c-Met Antibody Drug Conjugate

Technical Field

The present disclosure provides an antibody drug conjugate (ADC) having an IgG antibody that binds to a c-Met target conjugated at both Cys sites in the hinge region of an IgG antibody. The present disclosure further provides a method for treating a breast cancer comprising providing an effective amount of a c-Met ADC.

Background

HGF is a mesenchyme-derived pleiotrophic factor with mitogenic, motogenic and morphogenic activities on a number of different cell types. HGF effects are mediated through a specific tyrosine kinase, c-Met, and aberrant HGF and c-Met expression are frequently observed in a variety of tumors. (Maulik et al., *Cytokine & Growth Factor Reviews* (2002), 13:41-59; Danilkovitch-Miagkova & Zbar, *J. Clin. Invest.* (2002), 109(7):863-867). Regulation of the HGF/c-Met signaling pathway is implicated in tumor progression and metastasis. (Trusolino & Comoglio, *Nature Rev.* (2002), 2:289-300).

HGF binds the extracellular domain of the Met receptor tyrosine kinase (RTK) and regulates diverse biological processes such as cell scattering, proliferation, and survival. HGF-Met signaling is essential for normal embryonic development especially in migration of muscle progenitor cells and development of the liver and nervous system (Bladt et al., *Nature* 376, 768-771. 1995; Hamanoue et al. *J. Neurosci. Res.* 43, 554-564. 1996; Schmidt et al., *Proc. Natl. Acad. Sci. USA* 94, 11445-11450, 1995; Uehara et al., *Nature* 373, 702-705, 1995). Developmental phenotypes of Met and HGF knockout mice are very similar suggesting that HGF is the cognate ligand for the Met receptor (Schmidt et al., *Proc. Natl. Acad. Sci. USA* 94, 11445-11450, 1995; Uehara et al., *Nature* 373, 702-705, 1995). HGF-Met also plays a role in liver regeneration, angiogenesis, and wound healing (Bussolino et al., *J. Cell Biol.* 119, 629-641 1992; Nusrat et al., *J. Clin. Invest.* 93, 2056-2065 1994). The precursor Met receptor undergoes proteolytic cleavage into an extracellular subunit and membrane spanning subunit linked by disulfide bonds (Tempest et al., *Br. J. Cancer* 58, 3-7 1988). The subunit contains the cytoplasmic kinase domain and harbors a multi-substrate docking site at the C-terminus where adapter proteins bind and initiate signaling. Upon HGF binding, activation of Met leads to tyrosine phosphorylation and downstream signaling through Gab1 and Grb2/Sos mediated PI3-kinase and Ras/MAPK activation respectively, which drives cell motility and proliferation (Furge et al., *Oncogene* 19, 5582-5589 2000;

Hartmann et al., *J. Biol. Chem.* 269, 21936-21939 1994; Ponzetto et al., *Cell* 87, 531-542 1996; and Royal and Park, *J. Biol. Chem.* 270, 27780-27787 1995).

Met overexpression or gene-amplification has been observed in a variety of human cancers. For example, Met protein is overexpressed at least 5-fold in colorectal cancers and reported to be gene-amplified in liver metastasis (Di Renzo et al., *Clin. Cancer Res.* 1, 147-154, 1995; Liu et al., *Oncogene* 7, 181-185 1992). Met protein is also reported to be overexpressed in oral squamous cell carcinoma, hepatocellular carcinoma, renal cell carcinoma, breast carcinoma, and lung carcinoma (Jin et al., *Cancer* 79, 749-760 1997; Morello et al., *J. Cell Physiol.* 189, 285-290 2001; Natali et al., *Int. J. Cancer* 69, 212-217. 1996; Olivero et al., *Br. J. Cancer* 74, 1862-1868 1996; Suzuki et al., *Hepatology* 20, 1231-1236 1994). In addition, overexpression of mRNA has been observed in hepatocellular carcinoma, gastric carcinoma, and colorectal carcinoma (Boix et al., *Hepatology* 19, 88-91 1994; Kuniyasu et al., *Int. J. Cancer* 55, 72-75 1993; Liu et al., *Oncogene* 7, 181-185 1992).

A number of mutations in the kinase domain of Met have been found in renal papillary carcinoma which leads to constitutive receptor activation (Olivero et al., *Int. J. Cancer* 82, 640-643 1999; Schmidt et al., *Nat. Genet.* 16, 68-73 1997; Schmidt et al., *Oncogene* 18, 2343-2350 1999). These activating mutations confer constitutive Met tyrosine phosphorylation and result in MAPK activation, focus formation, and tumorigenesis (Jeffers et al., *Proc. Natl. Acad. Sci. USA* 94, 11445-11450 1997). In addition, these mutations enhance cell motility and invasion (Giordano et al., 2000; Lorenzato et al., *Cancer Res.* 62, 7025-7030 2002). HGF-dependent Met activation in transformed cells mediates increased motility, scattering, and migration which eventually leads to invasive tumor growth and metastasis (Jeffers et al., *Mol. Cell Biol.* 16, 1115-1125 1996; Meiners et al., *Oncogene* 16, 9-20 1998).

Met is a member of the subfamily of RTKs which include Ron and Sea (Maulik et al., *Cytokine Growth Factor Rev.* 13, 41-59 2002). Prediction of the extracellular domain structure of Met suggests shared homology with the semaphorins and plexins. The N-terminus of Met contains a Sema domain of approximately 500 amino acids that is conserved in all semaphorins and plexins. The semaphorins and plexins belong to a large family of secreted and membrane-bound proteins first described for their role in neural development (Van Vactor and Lorenz, *Curr. Biol.* 9, R201-204 1999). However, semaphorin overexpression has been correlated with tumor invasion and metastasis. A cysteine-rich PSI domain (also referred to as a Met Related Sequence domain) found in plexins, semaphorins, and integrins lies adjacent to the Sema domain followed by four IPT repeats that are

immunoglobulin-like regions found in plexins and transcription factors. A recent study suggests that the Met Sema domain is sufficient for HGF and heparin binding (Gherardi et al., (2003). Functional map and domain structure of Met, the product of the c-Met protooncogene and receptor for hepatocyte growth factor/scatter factor. *Proc. Natl. Acad. Sci. USA* 2003). Furthermore, Kong-Beltran et al. (*Cancer Cell* (2004), 6:61-73) have reported that the Sema domain of Met is necessary for receptor dimerization and activation.

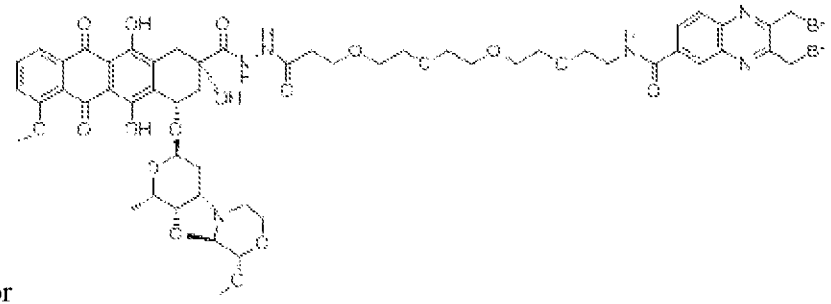
C-Met, a transmembrane receptor tyrosine kinase, plays a key role in malignant transformation of epithelial cells by activating signal transduction pathways essential for cellular proliferation, survival, migration and invasion. C-Met overexpression, with or without gene amplification, has been reported in primary breast cancers and correlate with poor prognosis. C-Met signaling inhibition, such as tyrosine kinase inhibitors (TKIs), usually not sufficient for sustained treatment efficacy. Therefore, we believe that antibody drug conjugates (ADCs) offer the promise and potential of delivering potent anti-tumor activity with the advantage of reduced side effects.

