

Ajinomoto Co., Inc. v. AbTis Co., Ltd.

Case No.: IPR2025-00283

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

Patent Owner (AbTis) Demonstrative Slides

Friday, May 8, 2026

9:00 A.M. Eastern

ABTIS EXHIBIT 2013
Ajinomoto v. AbTis
IPR2025-00283

- Proposed Substitute Claims 14, 15, and 16 Have Written Description Support
- The Proposed Amended Claims Are Not Anticipated
- The Claims are Enabled and Not Indefinite
- Proposed Substitute Claims 14, 15, and 16 Are Not Obvious

- **Proposed Substitute Claims 14, 15, and 16 Have Written Description Support**
- The Proposed Amended Claims Are Not Anticipated
- The Claims are Enabled and Not Indefinite
- Proposed Substitute Claims 14, 15, and 16 Are Not Obvious

Proposed Substitute Claims 14, 15, and 16

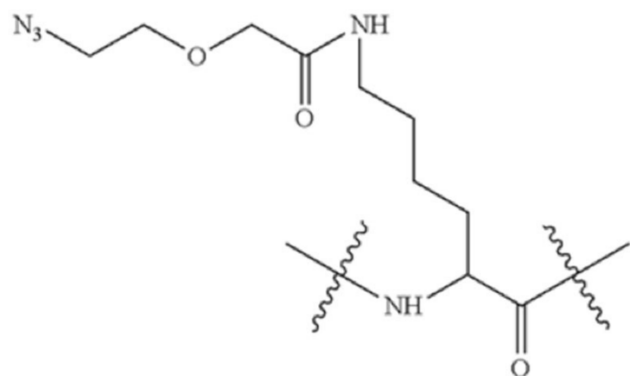
Claim 14. A modified antibody comprising biorthogonal click chemistry functional group,

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

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

wherein the 248 position is determined by an EU numbering system, and

wherein the modified lysine has the following structure:



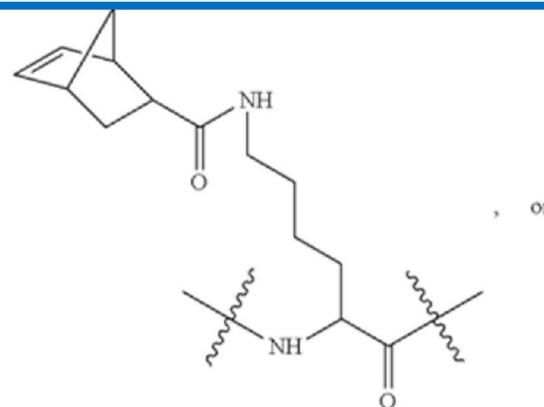
Claim 15. A modified antibody comprising biorthogonal click chemistry functional group,

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

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

wherein the 248 position is determined by an EU numbering system, and

wherein the modified lysine has the following structure:



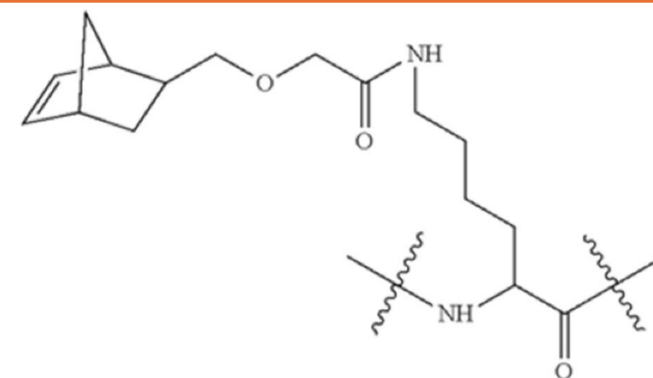
Claim 16. A modified antibody comprising biorthogonal click chemistry functional group,

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

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

wherein the 248 position is determined by an EU numbering system, and

wherein the modified lysine has the following structure:



Mot. to Amend. (Paper 23), Appx. A.

Claim limitations 14[pre], 15[pre], 16[pre]

Claim 14. A modified antibody comprising biorthogonal click chemistry functional group,

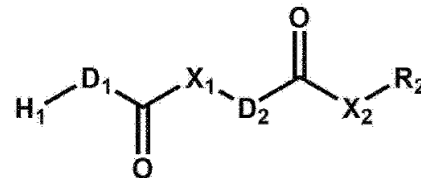
Claim 15. A modified antibody comprising biorthogonal click chemistry functional group,

Claim 16. A modified antibody comprising biorthogonal click chemistry functional group,

Mot. to Amend. (Paper 23), Appx. A

[0013] The present application provides A compound of Formula 2:

[0014] [formula 2]



[0015] wherein, H₁ is a first click chemistry functional group, D₁ is selected from a covalent bond, C₁₋₄alkylene, C₂₋₄alkenylene, C₂₋₄alkynylene, and C₃₋₈cycloalkylene, X₁ is S, D₂ is selected from C₁₋₇alkylene, C₂₋₇alkenylene, C₂₋₇alkynylene, and C₃₋₈cycloalkynylene, X₂ is O, R₂' is N-succinimide, p-nitrophenyl, or pentafluorophenyl.

[0016] Also, the present application provides the compound wherein H₁ is selected from terminal alkyne, azide, strained alkyne, diene, dienophile, alkene, thiol, and tetrazine. Furthermore, the present application provides the compound wherein H₁ is selected from norbornene, tetrazine, azide and dibenzocyclooctyne-amine.

[0017] Additionally, the present application provides the compound wherein R₂' is N-succinimide.

Ex. 2002, ¶¶13-16

[0242] In specific embodiments, R₁' may include a click-chemistry functional group. Also, the click-chemistry functional group may include one or more selected from an alkyne, an azide, a strained alkyne, a diene, a dienophile, an alkene, a thiol, and a tetrazine. Furthermore, the click-chemistry functional group may be selected from an azide, or a strained alkyne. Further, the click-chemistry functional group may be selected from an azide, or dibenzocyclooctyne-amine. Additionally, the click-chemistry functional group may be selected from a diene, or a dienophile. Further, the click-chemistry functional group may be selected from a tetrazine, or a norbornene.

Ex. 2002, ¶242

Claim limitations 14[a], 15[a], 16[a]

Claim 14[a].

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

Claim 15[a].

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

Claim 16[a].

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

Mot. to Amend. (Paper 23), Appx. A

¶ 67. The record before us shows that a person of ordinary skill in the art reading the specification could “immediately discern” (*Purdue Pharma L.P.*, 230 F.3d at 1323) that it described and contemplated “modified antibodies” comprising exactly one modified heavy chain or three or more modified heavy chains from the applications.

Prelim. Guidance (Paper 27), 7

[0580] In specific embodiments, the antibody may be a human antibody. In other specific embodiments, the antibody may be a non-human animal antibody. In specific embodiments, the antibody may be immunoglobulin G (IgG). In specific embodiments, the antibody may be a whole antibody. In other specific embodiments, the antibody may be a fragment of the antibody. In specific embodiments, the antibody may be a wild-type antibody. In other specific embodiments, the antibody may be a manipulated antibody.

Ex. 2002, ¶580; Ex. 2003, ¶579

Claim limitations 14[b], 15[b], 16[b]

Claim 14[b].

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

Claim 15[b].

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

Claim 16[b].

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

Mot. to Amend. (Paper 23), Appx. A

[0008]

The present invention provides technology for specifically transferring a chemical functional group to a certain site of an antibody. In one specific embodiment, the present invention provides technology for specifically transferring a chemical functional group to lysine 246 in the antibody. In another specific embodiment, the present invention provides technology for specifically transferring a chemical functional group to lysine 248 in the antibody. In still another specific embodiment, the present invention provides technology for specifically transferring a chemical functional group to lysine 246 and 248 in the antibody.

Ex. 2002, ¶18

[0228]

In specific embodiments, the antibody according to the present invention may include a sequence of SEQ ID NO: 1 or derivatives thereof. Also, the antibody according to the present invention may include a derivative of SEQ ID NO: 1 in which lysine 246 is substituted. In addition, the antibody according to the present invention may include a derivative of SEQ ID NO: 1 in which lysine 248 is substituted. Furthermore, the antibody according to the present invention may include a derivative of SEQ ID NO: 1 in which lysine 246 and 248 are substituted.

Ex. 2002, ¶228

Claim limitations 14[c], 15[c], 16[c]

Claim 14[c].

... wherein the 248 position is determined by an EU numbering system, and

Claim 15[c].

... wherein the 248 position is determined by an EU numbering system, and

Claim 16[c].

... wherein the 248 position is determined by an EU numbering system, and

Mot. to Amend. (Paper 23), Appx. A

[0225] In the present invention, when reference to an amino acid sequence of the Fc domain of the antibody is made, numbers in the sequence are numbered according to the EU numbering system unless stated otherwise. The EU numbering system has been widely used as a sequencing system for the Fc domain after research on the sequence of IgG, as described in Edelman GM, *et al.*, The covalent structure of an entire gamma-G immunoglobulin molecule; Proc. Natl. Acad. Sci. USA., 1969 May; 63(1): 78-85.

Ex. 2002, ¶225

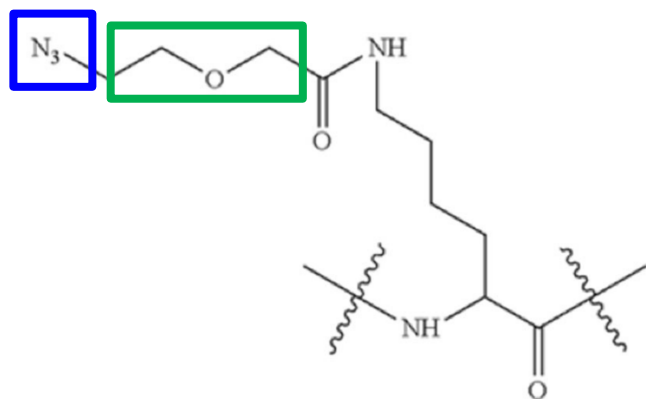
[0227] A labeling site of an antibody may be designed in consideration of the criteria for the labeling site, that is, (1) a site spaced apart from a paratope; and (2) a site spaced apart from a recognition site of FcR including FcRn. Examples of the amino acids used in a bioconjugation reaction typically include lysine, cysteine, and tyrosine. Lysine 246 (Lys₂₄₆) and lysine 248 (Lys₂₄₈) present in an Fc domain of the antibody are residues that satisfy all the requirements, and thus are both desirable labeling sites. A sequence of the Fc domain including the Lys₂₄₆ and Lys₂₄₈ residues is GPSVFLFPPKPKDTLMI, and the sequence and numbers in the sequence numbered according to the EU numbering system are shown in FIG. 1 (FIG. 1, SEQ ID NO: 1).

Ex. 2002, ¶227

Claim limitation 14[d]

Claim 14[d].

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



Mot. to Amend. (Paper 23), Appx. A

- [1290] 3.2. Synthesis of Antibody-Azide
- [1291] Synthesis method of Trastuzumab-Azide (4)
- [1292] Introduction reaction using Compound IV-SSFI (Dap)
- [1293] Synthesis of Ab (246/248 Lys)-azide was carried out in a buffer using Compound IV-SSFI (Dap). A 1× PBS buffer (0.01% Tween 20, pH 7.4) was used as the reaction buffer. To introduce an azide at a certain site of an antibody (trastuzumab, 4 mg/mL), 10 equivalents of Compound IV-SSFI (Dap) was added per one antibody, and reacted at room temperature for 24 hours, and the reaction monitoring and termination were confirmed by HIC-HPLC. As the binding of norbornene to the antibody proceeds, the peaks on the chromatogram were observed to shift from 6 minutes to 6.3 minutes, thereby confirming a degree of progression of the reaction. The Ab-norbornene conjugate was dialyzed three times using a 1× PBS buffer (pH 7.4), and purified using a size exclusion chromatography technique.
- [1294] Observation of the binding reaction between trastuzumab and Compound IV-SSFI (Dap) according to reaction time is shown in FIG. 48.

Ex. 2002, ¶¶ 1318-19

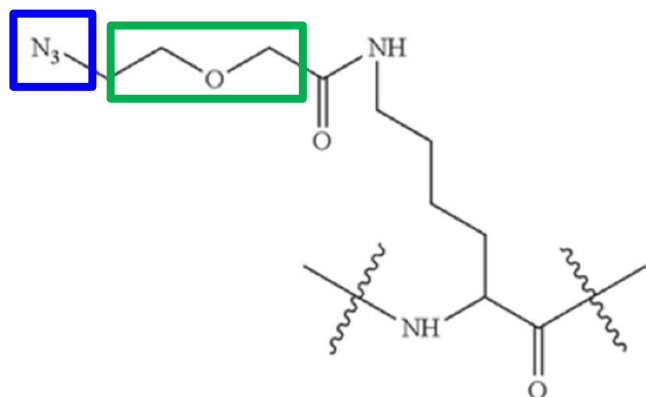
- [1318] 3.4. Confirmation of structure of Trastuzumab-Azide
- [1319] The antibody-azide complex in which an azide linker was bound to an antibody via Compound IV-SSFI (Dap) was confirmed using mass spectrometry. A molecular weight increase of 249 Da was confirmed when two molecules of an azide compound were bound to trastuzumab. The measured mass spectrum of trastuzumab is shown in FIG. 56, and the mass spectrum of the antibody-azide complex to which two azide molecules were bound is shown in FIG. 57.

