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

PETITION FOR *INTER PARTES* REVIEW

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EXHIBIT LIST

Ex #	Exhibit Description
1001	U.S. Patent No. 11,896,675 ("the '675 Patent")
1002	Declaration of Dr. Lawrence Nathan Tumey
1003	Declaration of Dr. Tatsuya Okuzumi
1004	WO 2020/184944
1005	CA 3132959A1 (Canadian National Stage of WO 2020/184944)
1006	Yamada et al., *Development of a Novel Chemical Site-Specific Conjugation Platform for ADCs – Ajicap™ Technology*, Poster Presentation from PEPTALK 2019, THE PROTEIN SCIENCE WEEK, Jan. 14-18, 2019 ("PepTalk Poster")
1007	Okuzumi, *Technology of Site Specific Conjugation for Next Generation ADCs*, Luncheon Presentation from PEPTALK 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, *PepTalk 2019 - CHI's 18th Annual Meeting - The Protein Science Week: Antibody-Drug Conjugates, San Diego, CA, USA*, IDDB MEETING REPORT, January 25, 2019 ("PepTalk 2019 Annual Meeting Report")
1013	PepTalk 2019 Conference Program
1014	Croasdell, *18th Annual PepTalk: The Protein Science Week – Antibody-Drug Conjugates: Next-Gan Engineering*, DRUGS OF THE FUTURE, 2019, 44(3): 241-245

Ex #	Exhibit Description
1015	Photographs from Luncheon Presentation
1016	Photographs from Poster Presentation
1017	Email exchange with Dr. Igor D'Angelo providing a copy of PepTalk Presentation
1018	Email exchange with Dr. Bernhard Valldorf providing a copy of PepTalk Presentation
1019	Email exchange with Dr. Michael Szardenings providing a copy of PepTalk Presentation
1020	Email exchange with Susan Lee providing a copy of PepTalk Presentation
1021	Email exchange with Professor Rolf G. Werner providing a copy of PepTalk Presentation
1022	LinkedIn profile of Dr. Igor D'Angelo
1023	LinkedIn profile of Dr. Bernhard Valldorf
1024	LinkedIn profile of Dr. Michael Szardenings
1025	LinkedIn profile of Susan Lee
1026	Lambert and Berkenblit, *Antibody–Drug Conjugates for Cancer Treatment*, ANNU. REV. MED., 2018, 69: 191-207.
1027	Birrer et al., *Antibody-Drug Conjugate-Based Therapeutics: State of the Science*, J. NAT'L CANCER INST., 2019, 111(6): 538-549
1028	Schumacher et al., *Current Status: Site-Specific Antibody Drug Conjugates*, J. CLIN. IMMUNOL., 2016, 36: S100-S107.
1029	Nejadmoghaddam et al., *Antibody-Drug Conjugates: Possibilities and Challenges*, AVICENNA J MED BIOTECHNOL., 2019, (1):3-23.

Ex #	Exhibit Description
1030	9th Annual World ADC Conference Program, November 12-15, 2018
1031	Mendelsohn, *Technology of Site Specific Conjugation for Next Generation ADCs*, Presentation from WORLD ADC 2018, Nov. 13, 2018
1032	Oxford English Dictionary definition of "terminal"
1033	Tam et al., *Functional, Biophysical, and Structural Characterization of Human IgG1 and IgG4 Fc Variants with Ablated Immune Functionality*, ANTIBODIES, 2017, 6(12): 10.3390/antib6030012.
1034	Lu et al., *Beyond binding: antibody effector functions in infectious diseases*, NAT. REV. IMMUNOL., 2018, 18(1): 46–61.
1035	Prosecution History for the '675 Patent
1036	Amblard *et al*., *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*, CHEM. REV., 2009, 109(9): 4207-4220.
1037	U.S. 2023/0158167 (U.S. pre-grant publication of U.S. Application 16/980,503)
1038	Japanese Patent Application No. 2018-113962
1039	Verified English Translation of Japanese Pat. App. No. 2018-113962
1040	Verified English translation of application US Ser. No. 62/815,557

I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real-Party-In-Interest (§ 42.8(b)(1))

The real-party-in-interest for this Petition is Ajinomoto Co., Inc.

B. Related Matters (§ 42.8(b)(2))

Petitioner is not aware of any other current litigations or administrative proceedings involving the ’675 Patent that would affect, or be affected by, a decision in this proceeding.

C. Lead and Back-Up Counsel (§ 42.8(b)(3))

Lead-Up Counsel: Stephen Maebius – Registration No. 35,264

Back-Up Counsel: Jason N. Mock – Registration No. 69,186

Address: Foley & Lardner LLP, 3000 K St. NW, Washington, DC. 20008

Fax: 202.672.5399

D. Service Information (§ 42.8(b)(4))

Please address all correspondence to the lead counsel at the address shown above. Petitioner also consents to electronic service by email at:

FOLEY_AJINOMOTO_IPR2025_0283@foley.com

Service by post may be sent to:

FOLEY & LARDNER LLP

3000 K. Street NW

Washington, D.C. 20007-5109

II. REQUIREMENTS FOR PETITION UNDER 37 C.F.R. § 42.104

A. Ground for Standing

Petitioner certifies that the patent for which review is sought is available for *inter partes* review and petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in the petition.

B. Identification of Challenged Claims and Relief Requested

Petitioner requests that claims 1-13 of the '675 Patent (EX1001) be held unpatentable and therefore cancelled based on the grounds for unpatentability detailed below.

A petition for *inter partes* review must demonstrate "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). This Petition meets the threshold; each of the elements of claims 1-13 of the '675 Patent is disclosed, taught, or suggested in the prior art.

Ground	Challenged Claims	Description
1	1-13	Anticipated by CA 3132959 (EX1005)
2	1, 4, 8-10	Anticipated by PepTalk Poster (EX1006)
3	1-13	Obvious over PepTalk Poster (EX1006), alone or in combination with Yamada (EX1008) and Matsuda (EX1010)
4	1, 4, 8-10	Anticipated by PepTalk Presentation (EX1007)

Ground	Challenged Claims	Description
5	1-13	Obvious over PepTalk Presentation (EX1007), alone or in combination with Yamada (EX1008) and Matsuda (EX1010)
6	1, 4, 8-10	Anticipated by Yamada (EX1008)
7	1-13	Obvious over Yamada (EX1008) in view of Matsuda (EX1010)

III. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") as of the earliest claimed priority date or the filing date of the '675 Patent 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. EX1002, ¶36.

IV. TECHNICAL SUMMARY AND BACKGROUND

Antibody-drug conjugates (ADCs) are immunoconjugates comprising an antibody tethered to a cytotoxic drug (known as the payload) via a chemical linker.

ADCs are designed to selectively deliver the toxic payload directly to a target cell, such as a cancer cell. EX1026, 192. This targeted drug delivery couples the precision of antibody targeting with payloads that are generally too toxic for systemic administration alone by reducing toxicities in patients through limited exposure of normal tissues to the payload. EX1027, 538. As of 2019, the pace of ADC development was accelerating, with the number of investigational agents in human trials having more than tripled over the prior 5 years, underscoring the interest in developing this technology. *Id*., 544; EX1002, ¶59.

As of 2019, there were four FDA-approved ADCs, and all employed random conjugation of the cytotoxic drug to either lysine or cysteine residues in the antibody backbone, resulting in a heterogeneous mixture of conjugates with different drug-antibody ratios (DARs). EX1027, 541. 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 motivation in the art to pursue technologies for site-specific conjugation. *Id*.; EX1002, ¶60-61.

Approaches for fine-tuning DARs through site-specific conjugation were considered "highly desirable," and a number of methodologies were in development, including site-specific chemical conjugation to cysteine residues, incorporation of unnatural amino acids into the antibody component for later conjugation, "tub-tag labeling," along with other enzymatic and chemoenzymatic approaches. EX1028,

S101-S105. Thus, by March 2019, it was known that the antibody conjugation site, a well-defined DAR, and homogeneity of the ADC product, were important parameters for ADC development and numerous methodologies were being pursued to implement site-specific conjugation. EX1029, 1, 13-14; EX1002, ¶62.

One 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 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. EX1012, 6; EX1002, ¶63.

Ajinomoto publicly disclosed its AJICAP™ platform at the 9th Annual World ADC conference in San Diego on November 13, 2018 (EX1030, 21; EX1031), and again—in the form of a poster presentation and a luncheon presentation—at the 18th Annual PepTalk conference in San Diego on January 16, 2019 (EX1013, 32; EX1006; EX1007). Both the World ADC and PepTalk conference presentations

provided detailed disclosure of how AJICAP™ could specifically modify the lysine residue at position 248 of IgGs with a wide range of bio-orthogonal click-chemistry functional groups compatible with a wide range of drug-linkers to yield ADCs with a site-specific, controlled DAR of 2. EX1031; EX1006; EX1007.

Thereafter, on March 8, 2019, AbTis filed U.S. Provisional Appl. 62/815,557, which is the earliest application in the ’675 Patent’s asserted priority claim.

V. THE ’675 PATENT

A. Claims

The ’675 Patent contains 13 claims, of which only claim 1 is 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.

Claim 1 recites an antibody (or fragment) that is modified at the lysine residue at position 248 of the heavy chain(s) to include a terminal bio-orthogonal click-

chemistry functional group, and not include a hydroxyl, carboxyl, thiol, amino, or aldehyde group.

The ’675 Patent acknowledges that random attachment approaches were initially used to prepare ADCs. EX1001, 1:55-65; EX1002, ¶50-51. The ’675 Patent also discloses that random conjugation could interfere with the antibody’s ability to recognize its target. EX1001, 1:66-2:7. 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. EX1001, 2:8-20; EX1002, ¶52. According to the ’675 Patent, relying on existing modification methods was “ineffective in technical and economic aspects.” EX1001, 2:8-20.

The ’675 Patent also specifically cites WO 2018/199337 (“Yamada”; EX1008) and acknowledges the technology claimed therein. EX1001, 34:3-9, 69:48-51, 70:12-15, 71:36-39, 72:16-19, 82:52-56.

The ’675 Patent notes 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. Notably, the claims of the ’675 Patent do not exclude a cross-linker including two NHS esters. EX1002, ¶54. The ’675 Patent also concedes that Yamada “aims 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.

Like Yamada, 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.

B. Priority of the '675 Patent

The '675 Patent issued on February 13, 2024 and was filed on January 16, 2023, as U.S. Appl. No. 18/154,998 ("the '998 application"). The '675 Patent is a continuation of U.S. Appl. No. 16/980,503 ("the '503 application"; filed on September 14, 2020; EX1037), which is still pending. The '503 application is a national stage entry of PCT/KR2020/003282 (filed March 9, 2020) and purported English translation thereof as mandated by 35 U.S.C. § 371, which claims priority to U.S. Provisional Appl. 62/815,557 (filed March 8, 2019; EX1040).

Although the '675 Patent claims priority to the '503 application, the '675 Patent specification and the identical '503 application specification fail to provide adequate written description for the claims of the '675 Patent, as explained in Section

VII. Further, there is additional material in the ’503 application that is not present in U.S. 62/815,557, providing separate reasons for denial of priority to this application as well. Accordingly, the ’675 Patent is not entitled to the benefit of priority to the ’503 application or any earlier filed application in the priority chain.

VI. CLAIM CONSTRUCTION

Claims in an *inter partes* review are construed according to the standard articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). 37 C.F.R. § 42.100(b); 83 Fed. Reg. 51340, 51340-59. Claim construction begins with the language of the claims. *Phillips,* 415 F.3d at 1312-14. The “words of a claim are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, *i.e.*, as of the effective filing date of the patent application.” *Id.* at 1312-13; *see also In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). A claim should be interpreted in light of “the words of the claims themselves,” the specification, and the prosecution history of the patent. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582-83 (Fed. Cir. 1996).

A. Construction of “antibody”

The ’675 Patent explicitly defines “antibody” at column 23, lines 40-54 as:

> [T]he 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.

Additionally, the ’675 Patent states at col. 47, lines 52-57:

> [T]he 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.

Thus, the term “antibody” encompasses any type of immunoglobulin molecule or a fragment thereof, including human and non-human immunoglobulin molecules, as well as recombinant proteins, fusion proteins, chimeric protein, wild-type or manipulated antibodies, and “the like, which have the same or similar structures.” Notably, col. 47, line 55 states that the antibody “may be” an IgG, which indicates that “antibody” should be construed as not only IgG, but also IgM, IgA, IgE, and IgD. The term “antibody” is not limited to any particular binding target. EX1002, ¶65-67.

B. Construction of "fragment"

Unlike the term "antibody," the '675 Patent does not explicitly define the term "fragment." However, the definition of "antibody" provides context. Column 23, lines 44-48 of the '675 Patent states, "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." Thus, the term "fragment" must include fragments that have the ability to bind a target antigen and fragments that do not bind an antigen (e.g., an Fc fragment).

Accordingly, the term "fragment" encompasses all known antibody fragments including, but not limited to, (i) Fab fragments; (ii) $F(ab')_2$ fragments; (iii) Fd fragments; (iv) Fv fragments, (v) dAb fragments; (vi) isolated complementarity determining regions (CDR); (vii) single chain Fv (scFv) constructs; and (viii) Fc fragments. EX1002, ¶68.

C. Construction of "at 248 position of heavy chain amino acid sequence"

The claim limitation "at 248 position of heavy chain amino acid sequence" was not discussed or commented on during prosecution of the '675 Patent. However, the specification and claims make clear that the position number "is determined by an EU numbering system" (EX1001, claim 1; 27:61–28:2), and the specification also suggests that this position is commonly "a lysine residue of an Fc domain of the

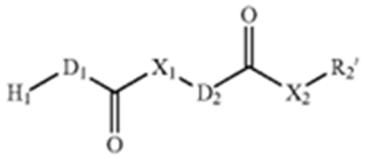
antibody" (EX1001, 6:44-45, 6:54-55, 6:64-65, 7:9-10, 28:1-13; *see also* Figs. 1, 2, 5, 7).

Because EU numbering is a widely accepted system for determining amino acid positions within an antibody, and this position may be within an Fc domain (e.g., if the antibody is an IgG), the POSA would understand how to determine which position within an antibody heavy chain is "at 248 position of heavy chain amino acid sequence" or a corresponding position for a fragment. 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. EX1002, ¶69-70.

D. Construction of "terminal"

Claim 1 recites, "wherein the modified lysine residue does not comprise a terminal bio-reactive functional group…." "Terminal" is not explicitly defined in the '675 Patent specification, but it is utilized in, for example, col. 3, lines 20-23, which states, "the present application provides the compound wherein H_1 is selected from terminal alkyne, azide, strained alkyne, diene, dienophile, alkene, thiol, and tetrazine." This statement is made in reference to "Formula 2":

[formula 2]



The H_1 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.

This is consistent with the Oxford English Dictionary definition of "terminal": "Occurring at the end…forming the last member of a series or succession." EX1032.

Accordingly, "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., H_1 in Formula 2 and other similar formulas disclosed in the '675 Patent).

E. Other Claim Terms Not Construed Herein

Petitioner reserves the right to oppose the interpretation or construction of any claim terms that may be offered or applied in this proceeding and to address modified constructions adopted during this proceeding.

VII. THE '675 PATENT IS NOT ENTITLED TO PRIORITY EARLIER THAN JANUARY 16, 2023

A. Patent Owner Bears Burden of Proof of Establishing Entitlement to the Priority Claim

Entitlement of the '675 Patent to claim priority benefit to U.S. provisional application 62/815,557 ("the '557 application"), or any of the other applications in

the priority chain (e.g., the ’503 application) was acknowledged but never explicitly discussed during prosecution of the ’675 Patent. Petitioner bears the burden of demonstrating that a priority determination is incorrect only when the priority determination was expressly considered by the Patent Office during prosecution. *Microsoft Corp. v. Raniere*, IPR2016-00663, Paper 10 at 6 n.3 (Nov. 10, 2016) (“the burden of proving insufficient disclosure in the parent application [is] on the patent challenger” where priority was addressed by the Patent Office); *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008) (patent challenger has the burden of showing claims lack priority where the Patent Office previously found priority established); *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1573-74 (Fed. Cir. 1985) (same).

Because priority entitlement was never expressly considered by the examiner or discussed during prosecution, entitlement to priority cannot be presumed. *Core Survival, Inc., v. S & S Precision, LLC*, PGR2015-00022, Paper 8, 8 (PTAB Feb. 19, 2016) (“[A]lthough the patent challenger has the ultimate burden of persuasion, a patentee must demonstrate entitlement to a priority date when the patentee relies on that priority date to overcome an anticipation or obviousness argument.”); *see also Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1379-80 (Fed. Cir. 2015); *In re NTP, Inc.*, 654 F.3d 1268, 1270, 1276 (Fed. Cir. 2011); *Liberty Mutual Ins. Co. v. Progressive Cas. Ins. Co.*, CBM2013-00009, Paper 10 (Mar. 28, 2013)

("[E]ntitlement to a priority date for any claim is a matter for which [Patent Owner] bears the burden of proof.").

B. Priority of the '675 Patent Can Be Challenged in an IPR

The PTAB has held that it is permissible to challenge a patent's priority based on deficiencies under § 112 through the application of intervening prior art against the claims. *See, e.g.*, *Daiichi Sankyo Co. Ltd., v. Alethia Biotherapeutics*, IPR2015-00291, Paper 75 at 6-20 (PTAB. June 14, 2016); *see also SAP America, Inc., v. PI-Net Int'l, Inc.*, IPR2014-00414, Paper 11 at 11-16 (PTAB Aug. 18, 2014); *Bioactive Labs. v. BTG Int'l Inc.*, IPR2015-01305, Paper 19 (PTAB Dec. 15, 2015). The Federal Circuit has also held that right of priority may be properly contested when intervening art is asserted, even when the patent issued from a "series of continuations." *NTP*, 654 F.3d at 1270, 1278 ("[A] continuation application is required to have an identical written description to that of its parent, this [priority entitlement] can only be determined by examining the parent application.").

C. Benefit of Priority Under 35 U.S.C. § 120 Requires Fulfillment of 35 U.S.C. § 112

35 U.S.C. §§ 120 and 365(c) provide that a claim in a U.S. application or patent is entitled to the benefit of the filing date of an earlier U.S. application or international application only if, among other things, the claimed invention is disclosed in the earlier application in a manner required by 35 U.S.C. § 112.

The ’675 Patent should only be accorded benefit of priority to January 16, 2023, the filing date of the application that issued as the ’675 Patent, because the parent ’503 application, which is identical to the PCT, and the underlying provisional, U.S. 62/815,557 (EX1040), fail to satisfy the written description requirement under 35 U.S.C. § 112(a).