Summary

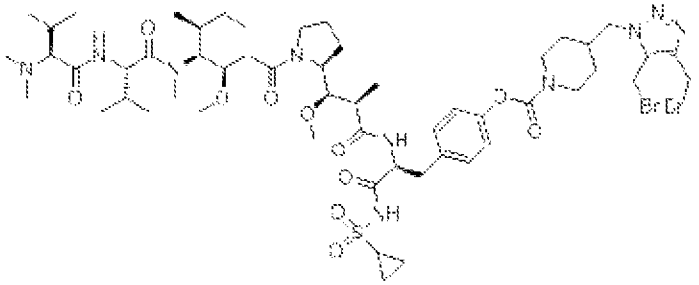
The present disclosure provides and antibody drug conjugate (ADC) having an IgG antibody that binds to a c-Met target conjugated at both Cys sites in the hinge region of an IgG antibody. The present disclosure further provides a method for treating a breast cancer comprising providing an effective amount of a c-Met ADC.

We generated antibody drug conjugates containing a novel human anti-c-Met antibody (STI-0602) (described in United States Patent application serial number 13/924,492 filed 21 June 2013, the disclosure of which is incorporated by reference herein) with either a tubulin inhibitor or DNA damaging agent, such as doxorubicin analogs. The ADC conjugates retained binding affinity and showed potent cell killing in a variety of c-Met positive cell lines.

The present disclosure provides an antibody drug conjugate (ADC) composition comprising an IgG antibody that binds to c-Met, a conjugation linker moiety that binds to both Cys residues in the hinge region of an IgG antibody and a toxin moiety. Preferably, the toxin moiety is a tubulin inhibitor or a doxorubicin analog. Preferably, the antibody is an IgG antibody from the H8 (heavy/light SEQ ID NOs 19/20) family or is a B12 (heavy/light SEQ ID NOs 7/8), wherein the H8 antibody family is selected from the group consisting of H8-A2, H8-9, H8-9EE8L3, H8-C1, H8-D4, H8-D5, H8-D6, H8-D10, H8-E5, H8-G7, H8-H6, H8-2A2, H8-2B1, H8-2B2, H8-2B4, H8-2B7, H8-A7P, H8-9EH11L, H8-9EH11L, and H8-6AG2H3. Preferably, the conjugated toxin is

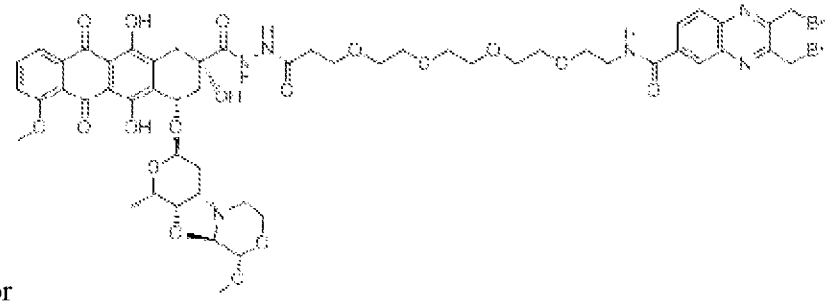


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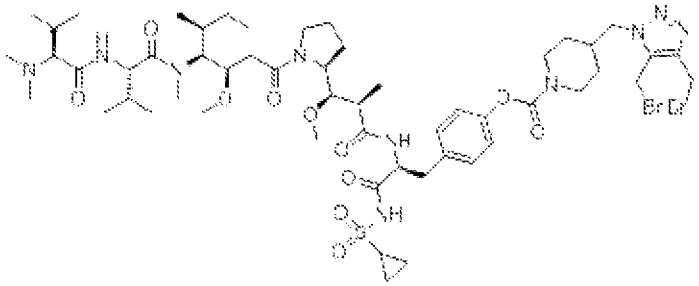


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The present disclosure provides a method for treating breast cancer, comprising administering an effective amount of an antibody drug conjugate (ADC) composition comprising an IgG antibody that binds to c-Met, a conjugation linker moiety that binds to both Cys residues in the hinge region of an IgG antibody and a toxin moiety. Preferably, the toxin moiety is a tubulin inhibitor or a doxorubicin analog. Preferably, the antibody is an IgG antibody from the H8 (heavy/light SEQ ID NOs 19/20) family or is a B12 (heavy/light SEQ ID NOs 7/8), wherein the H8 antibody family is selected from the group consisting of H8-A2, H8-9, H8-9EE8L3, H8-C1, H8-D4, H8-D5, H8-D6, H8-D10, H8-E5, H8-G7, H8-H6, H8-2A2, H8-2B1, H8-2B2, H8-2B4, H8-2B7, H8-A7P, H8-9EH11L, H8-9EH11L, and H8-6AG2H3. Preferably, the conjugated toxin is



or 0276 Structure for conjugation and drug



0174 Structure for conjugation and drug.

Brief Description of the Figures

Figure 1 shows the effects of treatment with anti-cMet IgG1 antibody STI-0602 described herein with MDA-MB-231 and HS578T cells. The cells were plated at 10K cells/well overnight in complete RPMI and then treated with STI-0602 antibody in serum-free RPMI for 4 hours, starting at an initial concentration of 10 μg/ml, and the serially diluted 1:5 for a total of 8 different concentrations. After 4 hours, cells were stimulated with 50 ng/ml HGF diluted in serum-free RPMI for 15 minutes (media controls were left unstimulated). Cells were then lysed and frozen at -80 °C freezer overnight and phosphorylated c-Met levels were determined using a Cell Signaling ELISA kit.

Figure 2 shows a comparison of *in vivo* results achieved comparing 2 c-Met ADC doses (3 mg/kg and 10 mg/kg) to the c-Met antibody alone (STI-0602, also called H8-A2 and disclosed herein as heavy chain SEG ID NO.25 and light chain SEQ ID NO. 26) and control ADC The experimental detail is described in Example 1.

Figure 3 shows a comparison of *in vivo* results achieved comparing 2 c-Met ADC doses (3 mg/kg and 10 mg/kg) to the c-Met antibody alone and control ADC. The experimental detail is described in Example 1.

Figure 4 is a table showing the experimental detail described in Example 1. Figures 2 and 3 show the *in vivo* results.

Figure 5 shows a graph of three different ADC's, each with the STI 0602 anti c-Met IgG1 antibody and different toxins retain their binding affinities to c-Met TNBC cells. Mice were given a single iv dose at 10 mg/kg. Mean concentrations of total antibody and ADC in serum were determined by ELISA.

Figure 6 shows a graph of an ADC and a control STI 0602 anti c-Met IgG1 antibody have similar pharmacokinetic properties in mice. Mice were given a single iv dose at 10 mg/kg. Mean concentrations of total antibody and ADC in serum were determined by ELISA.

Figure 7 shows anti-c-Met ADC's specifically inhibit c-Met TNBC cell proliferation. In the top panel shows inhibition of cell proliferation in HS578T and the lower panel T47D.

Cells were plated at 4000 per well and treated with one of the three ADC's. After incubation for 4 days, proliferation was measured using a Cell Titer Glo assay.

Figure 8 shows that the anti-c-Met IgG1 antibody was internalized in a triple negative breast cancer cell line. Internalization of anti c-Met antibody IgG1 H8-A2 (also called STI-0602 SEQ ID NO. 25/SEQ ID NO. 26) in MDA-MB468. MDA-MB468 were plated overnight and incubated with 1μg/ml anti-C-Met H8A2 antibody for 180 min at 37 °C. Cells were stained with anti-AF488.