Ex. 2002, ¶¶ 1318-19

Claim limitation 14[d]

Claim 14[d].

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



Mot. to Amend. (Paper 23), Appx. A

[0573]

[Formula 8-2]

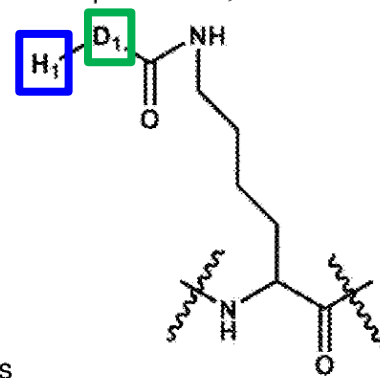
[0574]

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

21)

[0575]

wherein G is glycine, P is proline, S is serine, V is valine, F is phenylalanine, L is leucine, K is lysine, D is aspartic acid, T is threonine, M is methionine, I is isoleucine, and



[0576]

(K)' is

wherein H₁ is a first click-chemistry functional group, and

[0577]

D₁ is any alkylene, alkenylene, or alkynylene. The antibody or fragment thereof has H₁ connected via lysine 248 in an Fc domain thereof, or a site corresponding to the lysine 248.

[0578]

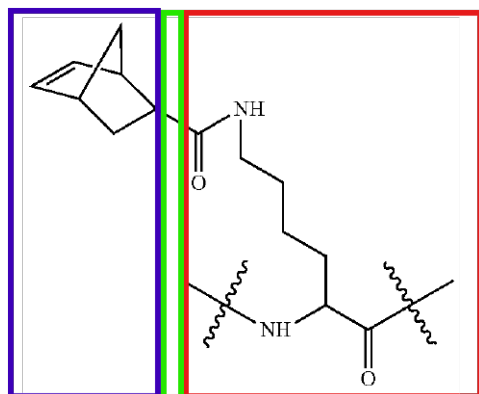
In specific embodiments, H₁ may include any one selected from an alkyne, an azide, a strained alkyne, a diene, a dienophile, an alkene, a thiol, and a tetrazine. Furthermore, H₁ may be an azide, or a strained alkyne. Further, H₁ may be an azide, or dibenzocyclooctyne-amine. Additionally, H₁ may be a diene, or a dienophile. Further, H₁ may be a tetrazine, or a norbornene. Alternatively, H₁ may be a tetrazine, or a trans-cyclooctene.

Ex. 2002, ¶¶ 573-78; Ex. 2004, ¶¶ 47, 52

Claim limitation 15[d]

Claim 15[d].

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



Mot. to Amend. (Paper 23), Appx. A

[1282]

Synthesis method of Trastuzumab-Norbornene (3)

[1283]

Introduction reaction using Compound III-SSFI (Dap, Dab, Orn, or Lys)

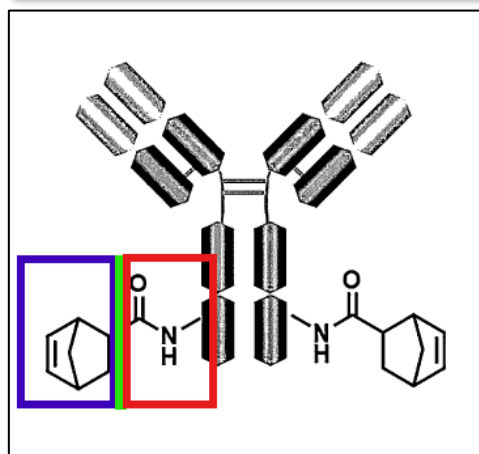
[1284]

Synthesis of Ab (246/248 Lys)-norbornene was carried out in a buffer using Compound III-SSFI (Lys). A 1× PBS buffer (0.01% Tween 20, pH 7.4) was used as the reaction buffer. To introduce norbornene at a certain site of an antibody (Herceptin or trastuzumab, 4 mg/mL), 10 equivalents of Compound III-SSFI (Dap, Dab, Orn, or Lys) was added per one antibody, and reacted at room temperature for 28 hours, and the reaction monitoring and termination were confirmed by HIC-HPLC. As the binding of norbornene to the antibody proceeds, the peaks on the chromatogram were observed to shift from 6.2 minutes to 6.4 to 6.7 minutes, thereby confirming a degree of progression of the reaction. The Ab-norbornene conjugate was dialyzed using a 1× PBS buffer (pH 7.4), and purified using a size exclusion chromatography technique.

[1285]

The reaction between Compound III-SSFI (Dap, Dab, Orn, or Lys) and the antibody is shown in FIG. 42, and the structure of the final product (i.e., Ab(246/248)-Norbornene) is shown in FIG. 43.

Ex. 2002, ¶¶1282-85

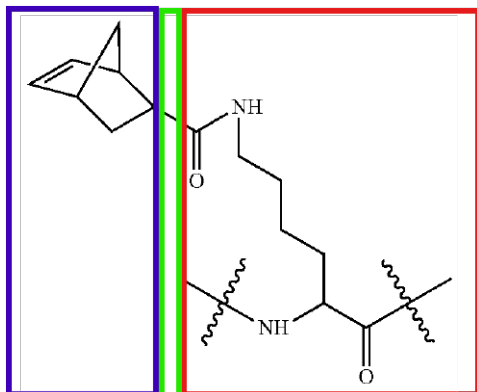


Ex. 2002, Fig. 43

Claim limitation 15[d]

Claim 15[d].

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



Mot. to Amend. (Paper 23), Appx. A

[0573]

[Formula 8-2]

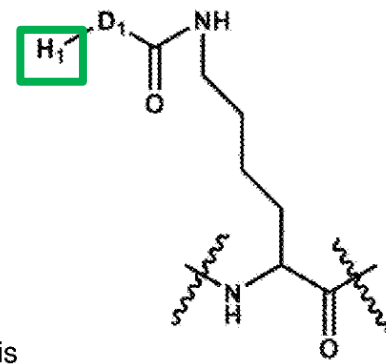
[0574]

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

21)

[0575]

wherein G is glycine, P is proline, S is serine, V is valine, F is phenylalanine, L is leucine, K is lysine, D is aspartic acid, T is threonine, M is methionine, I is isoleucine, and



[0576]

(K)' is

wherein H₁ is a first click-chemistry functional group, and

[0577]

D₁ is any alkylene, alkenylene, or alkynylene. The antibody or fragment thereof has H₁ connected via lysine 248 in an Fc domain thereof, or a site corresponding to the lysine 248.

[0578]

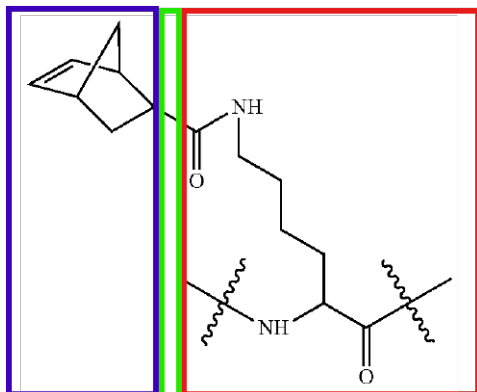
In specific embodiments, H₁ may include any one selected from an alkyne, an azide, a strained alkyne, a diene, a dienophile, an alkene, a thiol, and a tetrazine. Furthermore, H₁ may be an azide, or a strained alkyne. Further, H₁ may be an azide, or dibenzocyclooctyne-amine. Additionally, H₁ may be a diene, or a dienophile. Further, H₁ may be a tetrazine, or a norbornene. Alternatively, H₁ may be a tetrazine, or a trans-cyclooctene.

Ex. 2002, ¶¶573-78

Claim limitation 15[d]

Claim 15[d].

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



Mot. to Amend. (Paper 23), Appx. A

[0573]

[Formula 8-2]

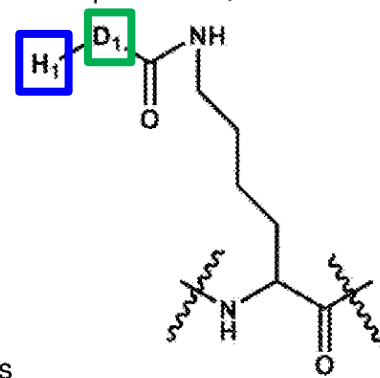
[0574]

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

21)

[0575]

wherein G is glycine, P is proline, S is serine, V is valine, F is phenylalanine, L is leucine, K is lysine, D is aspartic acid, T is threonine, M is methionine, I is isoleucine, and



[0576]

(K)' is

wherein H₁ is a first click-chemistry functional group, and

[0577]

D₁ is any alkylene, alkenylene, or alkynylene. The antibody or fragment thereof has H₁ connected via lysine 248 in an Fc domain thereof, or a site corresponding to the lysine 248.

[0578]

In specific embodiments, H₁ may include any one selected from an alkyne, an azide, a strained alkyne, a diene, a dienophile, an alkene, a thiol, and a tetrazine. Furthermore, H₁ may be an azide, or a strained alkyne. Further, H₁ may be an azide, or dibenzocyclooctyne-amine. Additionally, H₁ may be a diene, or a dienophile. Further, H₁ may be a tetrazine, or a norbornene. Alternatively, H₁ may be a tetrazine, or a trans-cyclooctene.

Ex. 2002, ¶¶ 573-78; Ex. 2004, ¶¶ 47, 52

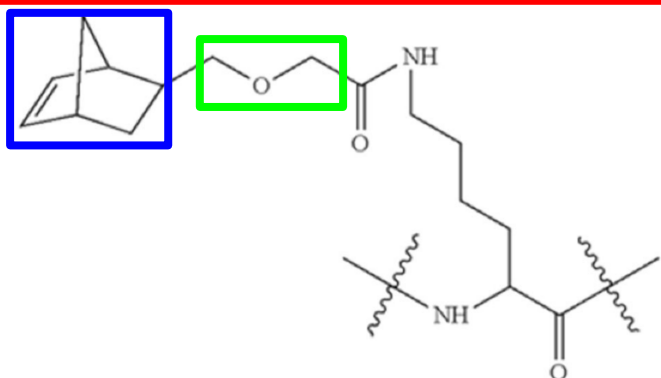
Claim limitation 16[d]

Claim 16. A modified antibody comprising biorthogonal click chemistry functional group, wherein the modified antibody comprises one or more modified heavy chain,

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

wherein the 248 position is determined by an EU numbering system, and

wherein the modified lysine has the following structure:



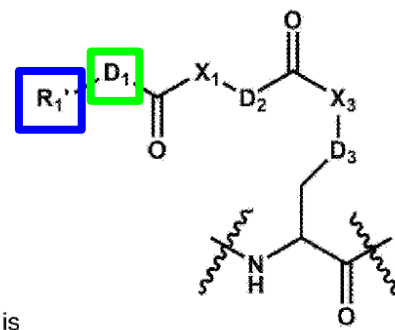
Mot. to Amend. (Paper 23), Appx. A

[0394] [Formula 5-2]

[0395] $(\text{Xaa})_{1-3}\text{-C-(Xaa)}_2\text{-H-(Xa}_1\text{)}'\text{-G-Xa}_2\text{-L-V-Xa}_3\text{-C-(Xaa)}_{1-3}$ (SEQ ID NO: 12)

[0396] wherein each Xaa is independently any amino acid except cysteine,

[0397] C is cysteine, H is histidine, G is glycine, Xa₂ is glutamic acid or asparagine, L is leucine, V is valine, Xa₃ is selected from tryptophan, naphthylalanine, and phenylalanine, and



[0398] (Xa₁)' is

[0399] wherein R₁' is a first chemical functional group,

[0400] D₁ is any alkylene, alkenylene, or alkynylene,

[0401] X₁ is an element that is more electronegative than carbon,

[0402] D₂ is any alkylene, alkenylene, or alkynylene,

[0403] D₃ is a covalent bond or a C₁₋₃ alkylene, and

[0404] X₃ is NH, O, or S.

[0405] In specific embodiments R₁' may include a click-chemistry functional group. Also, the click-chemistry functional group may include one or more selected from an alkyne, an azide, a strained alkyne, a diene, a dienophile, an alkene, a thiol, and a tetrazine. Furthermore, the click-chemistry functional group may be selected from an azide, or a strained alkyne. Further, the click-chemistry functional group may be selected from an azide, or dibenzocyclooctyne-amine. Additionally, the click-chemistry functional group may be selected from a diene, or a dienophile. Further, the click-chemistry functional group may be selected from a tetrazine, or a norbornene.

