

ANTI-DLL3 ANTIBODY AND METHOD OF MAKING AND USING THEREOF**CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims the benefit of the filing date of U.S. Provisional Application Ser. No. 63/599,433 filed November 15, 2023, under 35 U.S.C. 119(e), the entire disclosures of which are incorporated by reference herein.

TECHNICAL FIELD

10 The present disclosure generally relates to the technical field of antibodies, antibody therapy, cancer immunotherapy, pharmaceutical composition, and methods of treating diseases.

BACKGROUND

World-wide, lung cancers account for the most deaths in men and women when compared to any other cancer. The main types of lung cancer are non-small cell lung cancer and (NSCLC) and small cell lung cancer (SCLC). About 80% to 85% of lung cancers are NSCLC, including the subtypes of adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Originated from different types of lung cells, these subtypes are grouped together under NSCLC because their treatment and prognoses (outlooks) are often similar.

20 Small cell lung cancer (SCLC) is the most aggressive form of lung cancers and makes up 15% of all lung cancers [1]. There are 250,000 estimated new SCLC cases globally each year [2]. Of these, there are 30,000-35,000 new cases in the United States [3]. Globally, it is estimated that there are at least 200,000 deaths caused by SCLCs [4]. Number of cases and deaths vary year-to-year due to the strong link between smoking habits and SCLC, and the 30-year lag associated with smoking and cancer progression [5]. SCLC diagnoses are split up into two categories which are dependent on the severity and stage of the cancer: Limited-Stage SCLC (LS-SCLC) and Extensive-Stage SCLC (ES-SCLC). Patients diagnosed with LS-SCLC respond well to chemotherapy, with 75% exhibiting a complete response (CR). Conversely, patients diagnosed ES-SCLC rarely exhibit complete response rates above 30% [3]. In 2022, 80-85% of SCLC diagnoses were categorized under ES-SCLC [6]. Even in cases of responses to treatments, ES-SCLC is associated with high
30 levels of relapse, rapid proliferation, metastasis in the brain, and development of chemoresistance [6]. Due to this, patients diagnosed with ES-SCLC receive poor prognoses.

Delta-like canonical Notch ligand 3 (also known as Delta-Like Ligand 3, DLL3) is a member of the Delta/Serrate/Lag2 (DSL) family of Notch receptor ligands. Additional members in mammals include DLL1, DLL4, JAG1, and JAG2 [10]. Notch signalling is a highly conserved intercellular signalling pathway that influences multiple cellular processes, including differentiation, proliferation, survival, and apoptosis. Notch signalling has been shown to play an important role in the development of pulmonary neuroendocrine cells [11]. DLL3 is an inhibitory ligand of the Notch receptor and plays a critical role in Notch signalling. DLL3 binds Notch receptors via cis interactions, leading to a highly specific modulatory effect [12]. DLL3 is a single transmembrane
40 protein of 619 amino acids that compose a DSL domain, intracellular domain, and six epidermal

growth factor-like domains. The extracellular N-terminal DSL domain is highly conserved and is essential for binding to the Notch receptor. Under normal conditions, DLL3 is expressed in the Golgi apparatus; however, during pathogenesis, DLL3 is overexpressed and emerges on the cell membrane [10].

DLL3 is rarely detected in normal tissues but is highly expressed in SCLC. This highly specific expression profile has led to the development of a range of DLL3-specific therapeutics that target SCLC tumors. Indications for anti-DLL3 therapeutics also include additional tumors of neuroendocrine origin, including melanoma, glioblastoma multiforme, and small cell bladder cancer [11]. Furthermore, DLL3 has been suggested as a potential biomarker for better prognosis in patients with resectable pancreatic ductal adenocarcinoma (PDAC) [16]. Expression of DLL3 is regulated by achaete-scute homolog 1 (ASCL1), a transcription factor that is required for the normal development of pulmonary neuroendocrine cells. ASCL1 has been designated as an oncogenic driver in ~60% of all small cell lung cancers [11]. Furthermore, the Notch signalling pathway in SCLC is known to cause an upregulation in pro-oncogenic processes including: chemoresistance, differentiation, and proliferation [2]. DLL3 is an atypical ligand for Notch receptors, which is overexpressed on the surface of cancer cells in 80% of SCLCs with limited to no expression in normal lung tissue [7]. Through binding to Notch in a cis manner, DLL3 blocks cell to cell interactions and triggers internalization of Notch [8, 9]. The selective expression profile of DLL3 in neuroendocrine tumors, with low cytoplasmic expression in select normal tissues, make it a promising therapeutic target for the treatment of multiple cancer types, including SCLC.