Figure 9 shows an *in vivo* comparison of two doses of c-Met 0174 ADC at 3 mg/kg and 10 mg/kg and vehicle control with a c-Met antibody.

Figure 10 shows a single 1 mg/kg much lower dose of c-Met 0276 ADC and vehicle control. Tumor volume was measured twice weekly in all of the mice. Figure 10 provides these comparative data and it shows a significant effect for the lower 1 mg/kg dose when measuring tumor volume.

Figures 11A and 11B show that there was no significant weight change for these mice with either c-Met 0276 ADC (Figure 11A) or c-Met 0174 ADC (Figure 11B), compared to vehicle controls. These data suggest that there was no observed toxicity from either ADC tested.

Detailed Description

Antibody Component

The present disclosure provides a fully human antibody of an IgG class that binds to a c-Met epitope with a binding affinity of at least 10^{-6}M, which has a heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting

of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 35, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 77, SEQ ID NO. 78, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, and combinations thereof. Preferably, the fully human antibody has both a heavy chain and a light chain wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2 (called A1 herein), SEQ ID NO. 3/SEQ ID NO. 4 (called A2 herein), SEQ ID NO. 5/SEQ ID NO. 6 (called A8 herein), SEQ ID NO. 7/SEQ ID NO. 8 (called B12 herein), SEQ ID NO. 9/SEQ ID NO. 10 (called D6 herein), SEQ ID NO. 11/SEQ ID NO. 12 (called E1 herein), SEQ ID NO. 13/SEQ ID NO. 14 (called E6 herein), SEQ ID NO. 15/SEQ ID NO. 16 (called F3 herein), SEQ ID NO. 17/SEQ ID NO. 18 (called H6 herein), SEQ ID NO. 19/SEQ ID NO. 20 (called H8 herein), SEQ ID NO. 21/SEQ ID NO. 22 (called H8-9 herein), SEQ ID NO. 21/SEQ ID NO. 23 (called H8-9EE8L3 herein), SEQ ID NO. 24/SEQ ID NO. 22 (called H8-G3S herein), SEQ ID NO. 25/SEQ ID NO. 26 (called H8-A2 herein), SEQ ID NO. 27/SEQ ID NO. 28 (called H8-B6 herein), SEQ ID NO. 29/SEQ ID NO. 23 (called H8-C1 herein), SEQ ID NO. 24/SEQ ID NO. 30 (called H8-D4 herein), SEQ ID NO. 31/SEQ ID NO. 23 (called H8-D5 herein), SEQ ID NO. 24/SEQ ID NO. 23 (called H8-D6 herein), SEQ ID NO. 32/SEQ ID NO. 23 (called H8-D10 herein), SEQ ID NO. 33/SEQ ID NO. 22 (called H8-E5 herein), SEQ ID NO. 34/SEQ ID NO. 22 (called H8-G7 herein), SEQ ID NO. 24/SEQ ID NO. 35 (called H8-G9 herein), SEQ ID NO. 36/SEQ ID NO. 26 (called H8-H6 herein), SEQ ID NO. 29/SEQ ID NO. 22 (called H8-2A2 herein), SEQ ID NO. 37/SEQ ID NO. 38 (called H8-2B1 herein), SEQ ID NO. 34/SEQ ID NO. 23 (called H8-2B2 herein), SEQ ID NO. 37/SEQ ID NO. 23 (called H8-2B4 herein), SEQ ID NO. 32/SEQ ID NO. 39 (called H8-2B7 herein), SEQ ID NO. 32/SEQ ID NO. 22 (called H8-A7P herein), SEQ ID NO. 40/SEQ ID NO. 41 (called GCE-A10 herein), SEQ ID NO. 42/SEQ ID NO. 43 (called GCE-A11 herein), SEQ ID NO. 44/SEQ ID NO. 41 (called GCE-A13 herein), SEQ ID NO. 45/SEQ ID NO. 46 (called GCE-A14 herein), SEQ ID NO. 47/SEQ ID NO. 48 (called GCE-A16 herein), SEQ ID NO. 49/SEQ ID NO. 50 (called GCE-A18 herein), SEQ ID NO. 51/SEQ ID NO. 52 (called GCE-B2 herein), SEQ ID NO. 53/SEQ ID NO. 54 (called

GCE-B9 herein), SEQ ID NO. 45/SEQ ID NO. 55 (called GCE-B11 herein), SEQ ID NO. 56/SEQ ID NO. 57 (called GCE-B13 herein), SEQ ID NO. 58/SEQ ID NO. 57 (called GCE-B19 herein), SEQ ID NO. 59/SEQ ID NO. 60 (called GCE-BR1 herein), SEQ ID NO. 61/SEQ ID NO. 62 (called GCE-B20 herein), SEQ ID NO. 63/SEQ ID NO. 64 (called GCE-A19 herein), SEQ ID NO. 65/SEQ ID NO. 66 (called GCE-B10 herein), SEQ ID NO. 58/SEQ ID NO. 67 (called GCE-B5 herein), SEQ ID NO. 61/SEQ ID NO. 68 (called GCE-B4 herein), SEQ ID NO. 69/SEQ ID NO. 70 (called GCE-A26 herein), SEQ ID NO. 71/SEQ ID NO. 72 (called GCE-L1A-9 herein), SEQ ID NO. 49/SEQ ID NO. 73 (called GCE-H34-36 herein), SEQ ID NO. 74/SEQ ID NO. 73 (called GCE-H13-1 herein), SEQ ID NO. 61/SEQ ID NO. 73 (called GCE-H13-2 herein), SEQ ID NO. 44/SEQ ID NO. 73 (called GCE-H13-3 herein), SEQ ID NO. 40/SEQ ID NO. 73 (called GCE-H13-4 herein), SEQ ID NO. 75/SEQ ID NO. 73 (called GCE-H13-5 herein), SEQ ID NO. 69/SEQ ID NO. 73 (called GCE-H13-6 herein), SEQ ID NO. 76/SEQ ID NO. 73 (called GCE-H13-8 herein), SEQ ID NO. 21/SEQ ID NO. 77 (called H8-9EH11L herein), SEQ ID NO. 21/SEQ ID NO. 78 (called H8-9EG11L herein), SEQ ID NO. 79/SEQ ID NO. 20 (called H8-6AG2H3 herein), SEQ ID NO. 80/SEQ ID NO. 81 (called A1-2 herein), SEQ ID NO. 82/SEQ ID NO. 83 (called A1-4 herein), SEQ ID NO. 84/SEQ ID NO. 85 (called A1-6 herein), SEQ ID NO. 86/SEQ ID NO. 87 (called A1-8 herein), SEQ ID NO. 88/SEQ ID NO. 89 (called A1-9 herein), SEQ ID NO. 90/SEQ ID NO. 91 (called A1-24 herein), SEQ ID NO. 92/SEQ ID NO. 93 (called A1-32 herein), and combinations thereof.