D. All Applications in the Priority Chain Fail to Provide Adequate Written Description for the Claims of the ’675 Patent

A proper priority claim requires that “each application in the chain leading back to the earlier application must comply with the written description requirement.” *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565,1571 (Fed. Cir. 1997). Any earlier application must clearly convey to the skilled artisan the subject matter later claimed (*Martin v. Mayer*, 823 F.2d 500, 505 (Fed. Cir. 1987)).

Claim 1 of the ’675 Patent includes a negative limitation “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” (“the Negative Limitation”).

To support a negative limitation, the specification must “properly describ[e] alternative features of the patented invention” to indicate that the patentees “are merely excising the inventions of another, to which they are not entitled.” *Inphi Corporation v. Netlist, Inc.*, 805 F.3d 1350, 1355 (Fed. Cir. 2015). The specification

is not required to articulate advantages or disadvantages of each feature to later exclude the alternative feature. *Id.* at 1356-57. When determining whether a negative limitation is supported, "[t]he 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." *Rivera v. Int'l Trade Comm'n*, 857 F.3d 1315, 1322 (Fed. Cir. 2017).

The Federal Circuit has held that "[n]egative 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." *Santarus, Inc. v. Par Pharm., Inc*., 694 F.3d 1344, 1351 (Fed. Cir. 2012). The court has further explained "[t]hat is not to say that in all cases, a patentee may arbitrarily dissect its invention by amending the claims in order to avoid the prior art." *Inphi*, 805 F.3d at 1356. Thus, the specification should say *something* regarding the elements being excluded.

Here, the applications underlying the '675 Patent are entirely silent regarding terminal aldehyde groups. EX1002, ¶76-77; EX1037; EX1040. Terminal aldehyde groups are never disclosed or discussed in the context of a terminal bio-reactive functional group, nor is there any example using such a group. *Id*. Accordingly, the '675 Patent specification fails to provide "a reason to exclude the relevant limitation" and it would not be "possible for the patentee to support both the inclusion and

exclusion of the same material." *Santarus*, 694 F.3d at 1351. Rather, Patentee has "arbitrarily dissect[ed] its invention by amending the claims in order to avoid the prior art." *Inphi*, 805 F.3d at 1356.

Given the sheer number of potential bio-reactive functional groups that could theoretically be present at the terminus of a modified lysine, a skilled artisan could not immediately envisage every possible group that could be included or excluded (*Fujikawa v. Wattanasin,* 93 F.3d 1559, 1571 (Fed. Cir. 1996)), and therefore, the specification does not provide sufficient written description support for the Negative Limitation of claim 1.

Additionally, the Negative Limitation requires that the recited groups (i.e., hydroxy group, carboxyl group, thiol group, amino group, or aldehyde group) are not "a terminal bio-reactive functional group." The applications underlying the '675 Patent contain no discussion of "a terminal bio-reactive functional group." EX1037; Ex1040. This phrase is entirely absent. There is no disclosure (implicit or explicit) for drawing a subgenus to exclude the recited groups from the "terminal" position. *Id.* Thus, the recitation of this subgenus is without basis and apparently arbitrary.

None of the'675 Patent claims further limit or define the Negative Limitation of claim 1, and therefore, all of the claims lack sufficient written description for the same reason. Because the applications underlying the '675 Patent fail to satisfy the written description requirement with respect to claims 1-13 of the '675 Patent, there

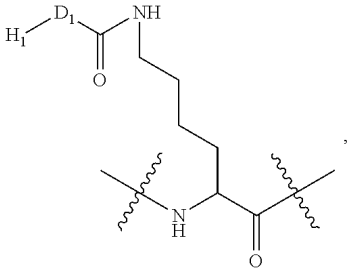
is a "break" in the priority chain and the claims cannot properly benefit from the priority of the '503 application or any application preceding it. As a result, the '675 Patent is entitled to priority only as of its immediate filing date on January 16, 2023.

E. Claims 2, 3, 5-7, 12, and 13 Lack Written Description Support

Beyond the lack of written description for the Negative Limitation, which affects every claim, claims 2, 3, 5-7, 12, and 13 additionally lack written description because the applications underlying the '675 Patent all fail to describe claim 2 and its dependencies.

Specifically, claim 2 recites:

…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.

This modified lysine is unique among other structures disclosed in the specification as it requires an amide bond not necessarily present in other examples. The only description in the '503 application 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. EX1002, ¶79; EX1037; EX1040.

However, there are many other known antibodies with different sequences at positions 237-253 that are not discussed or contemplated in the specification, yet still encompassed by the claims. For example, IgG1, IgG2, and IgG4 variants such as IgG1σ, IgG2σ, IgG4σ1, and IgG4σ2 do not comprise GPSVFLFPPKPKDTLMI (EX1033, 3), nor do other antibody isotypes such as IgA, IgM, IgD, and IgE (EX1034, 3). EX1002, ¶80; EX1037; EX1040.

The ’675 Patent discloses the modified lysine recited in claim 2 *only* in a specific subclass of antibodies (i.e., IgG1, IgG2, or IgG4), yet claim 2 is not limited to any particular antibody or fragment.

Legal precedent does “not compel the conclusion that a description of a species always constitutes a description of a genus of which it is a part” (*Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)), and disclosing a single context (i.e., Fc sequence) in which the claimed modified lysine structure does not provide written description for every potential combination if that

[1] 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.

disclosure is "not representative of the full variety or scope of the genus" (*AbbVie Deutschland Gmbh v. Janssen Biotech, Inc*., 759 F.3d 1285, 1290, 1299 (Fed. Cir. 2014)).

While disparate parts of the '675 Patent mention antibodies and "modified lysine" in generic ways, the disclosure of a broad genus (i.e., any antibody with any modified lysine) and a narrow genus (i.e., an IgG1, IgG2, or IgG4 with the recited modified lysine) does not provide proper written description for an intermediate genus (i.e., any antibody with the recited modified lysine) that was never disclosed or contemplated. *The Gentry Gallery, Inc. v. the Berkline Corporation*, 134 F.3d 1473, 1479-80 (Fed. Cir. 1998). Yet, that is precisely what claim 2 and the claims that depend therefrom (i.e., claims 5-7, 12, and 13) do.

"[T]he hallmark of written description is disclosure" (*Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010)) and allowing Patentee to claim an intermediate genus that includes undisclosed combinations of the recited modified lysine of claim 2 and any number of other adjacent sequences "flouts basic legal principles of the written description requirement" (*Amgen Inc. v. Sanofi, Aventisub LLC*, 872 F.3d 1367, 1378-79 (Fed. Cir. 2017)).

Accordingly, claims 2, 3, 5-7, 12, and 13 of the '675 Patent lack written description support in the applications underlying the '675 Patent. As a result, the '675 Patent is entitled to priority only as of its filing date on January 16, 2023. All

claims of the ’675 Patent lack priority entitlement to the underlying provisional (EX1037) for the same reasons set forth above and also because of new matter added in the later-filed applications (e.g., the PCT).

VIII. PRIOR ART BEFORE JANUARY 16, 2023

With respect to asserted prior art, Petitioner need only show that “the art must have existed as of the date of invention, presumed to be the filing date of the application until an earlier date is proved.” *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449 (Fed. Cir. 1986).

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

The ’959 Publication published on September 17, 2020, from Canadian Patent Application No. 3132959, which was the Canadian national stage of PCT/KR2020/003282, filed on March 9, 2020, which was published as WO2020/184944 (EX1004) on September 17, 2020. The ’959 Publication claims priority to U.S. Provisional Application No. 62/815,557, filed on March 8, 2019. Thus, the ’675 Patent and the ’959 Publication share essentially identical specifications, but the ’959 Publication is prior art to the ’675 Patent, assuming a priority date of January 16, 2023.

IX. PRIOR ART BEFORE MARCH 8, 2019

Each of the cited references discussed below existed and were available to the public prior to January 16, 2023 and also prior to the earliest claimed March 8, 2019, priority date.

A. PepTalk Poster (EX1006)

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" held from January 14-18, 2019, in San Diego, California ("the 2019 PepTalk conference"). PepTalk Poster is prior art to the '675 Patent before both its January 16, 2023 and March 8, 2019 priority dates.

1. PepTalk Poster Qualifies as a Printed Publication

Whether a reference qualifies as a "printed publication" under 35 U.S.C. § 102 is a legal conclusion based on underlying factual findings. *Valve Corp. v. Ironburg Inventions Ltd.*, 8 F.4th 1364, 1372 (Fed. Cir. 2021). To qualify as a printed publication, a reference must be sufficiently accessible to persons interested and ordinarily skilled in the art. *Id.* at 1373. Public accessibility is the touchstone of the inquiry, and "[t]he standard for public accessibility is whether interested members of the relevant public could locate the reference by reasonable diligence." *Weber, Inc. v. Provisur Techs., Inc.*, 92 F.4th 1059, 1067 (Fed. Cir. 2024) (citing *Valve*

Corp., 8 F.4th at 1376).

In the context of materials disseminated at conferences or meetings, factors to consider include the length of time the material was presented, expertise of the target audience, the nature of the conference or meeting, whether there were restrictions on public disclosure of the information, informal expectations of confidentiality versus sharing of the information, and ease of copying the information. *GoPro, Inc. v. Contour IP Holding LLC*, 908 F.3d 690, 694 (Fed. Cir. 2018); *In re Klopfenstein*, 380 F.3d 1345, 1350-52 (Fed. Cir. 2004); *Medtronic, Inc. v. Barry*, 891 F.3d 1368 (Fed. Cir. 2018). Free access is not required, and any cost required to attend a conference at which materials were disseminated must be considered in relation to the interested public, not the general public. *See Weber*, 92 F.4th 1068 n.6.

For example, in *In re Klopfenstein*, a poster displayed at a conference was found to be a printed publication because the poster was displayed for a matter of days, the attendees included interested persons of skill in the art, there was no reasonable expectation that the poster would not be copied, and the poster could be copied with relative ease. *In re Klopfenstein*, 380 F.3d at 1350-52.

Testimony from conference attendees can provide evidence of public accessibility, especially where attendees testify to the material having been disseminated, the circumstances under which it was disseminated, and whether any formal or informal expectations of confidentiality or non-disclosure existed. *Nobel*

Biocare Servs. AG v. Instradent USA, Inc., 903 F.3d 1365, 1376-77 (Fed. Cir. 2018).

Dr. Tatsuya Okuzumi is an Ajinomoto employee that attended the PepTalk 2019 conference. As detailed in Dr. Okuzumi's declaration (EX1003, ¶26-28), the PepTalk Poster was displayed throughout the day on January 16, 2019, at the PepTalk 2019 conference, which was "one of the largest annual gatherings of protein science researchers in the world" and "feature[d] renowned speakers from academia, biotech and pharma who bring global expertise and perspective to the forefront." EX1013, 2; EX1003, ¶11-13; EX1002, ¶35, 84. There were no specific expectations of confidentiality for the material presented in PepTalk Poster. EX1003, ¶13. Dr. Okuzumi attended the poster viewing sessions and stood with the poster to discuss it with any interested conference attendees. EX1003, ¶26-28. He made hard copies of the poster available to conference attendees and provided these hard copies to several conference attendees that viewed the poster and discussed it with him. *Id*.

Accordingly, PepTalk Poster qualifies as a printed publication because, as of January 16, 2019, it was disseminated at a conference attended by interested members of the art (EX1003, ¶11-12; EX1002, ¶35, 84); it was displayed without limitation throughout the day (EX1003, ¶26-28); the target audience and those in attendance at the conference were highly skilled (EX1003, ¶11-12; EX1002, ¶35, 84); there was no expectation of confidentiality (EX1003, ¶13); and there was no difficulty in copying the material because hard copies were provided to numerous

attendees (EX1003, ¶26-28). *GoPro, Inc.*, 908 F.3d at 694 (Fed. Cir. 2018); *Klopfenstein*, 380 F.3d at 1351-52.

B. PepTalk Presentation

PepTalk Presentation was presented on January 16, 2019, at the same 2019 PepTalk conference 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 of January 16, 2023, or March 8, 2019.

1. PepTalk Presentation Qualifies as a Printed Publication

In addition to the public accessibility factors discussed above, the Federal Circuit has found oral presentations are “printed publications” where they were presented orally to interested persons of skill and copies were disseminated without restriction. *See, e.g.*, *Mass. Inst. of Tech. v. AB Fortia*, 774 F.2d 1104, 1108-09 (Fed. Cir. 1985) (academic paper presented at conference was “printed publication” where “between 50 and 500 persons interested and of ordinary skill in the subject matter were actually told of the existence of the paper and informed of its contents by the oral presentation, and the document itself was actually disseminated without restriction to at least six persons”).

Dr. Tatsuya Okuzumi gave the PepTalk Presentation at a luncheon presentation session on January 16, 2019, that was open to all attendees of the conference and that did not require any additional registration or cost beyond that of

attending the 2019 PepTalk conference. EX1013, 32; EX1003, ¶14-15. The presentation lasted approximately 30 minutes and had around 30-50 attendees. *Id*. Following the presentation, Dr. Okuzumi discussed the presentation with Dr. Dixit, who himself presented on January 15, 2019 and Dr. Szardenings of the Fraunhofer Institute for Cell Therapy and Immunology. EX1003, ¶15-16, 20.

Shortly after the conference, on February 9, 2019, Dr. Okuzumi emailed copies of the slides that were displayed during the presentation to five individuals including Dr. Michael Szardenings, Dr. Igor D'Angelo, Dr. Bernhard Valldorf, Susan Lee, and Professor Rolf G. Werner. EX1003, ¶17-23; EX1017; EX1018; EX1019; EX1020; EX1021. All of these individuals are POSAs, as defined herein. *Id*. Additionally, the March 2019 issue of *Drugs of the Future* (which was available online as of 25 Jan. 2019) detailed Dr. Okuzumi's presentation, and the PepTalk 2018 18th Annual Meeting Report therein specifically noted that AJICAP™ "can be directly utilized for site-specific conjugation to the IgG at lysine 248" and "[t]he resulting ADC displays an ideal DAR of 2." EX1014, 244; EX1003, ¶24.

Accordingly, Peptalk Presentation qualifies as a printed publication because, prior to even the earliest priority date of the '675 Patent, the presentation was delivered to dozens of interested members of ordinary skill in the art (EX1003, ¶15); the presentation slides were disseminated to at least five conference attendees (*id*., ¶17-23); the target audience and those in attendance at the presentation were highly

skilled and interested in ADCs (*id*., ¶11-12; EX1002, ¶35, 84); there was no expectation of confidentiality (EX1003, ¶13); and subsequently published summaries of the presentation confirm that the information was understood and received by the target audience (EX1014, 244; EX1003, ¶24). *GoPro, Inc.*, 908 F.3d at 694; *Mass. Inst. of Tech*, 774 F.2d 1104.

C. WO 2018/199337 ("Yamada"; EX1008)

Yamada published on November 1, 2018, from PCT/JP2018/017345, filed on April 27, 2018, which claims priority to Japanese Patent Application No. 2017-090679, filed on April 28, 2017. Accordingly, Yamada is prior art to the '675 Patent under 35 U.S.C. § 102(a)(1) even if the '675 Patent is accorded its earliest claimed priority date. Because the PCT was published in Japanese, all citations are made to U.S. 2020/0190165 (EX1009), which is certified as an accurate translation of the corresponding PCT (EX1009, coversheet).

D. WO 2019/240288 ("Matsuda"; EX1010)

Matsuda published on December 19, 2019, from PCT/JP2019/023779, filed on June 14, 2019, which claims priority to Japanese Patent Application No. 2018-113962 (EX1038-1039), filed on June 14, 2018. Accordingly, Matsuda is prior art to the '675 Patent under 35 U.S.C. § 102(a)(2) even if the '675 Patent is accorded its earliest claimed priority date. Because the PCT was published in Japanese, all citations are made to U.S. 2021/0139541 (EX1011), which is certified as an accurate

translation of the corresponding PCT (EX1011, coversheet). All portions of EX1011 relied upon are found in EX1038/EX1039, and therefore the effective prior art date of Matsuda—WO 2019/240288 (EX1010) and US 2021/0139541 (EX1011)—is the Japanese priority date of June 14, 2018.

X. THE PRIOR ART RENDERS THE CHALLENGED CLAIMS UNPATENTABLE

This petition demonstrates a "reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a), and therefore each of the following grounds should be instituted for review. *SAS Inst., Inc. v. Iancu,* 138 S. Ct. 1348, 1360 (2018).

A. Ground 1 – Claims 1-13 Are Anticipated by the '959 Publication

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987). When there is a break in the chain of a priority claim, an earlier family member may anticipate a later issued patent within the same continuity chain. *Natural Alternatives Int'l, Inc. v. Iancu*, 904 F.3d 1375, 1377 (Fed. Cir. 2018). In *Natural Alternatives*, the eighth patent in a continuity chain was rejected by an examiner during an *inter partes* reexamination as anticipated by the first patent to issue in the continuity chain after it was determined that there was an error in the

priority claim of the fifth patent, which precluded the eighth patent from benefiting from its priority claim. *Id*. at 1377-78.

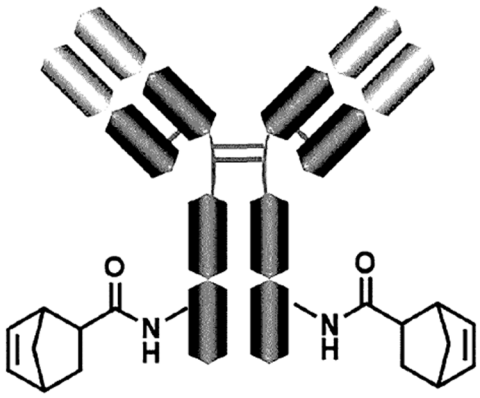
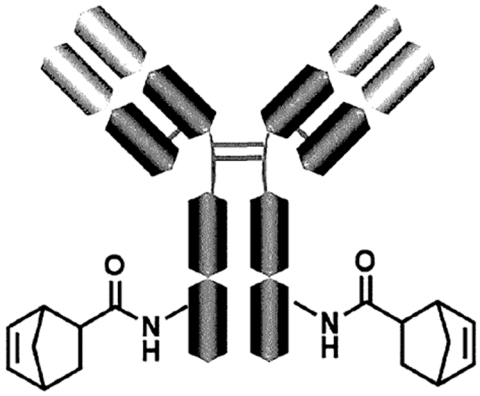
The ’959 Publication, which is the Canadian national stage entry of the PCT application in the ’675 Patent priority chain, can properly be asserted as prior art because the ’675 Patent is only entitled to priority as of its actual filing date, January 16, 2023. *See Daiichi Sankyo*, IPR2015-00291, Paper 75 at 6-20; *NTP*, 654 F.3d 1268 at 1278; *Nat. Alts. Int’l*, 904 F.3d. at 1377-78. Importantly, while the sections above discuss why the ’675 Patent specification and ’503 application do not sufficiently describe the ’675 Patent claims, the essentially identical disclosure of the ’959 Publication nevertheless anticipates all of the claims.