Ex. 2002, ¶¶394-405

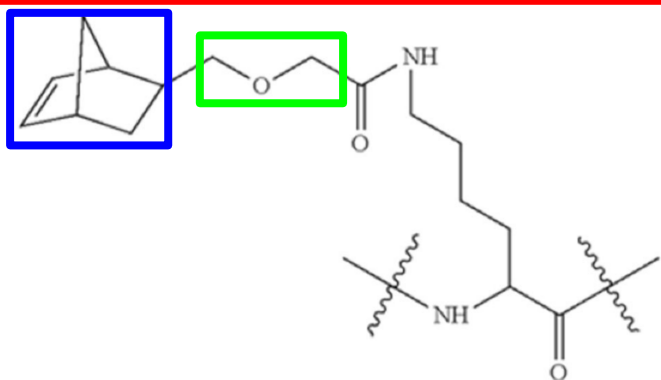
Claim limitation 16[d]

Claim 16. A modified antibody comprising biorthogonal click chemistry functional group, wherein the modified antibody comprises one or more modified heavy chain,

wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence,

wherein the 248 position is determined by an EU numbering system, and

wherein the modified lysine has the following structure:

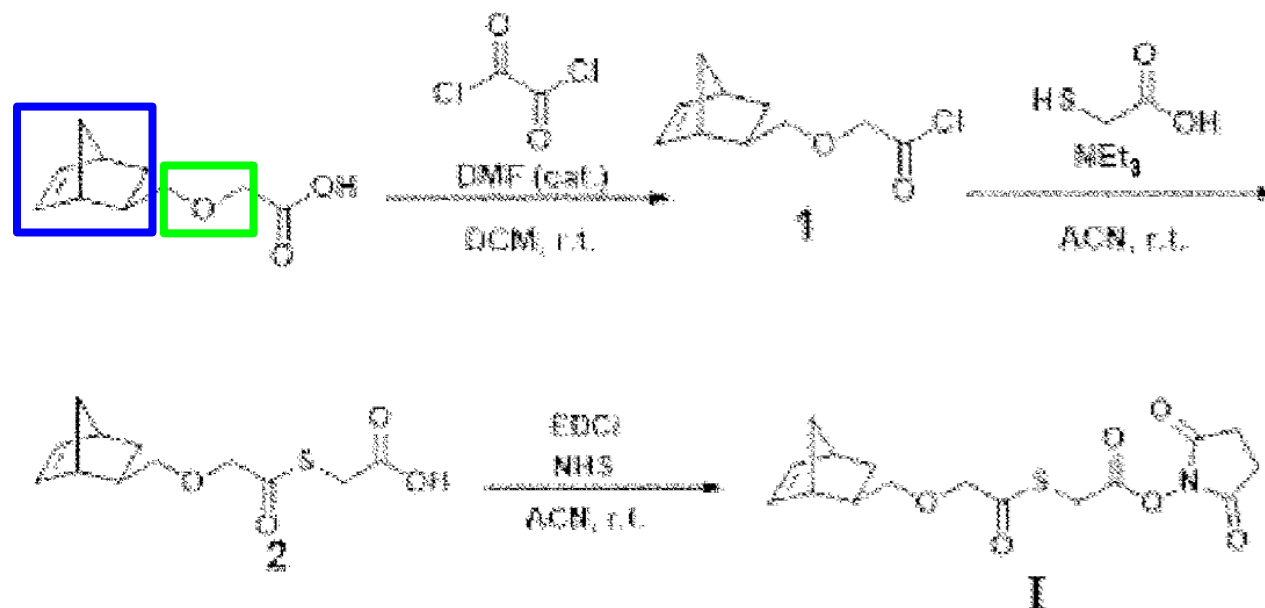


Mot. to Amend. (Paper 23), Appx. A

[0939] 1.1. Synthesis and confirmation of structure of linker (H₁-L₁)

[0940] 1.1.1.: Compound I (SO1 Linker: NHS & Norbornene)

[0941] [Scheme 6]



[0942] Synthesis of Compound I (Scheme 6, FIG. 15)

Ex. 2002, ¶¶939-942

Written Description Support for Proposed Substitute Claims 14 and 15

<u>Claim</u>	<u>'998 Application</u>	<u>'503 Application</u>
Proposed Substitute Claim 14		
14[pre]	[0008]-[0010], [0014]-[0017], [0232]-[0242], [0374]-[0413], [0572]-[0577], [0580], [0581], [0582]-[0587], [0590]-[0591], Figs. 21-22	[0007]-[0009], [0013]-[0016], [0231]-[0241], [0373]-[0412], [0571]-[0576], [0579], [0580], [0581]-[0586], [0589]-[0590], Figs. 21-22
14[a]	[0008], [0010], [0227], [0577], [0580]-[0581], [0585]-[0587], [0590]-[0591]	[0007], [0009], [0226], [0576], [0579]-[0580], [0584]-[0586], [0589]-[0590]
14[b]	[0008]-[0010], [0016], [0227], [0228], [0577], [0578], [0579], [0587], [0588], [0589], [1295]-[1298]	[0007]-[0009], [0015], [0226], [0227], [0576], [0577], [0578], [0586], [0587], [0588], [1294]-[1297]
14[c]	[0225], [0227], [0577], [0582]	[0224], [0226], [0576], [0581]
14[d]	[0013]-[0017], [0232]-[0249], [0395]-[0409], [0447]-[0452], [0575]-[0578], [0588], [0600]-[0606], [0980]-[0982], [1263], [1290]-[1294], [1318]-[1329], [1318]-[1329], Figs. 21-22, 48, 56-57	[0012]-[0016], [0231]-[0248], [0394]-[0408], [0446]-[0451], [0574]-[0577], [0587], [0599]-[0605], [0979]-[0981], [1262], [1289]-[1293], [1317]-[1328], [1317]-[1328], Figs. 21-22, 48, 56-57

Mot. to Amend. (Paper 23), at 10

Proposed Substitute Claim 15		
15[pre]	[0008]-[0010], [0014]-[0017], [0232]-[0242], [0374]-[0413], [0572]-[0577], [0580]-[0587], [0590]-[0591], Figs. 19 and 43	[0007]-[0009], [0013]-[0016], [0231]-[0241], [0373]-[0412], [0571]-[0576], [0579]-[0586], [0589]-[0590], Figs. 19 and 43
15[a]	<i>See Limitation 14[a]</i>	<i>See Limitation 14[a]</i>
15[b]	<i>See Limitation 14[b]</i>	<i>See Limitation 14[b]</i>
15[c]	<i>See Limitation 14[c]</i>	<i>See Limitation 14[c]</i>
15[d]	[0013]-[0017], [0232]-[0249], [0395]-[0409], [0452], [0575]-[0579], [0588]-[0589], [0938]-[0942], [0966]-[0968], [1162], [1254], [1282]-[1285], [1295]-[1298], Figs. 19, 42, 43, and 51-55	[0012]-[0016], [0231]-[0248], [0394]-[0408], [0451], [0574]-[0578], [0587]-[0588], [0937]-[0941], [0965]-[0967], [1253], [1281]-[1284], [1294]-[1297], Figs. 19, 42, 43, and 51-55

Mot. to Amend. (Paper 23), at 10-11

Written Description Support for Proposed Substitute Claim 16

Proposed Substitute Claim 16		
16[pre]	[0008]-[0010], [0014]-[0017], [0232]-[0242], [0374]-[0413], [0572]-[0577], [0580], [0581], [0582]-[0587], [0590]-[0591], Figs. 15 and 17	[0007]-[0009], [0013]-[0016], [0231]-[0241], [0373]-[0412], [0571]-[0576], [0579], [0580], [0581]-[0586], [0589]-[0590], Figs. 15 and 17
16[a]	See Limitation 14[a]	See Limitation 14[a]
16[b]	See Limitation 14[b]	See Limitation 14[b]
16[c]	See Limitation 14[c]	See Limitation 14[c]
16[d]	[0013]-[0017], [0232]-[0249], [0395]-[0409], [0447]-[0452], [0575]-[0579], [0588]-[0589], [0938]-[0942], [0955]-[0957], [1208], [1273]-[1277], [1295]-[1298], Figs. 15, 17, and 40-41	[0012]-[0016], [0231]-[0248], [0394]-[0408], [0446]-[0451], [0574]-[0578], [0587]-[0588], [0937]-[0941], [0954]-[0956], [1207], [1272]-[1276], [1294]-[1297], Figs. 15, 17, and 40-41

Mot. to Amend. (Paper 23), at 11

- Proposed Substitute Claims 14, 15, and 16 Have Written Description Support
- **The Proposed Amended Claims Are Not Anticipated**
- The Claims are Enabled and Not Indefinite
- Proposed Substitute Claims 14, 15, and 16 Are Not Obvious

Written Description Support – Proposed Claims 14, 15, 16

 US011896675B2	
(12) United States Patent Chung et al.	(10) Patent No.: US 11,896,675 B2 (45) Date of Patent: Feb. 13, 2024
(54) SITE-SPECIFIC ANTIBODY CONJUGATION AND ANTIBODY-DRUG CONJUGATE AS SPECIFIC EMBODIMENT THEREOF	FOREIGN PATENT DOCUMENTS
(71) Applicant: AbTis Co., Ltd. , Gyeonggi-do (KR)	CN 107496978 A 12/2017
(72) Inventors: Sang Jeon Chung , Gyeonggi-do (KR); Ju Hwan Kim , Gyeonggi-do (KR); Young Geun Lee , Gyeonggi-do (KR); Tae Jin Lee , Gyeonggi-do (KR); Jin Woo Seo , Gyeonggi-do (KR)	EP 3 299 383 A1 3/2018 EP 3617235 A1 3/2020 KR 10-2018-0002734 A 1/2018 KR 10-2020-0002858 A 1/2020 WO WO-2018-199337 A1 11/2018 WO WO-2020/184944 A1 9/2020
(73) Assignee: AbTis Co., Ltd. , Gyeonggi-do (KR)	OTHER PUBLICATIONS
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	Machine translation WO2018199337 (Aug. 4, 2023, pp. 1-378)* Van Gool, R. et al., Chemosynthetic Conjugation of Toxic Payloads to the Globally Conserved NGlycan of Native mAbs Provides Homogeneous and Highly Efficacious AntibodyDrug Conjugates, Bioconjugate Chemistry, 2015, 26, pp. 2233-2242. International Search Report from corresponding PCT Application No. PCT/KR2020/003282, dated Jun. 16, 2020. Written Opinion from corresponding PCT Application No. PCT/KR2020/003282, dated Jun. 16, 2020. Extended European Search Report from corresponding European Patent Application No. 20770235.8, dated Oct. 10, 2022. Kurosaki Hiromasa et al., "Irreversible Inhibition of Metallo-[beta]-lactamase (IMP-1) by 3-(30Mercaptopropionylsulfanyl)propionic Acid Pentadecylphenyl Ester", Angewandte Chemie International Edition, vol. 44, No. 25, Jun. 10, 2005, pp. 3861-3864. Office Action from corresponding Japanese Patent Application No. 2021-553121, dated Oct. 21, 2022. Yamaguchi, Y., et al., "Structure-Function Analysis and Development of Inhibitors of Metallo-β-lactamases Conferring Drug Resistance in Bacteria", Yakugaku Zasshi, vol. 135, No. 11, 2015, pp. 1299-1305. Office Action from corresponding Australian Patent Application No. 2020234994 dated Sep. 26, 2023. Tamura, T., et al., "Rapid labelling and covalent inhibition of intracellular native proteins using ligand-directed N-acetyl-N-alkyl sulfonamide", Nature Communications, 2018, 9, 1870, pp. 1-12. Notice of Allowance from corresponding Korean Application No. 10-2020-0029224, dated Jul. 25, 2023.
(21) Appl. No.: 18/154,998	
(22) Filed: Jan. 16, 2023	
(65) Prior Publication Data US 2023/0248842 A1 Aug. 10, 2023	
Related U.S. Application Data	
(63) Continuation of application No. 16/980,503, filed on Sep. 14, 2020.	
(60) Provisional application No. 62/815,557, filed on Mar. 8, 2019.	
(51) INT. CL. A61P 35/00 (2006.01) C07D 207/46 (2006.01) C07K 16/32 (2006.01) A61K 47/68 (2017.01)	
(52) U.S. CL. CPC A61K 47/6803 (2017.08); A61K 47/6855 (2017.08); A61K 47/6889 (2017.08); A61P 35/00 (2018.01); C07D 207/46 (2013.01); C07K 16/32 (2013.01)	
(58) Field of Classification Search CPC A61K 47/6803; A61K 47/6855; A61K 47/6889; A61P 35/00; C07D 207/46; C07K 16/32 USPC 424/133.1 See application file for complete search history.	
(56) References Cited U.S. PATENT DOCUMENTS 2012/0172575 A1 7/2012 Boons et al. 2018/0141976 A1 5/2018 Ito 2020/0190165 A1 6/2020 Yamada et al. 2021/0139541 A1 5/2021 Matsuda et al.	
	(57) ABSTRACT The present invention relates to technology capable of labeling a certain site of an antibody with a certain number of chemical functional groups or cargo moieties. The present invention may provide an antibody product having high uniformity. The present invention may provide an antibody product whose antibody functions are not degraded. That is, the present invention may provide an antibody product whose antibody binding affinity and half-life are not degraded. The present invention is of great significance as being the first technology allowing site-specific labeling of an antibody without any complicated processes. 13 Claims, 73 Drawing Sheets Specification includes a Sequence Listing.