The present disclosure provides a fully human antibody Fab fragment, having a variable domain region from a heavy chain and a variable domain region from a light chain, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences

selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 35, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 77, SEQ ID NO. 78, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, and combinations thereof. Preferably, the fully human antibody Fab fragment has both a heavy chain variable domain region and a light chain variable domain region wherein the antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID NO. 22, SEQ ID NO. 21/SEQ ID NO. 23, SEQ ID NO. 24/SEQ ID NO. 22, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 23, SEQ ID NO. 24/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 23, SEQ ID NO. 24/SEQ ID NO. 23, SEQ ID NO. 32/SEQ ID NO. 23, SEQ ID NO. 33/SEQ ID NO. 22, SEQ ID NO. 34/SEQ ID NO. 22, SEQ ID NO. 24/SEQ ID NO. 35, SEQ ID NO. 36/SEQ ID NO. 26, SEQ ID NO. 29/SEQ ID NO. 22, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 34/SEQ ID NO. 23, SEQ ID NO. 37/SEQ ID NO. 23, SEQ ID NO. 32/SEQ ID NO. 39, SEQ ID NO. 32/SEQ ID NO. 22, SEQ ID NO. 40/SEQ ID NO. 41, SEQ ID NO. 42/SEQ ID NO. 43, SEQ ID NO. 44/SEQ ID NO. 41, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 45/SEQ ID NO. 55, SEQ ID NO. 56/SEQ ID NO. 57, SEQ ID NO. 58/SEQ ID NO. 57, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 58/SEQ ID NO. 67, SEQ ID NO. 61/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 49/SEQ ID NO. 73, SEQ ID NO. 74/SEQ ID NO. 73, SEQ ID NO. 61/SEQ ID NO. 73, SEQ ID NO. 44/SEQ ID NO. 73, SEQ ID NO. 40/SEQ ID NO. 73, SEQ ID NO. 75/SEQ ID NO. 73, SEQ ID NO. 69/SEQ ID NO. 73, SEQ ID NO. 76/SEQ ID NO. 73, SEQ ID NO. 21/SEQ ID NO. 77, SEQ ID NO. 21/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 20, SEQ ID NO. 80/SEQ ID NO. 81, SEQ

ID NO. 82/SEQ ID NO. 83, SEQ ID NO. 84/SEQ ID NO. 85, SEQ ID NO. 86/SEQ ID NO. 87, SEQ ID NO. 88/SEQ ID NO. 89, SEQ ID NO. 90/SEQ ID NO. 91, SEQ ID NO. 92/SEQ ID NO. 93, and combinations thereof.

The present disclosure provides a single chain human antibody, having a variable domain region from a heavy chain and a variable domain region from a light chain and a peptide linker connection the heavy chain and light chain variable domain regions, wherein the heavy chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 1, SEQ ID NO. 3, SEQ ID NO. 5, SEQ ID NO. 7, SEQ ID NO. 9, SEQ ID NO. 11, SEQ ID NO. 13, SEQ ID NO. 15, SEQ ID NO. 17, SEQ ID NO. 19, SEQ ID NO. 21, SEQ ID NO. 24, SEQ ID NO. 25, SEQ ID NO. 27, SEQ ID NO. 29, SEQ ID NO. 31, SEQ ID NO. 32, SEQ ID NO. 33, SEQ ID NO. 34, SEQ ID NO. 36, SEQ ID NO. 37, SEQ ID NO. 40, SEQ ID NO. 42, SEQ ID NO. 44, SEQ ID NO. 45, SEQ ID NO. 47, SEQ ID NO. 49, SEQ ID NO. 51, SEQ ID NO. 53, SEQ ID NO. 56, SEQ ID NO. 58, SEQ ID NO. 59, SEQ ID NO. 61, SEQ ID NO. 63, SEQ ID NO. 65, SEQ ID NO. 69, SEQ ID NO. 71, SEQ ID NO. 74, SEQ ID NO. 75, SEQ ID NO. 76, SEQ ID NO. 79, SEQ ID NO. 80, SEQ ID NO. 82, SEQ ID NO. 84, SEQ ID NO. 86, SEQ ID NO. 88, SEQ ID NO. 90, SEQ ID NO. 92, and combinations thereof, and that has a light chain variable domain sequence that is at least 95% identical to the amino acid sequences selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 4, SEQ ID NO. 6, SEQ ID NO. 8, SEQ ID NO. 10, SEQ ID NO. 12, SEQ ID NO. 14, SEQ ID NO. 16, SEQ ID NO. 18, SEQ ID NO. 20, SEQ ID NO. 22, SEQ ID NO. 23, SEQ ID NO. 26, SEQ ID NO. 28, SEQ ID NO. 30, SEQ ID NO. 35, SEQ ID NO. 38, SEQ ID NO. 39, SEQ ID NO. 41, SEQ ID NO. 43, SEQ ID NO. 46, SEQ ID NO. 48, SEQ ID NO. 50, SEQ ID NO. 52, SEQ ID NO. 54, SEQ ID NO. 55, SEQ ID NO. 57, SEQ ID NO. 60, SEQ ID NO. 62, SEQ ID NO. 64, SEQ ID NO. 66, SEQ ID NO. 67, SEQ ID NO. 68, SEQ ID NO. 70, SEQ ID NO. 72, SEQ ID NO. 73, SEQ ID NO. 77, SEQ ID NO. 78, SEQ ID NO. 81, SEQ ID NO. 83, SEQ ID NO. 85, SEQ ID NO. 87, SEQ ID NO. 89, SEQ ID NO. 91, SEQ ID NO. 93, and combinations thereof. Preferably, the fully human single chain antibody has both a heavy chain variable domain region and a light chain variable domain region, wherein the single chain fully human antibody has a heavy chain/light chain variable domain sequence selected from the group consisting of SEQ ID NO. 1/SEQ ID NO. 2, SEQ ID NO. 3/SEQ ID NO. 4, SEQ ID NO. 5/SEQ ID NO. 6, SEQ ID NO. 7/SEQ ID NO. 8, SEQ ID NO. 9/SEQ ID NO. 10, SEQ ID NO. 11/SEQ ID NO. 12, SEQ ID NO. 13/SEQ ID NO. 14, SEQ ID NO. 15/SEQ ID NO. 16, SEQ ID NO. 17/SEQ ID NO. 18, SEQ ID NO. 19/SEQ ID NO. 20, SEQ ID NO. 21/SEQ ID

NO. 22, SEQ ID NO. 21/SEQ ID NO. 23, SEQ ID NO. 24/SEQ ID NO. 22, SEQ ID NO. 25/SEQ ID NO. 26, SEQ ID NO. 27/SEQ ID NO. 28, SEQ ID NO. 29/SEQ ID NO. 23, SEQ ID NO. 24/SEQ ID NO. 30, SEQ ID NO. 31/SEQ ID NO. 23, SEQ ID NO. 24/SEQ ID NO. 23, SEQ ID NO. 32/SEQ ID NO. 23, SEQ ID NO. 33/SEQ ID NO. 22, SEQ ID NO. 34/SEQ ID NO. 22, SEQ ID NO. 24/SEQ ID NO. 35, SEQ ID NO. 36/SEQ ID NO. 26, SEQ ID NO. 29/SEQ ID NO. 22, SEQ ID NO. 37/SEQ ID NO. 38, SEQ ID NO. 34/SEQ ID NO. 23, SEQ ID NO. 37/SEQ ID NO. 23, SEQ ID NO. 32/SEQ ID NO. 39, SEQ ID NO. 32/SEQ ID NO. 22, SEQ ID NO. 40/SEQ ID NO. 41, SEQ ID NO. 42/SEQ ID NO. 43, SEQ ID NO. 44/SEQ ID NO. 41, SEQ ID NO. 45/SEQ ID NO. 46, SEQ ID NO. 47/SEQ ID NO. 48, SEQ ID NO. 49/SEQ ID NO. 50, SEQ ID NO. 51/SEQ ID NO. 52, SEQ ID NO. 53/SEQ ID NO. 54, SEQ ID NO. 45/SEQ ID NO. 55, SEQ ID NO. 56/SEQ ID NO. 57, SEQ ID NO. 58/SEQ ID NO. 57, SEQ ID NO. 59/SEQ ID NO. 60, SEQ ID NO. 61/SEQ ID NO. 62, SEQ ID NO. 63/SEQ ID NO. 64, SEQ ID NO. 65/SEQ ID NO. 66, SEQ ID NO. 58/SEQ ID NO. 67, SEQ ID NO. 61/SEQ ID NO. 68, SEQ ID NO. 69/SEQ ID NO. 70, SEQ ID NO. 71/SEQ ID NO. 72, SEQ ID NO. 49/SEQ ID NO. 73, SEQ ID NO. 74/SEQ ID NO. 73, SEQ ID NO. 61/SEQ ID NO. 73, SEQ ID NO. 44/SEQ ID NO. 73, SEQ ID NO. 40/SEQ ID NO. 73, SEQ ID NO. 75/SEQ ID NO. 73, SEQ ID NO. 69/SEQ ID NO. 73, SEQ ID NO. 76/SEQ ID NO. 73, SEQ ID NO. 21/SEQ ID NO. 77, SEQ ID NO. 21/SEQ ID NO. 78, SEQ ID NO. 79/SEQ ID NO. 20, SEQ ID NO. 80/SEQ ID NO. 81, SEQ ID NO. 82/SEQ ID NO. 83, SEQ ID NO. 84/SEQ ID NO. 85, SEQ ID NO. 86/SEQ ID NO. 87, SEQ ID NO. 88/SEQ ID NO. 89, SEQ ID NO. 90/SEQ ID NO. 91, SEQ ID NO. 92/SEQ ID NO. 93, and combinations thereof.