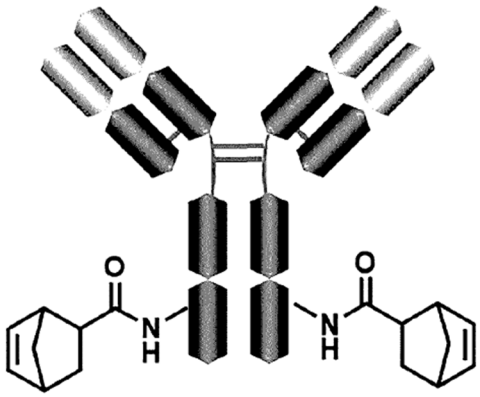
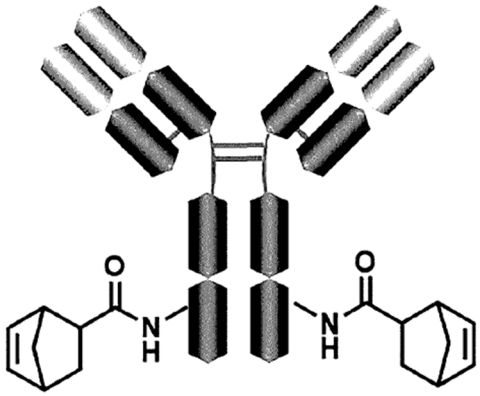
Although a prior art reference needs to be enabled, the enablement standard applied to prior art is a lower threshold than that of § 112. *Rasmusson v. Smithkline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005) (“The standard for what constitutes proper enablement of a prior art reference for purposes of anticipation under section 102, however, differs from the enablement standard under section 112.”). In other words, “section 112 ‘provides that the specification must enable one skilled in the art to ‘use’ the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure.’” *Id*. (quoting *In re In re Hafner*, 410 F.2d 1403, 1405 (CCPA 1969)). The Federal Circuit has further explained “anticipation does not require actual performance of suggestions in a disclosure.” *Id*.

at 1326 (quoting *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001)). Moreover, a species anticipates a genus (*In re Slayter,* 276 F.2d 408, 411 (CCPA 1960)), and the ’959 Publication discloses modified forms of trastuzumab with a modified lysine at position 248 that includes a bio-orthogonal click-chemistry functional group. EX1005, 222-241. As a result, the ’959 Publication anticipates claims 1-13

Claim 1 is anticipated by Example 3 (EX1005, 223-229), which details “Synthesis and confirmation of structure of antibody containing first click-chemistry functional group in site-specific manner.” Section 3.1 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). Both of these examples anticipate claim 1 because neither norbornene nor azide are excluded by the negative limitation of claim 1. In particular, “the structure of the final product” of Example 3.1 is shown in Fig. 43, which depicts each of the claim limitations. (*id*., 225.) The claim chart below shows exemplary anticipatory disclosures.

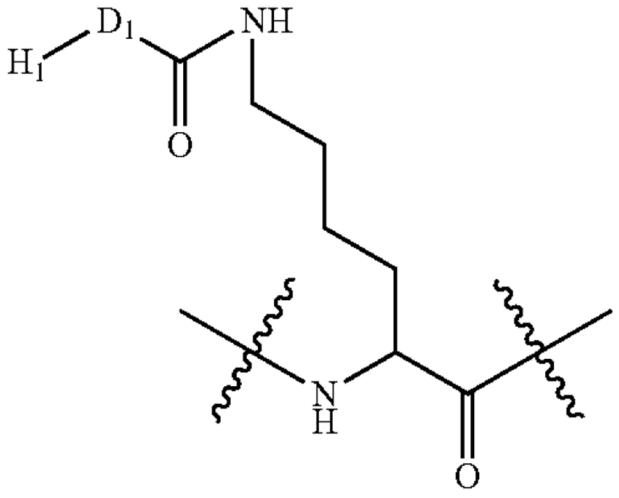
Claim 1 of the ’675 Patent	**Disclosure in the '959 Publication**
A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group	“[T]he structure of the final product (i.e., Ab(246/248)-Norbornene) is shown in FIG. 43.” *See* 225.

Claim 1 of the ’675 Patent	Disclosure in the '959 Publication
	 Fig. 43 *See also* Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1002, ¶93-100.
wherein the modified antibody comprises one or more modified heavy chain	 Fig. 43 *See also* Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1002, ¶101-104.
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	“Synthesis of Ab (246/248 Lys)-norbornene was carried out in a buffer using Compound III-SSFI (Lys).” *See* 225. “[T]he present invention provides technology for specifically transferring

Claim 1 of the ’675 Patent	Disclosure in the '959 Publication
	a chemical functional group to lysine 248 in the antibody.” *See* 3. *See also* Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1002, ¶105-110.
wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end	 Fig. 43 *See also* Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1002, ¶111-114.
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.	 Fig. 43 *See also* Example 3.1 (223-225) and Examples 3.2-3.4 (225-229); EX1002, ¶115-120.

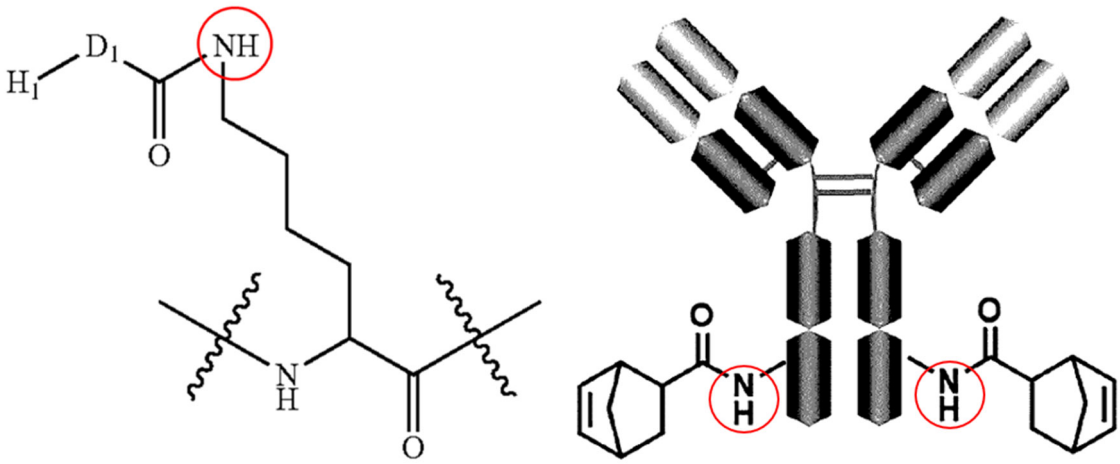
Claim 1 of the ’675 Patent	Disclosure in the '959 Publication

Claim 2 is anticipated by the same examples, as it recites a modified lysine with the 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.”

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. EX1002, ¶123.

Example 3.2, which discloses a trastuzumab modified with an azide group at lysine residues 248 (EX1005, 225-226, 229), also anticipates claim 2 as H_1 would be the azide and "the obvious choice for D_1 would be a short alkyl or cycloalkyl." EX1002, ¶124. Finally, the structure of claim 2 is also disclosed in Fig. 1, and the elements of claim 2 are described in pages 98-99. EX1002, ¶125-128.

Claim 3, which depends from claim 2, narrows D_1, but similarly includes the option where D_1 is a bond, and therefore this claim is also anticipated by Fig. 43. Pages 98-99 also disclose this limitation. EX1002, ¶131-133.

Claims 5-7 also depend from claim 2 and recite various possible groups represented by D_1, all of which are disclosed in pages 54-55 of the '959 Publication. EX1005, 58, 100; EX1002, ¶140-155.

Claim 4 depends from claim 1 and recites Formula 8-2, which provides a partial amino acid sequence of an IgG antibody. This formula is disclosed in pages 14-15 of the ’959 publication, and trastuzumab, the antibody used in Examples 3.1 and 3.2, is an IgG1.

Claim 8 depends from claim 1 and recites “wherein the modified antibody comprises two modified heavy chains.” The modified antibody shown in Fig. 43 shows two modified heavy chains. The modified trastuzumab-azide of Example 3.2 likewise indicates both heavy chains were modified. EX1005, 229; EX1002, ¶158. Pages 98-99 also disclose this limitation. EX1002, ¶159.

Claims 9, 10, 12, and 13 are identical except that claims 9 and 10 depend from claim 1, and claims 12 and 13 depend from claim 3. Claims 9 and 12 require a particular click-chemistry reaction (e.g., Huisgen 1,3-dipolar cycloaddition), and claims 10 and 13 require particular click-chemistry groups, including an azide or norbornene. Thus, both the trastuzumab-norbornene Example 3.1 provided in Fig. 43 (*see also* EX1005, 223-225) and Example 3.2 (*id.*, 225-226), which discloses a trastuzumab-azide, satisfy both these limitations because norbornene and azides are recited in claims 10 and 13 and can undergo Huisgen 1,3-dipolar cycloaddition or Diels-Alder reactions, as recited in claims 9 and 12. EX1002, ¶161-173, 183-192; EX1036.

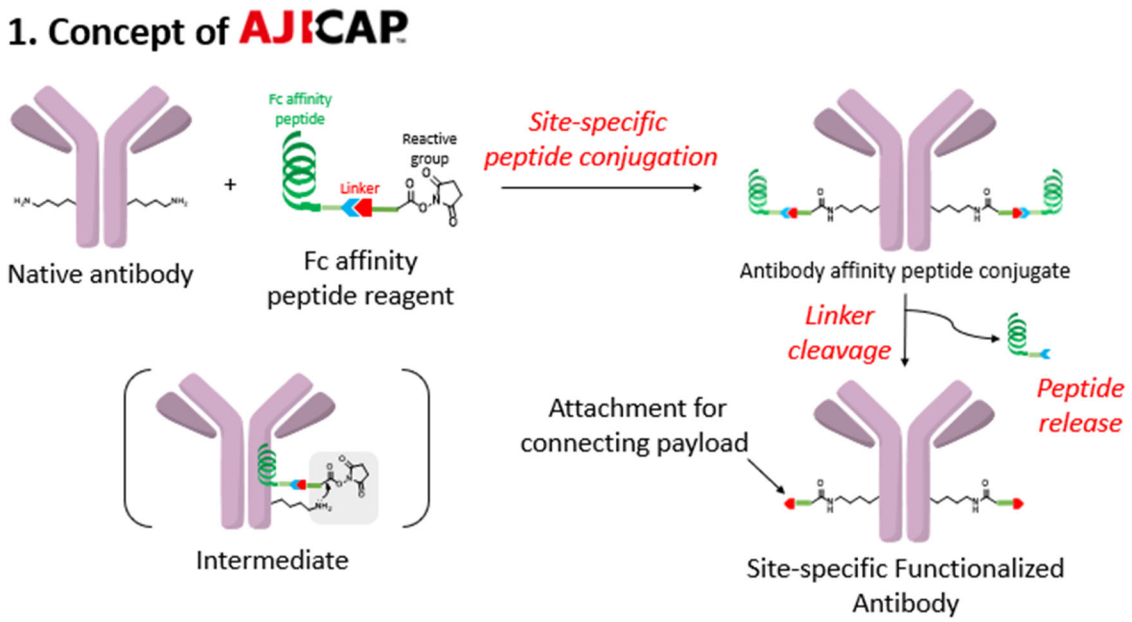
Claim 11 depends from claim 1 and recites structures of the modified lysine. Pages 5 and 171-172 of the '959 publication disclose precursors of those structures (EX1005, 5, 171-172; *see also* Figs. 17, 19, 22), and reacting the structure disclosed in 171-172 with trastuzumab, as shown in Example 3.2, would provide a modified lysine with the first structure shown in claim 11. EX1002, ¶176-179. Moreover, the middle structure shown in claim 11 is identical to the structure shown in Fig. 43, and synthesis of the final compound from its precursor is disclosed in EX1005, 165-174. EX1002, ¶190-181.

Accordingly, claims 1-13 are anticipated by the '959 publication (EX1005).

B. <u>Ground 2</u> – Claims 1, 4, and 8-10 Are Anticipated by PepTalk Poster

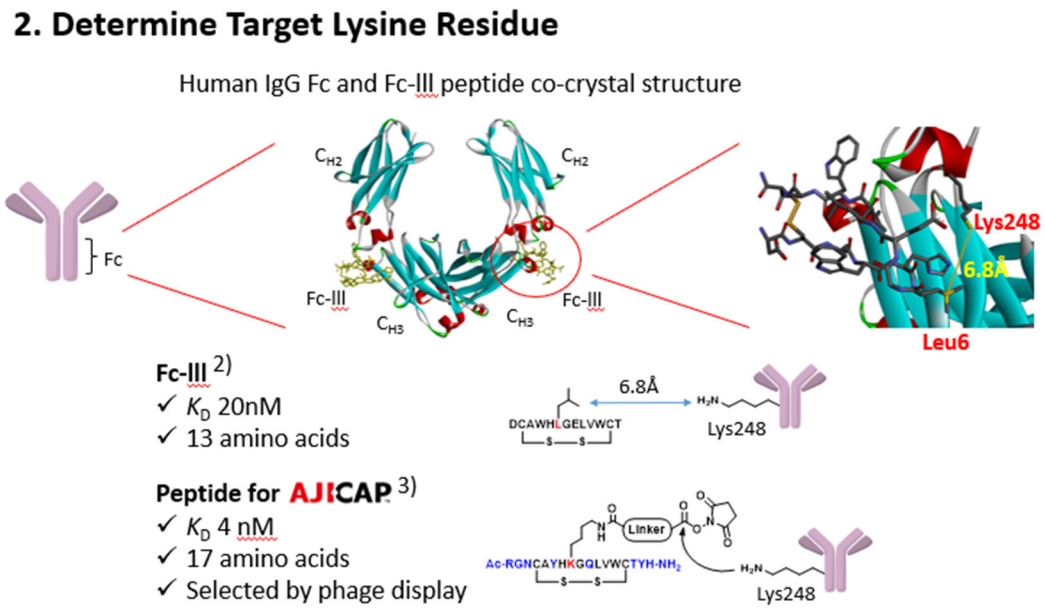
PepTalk Poster presents Ajinomoto's AJICAP™ technology for preparing ADCs through site-specific conjugation at lysine 248. PepTalk Poster includes four sections: Introduction, Methods, Results, and Conclusion. The Introduction provides overviews of ADCs, site-specific conjugation, and existing methods for site-specific conjugation. The Methods section summarizes Ajinomoto's method for site-specific conjugation. The Results section summarizes various safety and efficacy studies on the AJICAP™ technology. The Conclusion section summarizes the benefits of AJICAP™ relative to other technologies.

PepTalk Poster depicts a process for modifying an antibody to include a bio-orthogonal click-chemistry functional group as shown:

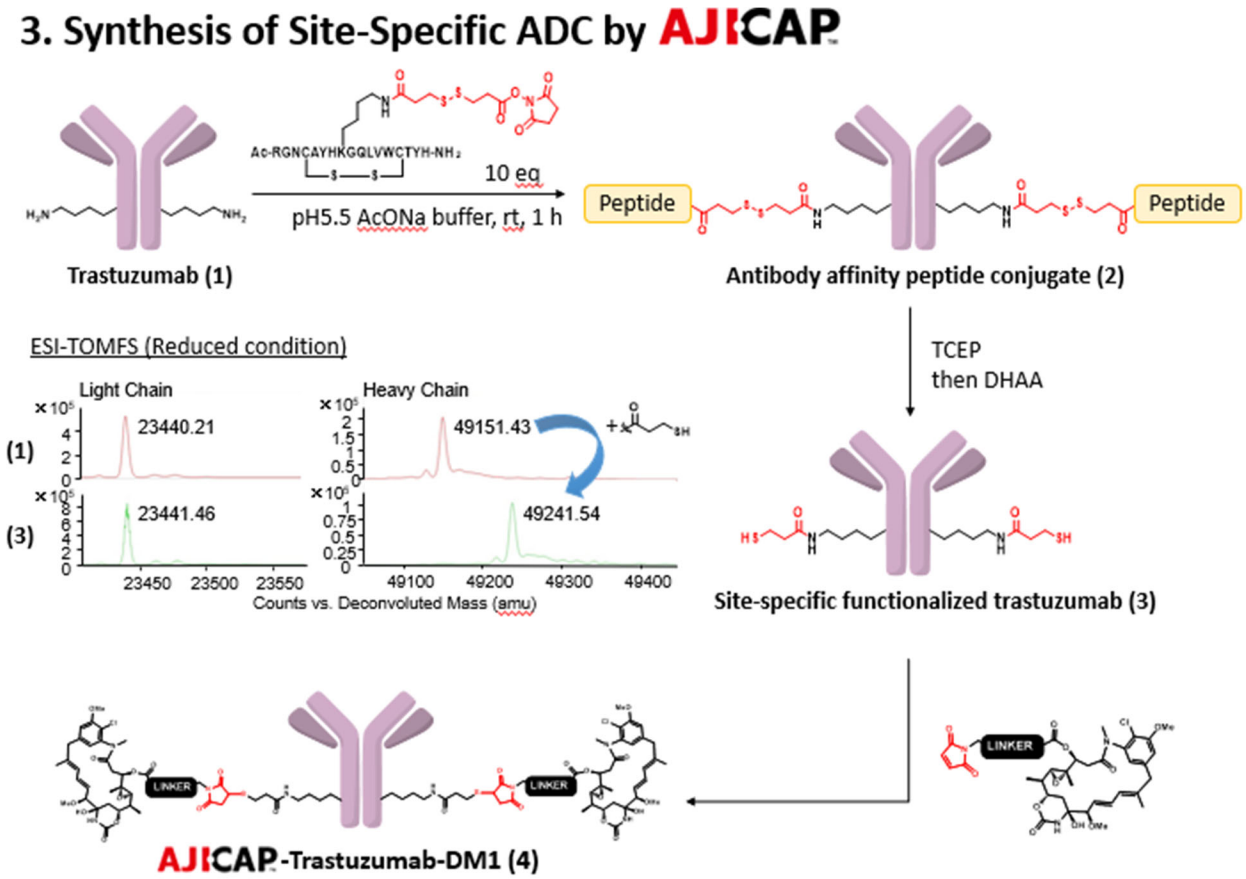


This figure shows an antibody being modified through "site-specific peptide conjugation" and "linker cleavage" to produce an "attachment for connecting payload." The "attachment for connecting payload" includes a bio-orthogonal click-chemistry functional group. EX1002, ¶196-197.

