2004, ¶53), this

assertion is a misstatement of fact (Dr. Tumey never previously opined on the support for claims 14-16) and illustrates Patent Owner’s misunderstanding of the applicable legal standards. While claims 14-16 lack enablement and written description because they are broader than the disclosure (i.e., they are not supported by the singular example of an antibody modified with the claimed structures), that singular example is sufficient to anticipate the claims. In other words, the proposed substitute claims are anticipated precisely because they are not supported, but the converse is not true.

Specifically, Example 3 (EX1005, 223-229) discusses “Synthesis of Ab (246/248 Lys)-norbornene” (*id.*, 223-225) and Section 3.2 discusses “Synthesis of Ab (246/248 Lys)-azide” (*id.*, 225-226). These examples anticipate claims 14-16, as shown in the claim chart below. To reduce redundancy, the claim chart combines the written limitations of proposed substitute claims 14-16 that are identical.

Proposed Substitute Claims 14-16	Disclosure in the '959 Publication
A modified antibody comprising bio-orthogonal click chemistry functional group,	Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1059, ¶23-25.
wherein the modified antibody comprises one or more modified heavy chain,	Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1059, ¶23-25.
wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and	“Synthesis of Ab (246/248 Lys)-norbornene was carried out in a buffer using Compound III-SSFI (Lys).” <i>See</i> 225. “[T]he present invention provides technology for specifically transferring a chemical functional group to <u>lysine 248</u> in the antibody.”

Proposed Substitute Claims 14-16	Disclosure in the '959 Publication
	<i>See 3.</i> <i>See also Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1059, ¶23-25.</i>
Proposed Substitute Claim 14	Disclosure in the '959 Publication
wherein the modified lysine has the following structure: 	Example 3.1 (223-225); EX1059, ¶23-25.
Proposed Substitute Claim 15	Disclosure in the '959 Publication
wherein the modified lysine has the following structure: 	“[T]he structure of the final product (i.e., Ab(246/248)-Norbornene) is shown in FIG. 43.”  Fig. 43 <i>See also Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1059, ¶23-25.</i>
Proposed Substitute Claim 16	Disclosure in the '959 Publication
wherein the modified lysine has the following structure:	Examples 3.2-3.4 (225-229); EX1059, ¶23-25.

Proposed Substitute Claims 14-16	Disclosure in the '959 Publication
	

Pages 5 and 171-172 of the '959 publication disclose precursors of the claimed structures (EX1005, 5, 171-172; *see also* Figs. 17, 19, 22), and reacting the structure disclosed in 171-172 with trastuzumab, as shown in Example 3.2, would provide a modified lysine with the structure of claim 14. EX1059, ¶23-25. The structure shown in claim 15 is identical to the structure shown in Fig. 43, and synthesis of the structure of claim 16 would occur from reacting its precursor disclosed in EX1005, 165-174. EX1059, ¶23-25. Claims 14-16 are anticipated by the '959 publication.

V. PROPOSED SUBSTITUTE CLAIMS 14-16 ARE OBVIOUS

Claims 14-16 are obvious for the reasons articulated in Grounds 3, 5, and 7 of the Petition. Petition, 49-56, 65-69, 80-84. The Petition did not discuss the structure of proposed substitute claim 15 because the Petition showed that the two other structures recited in claim 11 (i.e., those now shown in claims 14 and 16) were each obvious. Below, all of the recited structures and proposed substitute claims are analyzed and shown to be obvious.

A. Yamada Must Be Considered

Patent Owner reiterates that “Petitioner has not shown any ‘material error’ made by the USPTO during prosecution to satisfy its burden of proving that the ’675 Patent claims are unpatentable over Yamada.” MTA, 14. This assertion—which was raised and addressed during the discretionary denial phase—again falls flat.

The Examiner did not consider Yamada in combination with the PepTalk References, and the examiner materially erred in considering Yamada by overlooking that Yamada unambiguously discloses the “Negative Limitation” recited in claim 1. The Negative Limitation was the reason for the initial, improper allowance of the ’675 Patent. “[O]verlooking specific teachings of the relevant prior art where those teachings impact patentability” is “[a]n example of a material error.” *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 10 at 8 n.9 (PTAB Feb. 13, 2020) (precedential).