Several immunotherapies targeting DLL3 in advanced SCLC are in development, including bispecific antibodies (BsAbs), chimeric antigen receptor T cells (CAR-T), and antibody-drug conjugates (ADC). Tarlatamab is a first-in-class, half-life extended, bispecific T-cell engager (HLE BiTE) that binds DLL3 and CD3 to induce T-cell mediated lysis [13,14]. Tarlatamab was the first DLL3-targeted therapy to be clinically evaluated for SCLC and has shown manageable safety with promising activity in patients with pre-treated SCLC during Phase 1 studies. However, larger randomized studies with longer follow up is required to precisely determine safety and efficacy [13]. Nonetheless, Tarlatamab was granted accelerated approval for ES-SCLC in 2024 (IMDELLTRA™, Amgen). AMG119 (Amgen), a CAR-T, has also shown high potency and long-lasting anti-tumour activity [15]. Rovalpituzumab tesirine (ROVA-T) is a first-in-class antibody drug conjugate (ADC) from Abbvie/StemCentRx. ROVA-T has shown regression in SCLC; however, clinical activity was modest, and overall survival did not exceed the current standard care, topotecan [15]. Due to these reasons, development of ROVA-T has since been discontinued. While the majority of anti-DLL3 antibody-based therapy or cell therapy have shown promising pre-clinical and clinical data, no ADCs have been approved for clinical use [10]. Therefore, a need remains for the development of efficacious therapeutics to target neuroendocrine tumours that express DLL3, including ES-SCLC.

SUMMARY

The following summary is illustrative only and is not intended to be in any way limiting. In addition to the illustrative aspects, embodiments, and features described above, further aspects, embodiments, and features will become apparent by reference to the drawings and the following detailed description.

In one aspect, the application provides Delta-Like Ligand 3 (DLL3) binding peptides. In one embodiment, the binding peptides have a binding specificity to human DLL3. In one embodiment, the DLL binding peptide comprises a variable heavy (VH) chain and a variable light (VL) chain.

In one embodiment, the VH chain comprises: CDR H1 having an amino acid sequence of SEQ ID: 104 (TYYMT), CDR H2 having an amino acid sequence of SEQ ID: 105 (VIYASGGTYATWAKG),
10 CDR H3 having an amino acid sequence of SEQ ID: 106 (AYPDNGDGLDI), CDR H1 having an amino acid sequence of SEQ ID: 110 (RNVIN), CDR H2 having an amino acid sequence of SEQ ID: 111 (IIATAGDTYYANWAKG), CDR H3 having an amino acid sequence of SEQ ID: 112 (KYGDTFDL), CDR H1 having an amino acid sequence of SEQ ID: 116 (SHYFN), CDR H2 having an amino acid sequence of SEQ ID: 117 (IVYASGSTYYASWAKG), CDR H3 having an amino acid sequence of SEQ ID: 118 (DRSVAYSNI), or CDR H1 having an amino acid sequence of SEQ ID: 120 (TYGMT), CDR H2 having an amino acid sequence of SEQ ID: 105 (VIYASGGTYATWAKG), CDR H3 having an amino acid sequence of SEQ ID: 119 (AYPDSGDGLDI), and

In one embodiment, the VL chain comprises: CDR L1 having an amino acid sequence of SEQ ID: 101 (QASEDISGWLA), CDR L2 having an amino acid sequence of SEQ ID: 102 (WASNLAS), and
20 CDR L3 having an amino acid sequence of SEQ ID: 103 (QSTFYGTSDVAA), CDR L1 having an amino acid sequence of SEQ ID: 107 (QASQSISSYLS), CDR L2 having an amino acid sequence of SEQ ID: 108 (QASTLAS), and CDR L3 having an amino acid sequence of SEQ ID: 109 (QGYDSNSVENA), CDR L1 having an amino acid sequence of SEQ ID: 113 (QASQSIGGNLA), CDR L2 having an amino acid sequence of SEQ ID: 114 (SASKLAS), and CDR L3 having an amino acid sequence of SEQ ID: 115 (QQAWSYSNVDNT), or CDR L1 having an amino acid sequence of SEQ ID: 101 (QASEDISGWLA), CDR L2 having an amino acid sequence of SEQ ID: 102 (WASNLAS), and CDR L3 having an amino acid sequence of SEQ ID: 121 (QSTFGGTSDVAA).

In one embodiment, the VH chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 17, 19, 21, 23, 25, 27, 28, or 29. In one embodiment, the VL
30 chain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16, 18, 20, 22, 24, 26, or 30.