PepTalk Poster depicts that this site-specific modification occurs at lysine 248 (*id.*, ¶198):

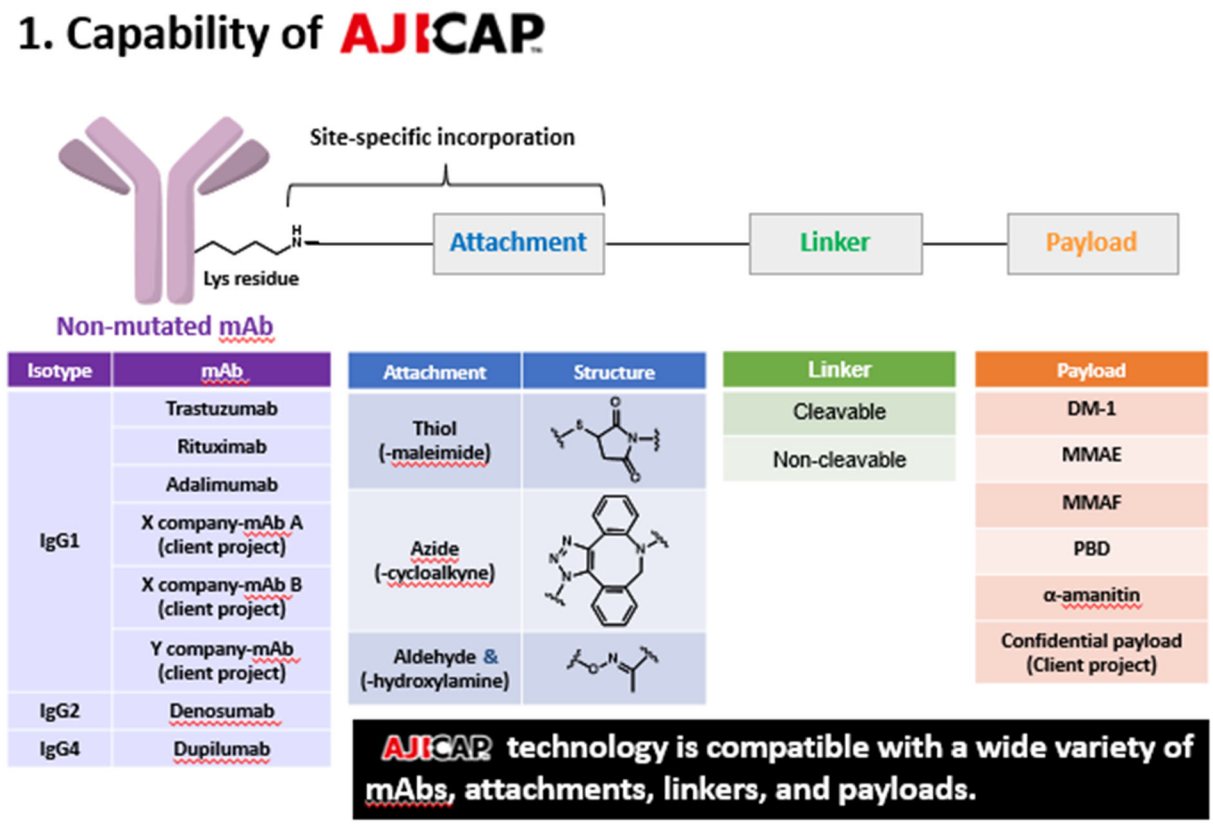


PepTalk Poster depicts an example in which trastuzumab (a human IgG1) is modified to include a bio-orthogonal click-chemistry functional group.



In this figure, trastuzumab is modified with a peptide conjugate that contains a precursor to a bio-orthogonal click-chemistry functional group, and a subsequent reaction cleaves/removes the peptide conjugate, leaving, in this example, a thiol group bound to lysine 248. A POSA understood that the thiol group shown in Step (3) is an example of a bio-orthogonal click-chemistry functional group. *Id.*, ¶199-201.

PepTalk Poster also discloses that AJICAP™ is compatible with a variety of antibodies, click-chemistry groups, and payloads.



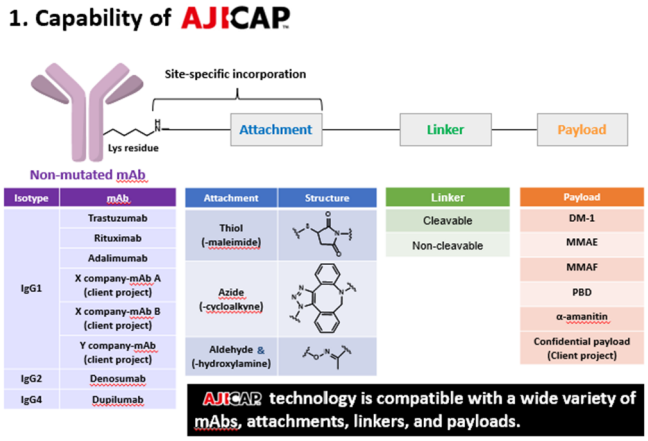
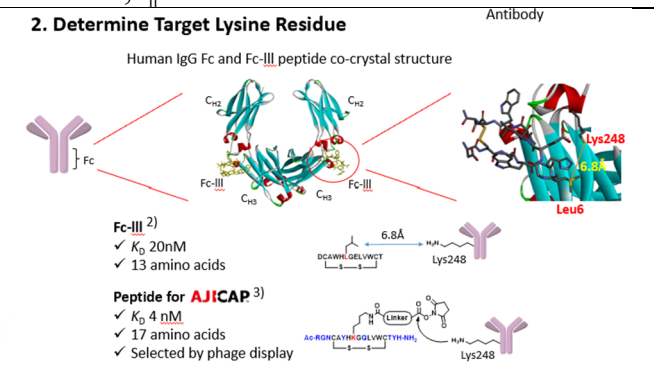
In the "Attachment" column above, PepTalk Poster discloses three examples of click-chemistry reactions that can be used with AJICAP™: thiol (-maleimide),

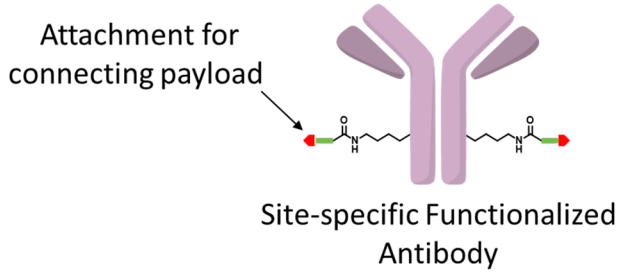
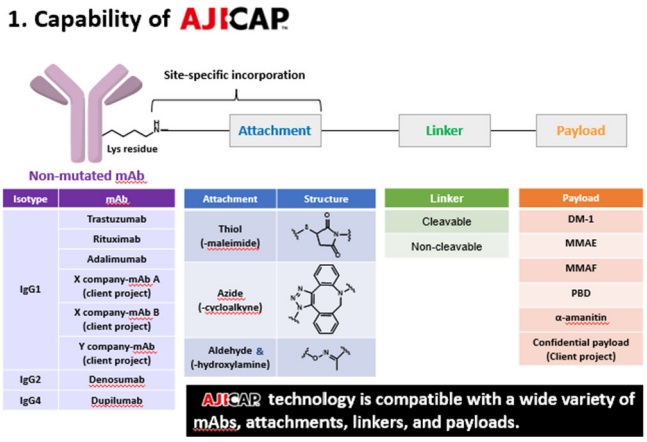
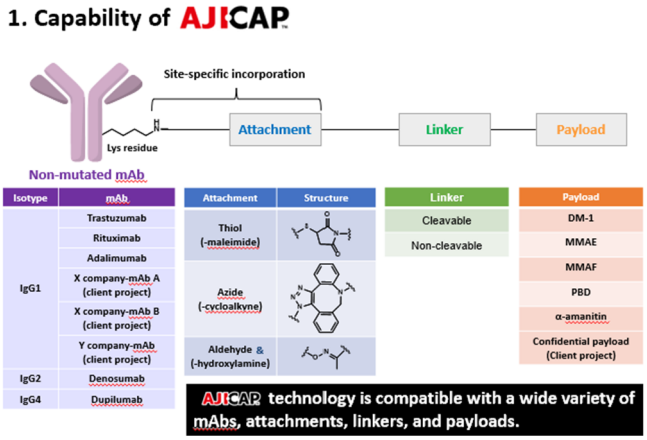
azide (-cycloalkyne), and aldehyde (-hydroxylamine). Each of these examples represents a pair of click-chemistry functional groups that participate in a click-chemistry reaction. A POSA understood that click-chemistry reactions are bio-orthogonal reactions, as the functional groups that participate in the reaction do not interact with proteins. *Id.*, ¶202-203.

A POSA also understood that the orientation of the click-chemistry functional groups is reversible. By disclosing the attachment "thiol-maleimide" (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 function equivalently. EX1002, ¶204. Thus, PepTalk Poster discloses both maleimide and a cycloalkyne (e.g., a dibenzocycloalkyne or "DBCA") functional groups, in addition to azide. *Id.*, ¶296. While claim 1 of the '675 Patent excludes a terminal thiol from the modified lysine, it does not exclude azide, DBCA, or maleimide.

1. Claim 1

The following claim chart aligns PepTalk Poster with claim 1. For the reasons discussed above and as shown in the chart below, claim 1 is anticipated.

Claim 1 of the ’675 Patent	Disclosure in PepTalk Poster
A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group	 EX1002, ¶194-205.
wherein the modified antibody comprises one or more modified heavy chain	*See above.* EX1002, ¶206-211.
wherein each of the modified heavy chain comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system	 EX1002, ¶198, 208, 212-216.

Claim 1 of the ’675 Patent	Disclosure in PepTalk Poster
wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end	  Attachment column shows bio-orthogonal click-chemistry functional groups. EX1002, ¶217-220.
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.	 An azide is not excluded (nor is maleimide or DBCA). EX1002, ¶221-226.

2. Claim 4

Claim 4 depends from claim 1 and recites a particular structure (i.e., formula 8-2; SEQ ID NO:21) in the heavy chain of the antibody. The recited sequence is a human IgG1, 2, or 4 CH2 domain with a modification (i.e., K') at position 248.

PepTalk Poster discloses preparation of a modified trastuzumab, which is a human IgG1, with a modification at lysine 248. The sequence recited in claim 4 is part of a human IgG1, 2, or 4 CH2 domain with a modification (i.e., K') at position 248. EX1002, ¶229-231. Accordingly, the modified heavy chain of trastuzumab disclosed in PepTalk Poster would necessarily comprise the claimed sequence, and claim 4 is anticipated.

3. Claim 8

Claim 8 depends from claim 1 and recites, "wherein the modified antibody comprises two modified heavy chains." Each of the modified antibodies shown in PepTalk Poster comprise two modified heavy chains. EX1006; EX1002, ¶233-241.

4. Claims 9 and 10

Claim 9 depends from claim 1 and recites, "wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a … Huisgen 1,3-dipolar cycloaddition…." Claim 10 depends from claim 1 and recites, "wherein the bio-orthogonal click chemistry functional group is selected from azide group…."

Regarding claim 10, PepTalk Poster teaches using an azide as a bio-orthogonal functional group, and therefore claim 10 is anticipated. EX1002, ¶247-250. Further, the click reaction between an azide and a terminal alkyne is a Huisgen 1,3-dipolar cycloaddition. EX1036; EX1002, ¶242-246. Accordingly, the limitations of claims 9 are taught through PepTalk Poster's disclosure of azide as a bio-orthogonal functional group. Thus, claims 9 and 10 are anticipated.

C. Ground 3 – Claims 1-13 Are Obvious Over PepTalk Poster in View of Yamada and Matsuda

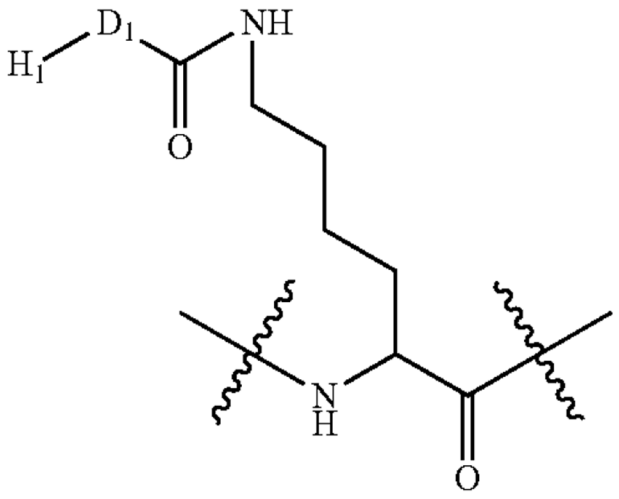
A "disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" *Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) (quoting *In re Fracalossi*, 681 F.2d 792, 794 (CCPA 1982)); *see also Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983). Accordingly, claims 1, 4, and 8-10 of the '675 Patent are rendered obvious by PepTalk Poster for at least the reasons discussed above.

Obviousness requires evaluation of the differences between the claimed subject matter and the prior art, and a showing that those differences would have been obvious to a POSA. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). For a claim to be obvious, there must have been some reason the POSA would have combined the cited prior art references or the teachings within a single reference in the manner required to arrive at the claimed invention, and he/she must have a reasonable expectation of success in arriving at the claimed invention. *KSR Int'l Co.*

v. Teleflex Inc., 550 U.S. 398, 416-17 (2007). However, "when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result." *Id*. at 416.

1. Claims 2 and 3

Claim 2 depends from claim 1 and recites a modified lysine with the 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." Claim 3 depends from claim 2 and requires D_1 is bond or that the recited alkylene, alkenylene, alkynylene, or cycloalkylene is unsubstituted.

PepTalk Poster, Yamada, and Matsuda disclose incorporating a terminal azide on lysine 248. EX1006; EX1009, 148; EX1011, p. 90, 92. The modified lysines disclosed in these references include the components recited in claims 2 and 3, and

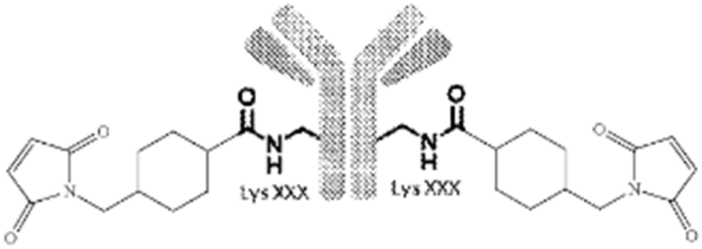
therefore these claims are nothing more than "the mere substitution of one element for another known in the field" and the substitutions "yield a predictable result." *KSR Int'l Co.*, 550 U.S. at 416.

PepTalk Poster discloses a modified trastuzumab with the following structure:

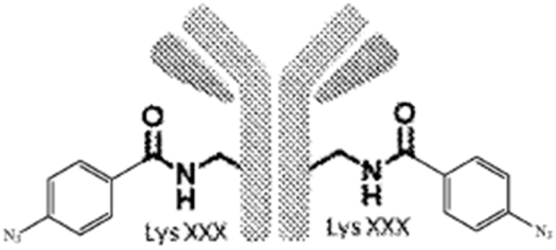
Site-specific functionalized trastuzumab (3)

This structure satisfies the requirements of claims 2 and 3 for D_1 with an unsubstituted C_2 alkylene, but H_1 is a thiol group (-SH), which is excluded by claim 1. EX1002, ¶257. However, PepTalk Poster also teaches the "attachment" (i.e., bio-orthogonal click-chemistry group) can be an azide. EX1002, ¶252-256. Substituting the thiol group above with an azide meets all limitations of claims 2 and 3. EX1002, ¶257, 265.

Examples 3-4 and 5-2-2 of Matsuda (reproduced below) include an unsubstituted C_6 cycloalkylene, consistent with the requirement of D_1 for claims 2 and 3. Thus, Matsuda teaches another example where known elements can be substituted with predictable results. EX1002, ¶259.



Example 3-4 (EX1011, p. 90)



Example 5-2-2 (EX1011, p. 92)

Similarly, Example 5-2-1 of Matsuda includes an unsubstituted C_5 alkylene (*id.*, 92), which is only one more carbon than claims 2 and 3 allow. A POSA would understand that this C_5 alkylene could be slightly longer or shorter and still function the same. EX1002, ¶260. The '675 Patent does not indicate any criticality regarding the recited upper limit of C_4. To the contrary, the '675 Patent discloses that "D_1 is ***any alkylene***, alkenylene, or alkynylene." EX1001, 48:14-30, *see also* 30:26-27 ("D1 may include any one selected from a C_{1-7} alkylene…"), 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. Where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *See In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

Accordingly, all of the elements of claims 2 and 3 are taught in PepTalk Poster, Yamada, and Matsuda, and a POSA could predictably combine these elements to arrive at the claims. EX1002, ¶251-265.

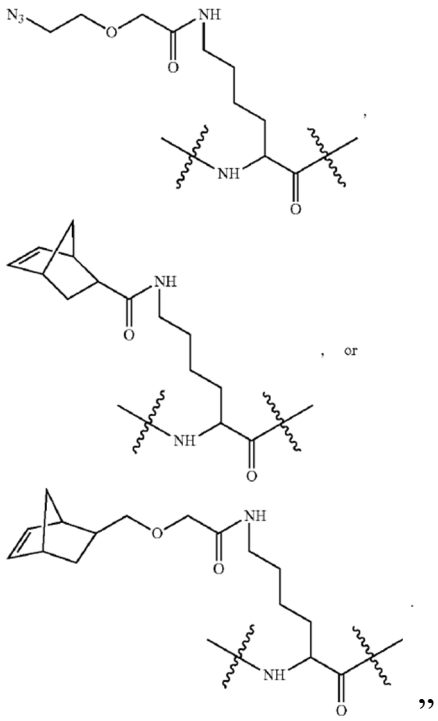
2. Claims 5-7 and 11

Claim 5 depends from claim 2 and recites, "wherein D_1 comprises one or more heteroatoms."

Claim 6 depends from claim 2 and recites, "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."

Claim 7 depends from claim 2 and recites, "wherein D_1 is —$CH_2CH_2OCH_2$— or —CH_2OCH_2—."