Patent Owner also acknowledges the Negative Limitation “permitted a wide range of other chemical moieties so long as they were not among those expressly excluded” (MTA, 5) and claims 14-16 “remove the negative limitation of disclaimed claim 1” (*id.*, 3). Thus, Patent Owner acknowledges the scope of claims 14-16 was never before the Examiner, and therefore any prior consideration of Yamada is moot.

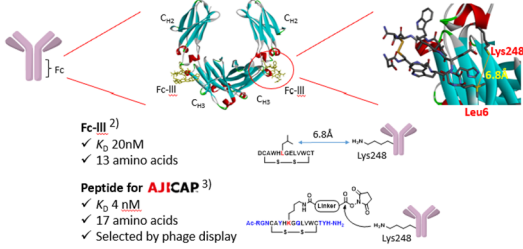
B. The Shared Limitations of the Proposed Substitute Claims Are Expressly Disclosed in the Art

All of the proposed substitute claims include the identical limitations:

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

All of these limitations are disclosed in PepTalk References (EX1006; EX1007), Yamada (EX1009), and Matsuda (EX1011), as shown in the claim chart below.

Proposed Substitute Claims 14-16	Disclosure in the Cited Art																													
A modified antibody comprising bio-orthogonal click chemistry functional group,	1. Capability of AJICAP  Non-mutated mAb <table><tr><th>Isotype</th><th>mAb</th><th>Attachment</th><th>Structure</th><th>Linker</th><th>Payload</th></tr><tr><td rowspan="5">IgG1</td><td>Trastuzumab</td><td rowspan="2">Thiol (-maleimide)</td><td rowspan="2"></td><td>Cleavable</td><td>DM-1</td></tr><tr><td>Rituximab</td><td>Non-cleavable</td><td>MMAE</td></tr><tr><td>Adalimumab</td><td rowspan="3">Azide (-cycloalkyne)</td><td rowspan="3"></td><td>MMAF</td></tr><tr><td>X company-mAb A (client project)</td><td>PBD</td></tr><tr><td>X company-mAb B (client project)</td><td>α-amanitin</td></tr><tr><td rowspan="2">IgG2</td><td>Denosumab</td><td rowspan="2">Aldehyde & (-hydroxylamine)</td><td rowspan="2"></td><td rowspan="2">Confidential payload (Client project)</td></tr><tr><td>Dupilumab</td></tr></table> AJICAP technology is compatible with a wide variety of mAbs, attachments, linkers, and payloads. EX1006 EX1007, 15, 16, 20. EX1009, FIGs 1-2, [1019]; <i>see also</i> [0151]-[0153], [0581]-[0591]. EX1011, [1018]-[1029],[1289]-[1290], and [1296]-[1298]. EX1002, ¶194-205, 290-298, 384-389.	Isotype	mAb	Attachment	Structure	Linker	Payload	IgG1	Trastuzumab	Thiol (-maleimide)		Cleavable	DM-1	Rituximab	Non-cleavable	MMAE	Adalimumab	Azide (-cycloalkyne)		MMAF	X company-mAb A (client project)	PBD	X company-mAb B (client project)	α-amanitin	IgG2	Denosumab	Aldehyde & (-hydroxylamine)		Confidential payload (Client project)	Dupilumab
Isotype	mAb	Attachment	Structure	Linker	Payload																									
IgG1	Trastuzumab	Thiol (-maleimide)		Cleavable	DM-1																									
	Rituximab			Non-cleavable	MMAE																									
	Adalimumab	Azide (-cycloalkyne)		MMAF																										
	X company-mAb A (client project)			PBD																										
	X company-mAb B (client project)			α-amanitin																										
IgG2	Denosumab	Aldehyde & (-hydroxylamine)		Confidential payload (Client project)																										
	Dupilumab																													

Proposed Substitute Claims 14-16	Disclosure in the Cited Art
wherein the modified antibody comprises one or more modified heavy chain,	EX1059, ¶26-27. <i>See above</i> for EX1006. EX1007, 15, 16, 20. EX1009, [0607]; <i>see also</i> FIG. 1-2, p. 147-148. EX1011, [1018]-[1029],[1289]-[1290], and [1296]-[1298]. EX1002, ¶206-211, 299-303, 390-393. EX1059, ¶26-27.
wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and	2. Determine Target Lysine Residue Antibody 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 EX1006 EX1007, 16, 18. EX1009, [0598], [1108]-[1109]; <i>see also</i>, Example 8, [1944]-[1971]. EX1011, [0329], [0431]. EX1002, ¶198, 208, 212-216, 304-308, 394-404. EX1059, ¶26-27.