In one embodiment, the VH chain and the VL chain have an amino acid sequence selected from SEQ ID NO: 17 and 16; 19 and 18; 21 and 20; 23 and 22; 25 and 24; 27 and 26; 28 and 22; 29 and 22; 29 and 30; or 28 and 30.

In one embodiment, the DLL3 binding peptide comprises a scFv domain. In one embodiment, the scFv domain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27,

28, 29, 30, 31, or 32. In one embodiment, the DLL3 binding peptide comprises a histidine residue linked to at least one end of the scFv domain.

In one embodiment, the DLL3 binding peptide comprises a Fab domain. In one embodiment, the Fc domain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 31, 32, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47.

In one embodiment, the DLL3 binding peptide further comprises a Fc domain linked to the Fab domain to provide a Fab-monoFc fusion protein.

10 In one embodiment, the DLL3 binding peptide comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29. In one embodiment, the DLL3 binding peptide comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 30, 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46.

In one aspect, the application provides antibodies or binding domains thereof having a binding specificity to human DLL3. The domain domains may be scFv domains or Fab domains. In some embodiments, the antibodies or binding domains may include a DLL3 binding peptide as disclosed herein.

20 In one embodiment, the antibody comprises a VH chain and a VL chain. In one embodiment, the VH chain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 17, 19, 21, 23, 25, 27, 28, or 29. In one embodiment, VL chain comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16, 18, 20, 22, 24, 26, or 30.

In one embodiment, the antibody comprises a heavy chain (HC) and a light chain (LC). In one embodiment, the HC comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% of sequence identity to SEQ ID NO: 37, 39, 41, 43, 45, or 31. In one embodiment, the LC comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% of sequence identity to SEQ ID NO: 32, 38, 40, 42, 44, or 46.

In one embodiment, the antibody comprises an amino acid sequence having at least 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% sequence identity to SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, or a combination thereof.

30 In one embodiment, the antibody comprises a mono-specific antibody, a bispecific antibody, a multi-specific antibody, a purified antibody, a humanized antibody, an IgG, or a combination thereof.

In one aspect, the application provides one or more isolated nucleic acid sequences encoding the antibodies, the binding domains, the DLL3 binding peptide as disclosed herein.

In one aspect, the application provides an expression vector or a host cell comprising the isolated nucleic acid sequences encoding the antibodies, the binding domains, the DLL3 binding peptide as disclosed herein.

In one aspect, the application provides an immunoconjugate. In one embodiment, the immunoconjugate comprises the antibody or DLL3 binding peptide conjugated to a drug unit through a linker. The example linker useful for such conjugation includes without limitation a covalent bond selected from an ester bond, an ether bond, an amine bond, an amide bond, a disulfide bond, an imide bond, a sulfone bond, a phosphate bond, a phosphorus ester bond, a peptide bond, a hydrazone bond or a combination thereof.

In one embodiment, the drug unit comprises a unit derived from a therapeutic agent, an imaging agent, a diagnostic agent, a radioisotope, or a combination thereof.

10 In one embodiment, the therapeutic agent comprises a cytotoxic agent, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof.

20 In one embodiment, the therapeutic agent comprises capecitabine, cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, epirubicin, pemetrexed, folinic acid, gemcitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lapatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, everolimus, temsirolimus, dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof.

In one embodiment, the radioisotope comprises deuterium, ¹³¹I, ³²P, ⁹⁰Sr, ⁹⁰Y, ⁸⁹Zr, ¹⁷⁷Lu, or a combination thereof., or a combination thereof.

In one aspect, the application provides pharmaceutical compositions. In one embodiment, the pharmaceutical composition comprises the antibodies or the DLL3 binding peptide. In one embodiment, the pharmaceutical composition comprises the immunoconjugate. In one embodiment, the pharmaceutical composition comprises a pharmaceutically acceptable carrier.

30 In one aspect, the application provides a method for producing the antibody of Claim 8, comprising culturing a host cell such that the DNA sequence encoding the antibody of Claim 8 is expressed, and purifying said antibody.

In one aspect, the application provides a method for producing the immunoconjugate of Claim 15, comprising conjugating the antibody of Claim 7 with the drug unit.

In one aspect, the application provides a method for treating or preventing a cancer, an autoimmune disease, or an infectious disease in a subject. In one embodiment, the method comprises administering to the subject an effective amount of the antibody or the DLL3 binding peptide. In one embodiment, the method comprises administering to the subject an effective amount of the immunoconjugate.