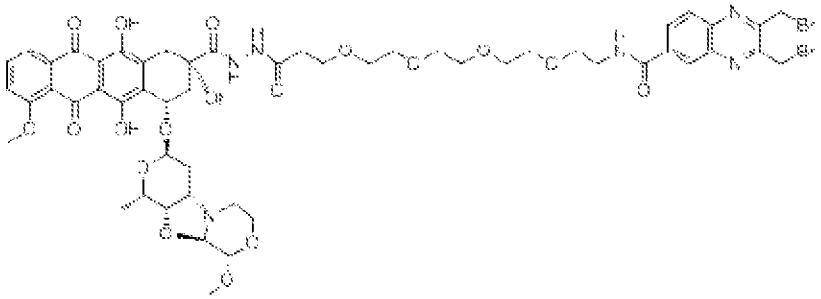
Preparation of cMet—DM1 ADC

Anti-c-Met antibody was buffer exchanged to phosphate buffer, pH from 6.5 to 7.5. Toxin-linker, SMCC-DM1 was dissolved in DMA (Dimethylacetamide) solution and added to antibody solution with Toxin/Antibody ratio from 7 to 10. The antibody-toxin solution was incubated at room temperature overnight. The unconjugated antibody was removed either gel-filtration chromatography or centrifugation filtration. The cMet-DM1 was characterized by HPLC. The drug antibody ratio (DAR) was calculated based on UV-VIS of cMet-DM1.

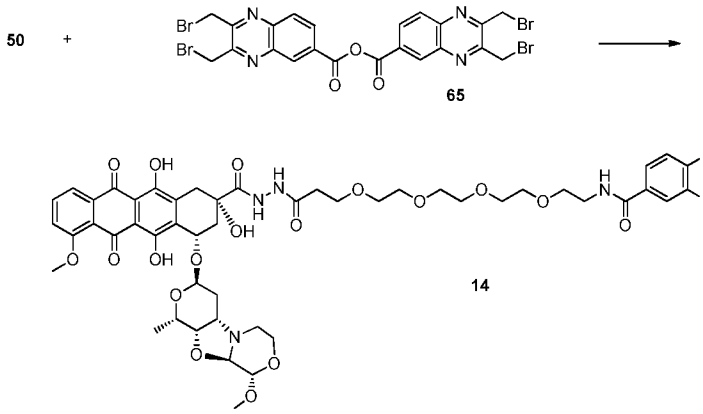
Preparation of cMet-Duo3

Anti-cMet antibody was reduced by TCEP (tris(2-carboxyethyl)phosphine), up to 20 mM. The excess of TCEP was removed by gel-filtration chromatography or centrifugal filtration. Toxin-Duo3-linker was dissolved in DMA solution and added to the reduced antibody with Toxin/antibody ratio from 4.5 to 6. After few hours' incubation at room temperature, the unconjugated Duo3-linker was removed by gel-filtration chromatography or centrifugal

filtration. The cMet-Duo3 was characterized by HPLC. The drug antibody ratio (DAR) was calculated based on UV-VIS or HIC-HPLC.

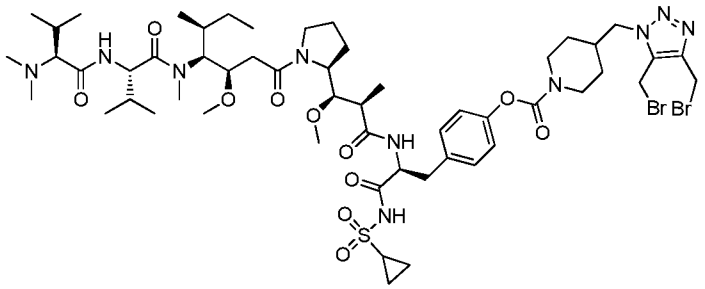


Structure of compound 030-0260 and preparation as follows:



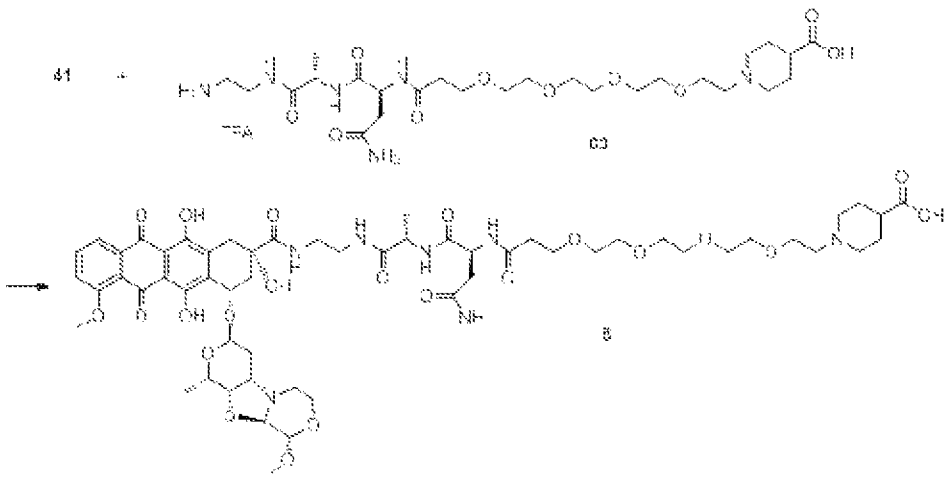
To a solution of compound 50 (18 mg, 0.02 mmol) in DCM (2 mL) was added compound 65 (15 mg), followed by DIEA (5 μL). The mixture was stirred at room temperature for 10 min. The reaction was then diluted with DCM (30 mL) and washed with aq. saturated $NaHCO_3$. The organic layer was concentrated and residue was purified by RP-HPLC to give compound 14 as a red solid after lyophilization (7 mg, 29%). MS m/z 1231.3 (M+H).

Structure of compound 030-0174



The synthesis of this compound was described as compound **8.**

Preparation of compound **8**



To compound **41** (72 mg, 0.10 mmol) in 3 mL of DMF was added DIEA (75 µL), and amine TFA **63** (86 mg, 0.12 mmol). The mixture was stirred at room temperature for 3 h, then diluted with DCM (40 mL). The mixture was washed with brine. The organic layer was dried and evaporated to dryness. The residue was purified by column (silica gel, DCM:MeOH, 9:1) to give compound **8** (63 mg, 52%). MS m/z 1214.5 (M+H).