Ex. 1001, Cover

(21) Appl. No.: **18/154,998**

(22) Filed: **Jan. 16, 2023**

(65) **Prior Publication Data**

US 2023/0248842 A1 Aug. 10, 2023

Related U.S. Application Data

(63) Continuation of application No. 16/980,503, filed on Sep. 14, 2020.

(60) Provisional application No. 62/815,557, filed on Mar. 8, 2019.

Ex. 1001, Cover

A motion to amend may not introduce new subject matter. 35 U.S.C. § 316(d)(3); 37 C.F.R. § 42.121(a)(2)(ii). Patent Owner contends proposed substitute claims 14–16 do not introduce new subject matter because each claim is supported by the specification for Application No. 18/154,998 (the “’998 application,” Ex. 2002), which issued as the ’675 patent, as well as Application No. 16/980,503 (the “’503 application,” Ex. 2003) of which the ’675 patent is a continuation. Mot. 8–11. For support, Patent Owner provides a table containing string citations to the ’998 and ’503 applications for each claim limitation. *Id.* at 10–11. We note that the specification of the ’998 application is identical to the specification of the ’503 application.

Prelim. Guidance (Paper 27), 5

'959 Publication is Not Prior Art

The '959 publication:

- has the **same priority date** as the '675 Patent
 - The '959 publication and the '675 Patent claim priority to the same provisional application
- has the **same inventors** as the '675 Patent
- was **published after** the '675 Patent's parent application

	Innovation, Sciences et Développement économique Canada Office de la Propriété Intellectuelle du Canada	Innovation, Science and Economic Development Canada Canadian Intellectual Property Office	CA 3132959 A1 2020/09/17 (21) 3 132 959
(12) DEMANDE DE BREVET CANADIEN CANADIAN PATENT APPLICATION (13) A1			
(86) Date de dépôt PCT/PCT Filing Date: 2020/03/09		(51) Cl.Int./Int.Cl. C07D 207/46 (2006.01), A61K 39/00 (2006.01), A61K 47/65 (2017.01), A61K 47/68 (2017.01), A61P 35/00 (2006.01), C07K 16/28 (2006.01), C07K 7/08 (2006.01)	
(87) Date publication PCT/PCT Publication Date: 2020/09/17		(71) Demandeurs/Applicants: ABTIS CO., LTD., KR; RESEARCH & BUSINESS FOUNDATION SUNGKYUNKWAN UNIVERSITY, KR	
(85) Entrée phase nationale/National Entry: 2021/09/08		(72) Inventeurs/Inventors: CHUNG, SANG JEON, KR; KIM, JU HWAN, KR; LEE, YOUNG GEUN, KR; LEE, TAE JIN, KR; ...	
(86) N° demande PCT/PCT Application No.: KR 2020/003282			
(87) N° publication PCT/PCT Publication No.: 2020/184944			
(30) Priorité/Priority: 2019/03/08 (US62/815,557)			
		* * *	
		(72) Inventeurs(suite)/Inventors(continued) SEO, JIN WOO, KR	

Ex. 1005, at Cover

(12) United States Patent Chung et al.	(10) Patent No.: US 11,896,675 B2 (45) Date of Patent: Feb. 13, 2024
(54) SITE-SPECIFIC ANTIBODY CONJUGATION AND ANTIBODY-DRUG CONJUGATE AS SPECIFIC EMBODIMENT THEREOF	FOREIGN PATENT DOCUMENTS
(71) Applicant: AbTis Co., Ltd., Gyeonggi-do (KR)	CN 107496978 A 12/2017 EP 3 299 383 A1 3/2018 EP 3617235 A1 3/2020 KR 10-2018-0002734 A 1/2018 KR 10-2020-0002858 A 1/2020 WO WO-2018-199337 A1 11/2018 WO WO-2020/184944 A1 9/2020
(72) Inventors: Sang Jeon Chung, Gyeonggi-do (KR); Ju Hwan Kim, Gyeonggi-do (KR); Young Geun Lee, Gyeonggi-do (KR); Tae Jin Lee, Gyeonggi-do (KR); Jin Woo Seo, Gyeonggi-do (KR)	OTHER PUBLICATIONS
(73) Assignee: AbTis Co., Ltd., Gyeonggi-do (KR)	Machine translation WO2018199337 (Aug. 4, 2023, pp. 1-378).*
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.	Van Geel, R. et al.; Chemoenzymatic Conjugation of Toxic Payloads to the Globally Conserved NGlycan of Native mAbs Provides Homogeneous and Highly Efficacious AntibodyDrug Conjugates, Bioconjugate Chemistry, 2015, 26, pp. 2233-2242.
(21) Appl. No.: 18/154,998	International Search Report from corresponding PCT Application No. PCT/KR2020/003282, dated Jun. 16, 2020.
(22) Filed: Jan. 16, 2023	Written Opinion from corresponding PCT Application No. PCT/KR2020/003282, dated Jun. 16, 2020.
(65) Prior Publication Data US 2023/0248842 A1 Aug. 10, 2023	Extended European Search Report from corresponding European Patent Application No. 20770235.8, dated Oct. 10, 2022.
Related U.S. Application Data	Kurosaki Hiromasa et al: "Irreversible Inhibition of Metallo-[beta]-lactamase (IMP-1) by 3-(30-Mercaptopropionylsulfanyl)propionic Acid Pentafluorophenyl Ester", Angewandte Chemie International Edition, vol. 44, No. 25, Jun. 10, 2005, pp. 3861-3864.
(63) Continuation of application No. 16/980,503, filed on Sep. 14, 2020.	Office Action from corresponding Japanese Patent Application No. 2021-553121, dated Oct. 21, 2022.
(60) Provisional application No. 62/815,557, filed on Mar. 8, 2019.	Yamaguchi, Y., et al.; "Structure-Function Analysis and Development of Inhibitors of Metallo-β-lactamases Conferring Drug Resistance in Bacteria", Yakugaku Zasshi, vol. 135, No. 11, 2015, pp. 1299-1305.
	Office Action from corresponding Australian Patent Application No. 2020234394 dated Sep. 26, 2023.
	Tamura, T., et al.; "Rapid labelling and covalent inhibition of intracellular native proteins using ligand-directed N-acyl-N-alkyl

Ex. 1001, at Cover

- Proposed Substitute Claims 14, 15, and 16 Have Written Description Support
- The Proposed Amended Claims Are Not Anticipated
- **The Claims are Enabled and Not Indefinite**
- Proposed Substitute Claims 14, 15, and 16 Are Not Obvious

The Claims Are Not Indefinite

- “[T]he preambles of the proposed substitute claims 14-16 each recite
 - ‘[a] modified antibody comprising a bioorthogonal click chemistry functional group,’ and
- the remaining limitations of the claims provide
 - the location and the structure of the claimed bioorthogonal click chemistry functional groups by reciting modified heavy chains and modified lysine residues described in the specification.”

Paper 27, at 3-4

The Proposed Substitute Claims Are Enabled

- Petitioner provides no expert evidence questioning enablement of the claimed compounds
 - One or more Heavy Chain: Dr. Tumey states a POSA knew “modification reactions such as those described in EX2002, paras. [1272]-[1329] could produce a trastuzumab molecule with one modified heavy chain, two modified heavy chains, or zero modified heavy chains.”
 - Dr. Zhou points out that a POSA would understand “DAR1”
 - “Antibody”: Petitioner questions enablement for antibodies with three or more heavy chains
 - The claims specify Lys 248 and a POSA would understand that
 - A POSA would understand the described synthetic routes

*Paper 27, at 9;
Tumey 2d Decl. ¶ 19;
Zhou 2d Decl. ¶ 47*

- Proposed Substitute Claims 14, 15, and 16 Have Written Description Support
- The Proposed Amended Claims Are Not Anticipated
- The Claims are Enabled and Not Indefinite
- **Proposed Substitute Claims 14, 15, and 16 Are Not Unpatentable for Obviousness**

Petitioner's Grounds 3, 5, and 7 References – Proposed Substitute Claims 14-16

Ground 3: PepTalk Poster, Yamada, Matsuda

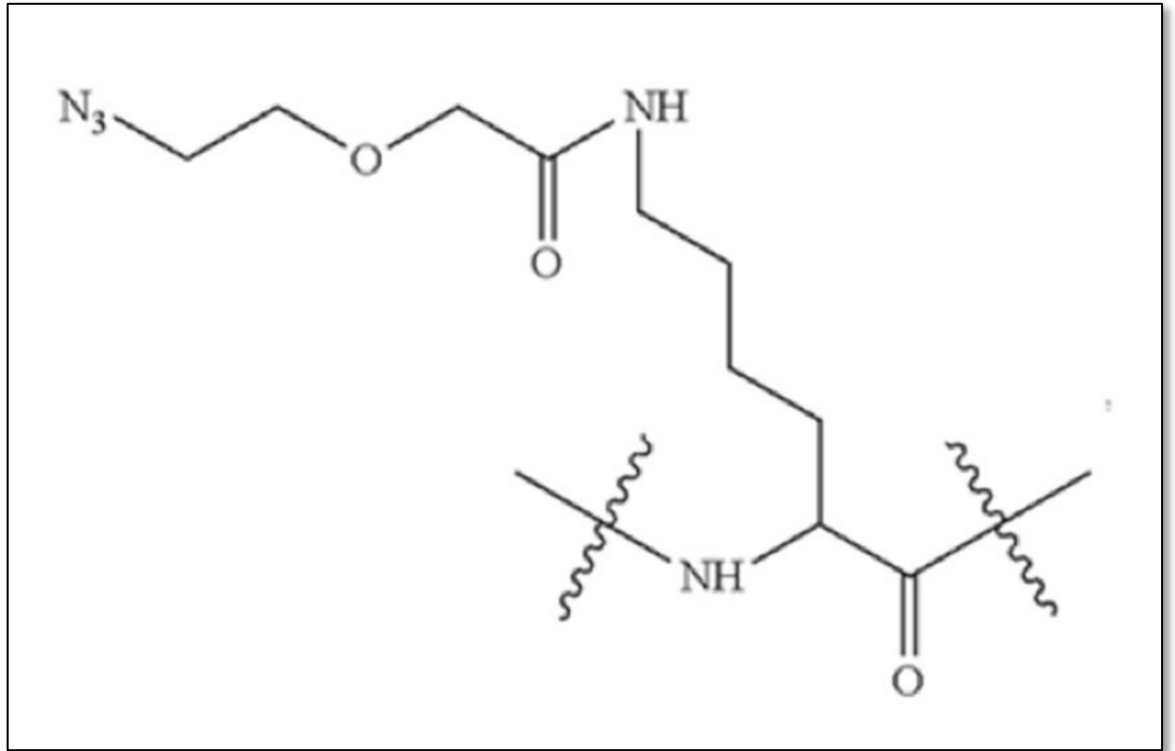
Ground 5: PepTalk Presentation, Yamada, Matsuda

Ground 7: Yamada, Matsuda

Paper 2, at 2-3

Proposed Substitute Claim 14

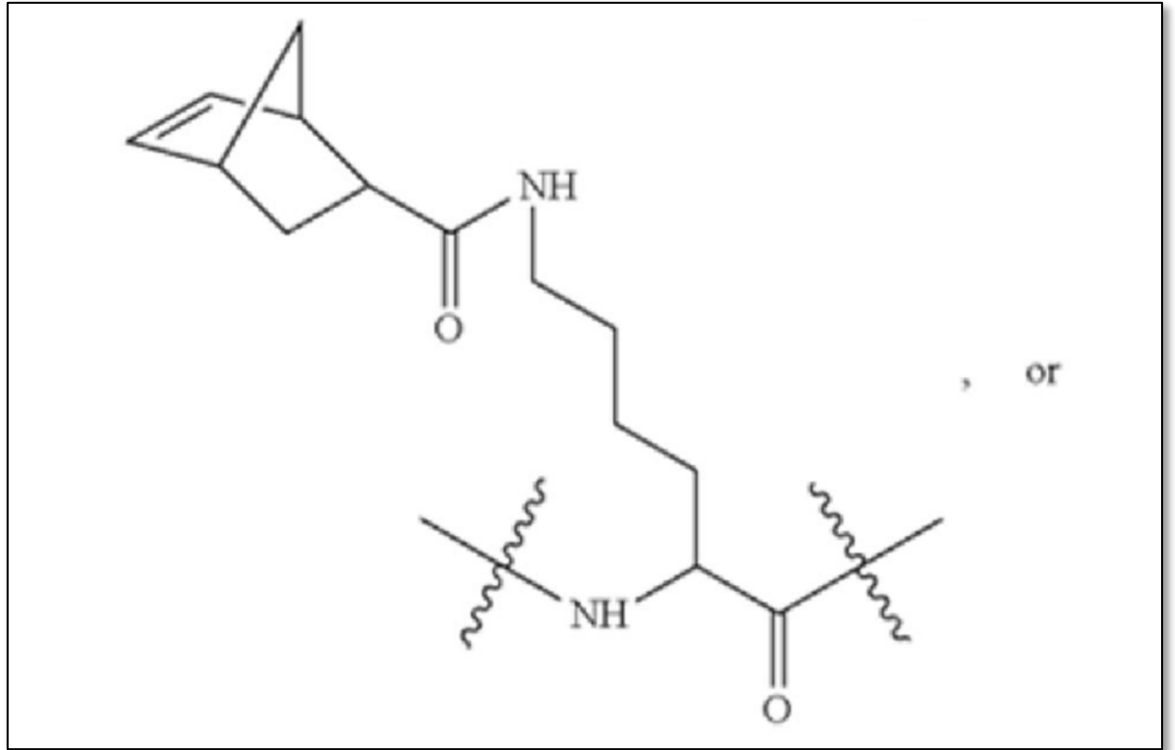
Claim 14. A modified antibody comprising biorthogonal click chemistry functional group, wherein the modified antibody comprises one or more modified heavy chain, wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and wherein the modified lysine has the following structure:



Mot. to Amend. (Paper 23), Appx. A

Proposed Substitute Claim 15

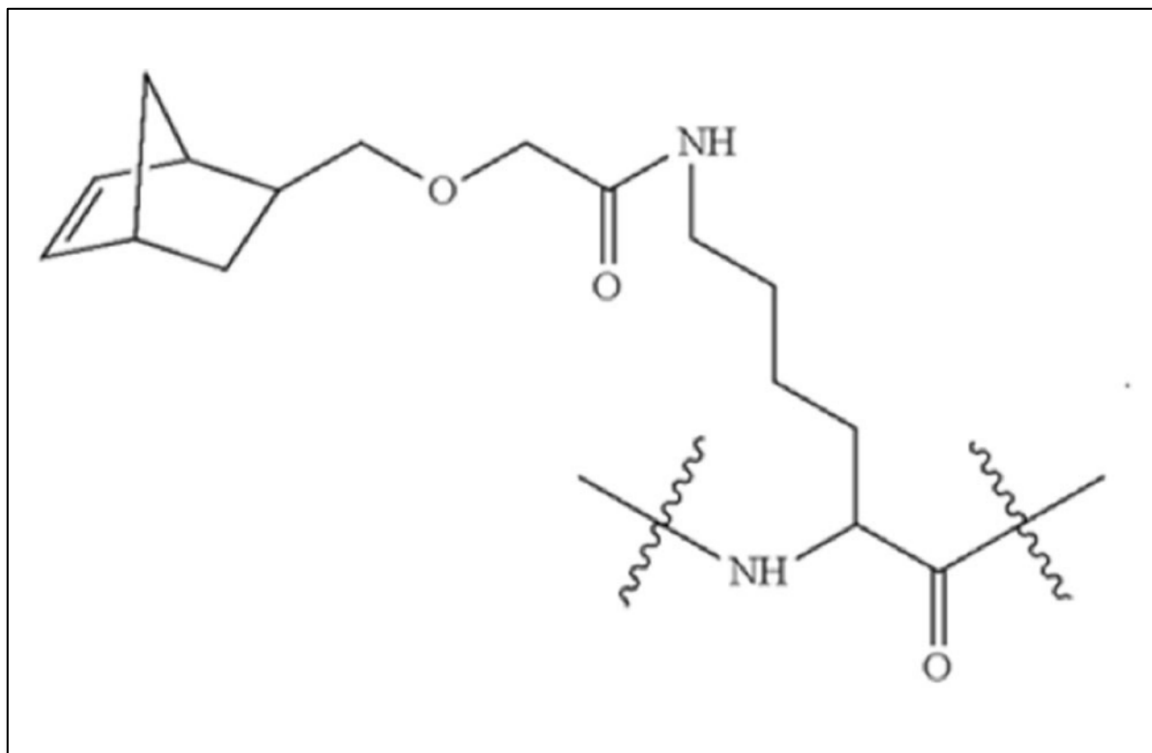
Claim 15. A modified antibody comprising biorthogonal click chemistry functional group, wherein the modified antibody comprises one or more modified heavy chain, wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and wherein the modified lysine has the following structure:



Mot. to Amend. (Paper 23), Appx. A

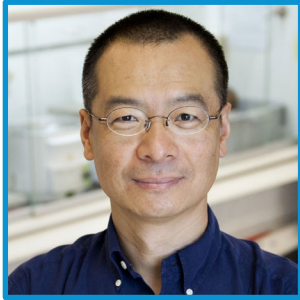
Proposed Substitute Claim 16

Claim 16. A modified antibody comprising biorthogonal click chemistry functional group, wherein the modified antibody comprises one or more modified heavy chain, wherein each of the modified heavy chains comprises a modified lysine residue at 248 position of heavy chain amino acid sequence, wherein the 248 position is determined by an EU numbering system, and wherein the modified lysine has the following structure:



Mot. to Amend. (Paper 23), Appx. A

No Dispute Over Level of Ordinary Skill



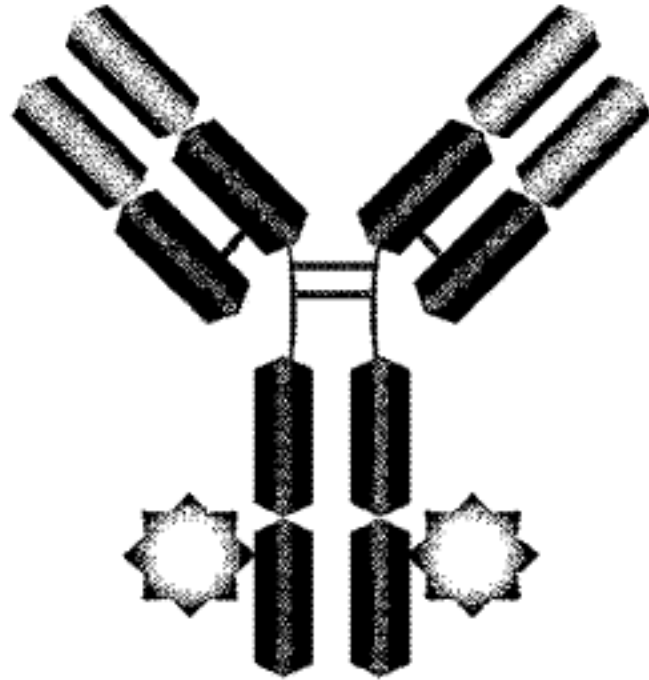
Sunny Zhou, Ph.D.
AbTis's Expert

Nathan Tumey, Ph.D.
Ajinomoto's Expert

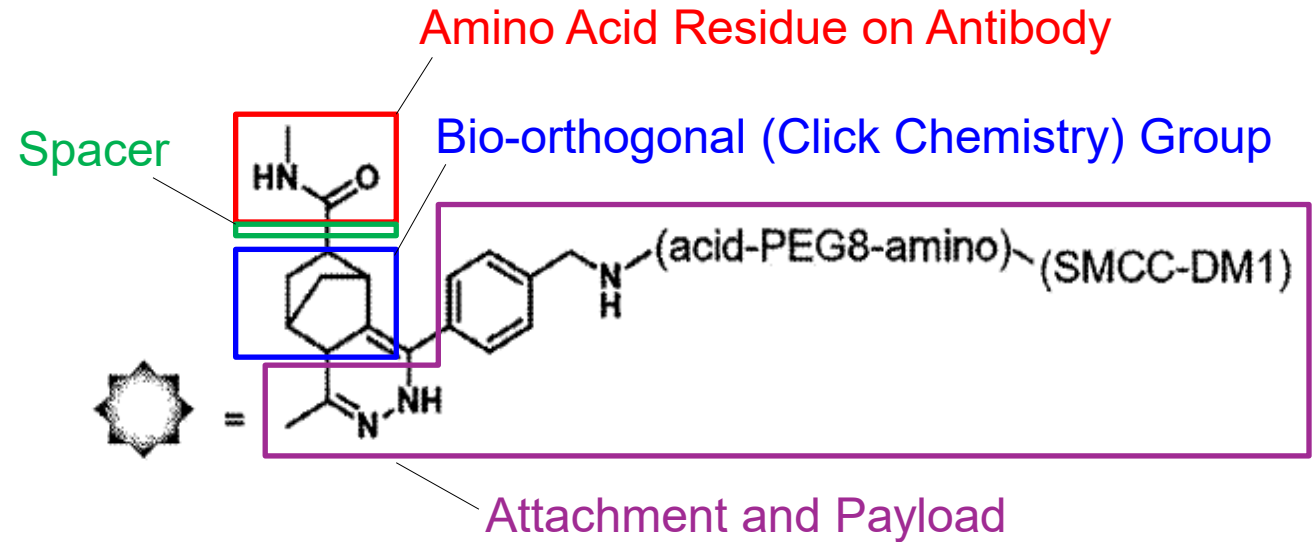


- A POSA in the field of the '675 Patent during the 2019–2023 timeframe would have had specialized knowledge in the field of antibody drug conjugates, which would entail
- (1) a Ph.D. degree in organic chemistry, biochemistry, medicinal chemistry, and/or pharmacology, along with at least 1-2 years of relevant applied research and/or industry experience in the field of antibodies or antibody-drug conjugates, or,
- Or, alternatively, (2) a Master's or Bachelor's degree in one of the aforementioned fields with at least 3-5 years, or 5-7 years, respectively, of relevant applied research and/or industry experience in the field of antibodies or antibody-drug conjugates.
- That person would have familiarity, gained through study, training, and/or experience, with the design and development of antibody-drug conjugates and antibody modifications. People of ordinary skill in the fields of antibodies and ADCs—both academics and industry professionals—routinely attend scientific conferences to share ideas and learn about new developments in the field.

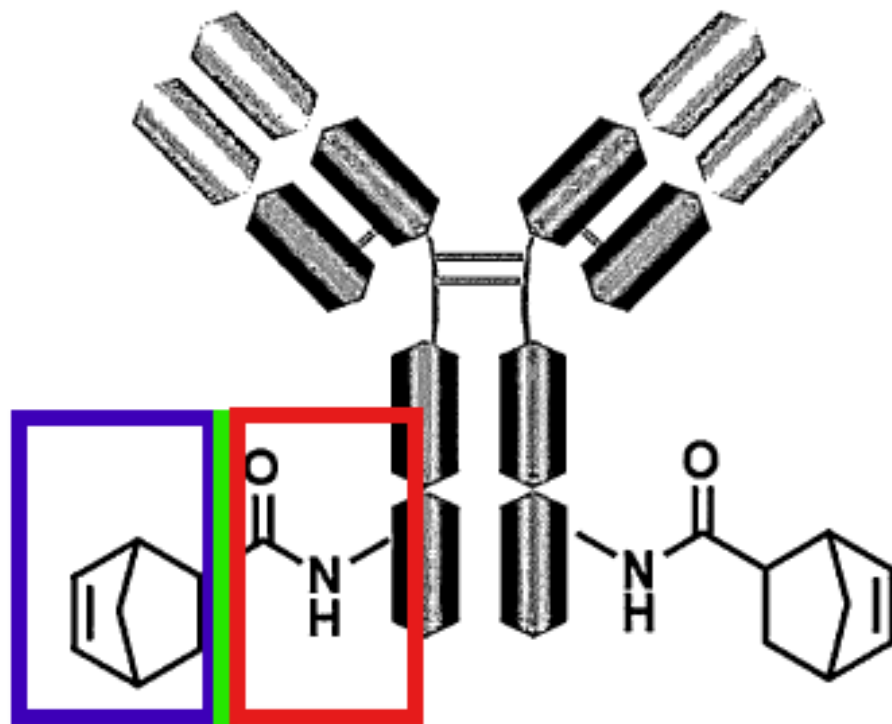
The Technology at Issue – Antibody-Drug Conjugates



'675 Patent, Ex. 1001 at Fig. 59.