Claim 11 depends from claim 1 and recites, "wherein the modified lysine residue has following structure:



Claims 5-7 and 11 are treated together because a disclosure of the first or third structure recited in claim 11 also satisfies the limitations of claims 5-7. While PepTalk Presentation does not explicitly teach the specific D_1 structures recited in claims 5-7 or the structures recited in claim 11, short alkyl or cycloalkyl linkers would be obvious to a POSA. EX1002, ¶267-268.

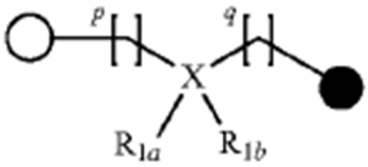
Further, Yamada specifically teaches the structures of claims 5-7 and 11. Yamada discloses an antibody regioselectively modified with a bio-orthogonal functional group at position 248 represented by (Formula (IV)):

L1-B-R′-T (IV)

where: L1 is a monovalent group with or without the bio-orthogonal functional group, B is a divalent group with or without the bio-orthogonal functional group, T

is the soluble protein (i.e., antibody), and R′ is a portion formed by a reaction between the soluble protein and a reactive group. EX1009, [0222], [1037], [1109], [1114], [0584]-[0588], [0677], [0678], [0697], [0702]-[0705], [0708]-[0710]; EX1002, ¶271-272.

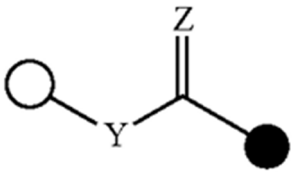
L1 can either be C1, which is a bio-orthogonal functional group (e.g., azide norbornene, etc.; *see* EX1009, [0626]-[0627]) or it can have a structure of:



(Lb')

in which the White Circle 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. EX1002, ¶273.

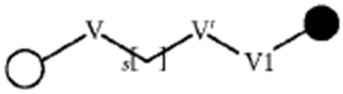
B can have a structure of:



(B-1)

in which 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 -CH_2-"; and Y can be -NH-, -O-, -CH_2-, or B-2:

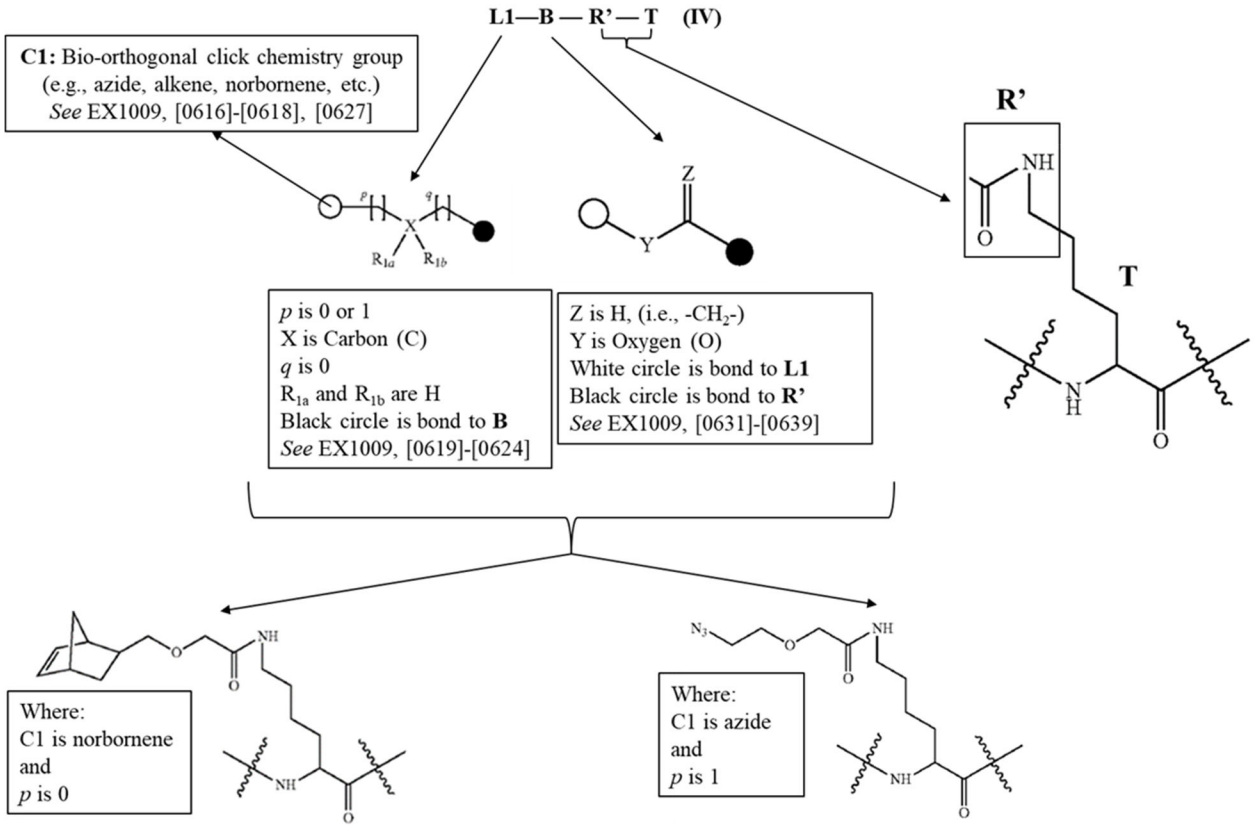


(B-2).

When Y is B-2, paragraphs [0634]-[0636] explain that V and V' can each independently be -NH-, -O-, -CH_2-, or a single bond; V1 is "a divalent group comprising a bioorthogonal functional group" or, optionally, a divalent group without a bioorthogonal functional group (EX1009, [1470]-[1472], [1480], [1571]), such as -O- (*id*., [1465]); and s is any integer from 0 to 10. EX1002, ¶274.

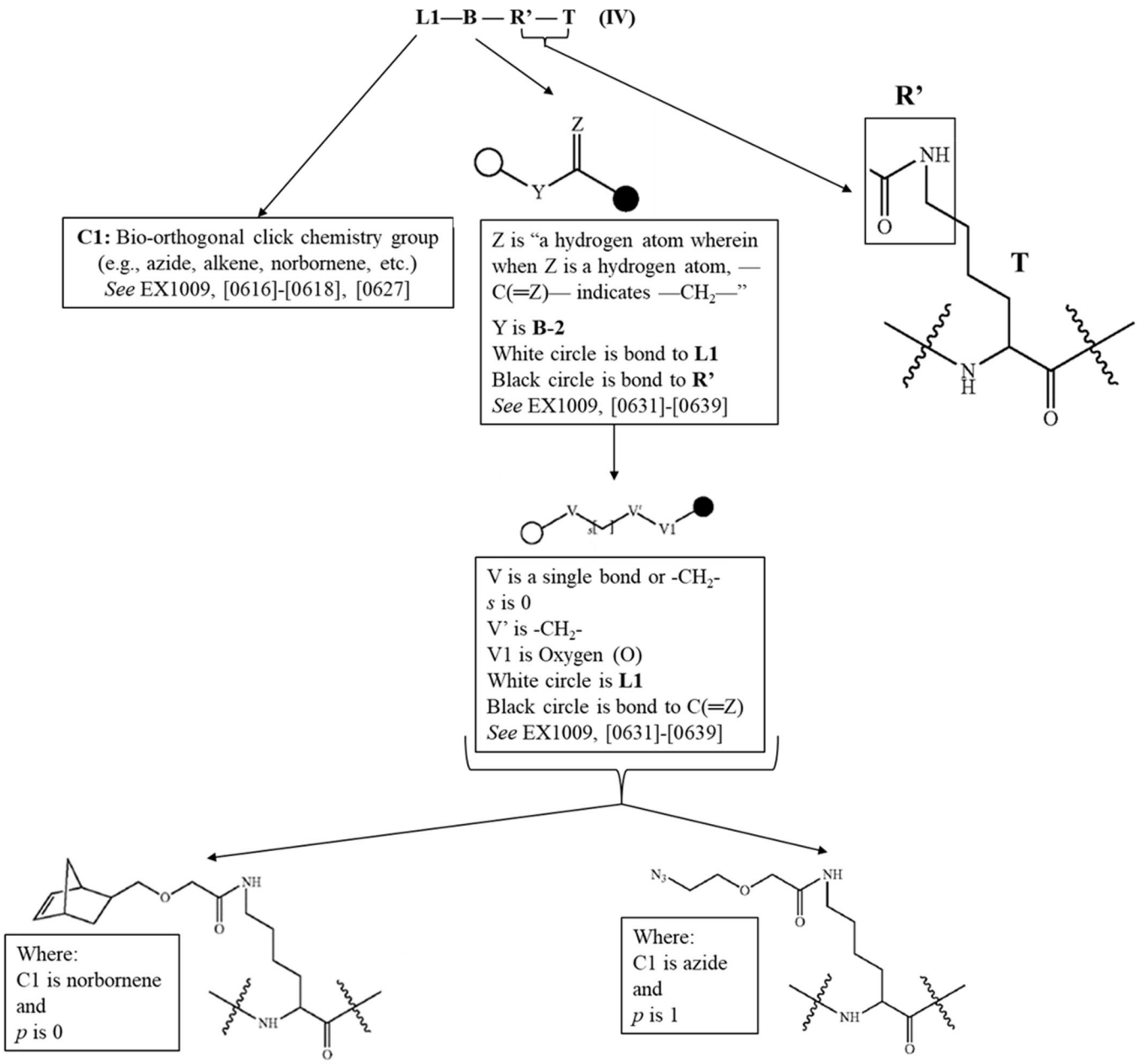
R′ is defined as "a portion formed by a reaction between a soluble protein and a reactive group," and Yamada describes "[e]xamples of a linking portion formed by a reaction between the reactive group specific to a side chain of a lysine residue and the amino group (NH2) present in the side chain of the lysine residue include an amide residue…." EX1009, [1510]. Thus, the amide portion of the structures from claims 2 and 11 are R′. EX1002, ¶275. Accordingly, there are two ways in which Formula (IV) can be completed to arrive at the first and third structures of claim 11:

Option 1:

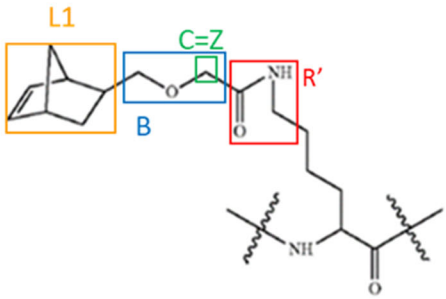


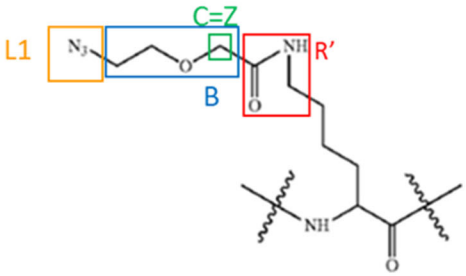
The components of the structures relative to Formula (IV) are denoted below for Option 1:

Option 2:



The components of the structures relative to Formula (IV) are denoted below for Option 2:

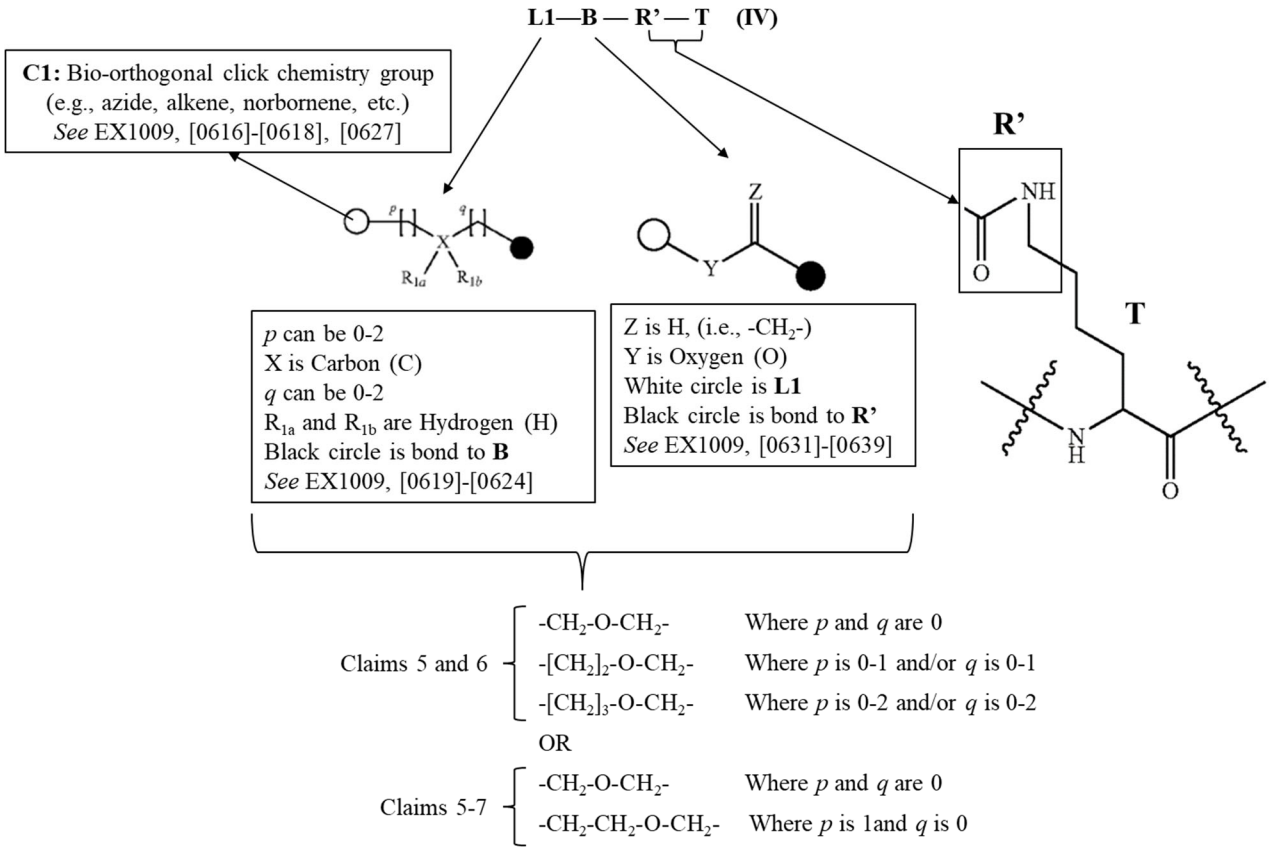




EX1002, ¶276.

Because the structures in claim 11 fall within the scope of the respective definitions of D_1 in claims 5-7, all of the elements of claims 5-7 are taught by Yamada, and combining these with PepTalk Poster would be nothing more than "the mere substitution of one element for another" to "yield a predictable result." *KSR Int'l Co.*, 550 U.S. at 416. EX1002, ¶276-277.

Claims 5-7 are further rendered obvious by multiple structures taught by Yamada. The flow chart below explains how Yamada's Formula (IV) reads on these claims:



See, EX1002, ¶278-280.

Thus, claims 5-7 and 11 are obvious over PepTalk Poster and Yamada, where all of the claim elements are disclosed and a POSA would combine them with a reasonable expectation of success. EX1002, ¶277, 280.

3. Claims 12 and 13

Claims 12 and 13 depend from claim 3. Claim 12 recites, "wherein the bio-orthogonal click chemistry functional group is a group capable of participating in a … Huisgen 1,3-dipolar cycloaddition …." Claim 13 recites, "wherein the bio-orthogonal click chemistry functional group is selected from azide group… and norbornene group."

As noted in Section X(C)(1), all of the limitations of claim 3 are taught or suggested in Peptalk Poster and Examples 3-4, 5-2-1, and 5-2-2 of Matsuda. EX1011, p. 90, 92. PepTalk poster, Matsuda, and Yamada all disclose an azide as a bio-orthogonal click-chemistry functional group. EX1006; EX1009, [0151], [0153], [0222], [1037]; EX1011, [0046]-[0047], [0592]-[0593], p. 90, 92.

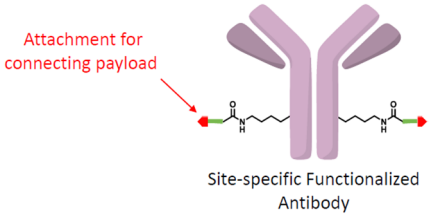
The click reaction between an azide and a terminal alkyne is a Huisgen 1,3-dipolar cycloaddition. EX1002, ¶281-284; EX1036. Accordingly, the limitations of claims 12 would be obvious to a POSA utilizing an azide as the click-chemistry functional group, and use of an azide is within the scope of claim 13. EX1002, ¶285-287.

D. <u>Ground 4</u> – Claims 1, 4, and 8-10 Are Anticipated by PepTalk Presentation (EX1007)

PepTalk Presentation also describes Ajinomoto's AJICAP™ technology for preparing ADCs through site-specific modification of lysine 248. PepTalk Presentation contains much of the same information as PepTalk Poster, with additional background (EX1007, 2-12), additional details regarding the AJICAP™ platform, its advantages/capabilities (*id*., 13-20), and further proof of concept (*id*., 21-32).

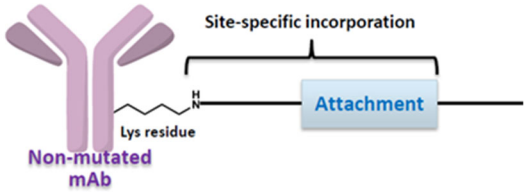
1. Claim 1

The claim chart below shows that PepTalk Presentation anticipates claim 1.

<table>
<tr><th>Claim 1 of the ’675 Patent</th><th>Disclosure in PepTalk Presentation</th></tr>
<tr><td>A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group</td><td>


EX1007, 15.