The cancer may be any DLL3 expressing cancer. In one embodiment, the cancer comprises lung cancer, small cell lung cancer (SCLC), large cell neuroendocrine carcinomas (LCNECs), medullary thyroid carcinomas (MTCs), cervical neuroendocrine carcinomas (CNECs), gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), bladder cancer, bladder NENs (BMENs), prostate cancer, NE prostate cancer (NEPC), merkel cell carcinoma (MCC), breast cancer, liver cancer, hepatocellular carcinoma (HCC), glioma, pancreatic cancer, or a combination thereof.

10 In one embodiment, the method further comprises co-administering an effective amount of a therapeutic agent. In one embodiment, the therapeutic agent comprises an antibody, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof. In one embodiment, the therapeutic agent comprises capecitabine, cisplatin, Cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, epirubicin, pemetrexed, folinic acid, gemcitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lapatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopanib, lapatinib, sunitinib, nilotinib, sorafenib, nab-palitaxel, Everolimus, temsirolimus, dabrafenib, vemurafenib, trametinib, 20 vintafolide, apatinib, crizotinib, periforsine, olaparib, bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof.

In one embodiment, the subject is a human.

In one aspect, the application provides solution comprising an effective concentration of the antibody, the DLL3 binding peptide, or the immunoconjugate. In one embodiment, the solution is blood plasma in a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

30 The foregoing and other features of this disclosure will become more fully apparent from the following description and appended claims, taken in conjunction with the accompanying drawings. Understanding that these drawings depict only several embodiments arranged in accordance with the disclosure and are, therefore, not to be considered limiting of its scope, the disclosure will be described with additional specificity and detail through use of the accompanying drawings, in which:

Figure 1 shows the results of direct sandwich ELISA for screening and identifying anti-DLL3 antibodies;

Figure 2 depicts FACS results showing the cross-species binding of chimeric antibodies to humans and cynomolgus monkeys DLL3-transfected CHO cells, compared to the background binding of the negative control;

- Figure 3** shows Bio-Layer Interferometry Affinity of chimeric antibodies bound recombinant human as well as recombinant cynomolgus monkey DLL3 at high affinity with KD values in 0.1 to 1 nM range;
- Figure 4** shows OCTET results indicating the cross-species binding of humanized anti-DLL3 clone 5018A1 GS to recombinant mouse and rat DLL3 by bio-layer interferometry at high affinity with KD values below 1 nM;
- Figure 5** shows OCTET results indicating the cross-species binding of humanized anti-DLL3 clones, SI-83M10 (5018A1 GS VH-N99S) and SI-83M8 (5029C10 FRS), to human DLL3 with high affinity and avidity at KD values within picomolar range;
- 10 **Figure 6** shows the flow cytometry histogram for screening purified antibodies indicating the surface and intercellular staining of humanized anti-DLL3 clones, SI-83M10 (5018A1 GS VH-N99S) and SI-83M8 (5029C10 FRS), and anti-DLL3 comparators, SI-83C1 (Rovalpituzumab) and SI-83C2 (Tarlata-mab), onto human cancer cell lines transiently transfected with a eukaryotic expression vector encoding human DLL3-EpCAM fusion construct (SEQ ID NO: 33), including (6A) ExpCHO cells, (6B) CORL279, (6C) NCI-H82, and (6D) MIA PaCa-2, where the black and grey lines represent stained and unstained cells, respectively;
- Figure 7** depicts the hierarchical clustering of the disclosed antibodies (5029C10, 5018A1, and 5257C8) and positive control antibodies (SI-83C1 and SI-83C2) in a binning matrix table, which indicates that 5018A1 recognizes a novel epitope;
- 20 **Figure 8** depicts antibody-dependent cell-mediated cytotoxicity (ADCC) of an anti-DLL3 antibody, SI-83M10 (a.k.a. 5018A1 GS VH-N99S) and controls ranging from 33 nM to 0.04 nM in a 3-fold serial dilution, including buffer alone, anti-DLL3 comparators (i.e., SI-83C1 and Rovalpituzumab), Rituximab (i.e., anti-CD20 antibody), and Cetuximab (i.e., anti-EGFR antibody) by using NK effector cells and Nuclear Red (NR) labeled target cells: (8A) DLL3-expressing Burkitt lymphoma cells (Daudi-NR), (8B) lung small cell carcinoma cells (COR-L279), (8C) CHO cells, and (8D) CHO expressing DLL3;
- Figure 9** depicts internalization of anti-DLL3 antibodies and lysosomal trafficking by using time-series live-cell fluorescence microscopy to quantify Red Calibrated Unit (RCU) indicative of the internalization and trafficking signals of an anti-DLL3 antibody (SI-83M10, 5018A1 GS VH-N99S),
- 30 anti-DLL3 comparator (SI-83C1, Rovalpituzumab), and an anti-CD20 antibody (Rituximab) at 10 nM concentrations in (9A) a DLL3-expressing lung small cell carcinoma line, COR-L279 cells; (9B) a DLL3-expressing epithelial cell line derived from a non-encapsulated primary lung tumor, SHP-77 cells, and (9C) DLL3-negative gastric cancer cell line, NUGC-4; showing that SI-83M10 was internalized more efficiently and trafficked more signals (indicative of cytotoxic payload in case of ADC) to lysosomes.
- Figure 10** shows the sequence alignment of heavy chains (10A) and light chain (10B) of lead and comparator anti-DLL3 antibodies, including SI-83M10, SI-83M8, 5257C8 BSM, FZ-AD005, GenSun mAb, Gocatamig, Obrixtamig, PT217, Rovalpituzumab (SI-83C1), and Tarlatamab (SI-83C2); and