Example 1

Upon receipt, animals were housed 5 mice per cage in a room with a controlled environment. Animals were provided rodent chow and water ad libitum. Acclimation of the mice to laboratory conditions was at least 72 hours prior to the start of cell administration and dosing. During the acclimation period, the animals' health status was determined. Only animals that are observed to be healthy prior to study initiation were used.

This example provides an *in vivo* experiment comparing treatment of mice with control (PBS), anti-c-Met IgG1 antibody (STI-0602 and STI-0607) and an ADC variant of both antibodies. The procedure first does a tumor cell inoculation & establishment of tumors:

a. U87 cells were cultured with 10% FBS U87 medium (EMEM) and harvested with 0.05% trypsin. Cells were washed 2 times with serum-free EMEM, counted, and resuspended at 5 x10^6 cells in 0.2 mL or, 25 x10^6 cells/mL in a 1:1 mix of serum-free EMEM and matrigel and injected subcutaneously into the upper right flank of each mouse.

b. Tumor growth was monitored by tumor volume measurement using a digital caliper starting Day 6-9 after inoculation, 2 times per week thereafter and prior to study termination.

c. Tumors were measured with digital calipers. The length (the longest dimension) and the width (the distance perpendicular to and in the same plane as the length) were measured. The formula for calculating tumor volume was TV (mm3) =½ x L x W2.

Treatments:

a. Once tumors were staged to the desired volume (average from 200 to 300 mm3), animals were randomized and mice with very large or small tumors culled. Mice were divided into 8 groups of 10 mice each, randomized by tumor volume.

b. Mice were treated with either vehicle or Test Article according to Figure 4. Mice received a total of 5 doses.

c. Tumor responses were monitored and study terminated once clear treatment trends are established and/or when tumor load in vehicle-treated mice reaches IACUC protocol limits (2000 mm^3).

Example 2

This example is an in vivo experiment comparing two disclosed c-Met ADCs in vivo with mice having (H292 non-small cell lung cancer line). ADC or vehicle control was administered iv to the tail in three weekly doses. Figure 9 shows two different doses of c-Met 0174 ADC at 3 mg/kg and 10 mg/kg and vehicle control. Tumor volume was measured twice weekly in all of the mice.

Figure 9 provides these comparative data and it shows a significant dose-dependent effect when measuring tumor volume. Figure 11B shows that there was no significant weight change for these mice, compared to vehicle control. These data suggest that there was no observed toxicity from the ADC.

Figure 10 shows a single 1 mg/kg much lower dose of c-Met 0276 ADC at and vehicle control. Tumor volume was measured twice weekly in all of the mice. Figure 10 provides these comparative data and it shows a significant effect for the lower 1 mg/kg dose when measuring tumor volume. Figure 11A shows that there was no significant weight change for these mice, compared to vehicle control. These data suggest that there was no observed toxicity from this ADC.

Sequence Listing

	Heavy chain variable domain region	Light chain variable domain region
A1	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGEINHSGSTNYNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARGRDGYDFDPWGQGTLVTVSS SEQ ID NO. 1	LPVLTQPASVSGSPGQSITISCTGTSSD VGGYNYVSWYQQHPGKAPKLMIYDVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSYRSSSALVVFGGGTK LTVL SEQ ID NO. 2

A2	QVQLQESGPGLVKPSGTLSLTCAVSGGSISRS NWWSWVRQPPGKGLEWIGEVYHSGSTNYNP SLKSRVTISVDKSKNQFSLKVNSVTAADTAVY YCARDSDGGYYFDYWGQGTLVTVSS SEQ ID NO. 3	LPVLTQPASVSGSPGQSITISCTGTSSD VGGYKYVSWYQQHPGKAPKLLIYDVT DRPSGVSNRFSGSQSGNTASLTISGLQ TEDEADYYCSSYTDNGALVVFGGGTK LTVL SEQ ID NO. 4
A8	QITLKESGAEVKKPGSSVKVSCKASGGTFSSY GISWVRQAPGQGLEWMGGIIPMFGTANYAQK FQGRVTITADESTSTAYMELSSLRSEDTAVYY CARDEVAPDYYGSGPSYGMDVWGQGTMVT VSS SEQ ID NO. 5	SYELMQPASVSGSPGQSITISCTGTSS DVGGYDHVSWYQQHPGKAPKLMIYAV RNRPSGVPDRFSGSKSGNTASLTISGL QAEDEADYYCSSYTSSLTYVFGTGTKV TVL SEQ ID NO. 6
B12	QVQLVESGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDYWGQGTTVTVSS SEQ ID NO. 7	QAVLTQPPSVSGSPGQSITISCTGTSS DVGTFNLVSWYQQHPGKAPKLIIYEVS KRPSDVSPRYSGSKSGTTASLTISVLQ TEDEADYYCCSYTTSSSYVFGIGTKVT VL SEQ ID NO. 8
D6	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC ARGRDGYDFDPWGQGTLVTVSS SEQ ID NO. 9	QSVLTQPPSASGSPGQSVTISCTGTSS DVGGYNYVSWYQQHPGKAPKLMIYEV SKRPSGVPDRFSGSKSGNTASLTVSG LQAEDEADYYCSSYAGSNNLVVFGGG TQLTVL SEQ ID NO. 10
E1	QVQLVQSGAEVKKPGASVKVSCKTSGYTFSG DYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPGRDYYYYDGMDVWGQGTTVTV SS SEQ ID NO. 11	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTVPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYDSSLSAYVFGTGT KVTVL SEQ ID NO. 12
E6	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYYC ARGGRVYSNYYMDVWGKGTTVTVSS SEQ ID NO. 13	QAVLTQPASVSGSPGQSITISCTGTRS DVGGYNYVSWYQQHPGKAPKLLVYDV SNRPSGVSNRFSGSQSGNTASLTISGL QTEDEADYYCSSYTDNSALVVFGGGT KVTVL SEQ ID NO. 14
F3	QVQLVESGPGLVKPSGTLSLTCAVSGGSISSS NWWSWVRQPPGKGLEWIGEIYHSGSTNYNP SLKSRVTISVDKSKNQFSLKLSSVTAADTAVYY CARSAYGDYFLDYWGQGTLVTVSS SEQ ID NO. 15	QSVLTQPASVSGSPGQSITISCTGTSS DVGGYNYVSWYQQHPGKAPKLLIYDV DSRPSGVSNRFSGSKSGNTASLTISGL QAEDEADYYCSSFTSSSTLVVFGGGT KVTVL SEQ ID NO. 16
H6	EVQLLESGGGLVQPGGSLRLSCAASGFTFSS YEMNWVRQAPGKGLEWVSYISSSGSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY YCARDGAATGDQIDYWGQGTLVTVSS SEQ ID NO. 17	AIRMTQSPAFMSATPGDKVNISYKASQ DVDDDMTWCQEKPGEAAIFIFQEAATL VPGIPPRLSGSGNGTDFTLTINNMESE DAAYYFCLQQDNFPLTFGQGTKVDIK SEQ ID NO. 18
H8	EVQLVQSGAEVKKPGASVKVSCKASGYTFSS YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDYWGQGTLVTVSS SEQ ID NO. 19	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAGVFGGGTKL TVL SEQ ID NO. 20
H8-9	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 21	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 22
H8-9EE8L3	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 21	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23