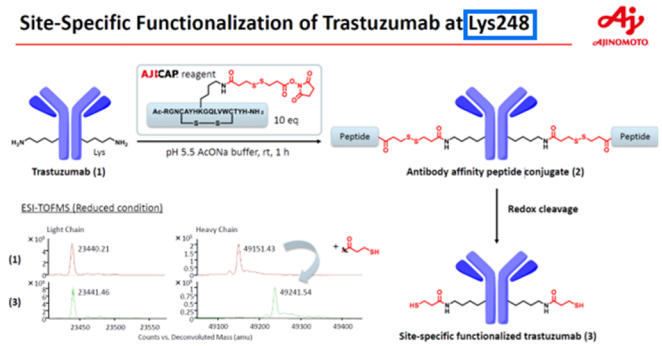
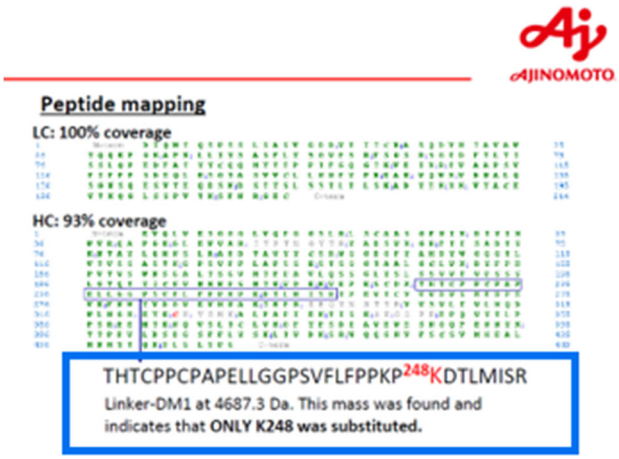
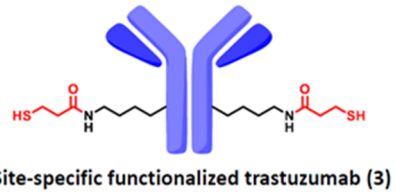
Id., 16.

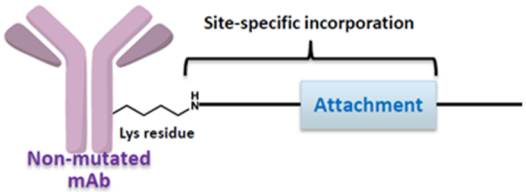


<table>
<tr><th>Isotype</th><th>mAb</th></tr>
<tr><td rowspan="6">IgG1</td><td>Trastuzumab</td></tr>
<tr><td>Rituximab</td></tr>
<tr><td>Adalimumab</td></tr>
<tr><td>X company-mAb A (client project)</td></tr>
<tr><td>X company-mAb B (client project)</td></tr>
<tr><td>Y company-mAb (client project)</td></tr>
<tr><td>IgG2</td><td>Denosumab</td></tr>
<tr><td>IgG4</td><td>Dupilumab</td></tr>
</table>
<table>
<tr><th>Attachment</th><th>Structure</th></tr>
<tr><td>Thiol (-maleimide)</td><td></td></tr>
<tr><td>Azide (-cycloalkyne)</td><td></td></tr>
<tr><td>Aldehyde & (-hydroxylamine)</td><td></td></tr>
</table>
Id., 20.

EX1002, ¶290-298.
</td></tr>
<tr><td>wherein the modified antibody comprises one or more modified heavy chain</td><td>See above.

EX1002, ¶299-303.</td></tr>
</table>

Claim 1 of the ’675 Patent	Disclosure in PepTalk Presentation
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	 EX1007, 16.  *Id.*, 18. EX1002, ¶304-308.
wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end	 *Id.*, 16.

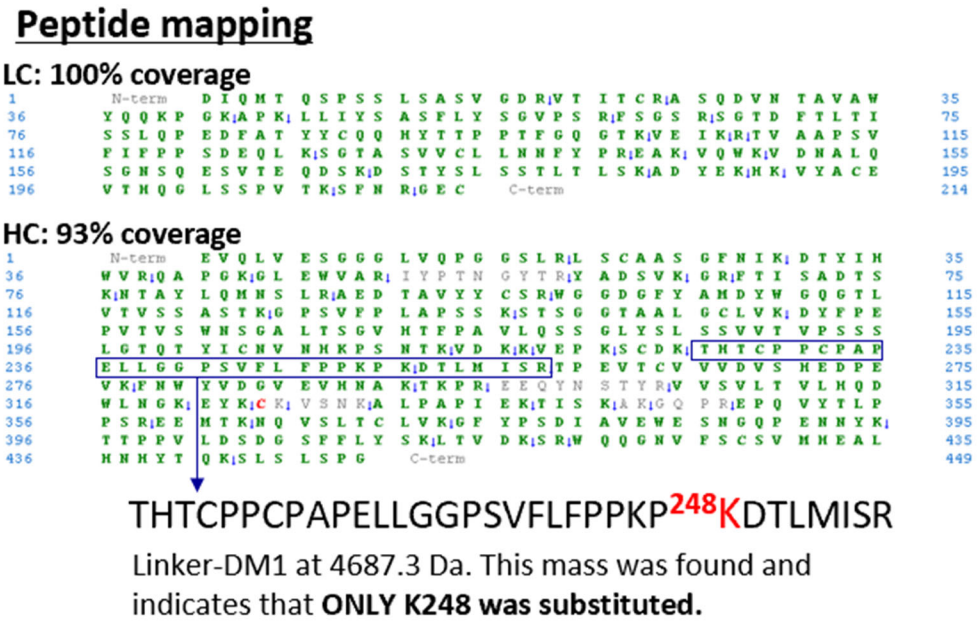
Claim 1 of the ’675 Patent	Disclosure in PepTalk Presentation
	 **Isotype** / **mAb**: IgG1: Trastuzumab; Rituximab; Adalimumab; X company-mAb A (client project); X company-mAb B (client project); Y company-mAb (client project); IgG2: Denosumab; IgG4: Dupilumab **Attachment** / **Structure**: Thiol (-maleimide); Azide (-cycloalkyne); Aldehyde & (-hydroxylamine) *Id.*, 20. EX1002, ¶309-312.
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.	EX1007, 20. *See above*. An azide is not excluded (nor is maleimide or DBCA). EX1002, ¶313-319.

Thus, PepTalk Presentation discloses each element of claim 1, thereby anticipating the claim. *Verdegaal Bros.*, 814 F.2d at 631.

2. Claim 4

Claim 4 depends from claim 1 and recites a particular sequence (i.e., formula 8-2, aka SEQ ID NO:21) in the heavy chain of the antibody. The recited sequence is a human IgG1, 2, or 4 CH2 domain with a modification (i.e., K’) at position 248.

PepTalk Presentation discloses preparation of a modified trastuzumab, which is a human IgG1, with a modification at lysine 248. EX1007, 16, 18, 20. Slide 18 discloses "ONLY K248 was substituted," as shown below:



Thus, slide 18 shows the same sequence recited in claim 4 being modified at position 248. Therefore, claim 4 is anticipated. EX1002, ¶320-328.

3. Claim 8

Claim 8 depends from claim 1 and recites, "wherein the modified antibody comprises two modified heavy chains." Each of the modified antibodies shown in PepTalk Presentation comprise two modified heavy chains. EX1007, 15-16, 18, 20; EX1002, ¶329-336.

4. Claims 9 and 10

With respect to claim 10, PepTalk Presentation teaches using an azide as a bio-orthogonal functional group. EX1007, 20; EX1002, ¶247-250. With respect to

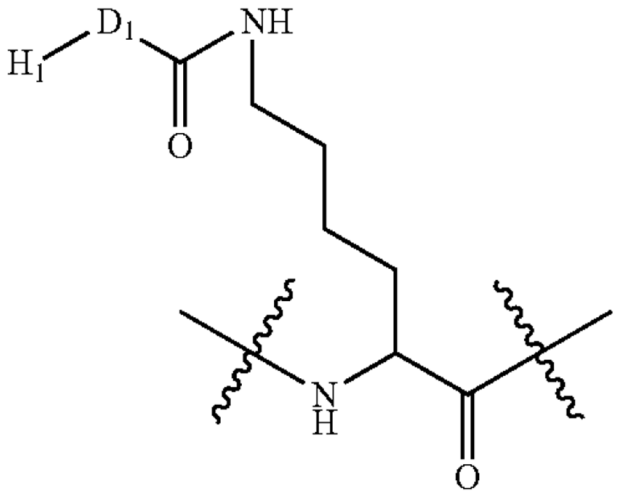
claim 9, the click reaction between an azide and a terminal alkyne is a Huisgen 1,3-dipolar cycloaddition. EX1036; EX1002, ¶337-341. Accordingly, claims 9 and 10 are anticipated.

E. <u>Ground 5</u> – Claims 1-13 Are Obvious Over PepTalk Presentation in View of Yamada and Matsuda

"[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" *Realtime Data, LLC*, 912 F.3d at 1373. Accordingly, claims 1, 4, and 8-10 of the '675 Patent are rendered obvious by PepTalk Presentation for at least the reasons discussed above.

1. Claims 2 and 3

Claim 2 depends from claim 1 and recites a modified lysine with the structure:

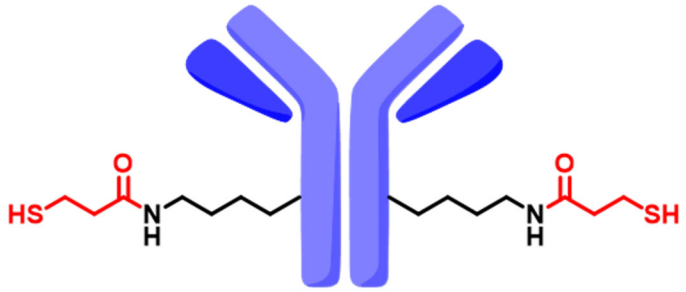


wherein H_1 is a click chemistry functional group, and D_1 is bond, or a C_{1-4} alkylene, C_{2-4} alkenylene, C_{2-4} alkynylene and C_{3-8} cycloalkylene." Claim 3 depends from

claim 2 and requires D_1 is bond or that the recited alkylene, alkenylene, alkynylene, or cycloalkylene is unsubstituted.

PepTalk Presentation, Yamada, and Matsuda disclose incorporating a terminal azide on lysine 248. EX1006, 15-16, 18, 20; EX1009, p. 148; EX1011, p. 90, 92. The modified lysines disclosed in these references include the components recited in claims 2 and 3, and therefore these claims are nothing more than "the mere substitution of one element for another known in the field," and the substitutions "yield a predictable result." *KSR Int'l Co.*, 550 U.S. at 416.

PepTalk Presentation discloses a modified trastuzumab with the following structure:

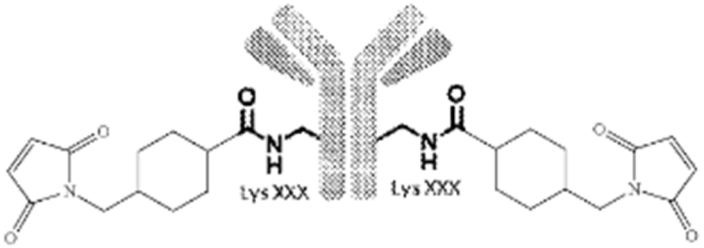


Site-specific functionalized trastuzumab (3)

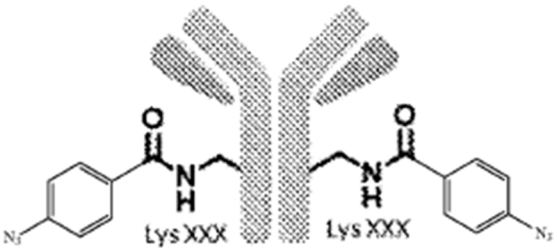
EX1007, 16. This structure satisfies the requirements of claims 2 and 3 for D_1 with an unsubstituted C_2 alkylene, but H_1 is a thiol group (-SH), which is excluded by claim 1. EX1002, ¶352. However, PepTalk Presentation also discloses the "attachment" (i.e., the bio-orthogonal click-chemistry group) can be an azide.

EX1007, 20; EX1002, ¶346-351. Substituting the thiol group above with an azide meets all of the limitations of claims 2 and 3. EX1002, ¶352.

Example 3-4 and 5-2-2 of Matsuda (reproduced below) include an unsubstituted C_6 cycloalkylene, consistent with the requirement of D_1 for claims 2 and 3, providing another example where known elements can be substituted with predictable results. EX1002, ¶354, 360.



Example 3-4 (EX1011, p. 90)



Example 5-2-2 (EX1011, p. 92)

Similarly, Example 5-2-1 of Matsuda includes an unsubstituted C_5 alkylene (*id.*, p. 92), which is only one more carbon than claims 2 and 3 allow. A POSA would understand that this C_5 alkylene could be slightly longer or shorter and still function effectively the same (EX1002, ¶355), and the ’675 Patent does not indicate any

criticality regarding the recited upper limit of C_4. EX1001, 48:14-30; *see In re Aller*, 220 F.2d at 456.

Accordingly, all of the elements of claims 2 and 3 are taught in PepTalk Presentation, Yamada, and Matsuda, and a POSA could predictably combine these elements to arrive at the claims. EX1002, ¶346-360.

2. Claims 5-7 and 11

Claims 5-7 and 11 are treated together because a disclosure of the first or third structures recited in claim 11 also satisfies the limitations of claims 5-7. While PepTalk Presentation does not explicitly teach the specific D_1 structures recited in claims 5-7 or the structures recited in claim 11, short alkyl or cycloalkyl linkers would be obvious to a POSA. EX1002, ¶362-363. Further, Yamada teaches the structures of claims 5-7 and 11.

As noted in Section X(C)(2), Yamada discloses an antibody regioselectively modified with a bio-orthogonal functional group at position 248 represented by (Formula (IV)):

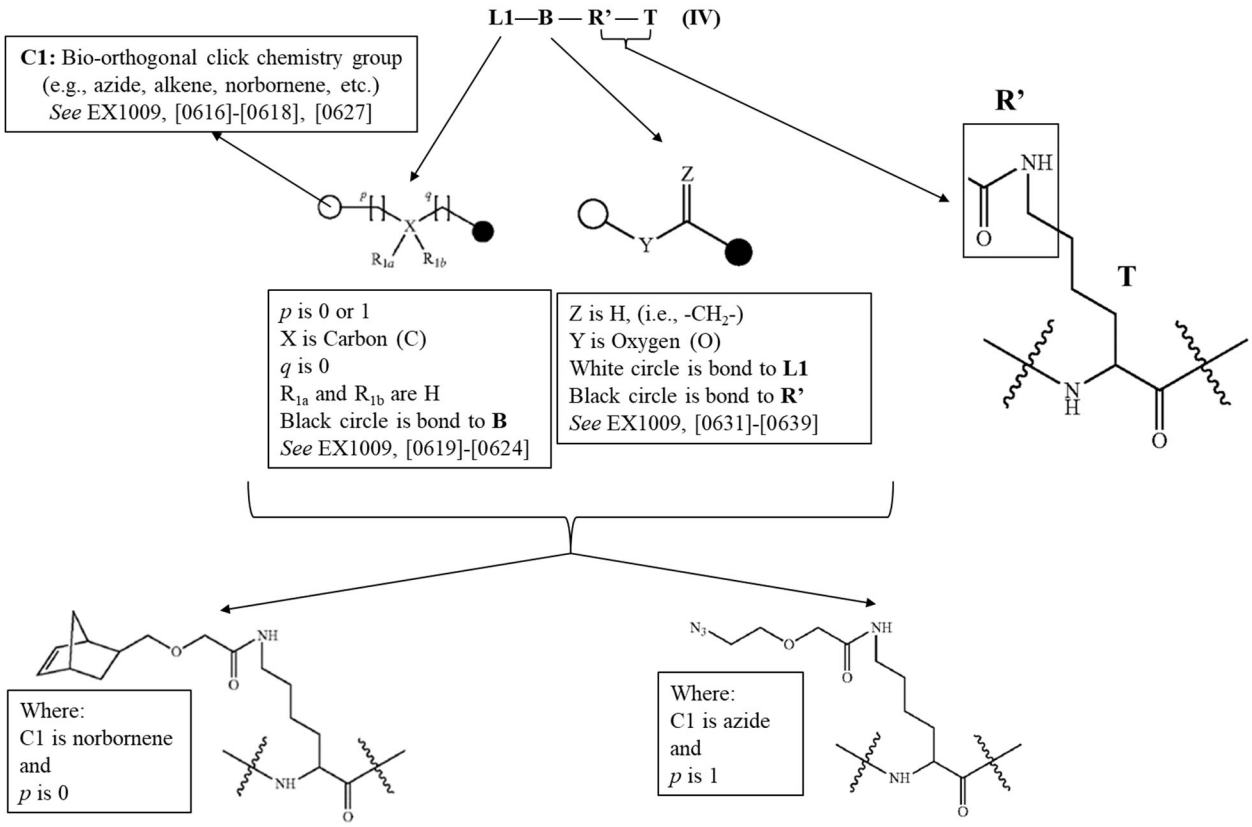
L1-B-R′-T (IV)

where: L1 is a monovalent group with or without the bio-orthogonal functional group, B is a divalent group with or without the bio-orthogonal functional group, T is the soluble protein (i.e., antibody), and R′ is a portion formed by a reaction between the soluble protein and a reactive group. EX1009, [0222], [1037], [1109],

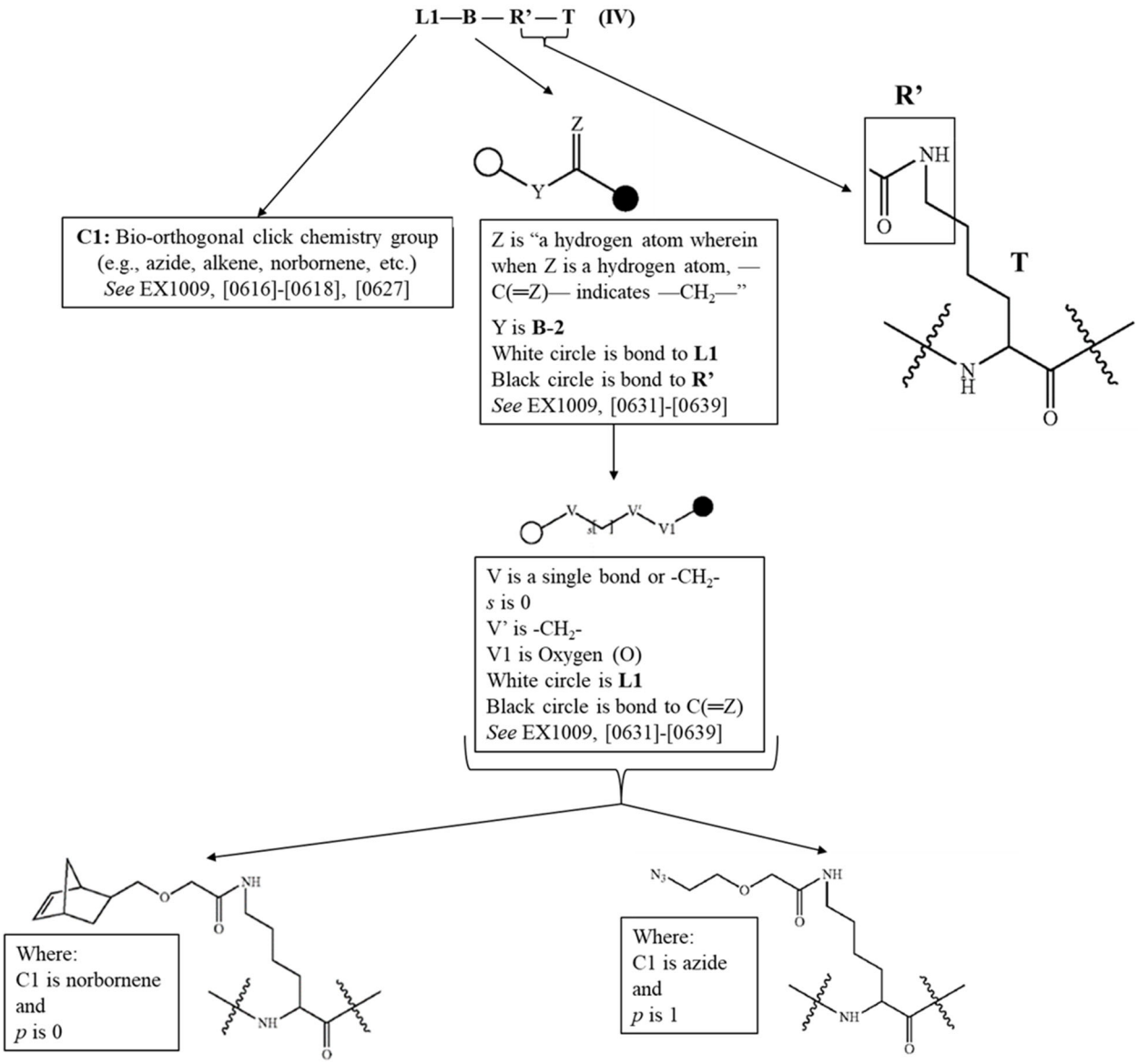
[1114], [0584]-[0588], [0677], [0678], [0697], [0702]-[0705], [0708]-[0710]; EX1002, ¶266-267.