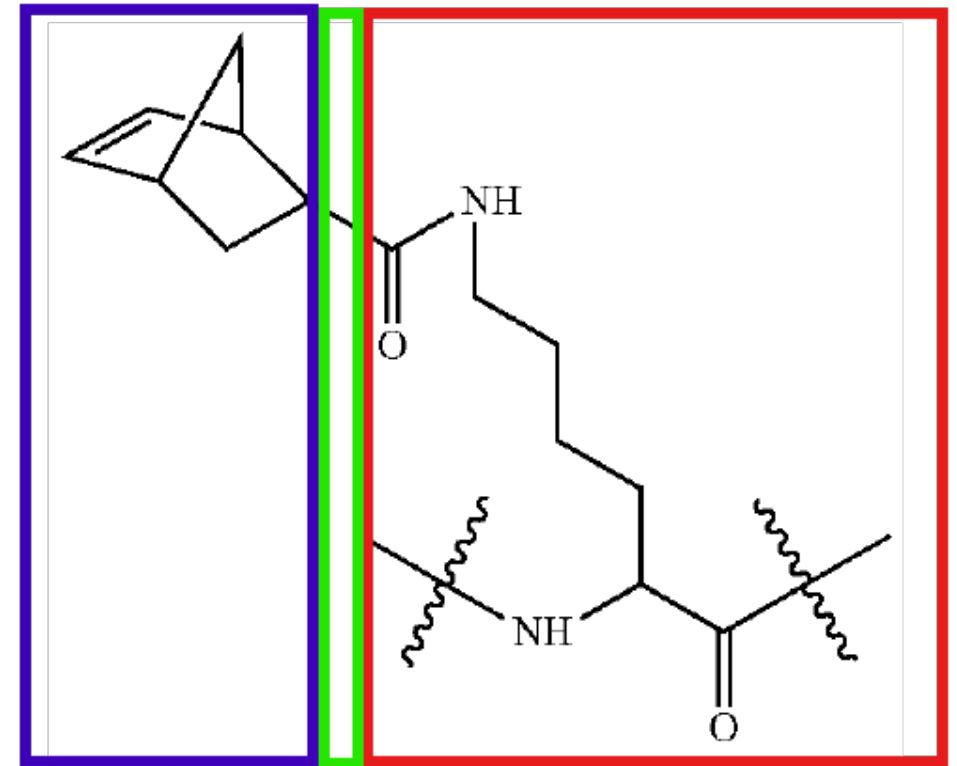
The Technology at Issue – Claimed Moieties



Bio-orthogonal (Click Chemistry) Group

Spacer

Amino Acid Residue on Antibody



IPR2025-0283
U.S. Patent No. 11,896,675

TRANSLATOR'S DECLARATION

I, Jon Johanning, certify that I am familiar with both the Japanese and the English languages, that I have reviewed the U.S. national stage publication, US 2020/0190165 (Exhibit 1009) and the WIPO publication, WO 2018/199337 (Exhibit 1008), and that US 2020/0190165 (Exhibit 1009) is a true, faithful, and accurate translation of the corresponding Japanese language WIPO publication, WO 2018/199337 (Exhibit 1008), with the following exceptions:

- Paragraph [0001], CROSS REFERENCES TO RELATED APPLICATIONS, was added to US 2020/0190165 (Exhibit 1009) and not present in WO 2018/199337 (Exhibit 1008).
- The paragraph numbering is different between US 2020/0190165 (Exhibit 1009) and WO 2018/199337 (Exhibit 1008).
- The claims (pages 397 to 446 of Exhibit 1008 and pages 185 to 186 of Exhibit 1009) are different.
- The sequence listing is incorporated into US 2021/0139541 (Exhibit 1011), and not present in WO 2019/240288 (Exhibit 1010). (It has been filed as a separate document.)
- Formulas have additional formula numbers in WO 2019/240288 (Exhibit 1010) in conformity with Japan Patent Office practice.

Aside from the foregoing exceptions, US 2020/0190165 (Exhibit 1009) is a true, faithful, and accurate translation of the corresponding Japanese language WIPO publication, WO 2018/199337 (Exhibit 1008)

I further declare that all statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

Exhibit 1009
AJINOMOTO CO., INC.
IPR2025-00283
Page 1 of 262

(54) COMPOUND HAVING AFFINITY SUBSTANCE TO SOLUBLE PROTEIN, CLEAVABLE PORTION AND REACTIVE GROUP, OR SALT THEREOF

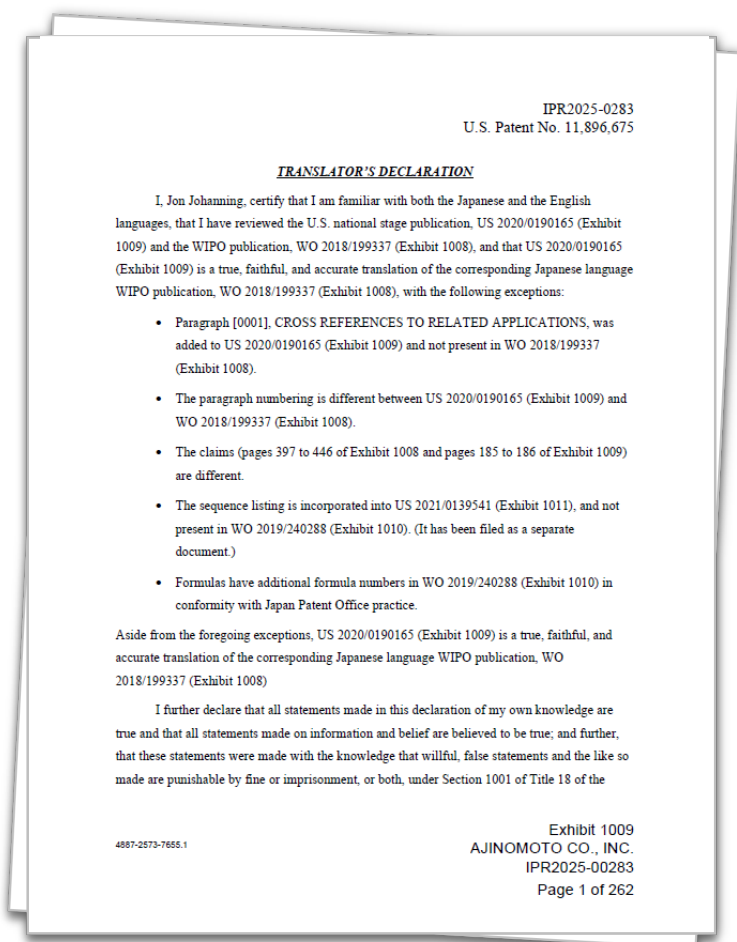
(71) Applicant: **Ajinomoto Co., Inc.**, Tokyo (JP)

(72) Inventors: **Kei Yamada**, Kawasaki-shi (JP);
Yutaka Matsuda, Kawasaki-shi (JP);
Tomohiro Fujii, Kawasaki-shi (JP);
Natsuki Shikida, Kawasaki-shi (JP);
Reiko Yuji, Kawasaki-shi (JP);
Kazutaka Shimbo, Kawasaki-shi (JP);
Yuji Ito, Kagoshima-shi (JP)

Yamada, Ex. 1009 at 3 of 262.

Yamada Discloses Billions of Potential Compounds

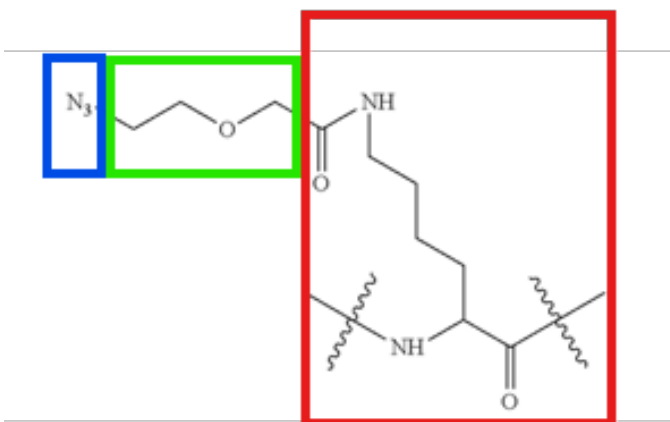
- *Yamada* does not identify the specific claimed compounds
- Petitioner asserts Formula IV ($L_1-B-R'-T$) discloses the claimed compounds
 - Formula (IV) is ($L_1-B-R'-T$)
 - L_1 provides **over 13 billion** potential compounds
 - B, R', and T can increase the number
- Dr. Tumey does not dispute the numbers
- *Yamada* does not teach toward the claimed compounds



Yamada, Ex. 1009 at 3 of 262; Tumey Dep. Tr., Ex. 2006 at 124:19-140:11

Yamada Does Not Disclose Claim 14

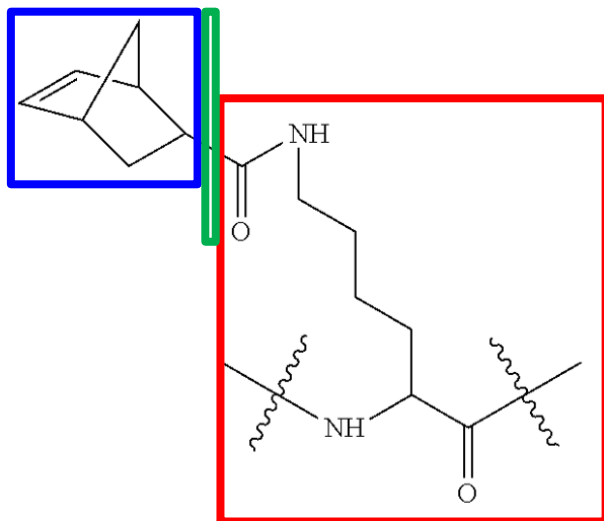
Claim 14



- *Yamada* does not specifically disclose an ether **spacer**
- *Yamada* discloses **Lys 248** among several alternatives
 - Other Lysine sites
 - Tyrosine sites
 - Tryptophan sites
- *Yamada* discloses an azide **bioorthogonal group** among **many** alternatives
 - 21 biorthogonal groups with some variation
 - A generic formula for other biorthogonal groups
- *Yamada* does not disclose a method of making the claimed compounds

Yamada Does Not Disclose Claim 15

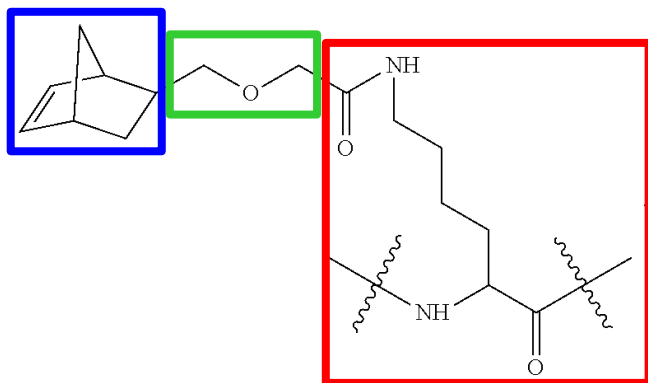
Claim 15



- *Yamada* does not specifically disclose no **spacer**
- *Yamada* discloses **Lys 248** among several alternatives
 - Other Lysine sites
 - Tyrosine sites
 - Tryptophan sites
- *Yamada* discloses a norbornene **bioorthogonal group** among **many** alternatives
 - 21 biorthogonal groups with some variation
 - A generic formula for other biorthogonal groups
- *Yamada* does not disclose a method of making the claimed compounds

Yamada Does Not Disclose Claim 16

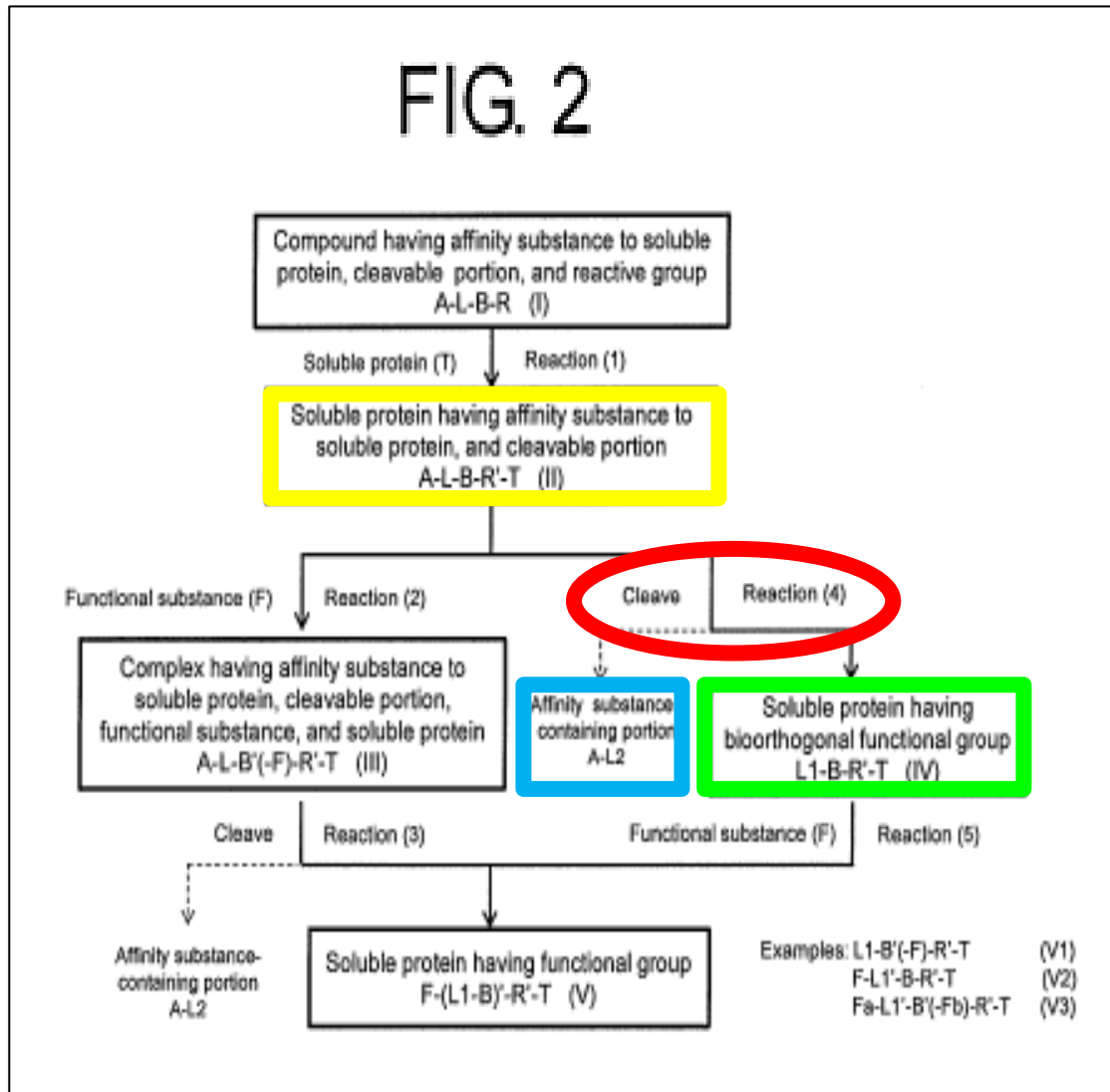
Claim 16



- *Yamada* does not specifically disclose an ether **spacer**
- *Yamada* discloses **Lys 248** among several alternatives
 - Other Lysine sites
 - Tyrosine sites
 - Tryptophan sites
- *Yamada* discloses a norbornene **bioorthogonal group** among **many** alternatives
 - 21 biorthogonal groups with some variation
 - A generic formula for other biorthogonal groups
- *Yamada* does not disclose a method of making the claimed compounds