H8-G3S	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 24	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 22
H8-A2	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGV APKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 25	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWAFGGGTK LTVL SEQ ID NO. 26
H8-B6	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 27	QLVLTQSPSVSVAPGQRVTISCSGSNS FTDNTYVSWYHHLPGTAPKLLIYDTNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 28
H8-C1	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGL APKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 29	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23
H8-D4	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 24	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RQSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 30
H8-D5	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGV AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 31	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23
H8-D6	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 24	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23
H8-D10	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGL AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 32	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23
H8-E5	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGY APKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 33	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 22
H8-G7	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGV AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 34	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 22

H8-G9	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 24	QLVLTQSPSVSVAPGQRVTISCSGSNS FSSNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 35
H8-H6	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGL AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 36	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWAFGGGTK LTVL SEQ ID NO. 26
H8-2A2	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGL APKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 29	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 22
H8-2B1	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGL APKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 37	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDTNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWAFGGGTK LTVL SEQ ID NO. 38
H8-2B2	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGV AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 34	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23
H8-2B4	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGL APKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 37	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWLFGGGTKL TVL SEQ ID NO. 23
H8-2B7	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGL AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 32	QLVLTQSPSVSVAPGQRVTISCSASNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 39
H8-A7P	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS EYMHWVRQAPGQGLEWMGWINPNSGNTGL AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 32	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 22
GCE-A10	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 40	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 41
GCE-A11	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYIHWVRQAPGQGLEWMGWINPNSGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPARDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 42	QSVVTQPPSVSGAPGQRVTISCLGSSS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRISGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYLFGTGTKV TVL SEQ ID NO. 43

GCE-A13	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 44	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 41
GCE-A14	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYIHWVRQAPGQGLEWMGWINPNSGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPARDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 45	QSVVTQPPSVSGAPGQRVTISCIGSSS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 46
GCE-A16	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYLHWVRQAPGQGLEWMGWINPNTGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPARDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 47	QSVVTQPPSVSGAPGQRVTISCIGSSS NIGAGYDVHWYQQLPGTAPKLLIYGNS NLPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYESSLSAYVFGTGTK VTVL SEQ ID NO. 48
GCE-A18	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPGRDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 49	QSVVTQPPSVSGAPGQRVTISCIGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 50
GCE-B2	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYMHWVRQAPGQGLEWMGWINPNTGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 51	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGYDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 52
GCE-B9	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 53	QSVVTQPPSVSGAPGQRVTISCLGSSS NIGAGHDVHWYQQLPGTAPKLLIYGNS NLPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVLFGTGTKV TVL SEQ ID NO. 54
GCE-B11	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYIHWVRQAPGQGLEWMGWINPNSGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPARDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 45	QSVVTQPPSVSGAPGQRVTISCIGSSS NIGAGYDVHWYQQLPGTAPKLLIYGNS NRISGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVLFGTGTKV TVL SEQ ID NO. 55
GCE-B13	QVQLVQSGAEVKKPGASVKVSCKASGSTFSG DYIHWVRQAPGQGLEWMGWINPNSGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPARDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 56	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVLFGTGTKV TVL SEQ ID NO.57
GCE-B19	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYIHWVRQAPGQGLEWMGWINPNSGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPGRDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 58	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVLFGTGTKV TVL SEQ ID NO. 57
GCE-BR1	QVQLVQSGAEVKKPGASVKVSCKASGSTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 59	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGYDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVLFGTGTKV TVL SEQ ID NO. 60

GCE-B20	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGMDVWGQGTTVTV SS SEQ ID NO. 61	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRISGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVLFGTGTKV TVL SEQ ID NO. 62
GCE-A19	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYYGLDVWGQGTTVTVS S SEQ ID NO. 63	QSVVTQPPSVSGAPGQRVTISCLGSSS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRISGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 64
GCE-B10	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYLHWVRQAPGQGLEWMGWINPNTGGTNYA QKFQGRVTMTRDTSISTAYMELSRLKSDDTAV YYCAREPARDYYYYDGLDVWGQGTTVTVSS SEQ ID NO. 65	QSVVTQPPSVSGAPGQRVTISCLGSSS NIGAGHDVHWYQQLPGTAPKLLIYGNS NLPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 66
GCE-B5	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYIHWVRQAPGQGLEWMGWINPNSGGTNYA QKFQGRVTMTRDTSISTAYMELSRLRSDDTA VYYCAREPGRDYYYYDGLDVWGQGTTVTVS S SEQ ID NO. 58	QSVVTQPPSVSGAPGQRVTISCLGSAS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAVVFGTGTK VTVL SEQ ID NO. 67
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GCE-A26	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 69	QSVVTQPPSVSGAPGQRVTISCLGSSS NIGAGHDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYLFGTGTKV TVL SEQ ID NO. 70
GCE-L1A-9	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPGRDYYYYDGMDVWGQGTTVTV SS SEQ ID NO. 71	QSVVTQPPSVSGAPGQRVTISCLGSSS NIGAGYDVHWYQQLPGTAPKLLIYGNS NRPSGVPDRFSGSKSGTSASLAITGLQ AEDEADYYCQSYSSSLSAYVFGTGTK VTVL SEQ ID NO. 72
GCE-H3B-36	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYMHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPGRDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 49	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO.73
GCE-H13-1	QVQLVQSGAEVKKPGASVKVSCKASGSTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPGRDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 74	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO. 73
GCE-H13-2	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGMDVWGQGTTVTV SS SEQ ID NO. 61	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO. 73

GCE-H13-3	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 44	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO. 73
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GCE-H13-5	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGMDVWGQGTTVTV SS SEQ ID NO. 75	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO. 73
GCE-H13-6	QVQLVQSGAEVKKPGASVKVSCKASGFTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPARDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 69	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO. 73
GCE-H13-8	QVQLVQSGAEVKKPGASVKVSCKASGYTFSG DYLHWVRQAPGQGLEWMGWINPNSGGTNY AQKFQGRVTMTRDTSISTAYMELSRLRSDDT AVYYCAREPGRDYYYYDGLDVWGQGTTVTV SS SEQ ID NO. 76	QSVVTQPPSVSGAPGQRVTISCTGSS SNIGAGYDVHWYQQLPGTAPKLLIYGN SNRPSGVPDRFSGSKSGTSASLAITGL QAEDEADYYCQSYSSSLSAYVFGTGT KVTVL SEQ ID NO. 73
H8-9EH11L	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 21	QLVLTQSPSVSVAPGQRVTISCSGSNS FIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 77
H8-9EG11L	EVQLVQSGAEVKKPGASVKVSCKASGYTFYS YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRGTTVSFDTWGQGTLVTVSS SEQ ID NO. 21	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNTYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAWVFGGGTK LTVL SEQ ID NO. 78
H8-6AG2H3	EVQLVQSGAEVKKPGASVKVSCKASGYTFSD YYMHWVRQAPGQGLEWMGWINPNSGNTGY AQKFQGRVTMTRNTSISTAYMELSSLRSEDTA VYYCARRATTVSFDYWGQGTLVTVSS SEQ ID NO. 79	QLVLTQSPSVSVAPGQRVTISCSGSNS NIGNNYVSWYHHLPGTAPKLLIYDNNK RPSGIPDRFSGSKSGTSATLGITGLQP GDEAHYYCGTWDSTLSAGVFGGGTKL TVL SEQ ID NO. 20
A1-2	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGESTHSGSTNYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGRDGYDFDAWGQGTLVTVSS SEQ ID NO. 80	LPVLTQPASVSGSPGQSITISCTGTSFD VGGYNYVSWYQQHPGKAPKLMIYDVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSFRSSSALVVFGGGTKL TVL SEQ ID NO. 81
A1-4	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGESSHSGSTNYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGRDGYYFDAWGQGTLVTVSS SEQ ID NO. 82	LPVLTQPASVSGSPGQSITISCTGTSSD VGGYPYVSWYQQHPGKAPKLMIYVVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSYRSSSALVVFGGGTQ LTVL SEQ ID NO. 83