A POSA would need only make selections of disclosed substituents for Formula (IV) as shown in the flow charts below to arrive at the first and third structures of claim 11:

Option 1:



Option 2:

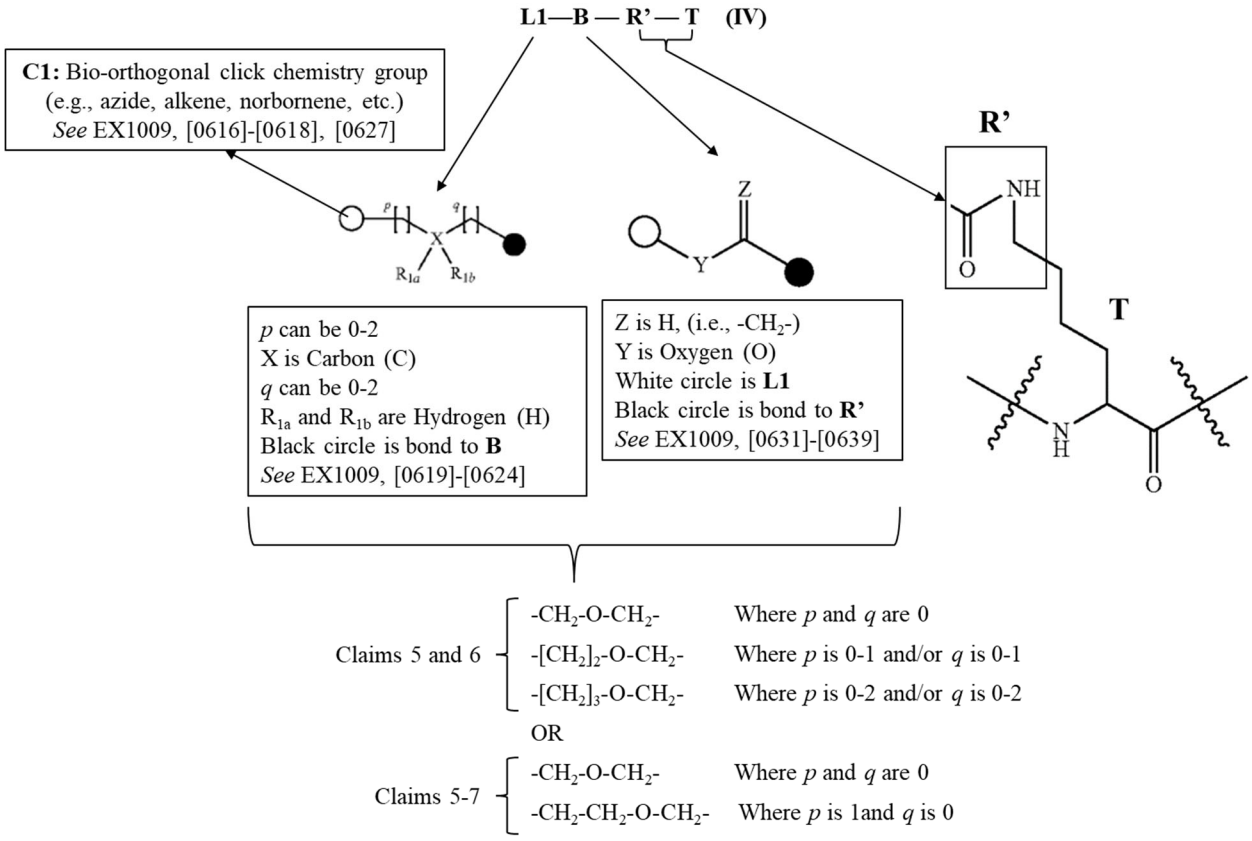


EX1009, [0626]-[0627], [0634]-[0636], [1510], [1465], [1470]-[1472], [1571]; EX 1002, ¶366-372.

Because the structures in claim 11 fall within the scope of the respective definitions of D_1 in claims 5-7, all of the elements of claims 5-7 were taught by Yamada, and combining these with PepTalk Poster would be nothing more than "the

mere substitution of one element for another" to "yield a predictable result." *KSR Int'l Co.*, 550 U.S. at 416. EX1002, ¶363-372.

Claims 5-7 are further rendered obvious by multiple structures taught by Yamada. The flow chart below explains how Yamada's Formula (IV) reads on these claims:



See, EX1002, ¶373-375; *see also id.*, ¶363.

Thus, claims 5-7 and 11 are obvious over PepTalk Presentation and Yamada because all of the claim elements are disclosed, and a POSA would combine them with a reasonable expectation of success. EX1002, ¶372, 375.

3. Claims 12 and 13

As noted above, in Section X(E)(1), all of the limitations of claim 3 are taught or suggested in Peptalk Presentation and Examples 3-4 and 5-2-1 of Matsuda (EX1011, p. 90, 92). PepTalk Presentation, Matsuda, and Yamada all disclose an azide as a bio-orthogonal click-chemistry functional group. EX1007, 15-16, 18, 20; EX1009, [0151], [0153], [0222], [1037]; EX1011, [0046]-[0047], [0592]-[0593].

The click reaction between an azide and a terminal alkyne is a Huisgen 1,3-dipolar cycloaddition. EX1002, ¶376-378; EX1036. Accordingly, the limitations of claims 12 would be obvious to a POSA utilizing an azide as the click-chemistry functional group, and use of an azide is within the scope of claim 13. EX1002, ¶380-382.

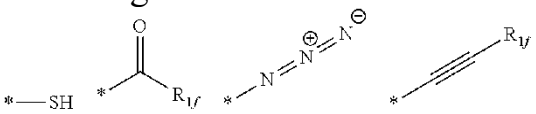
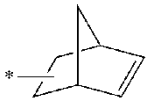
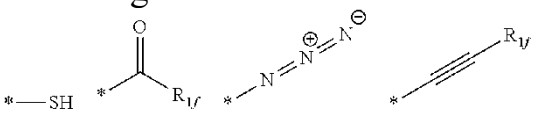
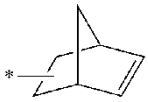
F. <u>Ground 6</u> – Claims 1, 4, and 8-10 Are Anticipated by Yamada

1. Claim 1

Yamada anticipates claim 1 because it explicitly discloses each element of claim 1 as summarized below.

Claim 1 of the '675 Patent	**Disclosure in Yamada**
A modified antibody or its fragment comprising bio-orthogonal click chemistry functional group	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**.

Claim 1 of the ’675 Patent	**Disclosure in Yamada**
	FIG. 1-2, [1019]; *see also* [0151]-[0153], [0581]-[0591]. EX1002, ¶384-389.
wherein the modified antibody comprises one or more modified heavy chain	(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** [0607] ; *see also* FIG. 1-2, p. 147-148. EX1002, ¶390-393.
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	(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**… [0598] … **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 residue**s and exposed tyrosine residues are present at the following positions… **(1) Exposed Lysine Residues** CH2 domain (position 246, **position 248**… [1108]-[1109] *See also*, Example 8, [1944]-[1971] EX1002, ¶394-404.

Claim 1 of the ’675 Patent	**Disclosure in Yamada**
wherein the modified lysine residue comprises a bio-orthogonal click chemistry functional group at terminal end	*See above.* … a bioorthogonal functional group selected from the group consisting of **an azide residue**, … an alkene residue, a tetrazine residue, a nitron residue, … a nitrile residue, a hydrazine residue, a ketone residue, a boronic acid residue, a cyanobenzothiazole residue, … a maleimide residue,… [0151] …wherein the bioorthogonal functional group is any one represented by the following:  …  … [0153] *See also*, structures in Table 3 and Table 4 EX1002, ¶405-412.
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.	…wherein the bioorthogonal functional group is any one represented by the following:  … 

Claim 1 of the ’675 Patent	Disclosure in Yamada
	… [0153]; showing both an azide and norbornene as the terminal bio-reactive functional groups, which are not excluded by the Negative Limitation. *See also*, [1500]-[1530] EX1002, ¶413-420.

Yamada discloses techniques for the regioselective modification of a soluble protein, such as a monoclonal IgG antibody. EX1005, [1108]-[1109]. Yamada provides several other examples of bio-orthogonal functional groups that can modify an antibody that are not excluded by the Negative Limitation, including azide groups, alkyne groups, alkene groups, halogens, tetrazines, nitrone groups, hydroxyamine groups, nitriles, hydrazine groups, etc. *Id*., [0151]-[0153], [1455]-[1458]. Yamada teaches preferred embodiments where the antibody is regioselectively modified at amino acid residues that are exposed to the surface of the antibody, such as position 248. *Id*., [1108]-[1109]; *see also* [1114]. Yamada discloses that modifying surfaced exposed lysine residues is preferred to maintain the function and structure of the antibody (*id*., [1108]), and Example 8 demonstrates that antibodies can be regioselectively modified at specific residues such as lysine 248. *See id*., [1945]-[1971].

Yamada also discloses the structure of an antibody regioselectively modified with a bio-orthogonal functional group at position 248 represented by (Formula (IV)):

L1-B-R′-T (IV)

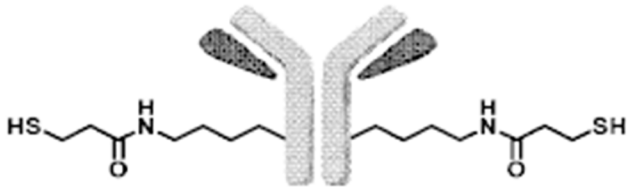
where: L1 is a monovalent group with or without the bio-orthogonal functional group, B is a divalent group with or without the bio-orthogonal functional group, T is the soluble protein (i.e., antibody), and R′ is a portion formed by a reaction between the soluble protein and a reactive group. EX1009, [0222], [1037], [1109], [1114], [0584]-[0588], [0677], [0678], [0697], [0702]-[0705], [0708]-[0710].

As noted in Section X(C)(2) and X(E)(2), Formula (IV) can be constructed in a variety of ways that are encompassed by claims 5-7 and 11 (EX1002, ¶266-280, 361-375), all of which depend indirectly from claim 1. Hence, these embodiments would all necessarily anticipate claim 1.

Beyond the embodiments that anticipate claims 5-7 and 11, even more simplistic interpretations of Formula (IV) would anticipate claim 1. For example, making L1 "a monovalent group comprising a bioorthogonal functional group"—one of two options for L1 in [0666]—and making B "a divalent group comprising no bioorthogonal functional group"—one of two options for B in [0667]—would anticipate claim 1 if (1) *any* of the bioorthogonal function groups disclosed in [0625]-[0627] other than those excluded by claim 1 (e.g., azide or norbornene) were

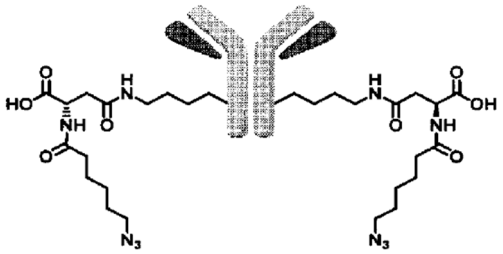
selected as the "monovalent group comprising a bioorthogonal functional group" of L1, and (2) <u>*any*</u> of the divalent groups disclosed in [0630] (e.g., "optionally substituted alkylene, optionally substituted cycloalkylene, optionally substituted aryl, an optionally substituted divalent heterocyclic group…") were selected as the "divalent group comprising no bioorthogonal functional group" of B. Because Yamada also discloses lysine 248 as a preferred modification site (*id*., [1108]-[1109], [1114], [1357]), a POSA could "at once envisage" members of the class encompassed by claim 1 of the '675 Patent (*In re Petering*, 301 F.2d 676, 681 (CCPA 1962), and therefore claim 1 is anticipated.

Further, Table 3 of Yamada includes examples of the resulting antibodies regioselectively modified with a bio-orthogonal functional group:

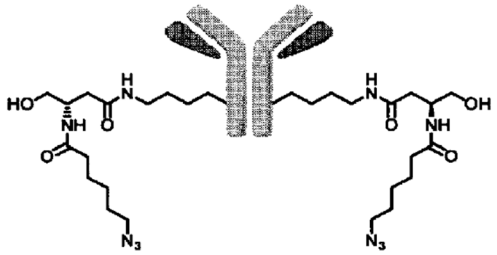


(Example 2-2);

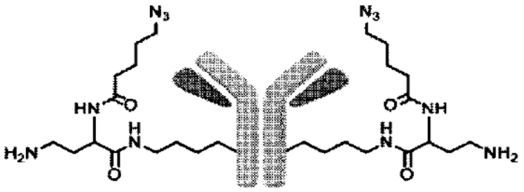
(Example 2-3);



(Example 11-1);



(Example 11-2); and



(Example 57).

Of the above examples, while many possess "a terminal bio-reactive functional group selected from terminal hydroxy group, terminal carboxyl group, terminal thiol group, terminal amino group, and terminal aldehyde group" that is excluded by the Negative Limitation, Yamada also discloses modifying antibodies to have a terminal azide and a terminal alkene, such as norbornene (*id.*, [0151]-[0153], [1455]), which are not terminal bio-reactive functional groups that are barred

by the claim. Further, the constructs of Yamada (e.g., Formula (IV)) in no way *require* terminal hydroxy, carboxyl, thiol, amino, or aldehyde.

For all of the foregoing reasons, Yamada anticipates claim 1.

2. Claim 4

Claim 4 depends from claim 1 and recites a particular sequence (formula 8-2, aka SEQ ID NO:21) in the heavy chain of the antibody corresponding to a human IgG1, 2, or 4 CH2 domain with a modification (K') at position 248.

Yamada teaches the modification of the lysine residue at position 248. EX1005, [1108]-[1109], [1114], [1357]. Further, Yamada teaches a peptide fragment of trastuzumab comprising the same sequence as recited in claim 4, further having a lysine residue modified with an azide or a thiol as a bio-orthogonal functional group. EX1005, [2080], [2557], and [2580] (SEQ ID NO: 40 of Yamada: THTCPPCPAPELLGGPSVFLFPPKPKDTLMISR; sequence corresponding to SEQ ID NO: 21 of the '675 Patent is underlined). EX1002, ¶438-439.

3. Claim 8

Claim 8 depends from claim 1 and recites, "wherein the modified antibody comprises two modified heavy chains."

Yamada teaches a modified antibody comprising two heavy chains. EX1005, [0607]-[0608], FIG. 1-2; EX1002, ¶466-468. Thus, claim 8 is anticipated.

4. Claims 9 and 10

With respect to claim 10, Yamada teaches using an azide as a bio-orthogonal functional group. EX1009, [0151]-[0153]; EX1002, ¶463-465. With respect to claim 9, the click reaction between an azide and a terminal alkyne is a Huisgen 1,3-dipolar cycloaddition. EX1036; EX1002, ¶459-462. Accordingly, Yamada teaches the limitations of claims 9 and 10, and the claims are anticipated.

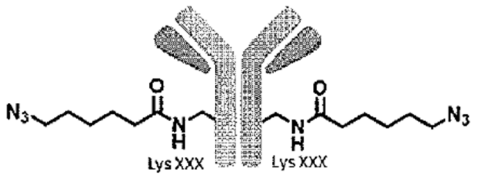
G. <u>Ground 7</u> – Claims 1-13 Are Obvious Over Yamada and Matsuda

"[A] disclosure that anticipates under § 102 also renders the claim invalid under § 103, for 'anticipation is the epitome of obviousness.'" *Realtime Data, LLC*, 912 F.3d at 1373. Accordingly, claims 1, 4, and 8-10 are rendered obvious by Yamada for at least the reasons above. The combination of Yamada and Matsuda also renders obvious claims 1-13 for the reasons below.

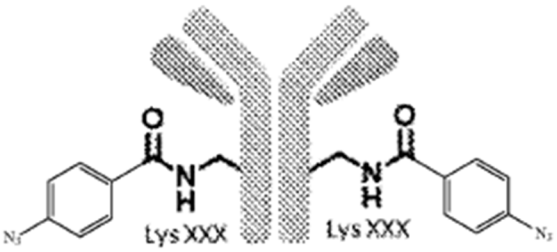
1. Claim 1

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 explains prior ADC production methods result in nonuniformity and varying DARs. EX1005, [0004]; EX1002, ¶421. The DAR can impact a variety of pharmacokinetic parameters (*id*.; EX1027, 541), and therefore a POSA would be motivated to regioselectively modify an antibody to prepare consistent DARs. EX1002, ¶421.