A “disclosure that anticipates under § 102 also renders the claim invalid under § 103, for ‘anticipation is the epitome of obviousness.’” *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019). Accordingly, the identical limitations

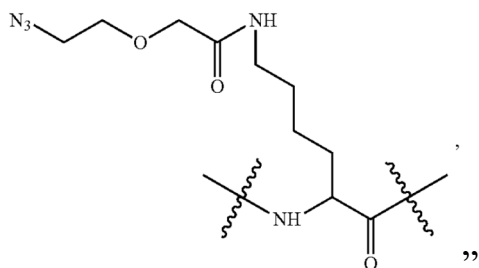
of claims 14-16 are obvious in view of PepTalk Poster (EX1006), PepTalk Presentation (EX1007), Yamada (EX1009), and/or Matsuda (EX1011).

The only distinctions between claims 14-16 are the modified lysine structures recited in each respective claim, which are discussed under the Grounds below.

C. Ground 7 – Claims 14-16 Are Obvious Over Yamada In View of Matsuda

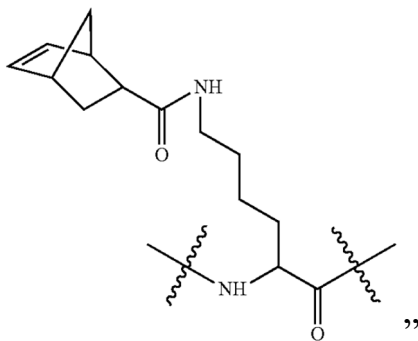
Proposed substitute claim 14 recites:

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



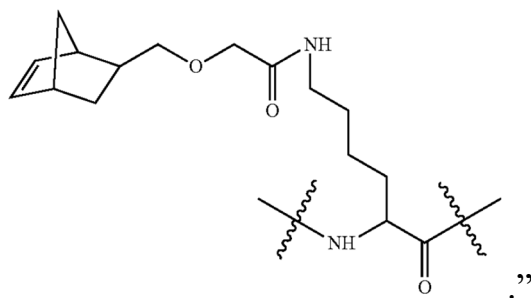
proposed substitute claim 15 recites:

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



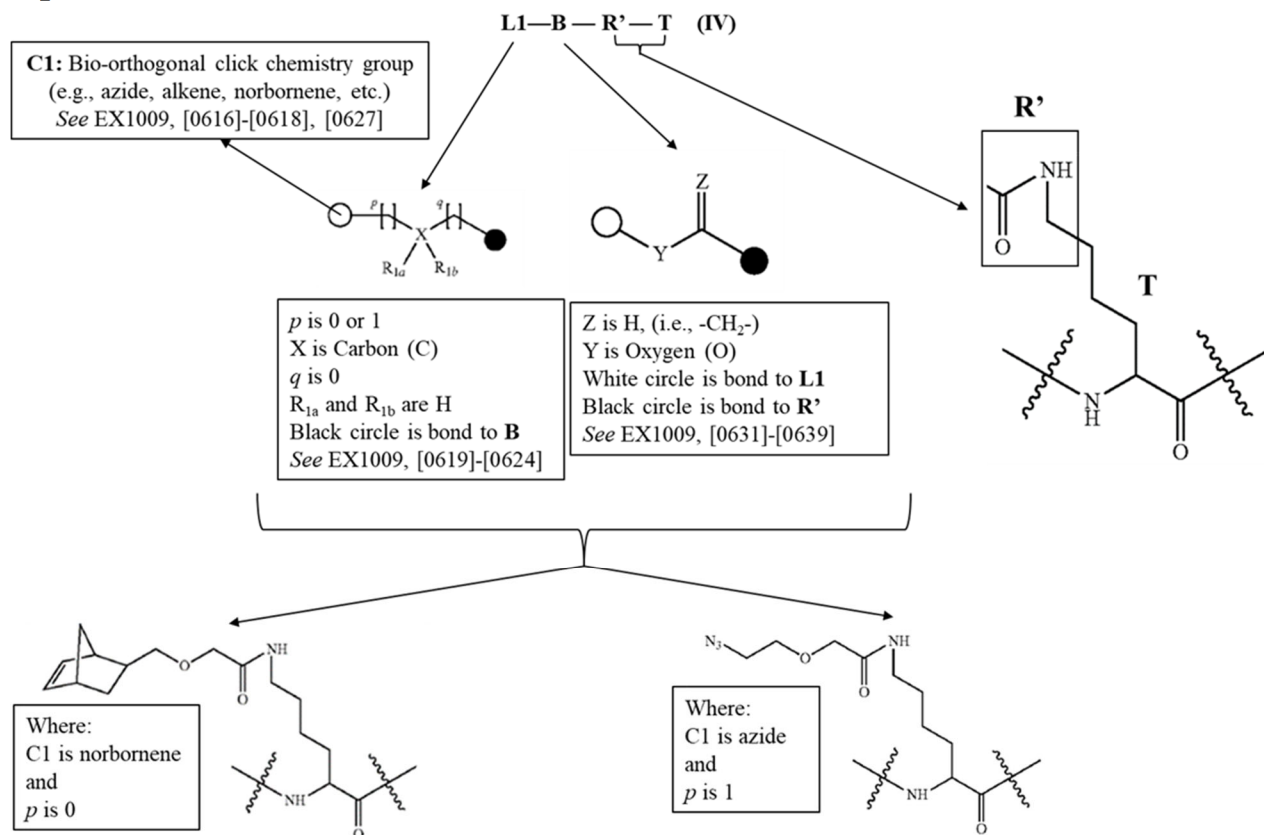
and proposed substitute claim 16 recites:

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



As provided in the Petition, the modified lysine structures recited in claims 14 and 16 are taught by Yamada's Formula (IV): L1-B-R'-T (IV). Petition, 49-56; EX1002, ¶¶267-277. There are at least two ways that the modified lysine structures recited in claims 14 and 16 can be assembled from Formula (IV):

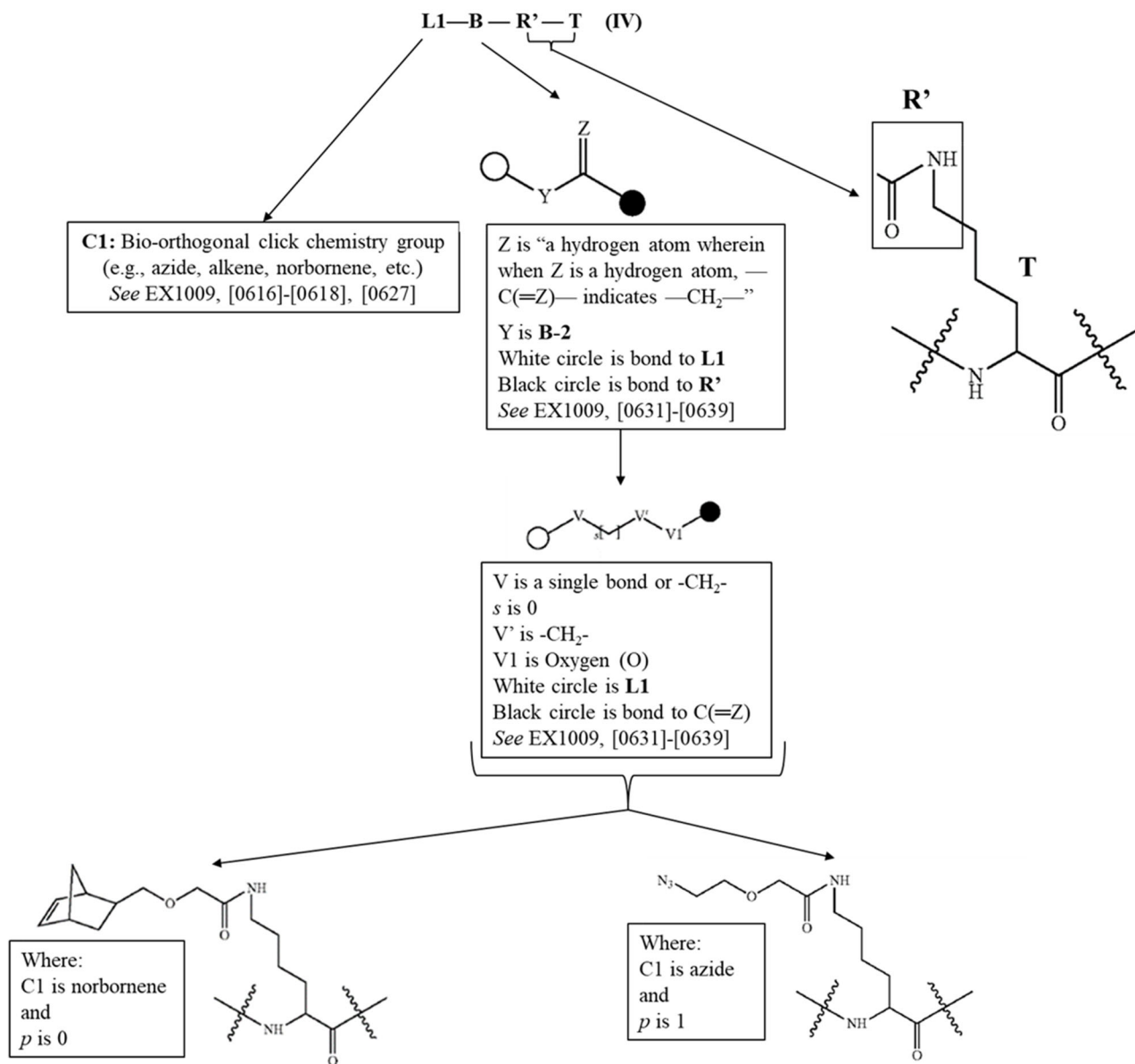
Option 1:



with the components of the structures relative to Formula (IV) for Option 1 being:



Option 2:



with the components of the structures relative to Formula (IV) for Option 2 being :



EX1002, ¶276.

There is no dispute that Yamada teaches the necessary components for Formula (IV) to arrive at the structures of claims 14 and 16 (EX1059, ¶29-30, 38), and there was also motivation to select these components (EX1059, ¶31-36, 39-43).

Patent Owner argues there was “no reason to choose any one of the functional groups in the claims” (MTA, 17), but this is not true. Claim 14 includes an azide on the modified lysine and both claims 15 and 16 include a norbornene. Not only were azide and norbornene both disclosed as suitable functional groups in Yamada and Matsuda, azide and norbornene were also among the most well-established and commonly used click chemistry groups at the time. EX1059, ¶31-32, 39; EX1050; EX1053; EX1054; EX1055. A POSA would be motivated to select them.

A POSA would also be motivated to select the linkers connecting the click chemistry groups to the lysines in claims 14-16. Short linkers—like those in claims 14 and 16—were preferred (EX1002, ¶256, 267, 351, 362) because they provide flexibility, which can be helpful for subsequent reactions, and both Yamada and Matsuda (as well as the PepTalk References) disclose short alkyl linkers similar to those in the claims. EX1059, ¶33-36, 39-43. The inclusion of an oxygen heteroatom,

as in the linkers of claims 14 and 16, would have been desirable to a POSA because an oxygen heteroatom would provide stability in a variety of reaction conditions and improve solubility in circulation. *Id.*, ¶34, 50. Both Yamada and Matsuda provide multiple examples of linkers with a heteroatom (including oxygen, specifically), underscoring the proven motivation and feasibility of including a heteroatom in the linker. *Id.*, ¶35, 50-52, 75; EX1009, [0622], [0633]; EX1011, [1154], [1161]-[1168].

With respect to claim 16, a POSA would have been motivated to keep molecules simple by preparing a modified lysine with no linker. EX1059, ¶41. A structure like that of claim 16 could serve as a standard of comparison (i.e., control) for assessing the impact of adding to/altering the linker, which was a scientific need that would motivate a POSA to prepare the modified lysine of claim 15. *Id.*

While Patent Owner alleges that “Yamada does not identify any preference, advantage, or motivation to choose the claimed options” (MTA, 18), this assertion is inaccurate and ignores the fact that “the requisite motivation can come from any number of sources and need not necessarily be explicit in the art.” *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008).