A1-6	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGEITHSGSTNYNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARGRDGYDIDAWGQGTLVTVSS SEQ ID NO. 84	LPVLTQPASVSGSPGQSITISCTGTSW DVGGYPYVSWYQQHPGKAPKLMIYDV SDRPSGVSTRFSGSKSGNTASLTISGL QAEDEADYYCSSYRSVSALVVFGGGT KLTVL SEQ ID NO. 85
A1-8	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGEISHSGSTNYNP SLESRVTISVDTSKNQFSLKLSSVTAADTAVYY CARGRDGYDLDRWGQGTLVTVSS SEQ ID NO. 86	LPVLTQPASVSGSPGQSITISCTGTSSD VGGYPYVSWYQQHPGKAPKLMIYRVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSYRSSAALVVFGGGTK LTVL SEQ ID NO. 87
A1-9	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGEISHSGSTNYNP SLKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARGRDGYYLDQWGQGTLVTVSS SEQ ID NO. 88	LPVLTQPASVSGSPGQSITISCTGTSSD VGGYNYVSWYQQHPGKAPKLMIYNVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSFRSSSALVVFGGGTKL TVL SEQ ID NO. 89
A1-24	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGESTHSGSTNYN PSLESRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGRDSYDFDAWGQGTLVTVSS SEQ ID NO. 90	LPVLTQPASVSGSPGQSITISCTGTSFD VGGYNYVSWYQQHPGKAPKLMIYDVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSFRSSAALVVFGGGTKL TVL SEQ ID NO. 91
A1-32	QVQLQESGPGLVKPSQTLSLTCTVSGGSISSG GYYWSWIRQHPGKGLEWIGESTHSGSTNYN PSLDSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGRDGYYLDQWGQGTLVTVSS SEQ ID NO. 92	LPVLTQPASVSGSPGQSITISCTGTSFD VGGYPYVSWYQQHPGKAPKLMIYDVS DRPSGVSTRFSGSKSGNTASLTISGLQ AEDEADYYCSSFRSSAALVVFGGGTKL TVL SEQ ID NO. 93

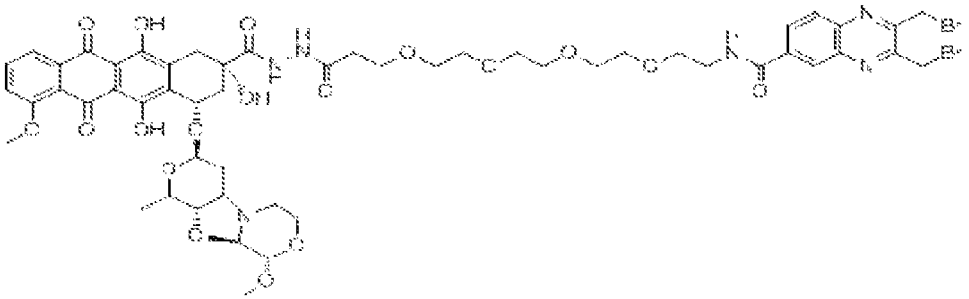
We claim:

1. An antibody drug conjugate (ADC) composition comprising an IgG antibody that binds to c-Met, a conjugation linker moiety that binds to both Cys residues in the hinge region of an IgG antibody and a toxin moiety.

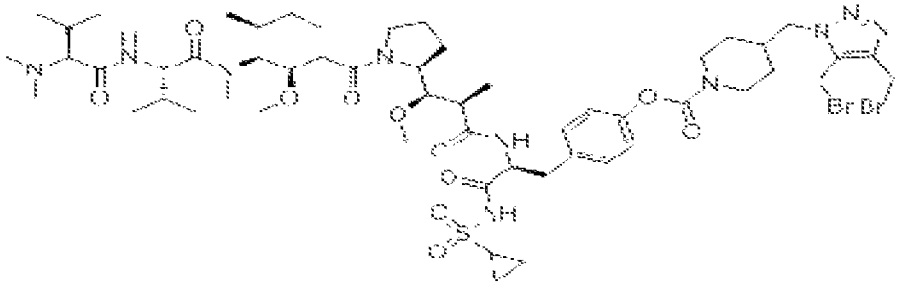
2. The ADC composition of claim 1, wherein the toxin moiety is a tubulin inhibitor or a doxorubicin analog.

3. The ADC composition of claim 1, wherein the antibody is an IgG antibody from the H8 (heavy/light SEQ ID NOs 19/20) family or is a B12 (heavy/light SEQ ID NOs 7/8), wherein the H8 antibody family is selected from the group consisting of H8-A2, H8-9, H8-9EE8L3, H8-C1, H8-D4, H8-D5, H8-D6, H8-D10, H8-E5, H8-G7, H8-H6, H8-2A2, H8-2B1, H8-2B2, H8-2B4, H8-2B7, H8-A7P, H8-9EH11L, H8-9EH11L, and H8-6AG2H3.

4. The ADC composition of claim 1, wherein the conjugated toxin is



or



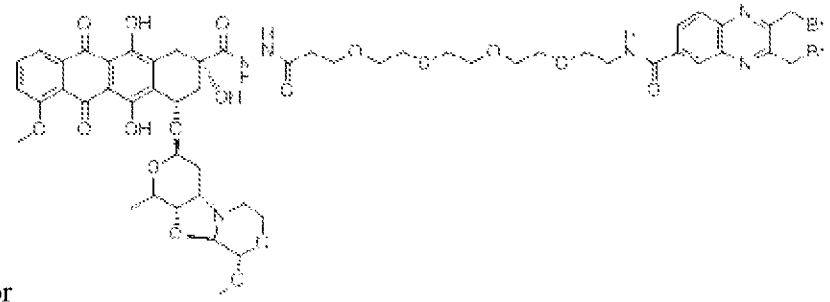
5. A method for treating breast cancer, comprising administering an effective amount of an antibody drug conjugate (ADC) composition comprising an IgG antibody that binds to c-Met, a conjugation linker moiety that binds to both Cys residues in the hinge region of an IgG antibody and a toxin moiety.

6. The method for treating breast cancer of claim 5, wherein the toxin moiety is a tubulin inhibitor or a doxorubicin analog.

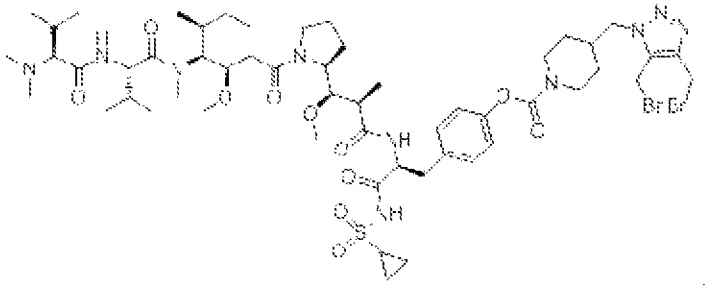
7. The method for treating breast cancer of claim 5, wherein the antibody is an IgG antibody from the H8 (heavy/light SEQ ID NOs 19/20) family or is a B12 (heavy/light SEQ ID NOs 7/8), wherein the H8 antibody family is selected from the group consisting of H8-A2, H8-9, H8-9EE8L3, H8-C1, H8-D4, H8-D5, H8-D6, H8-D10, H8-E5, H8-G7, H8-H6,

H8-2A2, H8-2B1, H8-2B2, H8-2B4, H8-2B7, H8-A7P, H8-9EH11L, H8-9EH11L, and H8-6AG2H3.

8. The method for treating breast cancer of claim 5, wherein the conjugated toxin is



or



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