Matsuda provides further motivation for a POSA to regioselectively modify an antibody at lysine 248 according to claim 1. 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 (Example 5-2-1 and Example 5-2-2; *id.*, [1018]-[1029],[1289]-[1290], and [1296]-[1298]) as shown below:



(Example 5-2-1, p. 92);



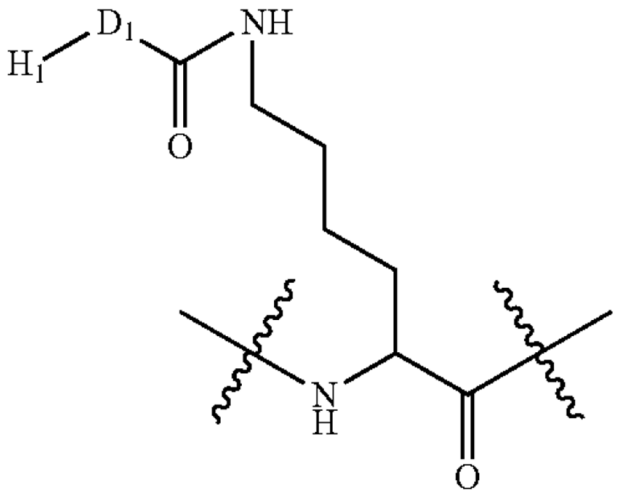
(Example 5-2-2, p. 92).

Thus, Yamada and Matsuda both suggest regioselectively modifying Lys248 with a terminal bio-orthogonal functional group, and Matsuda provides specific examples of azide-containing modifications that comply with the Negative Limitation of claim 1 (EX1011, p. 92). Yamada alone renders claim 1 obvious, but

taken together with Matsuda, a POSA would be motivated and able to prepare a modified antibody according to claim 1 with a reasonable expectation of success.

2. Claims 2 and 3

Claim 2 depends from claim 1 and recites a modified lysine with the structure:



wherein H_1 is a click-chemistry functional group, and "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." Claim 3 depends from claim 2 and requires D_1 is bond or that the recited alkylene, alkenylene, alkynylene, or cycloalkylene is unsubstituted.

Matsuda Examples 3-4 include a C_6 cycloalkylene, consistent with the recited requirement of D_1, and a maleimide for H_1. Accordingly, all of the elements of claim 2 are taught in Matsuda Examples 3-4, and therefore claim 2 is obvious.

Similarly, Matsuda Example 5-2-1 includes a C_5 alkylene, which is only one more carbon than claim 2 allows. The specification of the '675 Patent does not indicate any criticality regarding the recited upper limit of C_4. Rather, the '675 Patent

discloses that "D_1 is ***any alkylene***, alkenylene, or alkynylene." EX1001, 48:14-30; *see In re Aller*, 220 F.2d at 456.

Accordingly, all of the elements of claims 2 and 3 are taught in Yamada and Matsuda, and a POSA could predictably combine these elements to arrive at the claims. EX1002, ¶424-437. Thus, claim 2 is obvious over Yamada and Matsuda.

3. Claim 4

In addition to Yamada disclosing all of the limitations of claim 4 (discussed above), Matsuda teaches the same peptide fragment of trastuzumab disclosed in Yamada, THTCPPCPAPELLGGPSVFLFPPKPKDTLMISR, with a lysine modified with an azide at positions 246 or 248. EX1011, [1312]. Accordingly, the limitations of claim 4 are anticipated/rendered obvious by Yamada and Matsuda. EX1002, ¶439-441.

4. Claims 5-7 and 11

Claims 5-7 and 11 are treated together in this section for the same reasons discussed above: a disclosure of the first or third structures recited in claim 11 also satisfies the limitations of claims 5-7.

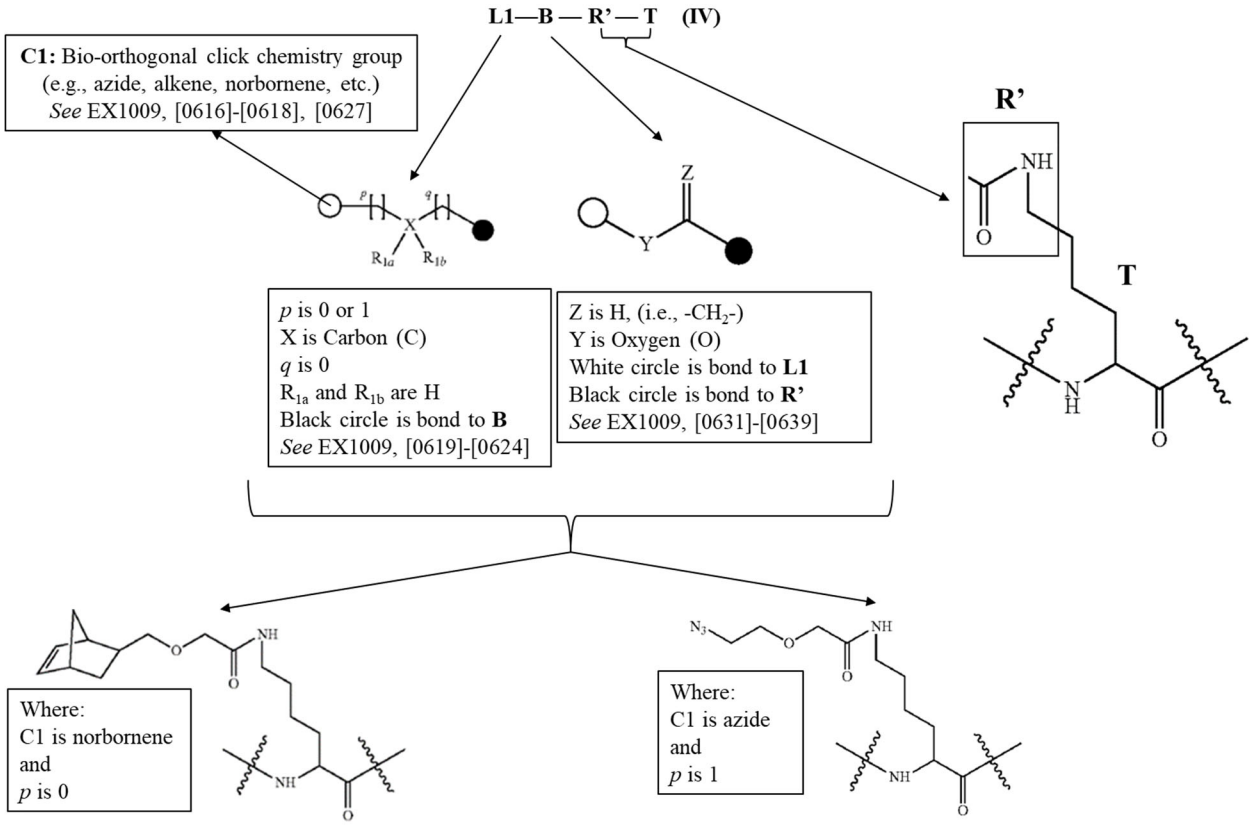
As noted in Sections X(C)(2) and X(E)(2), Yamada discloses an antibody regioselectively modified with a bio-orthogonal functional group at position 248 represented by (Formula (IV)):

L1-B-R′-T (IV)

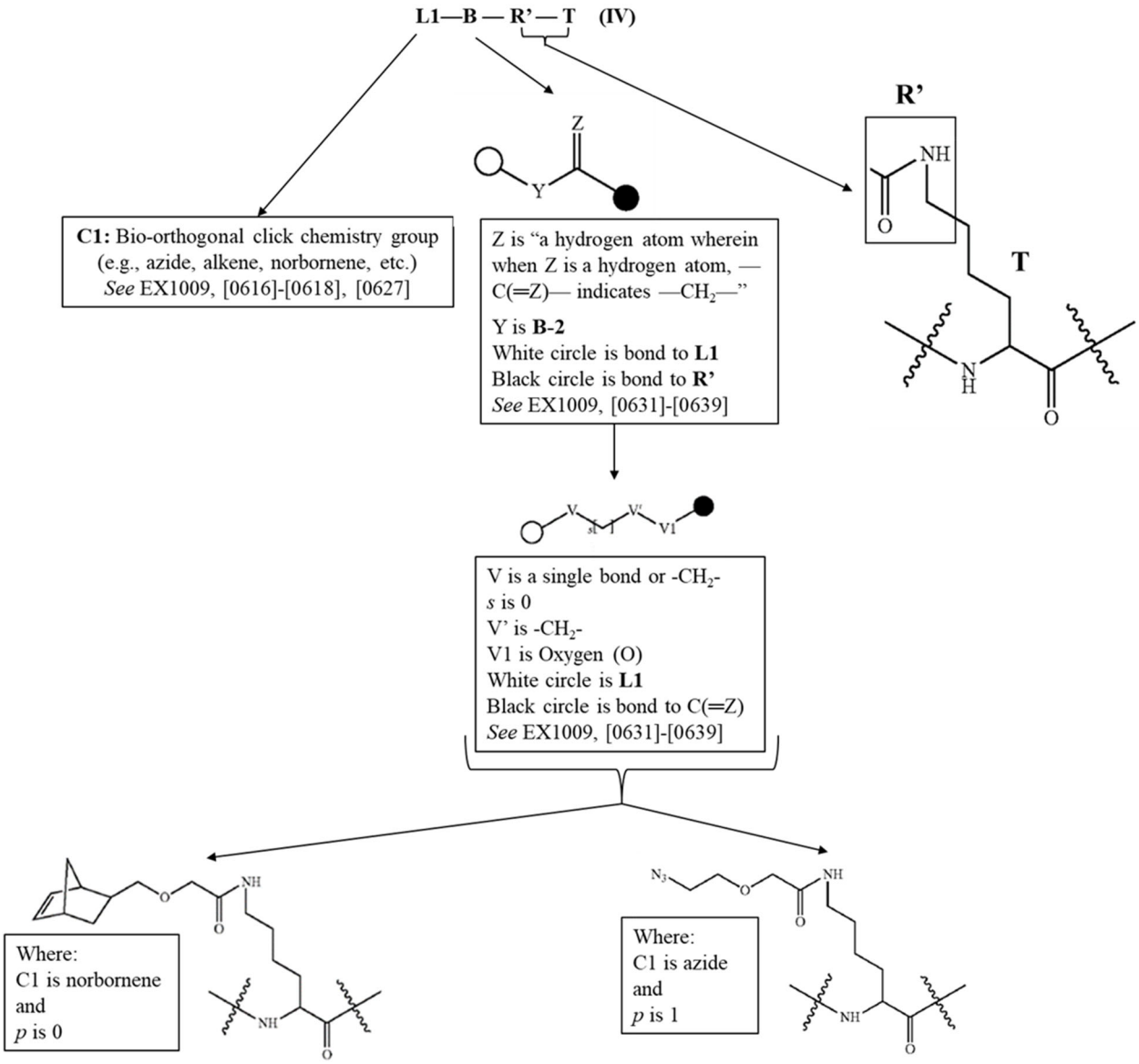
where: L1 is a monovalent group with or without the bio-orthogonal functional group, B is a divalent group with or without the bio-orthogonal functional group, T is the soluble protein (i.e., antibody), and R′ is a portion formed by a reaction between the soluble protein and a reactive group. EX1009, [0222], [1037], [1109], [1114], [0584]-[0588], [0677], [0678], [0697], [0702]-[0705], [0708]-[0710]; EX1002, ¶445-446.

A POSA need only make selections of disclosed substituents for Formula (IV) as shown in the flow charts below to arrive at the first and third structures of claim 11:

Option 1:



Option 2:

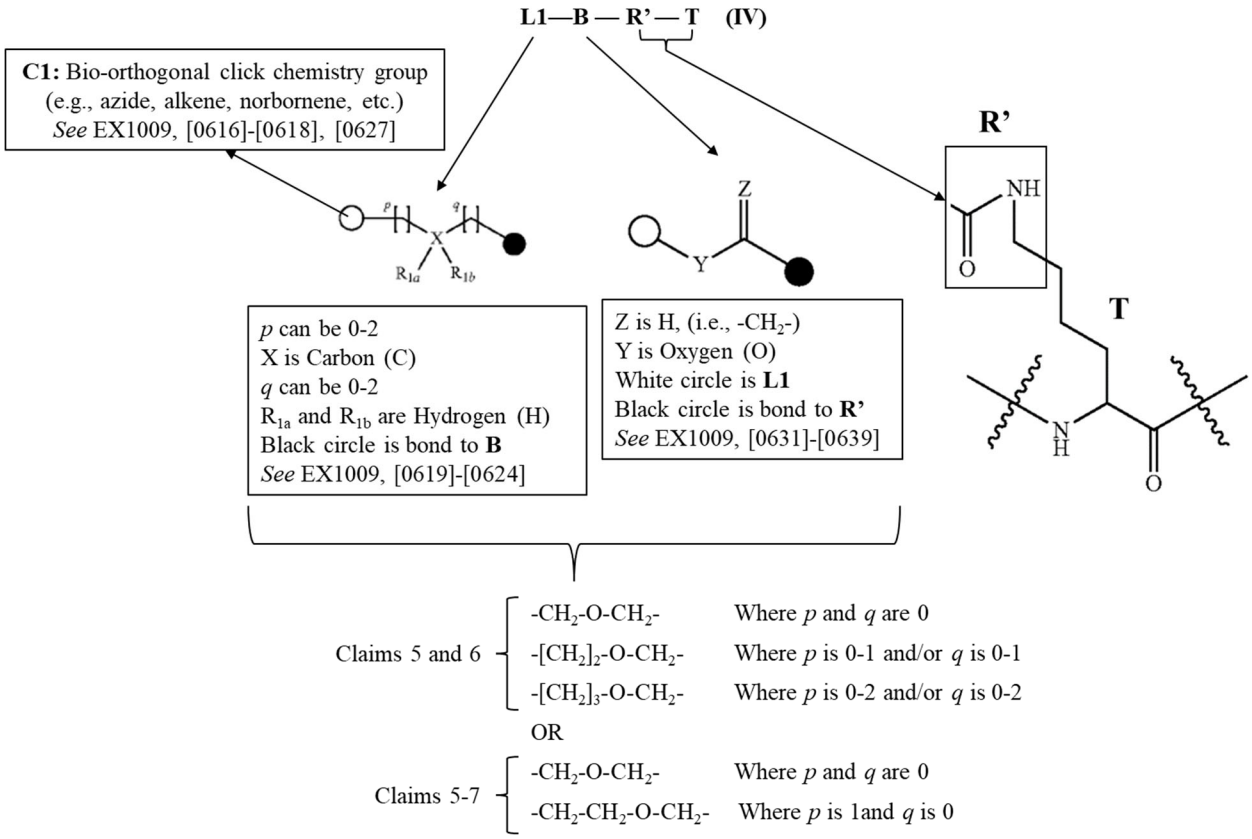


EX1009, [0626]-[0627], [0634]-[0636], [1510], [1465], [1470]-[1472], [1571]; EX 1002, ¶447-451.

Because the structures in claim 11 fall within the scope of the respective definitions of D_1 in claims 5-7, all of the elements of claims 5-7 and 11 are taught in

Yamada, and combining these elements as disclosed in Yamada or with Matsuda was nothing more than "the mere substitution of one element for another" to "yield a predictable result." *KSR Int'l Co.*, 550 U.S. at 416. EX1002, ¶447-451.

Claims 5-7 are further rendered obvious by multiple structures taught by Yamada. The flow chart below explains how Yamada's Formula (IV) reads on these claims:



See, EX1002, ¶452-454.

Thus, claims 5-7 and 11 are obvious, if not anticipated by, Yamada because all of the claim elements are disclosed and a POSA could readily combine them with a reasonable expectation of success. EX1002, ¶453, 454.

5. Claim 8

Yamada anticipates claim 8 as discussed above. Additionally, Matsuda Examples 5-2-1, 5-2-2 and 3-4 each disclose modified antibodies that comprise two modified heavy chains. *See, e.g.*, EX1011, p. 90, 92. Thus, the limitations of claim 8 are explicitly taught by Yamada and Matsuda, and the claim is obvious.

6. Claims 9, 10, 12, and 13

Claims 9, 10, 12, and 13 are identical except that claims 9 and 10 depend from claim 1, and claims 12 and 13 depend from claim 3. Claims 9 and 12 require a particular click-chemistry reaction (e.g., Huisgen 1,3-dipolar cycloaddition) and claims 10 and 13 require particular click-chemistry groups, including an azide. Both Yamada and Matsuda disclose antibodies modified with an azide (EX1009, [0151]-[0153]; EX1011, p. 92), thus satisfying these limitations because azides are recited in claims 10 and 13 and can undergo Huisgen 1,3-dipolar cycloaddition or Diels-Alder reactions, as recited in claims 9 and 12. EX1002, ¶459-472; EX1036.

XI. THE PETITION SHOULD NOT BE DENIED UNDER SECTION 325(D)

The PepTalk Poster, PepTalk Presentation, and Matsuda were not of record or considered by the Office during prosecution of the ’675 Patent.

While Yamada was cited during prosecution as anticipating several claims (EX1035, 327), the Office Action citing Yamada mischaracterized this reference. The Examiner did not reject then-pending claim 58 as anticipated or obvious over

Yamada, and in response to the rejection, Patentee simply amended the independent claim (then-pending claim 54) to incorporate the limitations of claim 58 without making any substantive arguments (EX1035, 304, 3112). After this amendment, the claims were allowed without further rejection.

At the time of the rejection claim 58 recited:

> The modified antibody of claim 54, 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.

As detailed above, Yamada discloses this limitation, and therefore the Examiner's interpretation of Yamada was inaccurate. Claim 58 should have been rejected as well.

When applying § 325(d), "the Board uses the following two-part framework: (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims." *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13,2020) (precedential).

Here, Petitioner presents multiple references never considered by the Office. With respect to Yamada—the one reference that was considered—the Office's prior

interpretation of Yamada was incorrect, and this misinterpretation led to the grant of the patent (i.e., the Office erred in a manner material to the patentability of challenged claims). Therefore, the Petition and any grounds relying on Yamada should not be denied institution under § 325(d).

XII. CONCLUSION

For the reasons set forth above, claims 1-13 of the ’675 Patent are unpatentable. Petitioner requests that an *inter partes* review be instituted and all challenged claims be cancelled.

Respectfully submitted,

Dated: December 24, 2024

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

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,868 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: December 24, 2024

/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 petition for *inter partes* review and all Exhibits and other documents filed together with the petition were served on December 24, 2024, by delivering a copy to FEDERAL EXPRESS directed to the attorneys of record for the patent at the following address:

C/O Kisuk Lee
Harness Dickey
7700 Bonhomme, Suite 400
St. Louis, MO 63105

Respectfully submitted,

Dated: Decmeber 24, 2024

/Stephen B Maebius/

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

PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(A) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No.: 19-0741.

Respectfully submitted,

Dated: December 24, 2024

/Stephen B Maebius/

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