Patent Owner also argues that obviousness cannot be premised on Yamada’s Formula (IV) because “Petitioner fails to show that *Yamada* teaches the modified residues of the substitute claims are scientifically feasible.” MTA, 21. This argument is also unavailing. Yamada does not need to provide a synthetic scheme for a POSA

to select the disclosed components in Formula (IV) and arrive at claims 14-16. A reference is “enabling” if “one of ordinary skill in the art could have combined the publication’s description of the invention with his [or her] own knowledge to make the claimed invention.” *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1984). Even if one could not prepare the claimed structures from Yamada’s synthetic scheme in Figure 2, Yamada discloses all of the components of the claimed structures and suggests combining them. That alone is sufficient to render the claims obvious. *Beckman Instruments v. LKB Produkter A&B*, 892 F.2d 1847, 1551 (Fed. Cir. 1989) (“Even if a reference discloses an inoperative device, it is prior art for all that it teaches.”); *Symbol Techs. Inc. v. Opticon Inc.*, 9235 F.2d 1569, 1578 (Fed. Cir. 1991).

Patent Owner attempts to cloud the issue by focusing only on Yamada’s Figure 2 scheme, and misled its expert into considering only Yamada while ignoring any other teaching/knowledge in the art (EX1060, 208:5-11). But Patent Owner’s assertions of “scientific feasibility” are legally moot because the level of skill and knowledge in the art would have allowed a POSA to make the claimed modified lysines independently of the specific reaction scheme disclosed in Figure 2 of Yamada. EX1059, ¶¶55-63. There were multiple well-established synthetic routes for creating the claimed lysine structures (*id.*, ¶¶57-61; EX1056; EX1057), including Figure 1 of Matsuda, which is a synthetic scheme that is highly similar to the ’675 Patent’s and could create the claimed structures (EX1059, ¶¶62-36).

D. Grounds 3 and 5 – Claims 14-16 Are Obvious Over PepTalk Poster or PepTalk Presentation in View of Yamada and Matsuda

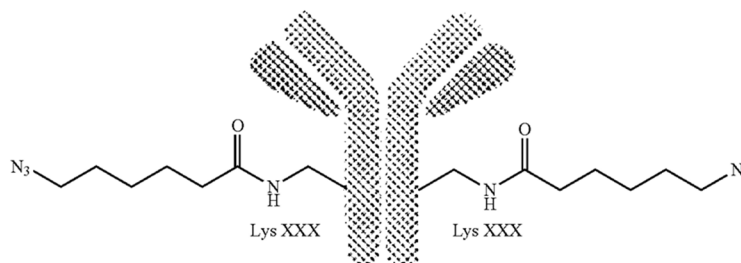
Patent Owner argues that “the PepTalk References would teach away from using the AJICAP technology” because “the PepTalk References disclose a second generation.” MTA, 24-25. This argument is flawed for multiple reasons. AJICAP was presented at the PepTalk Conference to encourage adoption and to seek collaboration with industry partners; the antithesis of teaching away. A POSA would not infer “deficiencies and imminent obsolescence” in the PepTalk References when both references explicitly state that AJICAP “provides significant advantages for next generation ADCs.” EX1006; EX1007, 33.

Dr. Zhou similarly argues although the PepTalk Poster References “mention[] ‘lysine residue 248’ as an example, it does not state that it is the exclusive lysine binding site.” EX2004, ¶57, 71. This interpretation of the PepTalk References is so strained it calls into question Dr. Zhou’s credibility. These references do not merely “mention” modification of lysine 248; lysine 248 is the only residue that is discussed, used, or tested, and the test results show that modification of lysine 248 provided desirable results. EX1059, ¶50-53.