Yamada Does Not Disclose The Claimed Compounds

FIG. 2



- Yamada only discloses compounds as products of a reaction scheme
 - That scheme requires cleaving L to form L_1 and L_2
 - Each example compound has a cleaved group
- Petitioner admits *Yamada's* scheme cannot make the claimed compounds
 - The claimed compounds do not include substituents that could be an L_1 resulting from cleaving an L
- Yamada, read as a coherent whole, cannot disclose the claimed compounds to a POSA

Yamada, Ex. 1009 ¶¶[582]-[639], [1465], [1470], [1472], and [1480]

Dr. Tumey Admits *Yamada* Provides No Synthesis for the Claims



*“Although **Yamada’s synthesis scheme in Figure 2 could not be used to prepare the structures now recited in proposed substitute claims 14-16**, a person of ordinary skill in the art would have understood that Figure 2 of Yamada was not the only possible approach for preparing a modified lysine.”*

Tumey 2d Decl., Ex. 1059 ¶¶ 56

Dr. Tumey Uses Hindsight To Fill The Gaps In *Yamada*



*“Clearly Dr. Zhou’s pronouncement that construction of the claimed structures is ‘scientifically infeasible’ is incorrect **because AbTis has apparently prepared a modified version of trastuzumab with each of the claimed structures.**”*

“Therefore, the synthesis itself is not ‘scientifically infeasible,’ nor would a person of ordinary skill have viewed it as such prior to the earliest claimed priority date of the ‘675 Patent.”

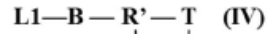
Tumey 2d Decl., Ex. 1059 ¶¶ 55.

Petitioner Begins With The Compounds of Claims 14 and 16

Claims 14 and 16

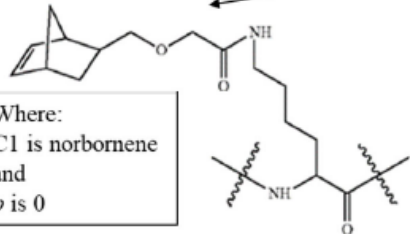
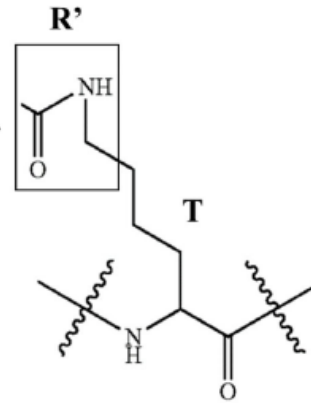
Option 1:

C1: Bio-orthogonal click chemistry group
(e.g., azide, alkene, norbornene, etc.)
See EX1009, [0616]-[0618], [0627]

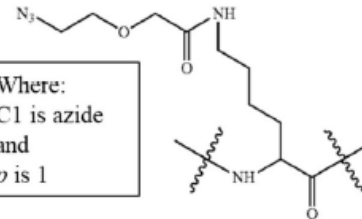


p is 0 or 1
 X is Carbon (C)
 q is 0
 R_{1a} and R_{1b} are H
Black circle is bond to **B**
See EX1009, [0619]-[0624]

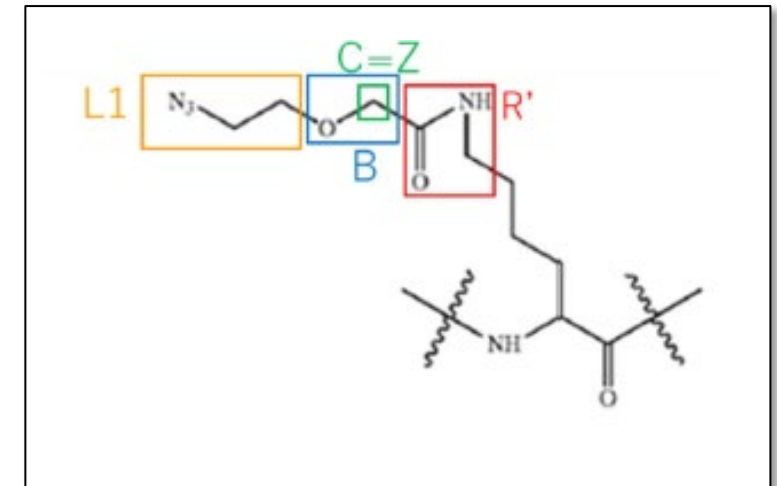
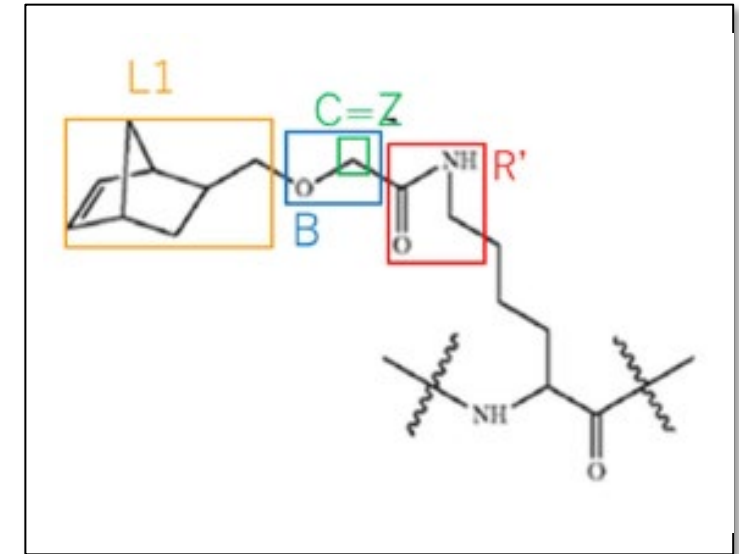
Z is H, (i.e., $-\text{CH}_2-$)
 Y is Oxygen (O)
White circle is bond to **L1**
Black circle is bond to **R'**
See EX1009, [0631]-[0639]



Where:
C1 is norbornene
and
 p is 0



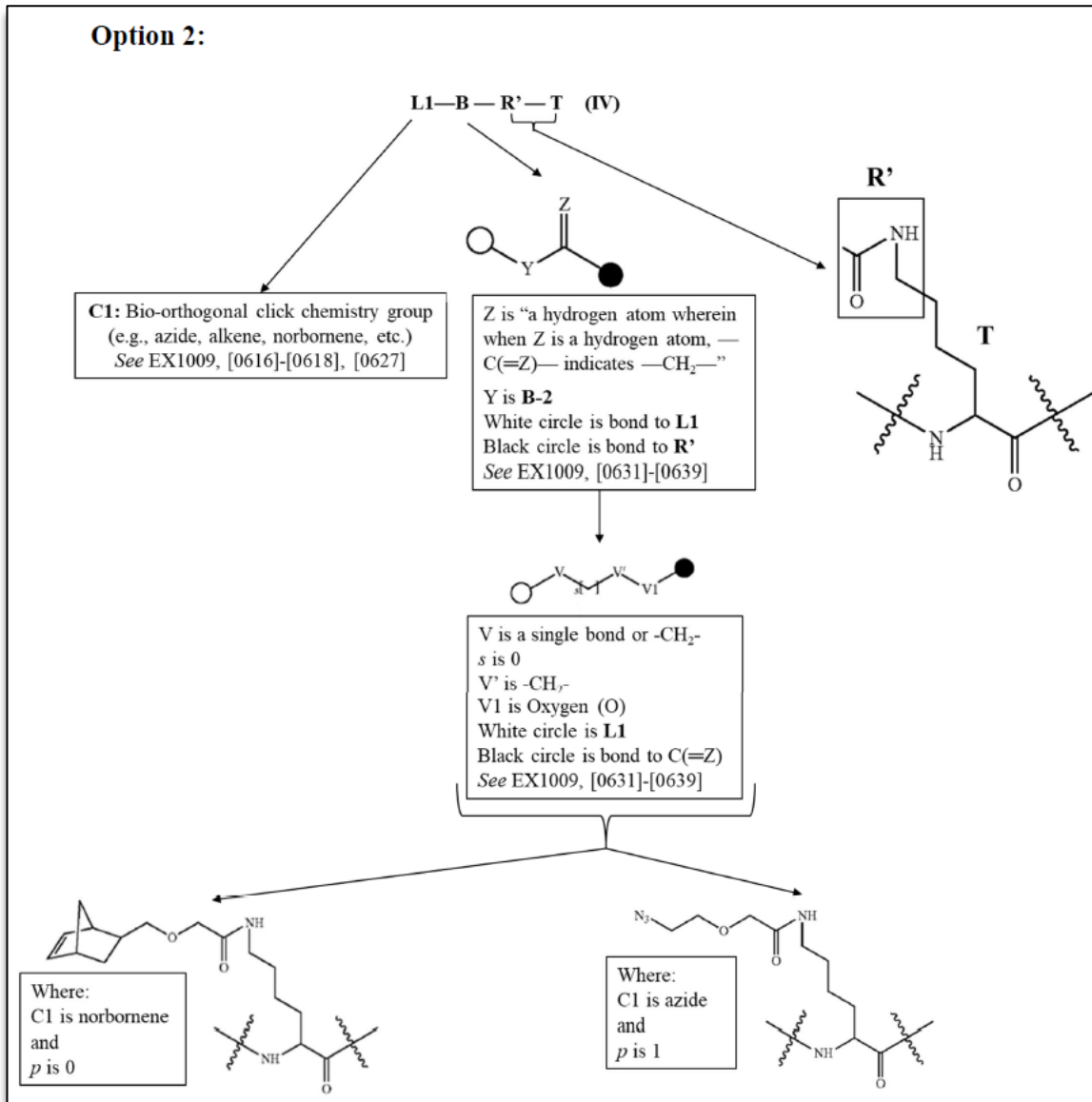
Where:
C1 is azide
and
 p is 1



Tumey Decl. Ex. 1002 ¶ 276.

Petitioner Begins With The Compounds of Claims 14 and 16

Claims 14 and 16



Gaps Between *Yamada* and the Claims

- No reason to select **Lys 248**
- No reason to select $-C-O-C-$ ether **spacer**
- No reason to select $-C-C-O-C-$ ether **spacer**
- No reason to select norbornene **bio-orthogonal group**
- No reason to select azide **bio-orthogonal group**
- No operative synthetic scheme
- Billions of potential compounds

Tumey Decl. Ex. 1002 ¶ 276.

Occam's Razor Can't Cut It

Claim 15

- Petitioner does not cite any prior art disclosing no **spacer** (i.e. a single bond as a spacer).
- Given the lack of available art, Dr. Tumey relied on “Occam’s Razor”
- *“As discussed during my deposition, there is an implicit motivation to keep molecules simple, a la **Occam’s razor**. EX2006, 152:8-22. As a result, a person of ordinary skill preparing a modified lysine with a norbornene as the terminal bioorthogonal click chemistry group **would logically start by preparing the simplest structure, which is the structure recited in proposed substitute claim 15**. This structure, which lacks a spacer/linker, would serve as the standard of comparison (i.e., control) to determine the functional impact of adding a spacer/linker. In other words, there is always a logical and implicit need to begin one’s development with the simplest modification and then iterate and develop from there.”*
- The lack of art and reliance on claim 15 itself shows Ajinomoto’s obviousness position is based on impermissible hindsight.