With respect to claim 14, the PepTalk References teach an azide as a suitable bio-orthogonal click chemistry group to modify the lysine at position 248, and they disclose a linker that differs from the linker of claim 14 only with respect to the oxygen ether. EX1006, “Capability of AJICAP™”, “Synthesis of Site-Specific ADC

by AJICAP™”; EX1007, 16, 20. EX1059, ¶47, 49. Yamada and Matsuda likewise disclose the use of an azide, and Matsuda discloses an azide structure that only differs from claim 14 by having a carbon in the beta position instead of an oxygen:

5-2-1

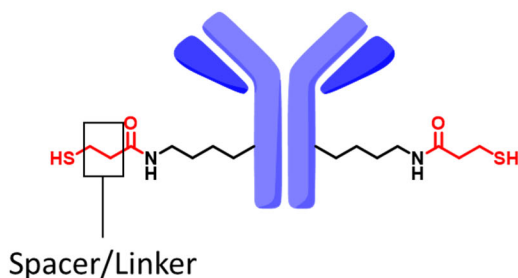


EX1059, ¶44, 46; EX1009, FIG. 1-2, [0151]-[0153], [0581]-[0598], [0607], [1019]
[1108]-[1109], [1944]-[1971] EX1011, 92, [[0593], [0739].

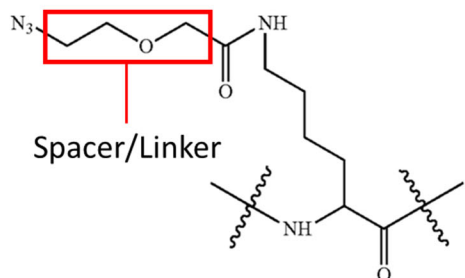
There are numerous benefits to incorporating an oxygen into the linker, and therefore a POSA would be motivated to incorporate an oxygen. EX1059, ¶33-36, 47. Additionally, both Yamada and Matsuda provide examples of incorporating a heteroatom into the linker, including examples of incorporating oxygen. EX1059, ¶44, 67; EX1002, ¶453; EX1009, [0622], [0633]; EX1011, [1154], [1161]-[1168].

Thus, a POSA would have been motivated to substitute the thiol in the structure below with an azide and to alter the linker to include an oxygen:

Disclosed in PepTalk References



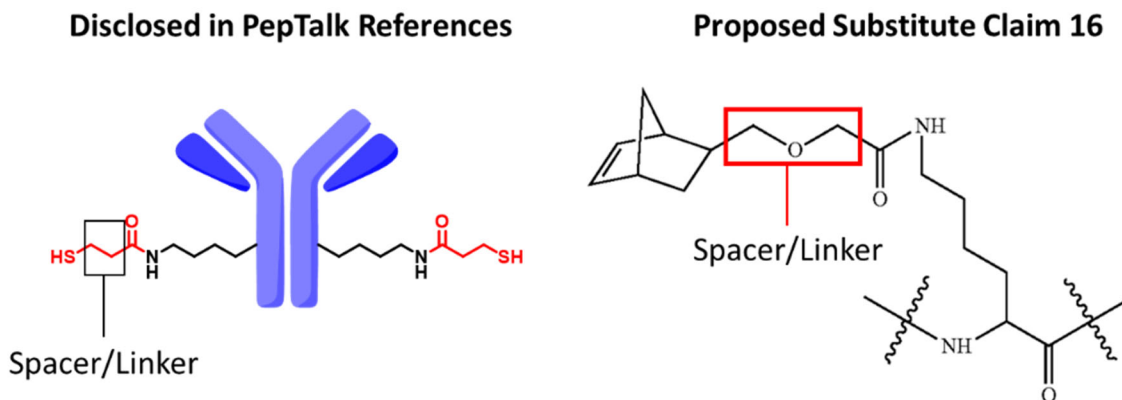
Proposed Substitute Claim 14



EX1006, “Capability of AJICAP™”; EX1007, 16; EX1059, ¶47.

Additional motivation and expectation of successfully making the structure is found in Yamada’s Formula (IV), which discloses and suggests combination of all of the components (*see* discussion of Yamada, *supra*; EX1002, ¶267-277), and Matsuda, which discloses an azide structure barely differing from claim 14 (EX1011, p. 92) along with a synthetic scheme that a POSA would use to produce the claimed structure (EX1059, ¶62-63).

With respect to claims 15 and 16, although PepTalk References do not explicitly disclose norbornene, the utility of norbornene was well-established, and Yamada and Matsuda both explicitly suggest it. EX1059, ¶39-42, 48, 49. The linker exemplified in the PepTalk References is highly similar to the linkers in claims 15 and 16, as well:



EX1006, “Synthesis of Site-Specific ADC by AJICAP™”; EX1007, 16; EX1059, ¶56. For claim 16, there was motivation to alter the linker to include an oxygen heteroatom (EX1059, ¶48, 67; EX1048, EX1052), and both Yamada and Matsuda disclosed examples of heteroatoms in the linker (EX1009, [0622], [0633]; EX1011, [1154], [1161]-[1168]). For claim 15, one of the only ways the structure in the PepTalk References could be simplified is by removing the two carbon linker entirely, which a POSA would have been motivated to do. EX1059, ¶48-49, 41.

Additional motivation and expectation of successfully making these structures is found in Yamada’s Formula (IV), which discloses and suggests combination of all of the components (*see* discussion of Yamada, *supra*; EX1002, ¶267-277), along with Matsuda, which discloses a synthetic scheme that could be used to produce the structures (EX1059, ¶62-63) and the general skill in the art (EX1059, ¶56-61).

Accordingly, claims 14-16 are obvious over either of the PepTalk References in view of Yamada and Matsuda.

E. Matsuda Does Not Teach Away from Using Heteroatoms

The legal standard for “teaching away” is not satisfied when a reference “merely expresses a general preference for an alternative invention” (*UCB, Inc. v. Actavis Labs, UT, Inc.*, 65 F.4th 679, 692 (Fed. Cir. 2023)) and “a known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use” (*In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)).

Matsuda’s suggestion that a single reaction with compounds 26 or 60 “had not progressed” does not mean that the reaction did not work at all or would not work under other conditions. EX1059, ¶¶64-67; EX1060, 160:5-22; 163:3-19. The experiment with compound 26 was only performed under one set of reaction conditions and the conditions for compound 60 were not disclosed. Altering any number of parameters (incubation time, temperature, or pH) might lead the reaction to proceed, and it was common to optimize reaction conditions over iterative experiments. EX1059, ¶¶66-67. Not “progressing” under the single disclosed set of conditions is not a “teaching away” because a POSA would understand that other conditions could work. *Id.*

Moreover, both Matsuda and Yamada provide multiple examples of a linker with a heteroatom, including a beta (β)-heteroatom such as oxygen. EX1059, ¶¶67; EX1009, [0622], [0633]; EX1011, [1154], [1161]-[1168]. Matsuda’s disclosure of

compounds 26 and 60 is not tantamount to a “teaching away.”

F. There is Nothing Unexpected or Critical About the Claimed Structures

Neither Patent Owner nor Dr. Zhou have provided any evidence that the modified lysine structures recited in proposed substitute claims 14-16 possess any unexpected technical benefits or functions (EX1059, ¶68), nor have they provided any evidence that the selection of bio-orthogonal click chemistry groups was critical. Rather, the substitute claims utilize some of the most well-established and common click chemistry groups and short linkers that were commonly exemplified in the references of record. A POSA would have had a reasonable expectation of successfully making the claimed structures and would have ample motivation to do so, and therefore the proposed amended claims are obvious.

VI. CONCLUSION

For the reasons set forth above, the Patent Owner’s Motion to Amend should be denied, proposed substitute claims 14-16 should not be entered, and claim 11 of the ’675 Patent should be canceled as unpatentable.

Respectfully submitted,

Dated: January 23, 2026

By: /Stephen B Maebius/
Stephen Maebius
Registration No. 35,264
Foley & Lardner LLP
Counsel for Petitioner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petitioner's Opposition to Patent Owner's Motion to Amend was served on January 23, 2026, by electronic mail to the attorneys of record for Patent Owner at the following address:

Jason A. Engel
Jason.Engel.PTAB@klgates.com

Anna Rebekah Hill
Rebekah.hill@klgates.com

Devon C. Beane
devon.beane@klgates.com

K&L GATES LLP
70 W. Madison Street, Suite 3100
Chicago, IL 60602

Respectfully submitted,

Dated: January 23, 2026

/Stephen B Maebius/
Stephen B. Maebius
Registration No. 35,264
Foley & Lardner LLP
Counsel for Petitioner