*Tumey 2d Decl. Ex. 1059 ¶ 41;
Zhou 2d Decl., Ex. 2012 ¶ 35.*

Matsuda Teaches Away from Ether Spacer

IPR2025-0283
U.S. Patent No. 11,896,675

TRANSLATOR'S DECLARATION

I, Frank McGee, certify that I am familiar with both the Japanese and the English languages, that I have reviewed the U.S. national stage publication, US 2021/0139541 (Exhibit 1011) and the WIPO publication, WO 2019/240288 (Exhibit 1010), and that US 2021/0139541 (Exhibit 1011) is a true, faithful, and accurate translation of the corresponding Japanese language WIPO publication, WO 2019/240288 (Exhibit 1010), with the following exceptions:

- Paragraph [0001], CROSS REFERENCES TO RELATED APPLICATIONS, was added to US 2021/0139541 (Exhibit 1011) and not present in WO 2019/240288 (Exhibit 1010).
- The paragraph numbering is different between US 2021/0139541 (Exhibit 1011) and WO 2019/240288 (Exhibit 1010).
- The sequence listing is incorporated into US 2021/0139541 (Exhibit 1011), and not present in WO 2019/240288 (Exhibit 1010). (It has been filed as a separate document.)
- Formulas have additional formula numbers in WO 2019/240288 (Exhibit 1010) in conformity with Japan Patent Office practice.
- There are 21 claims in US 2021/0139541 (Exhibit 1011), and 37 claims in WO 2019/240288 (Exhibit 1010).
- There is an additional cited document in paragraph 0003 of US 2021/0139541 (Exhibit 1011).

Aside from the foregoing exceptions, US 2021/0139541 (Exhibit 1011) is a true, faithful, and accurate translation of the corresponding Japanese language WIPO publication, WO 2019/240288 (Exhibit 1010).

I further declare that all statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true; and further,

4887-2573-7655.1

Exhibit 1011
AJINOMOTO CO., INC.
IPR2025-00283
Page 1 of 216

(71) Applicant **Ajinomoto Co., Inc.**, Tokyo (JP)

(72) Inventors: **Yutaka MATSUDA**, Kawasaki-shi (JP);
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Kei YAMADA, Kawasaki-shi (JP);
Natsuki SHIKIDA, Kawasaki-shi (JP);
Kazutaka SHIMBO, Kawasaki-shi (JP);
Tomohiro FUJII, Kawasaki-shi (JP);
Shigeo HIRASAWA, Kawasaki-shi (JP)

Matsuda, Ex. 1011 at 3 of 216.

Matsuda Teaches Away From Ether Spacer

Claims 14 and 16

- Matsuda discloses beta (β)-heteroatom **spacer** substituents
 - e.g., compounds 26 (ether) and 60 (alkyl amino)
- Matsuda groups these compounds together in its Comparative Example 1
- Matsuda concludes that the antibody modification reactions “had not progressed” for each compound with a beta (β)-heteroatom
 - Despite extended incubation
- A POSA would understand *Matsuda* to expressly teach away from the **spacer** substituents in proposed claims 14 and 16.

Zhou Decl., Ex. 2004 ¶¶ 106-110;

Zhou 2d Decl., Ex. 2012 ¶¶35;

Matsuda, Ex. 1011 ¶¶[1014], [1023], [1150]-[1152]

PepTalk References Do Not Remedy the Deficiencies of Yamada and Matsuda

Yamada Inventors

(71) Applicant **Ajinomoto Co., Inc.**, Tokyo (JP)

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Reiko Yuji, Kawasaki-shi (JP);
Kazutaka Shimbo, Kawasaki-shi (JP);
Yuji Ito, Kagoshima-shi (JP)

Yamada, Ex. 1009 at 3 of 262

Matsuda Inventors

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Kazutaka SHIMBO, Kawasaki-shi (JP);
Tomohiro FUJII, Kawasaki-shi (JP);
Shigeo HIRASAWA, Kawasaki-shi (JP)

Matsuda, Ex. 1011 at 3 of 216

Development of a Novel Chemical Site-Specific Conjugation Platform for ADCs - **AJICAP** Technology -



Kei Yamada^{1,2}, Tomohiro Fujii¹, Takuya Seki¹, Yuri Ooba¹, Takahiro Narita¹, Akira Nakayama¹, Yoshiro Kitahara¹, Natsuki Shikida¹, Kazutaka Shimbo¹, Kunio Nakata¹, Tatsuya Okuzumi¹, Yuji Ito², Yutaka Matsuda³, Zahra Khedri³ and Brian A. Mendelsohn³

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Ajinomoto Co., Inc.

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Chemistry

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- **Tomohiro Fujii**
- **Noriko Hatada**
- Shigeo Hirasawa

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- Yuri Ooba
- Akira Nakayama
- Takahiro Narita
- Yoshiro Kitahara

Analysis

- **Natsuki Shikida**
- Kunio Nakata
- **Kazutoshi Takahashi**
- **Reiko Yuji**
- **Kazutaka Shimbo**

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- Vladimir Spasojevic

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- **Yutaka Matsuda**
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- Veronica Robles

Analysis

- Samuel Janssen
- Josh Toschi
- Moi Keenan
- Sou Boutsaboualoy



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- **Yuji Ito**



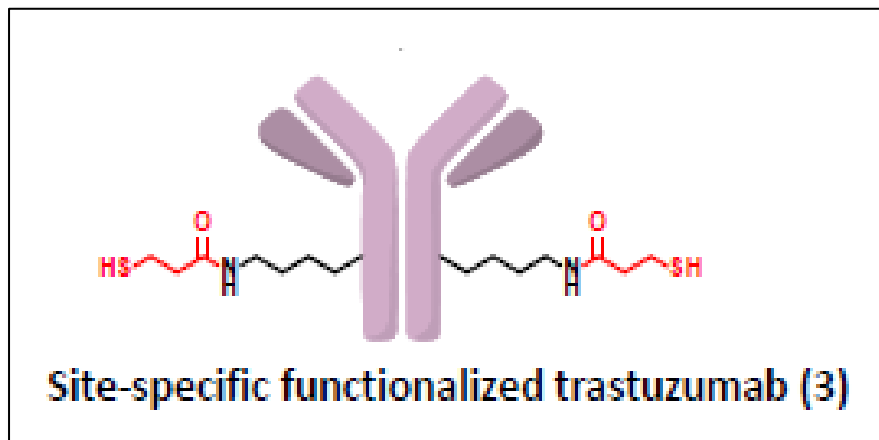
**Kamakura
Techno-Science, Inc.**

PepTalk Poster, Ex. 1006, at 1

PepTalk Presentation, Ex. 1007, 38

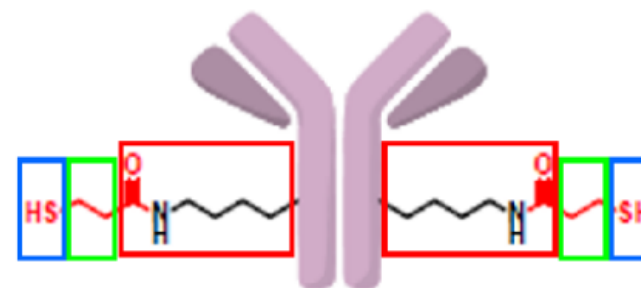
The PepTalk References do not disclose compounds with ether spacer

Claims 14 and 16



PepTalk Poster, Ex. 1006 at 1.

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



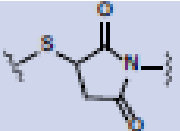
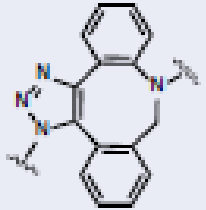
Site-specific functionalized trastuzumab (3)

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

Zhou Decl., Ex. 2004, para. 59

The PepTalk References do not disclose norbornene

Claims 15 and 16

Attachment	Structure
Thiol (-maleimide)	
Azide (-cycloalkyne)	
Aldehyde & (-hydroxylamine)	

3. Wide drug-linker compatibility: reactive group compatibility includes thiol, alkyne, azide, etc

PepTalk Poster, Ex. 1006 at 1

The PepTalk References Do Not Teach Toward Lys248

Claims 14, 15 and 16

- Technology disclosed is “ongoing experimental investigation, not an established or routine practice.” (Ex. 2004, at para. 39)
- The PepTalk References disclose a Second Generation
- The second generation specifies compatibility with sites other than Lys248
- A POSA would understand it to teach more broadly than Lys248

✓ Expansion of conjugation sites (LysXXX, LysYYY, etc.) through peptide SAR

PepTalk Poster, Ex. 1006 at 1

Occam's Razor Can't Cut It

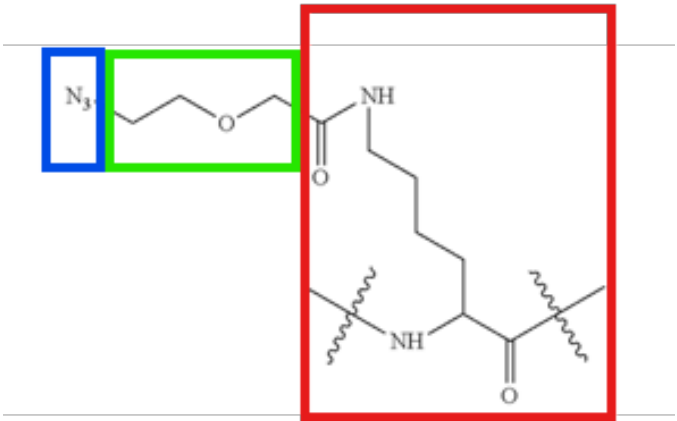
Claim 15

- Petitioner does not cite any prior art disclosing no **spacer** (i.e. a single bond as a spacer).
- Given the lack of available art, Dr. Tumey relied on “Occam’s Razor”
- *“As discussed during my deposition, there is an implicit motivation to keep molecules simple, a la **Occam’s razor**. EX2006, 152:8-22. As a result, a person of ordinary skill preparing a modified lysine with a norbornene as the terminal bioorthogonal click chemistry group **would logically start by preparing the simplest structure, which is the structure recited in proposed substitute claim 15**. This structure, which lacks a spacer/linker, would serve as the standard of comparison (i.e., control) to determine the functional impact of adding a spacer/linker. In other words, there is always a logical and implicit need to begin one’s development with the simplest modification and then iterate and develop from there.”*
- The lack of art and reliance on Claim 15 itself shows Ajinomoto’s obviousness position is based on impermissible hindsight.

*Tumey 2d Decl. Ex. 1059 ¶ 41;
Zhou 2d Decl., Ex. 2012 ¶ 35.*

The Gaps Between the Prior Art and Claim 14

Claim 14

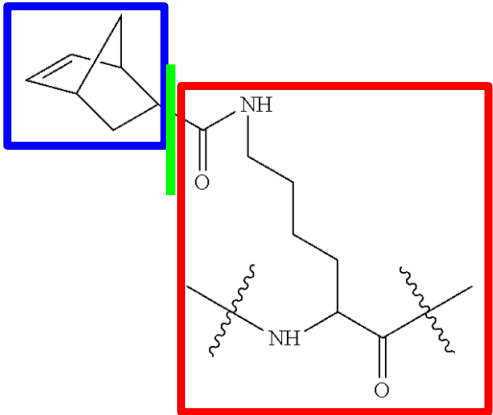


	Azide	Ether-spacer	Lysine-248	Synthesis
Yamada	✓	?	?	X
Matsuda	?	✗	?	✗
PepTalk References	✓	X	?	X

Ex. 2004, ¶¶58, 72; MTA, 20-21, 24

The Gaps Between the Prior Art and Claim 15

Claim 15

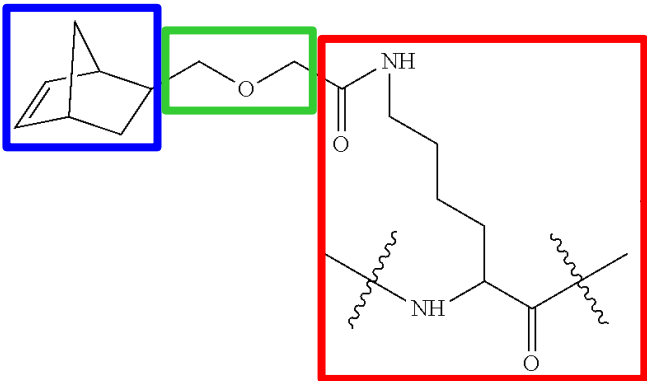


	Norbornene	No spacer	Lysine-248	Synthesis
Yamada	?	X	?	X
Matsuda	?	X	?	X
PepTalk References	X	X	?	X

Ex. 2004, ¶158, 72, 94-97; MTA, 20-25

The Gaps Between the Prior Art and Claim 16

Claim 16



	Norbornene	Ether-spacer	Lysine-248	Synthesis
Yamada	?	?	?	X
Matsuda	?	⊘	?	⊘
PepTalk References	X	X	?	X

Ex. 2004, ¶158, 72; MTA, 20-21, 24

The Gaps Between the Asserted Prior Art and the Claims

- Petitioner does not cite any prior art disclosing the claimed **spacers**
 - No single bond as a spacer (claim 15)
 - No C-C-O-C ether spacer (claim 14)
 - No C-O-C ether spacer (claim 16)
- Petitioner provides no motivation to select the claimed **Lys248 position**
- Petitioner provides no motivation to select the claimed **bio-orthogonal groups (azide or norbornene)**
- Petitioner provides no prior art synthesis for the claimed compounds
- Petitioner's analyses begin with the claimed compounds themselves, and provide no motivation or reasonable expectation of success