Figure 11 depicts the sequence similarity between SI-83M10, SI-83M8, or 5257C8 BSM and the average of the remaining comparators by showing the percentage identity of CDRs (11A), framework only (11B), and variable region (CDRs + framework) (11C).

DETAILED DESCRIPTION

In the following detailed description, reference is made to the accompanying drawings, which form a part hereof. In the drawings, similar symbols typically identify similar components, unless context dictates otherwise. The illustrative embodiments described in the detailed description, drawings, and claims are not meant to be limiting. Other embodiments may be utilized, and other changes may be made, without departing from the spirit or scope of the subject matter presented herein. It will be readily understood that the aspects of the present disclosure, as generally described herein, and illustrated in the Figures, can be arranged, substituted, combined, separated, and designed in a wide variety of different configurations, all of which are explicitly contemplated herein.

The present disclosure provides, among others, peptides, proteins including for example antibody-like proteins, isolated antibodies or their binding fragments thereof, methods of making such peptides, proteins, or antibodies, monoclonal and/or recombinant monospecific antibodies or their binding fragments thereof, multi-specific antibodies or their binding fragments thereof, peptide-, protein-, or antibody-drug conjugates and/or immuno-conjugates composed from such peptides, proteins, antibodies or antigen binding fragments, pharmaceutical compositions containing the peptides, proteins, antibodies, monoclonal and/or recombinant monospecific antibodies or their binding fragments thereof, multi-specific antibodies or their binding fragments thereof, peptide-, protein-, antibody-drug conjugates and/or immuno-conjugates, the methods for making the peptides, proteins, antibodies and compositions, and the methods for treating cancer using the peptides, proteins, antibodies and compositions disclosed herein.

The terms “a”, “an” and “the” as used herein are defined to mean “one or more” and include the plural unless the context is inappropriate.

The terms “polypeptide”, “peptide”, and “protein”, as used herein, are interchangeable and are defined to mean a biomolecule composed of amino acids linked by a peptide bond.

The term “antigen” refers to an entity or fragment thereof which can induce an immune response in an organism, particularly an animal, more particularly a mammal including a human. The term includes immunogens and regions thereof responsible for antigenicity or antigenic determinants.

The terms “antigen- or epitope-binding portion or fragment”, “variable region”, “variable region sequence”, or “binding domain” refer to fragments of an antibody that are capable of binding to an antigen (such as EGFR in this application). The antigen-binding fragment (Fab) is a region (Fab region) on an antibody that binds to antigens. These fragments may be capable of the antigen-binding function and additional functions of the intact antibody. Examples of binding fragments include, but are not limited to, a single-chain Fv fragment (scFv) consisting of the

variable light chain (VL) and variable heavy chain (VH) domains of a single arm of an antibody connected in a single polypeptide chain by a synthetic linker, or a Fab fragment which is a monovalent fragment consisting of the VL, constant light (CL), VH and constant heavy 1 (CH1) domains.

Antibody fragments can be even smaller sub-fragments and can consist of domains as small as a single CDR domain, in particular the CDR3 regions from either the VL and/or VH domains (for example see Beiboer et al., J. Mol. Biol. 296:833-49 (2000)). Antibody fragments are produced using conventional methods known to those skilled in the art. The antibody fragments can be screened for utility using the same techniques employed with intact antibodies.

10 The "antigen- or epitope-binding portion or fragment", "variable region", "variable region sequence", or "binding domain" may be derived from an antibody of the present disclosure by a number of art-known techniques. For example, purified monoclonal antibodies can be cleaved with an enzyme, such as pepsin, and subjected to HPLC gel filtration. Papain digestion of antibodies produces two identical antigen binding fragments, called "Fab" fragments, each with a single antigen binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen combining sites and is still capable of cross-linking antigen. The appropriate fraction containing Fab fragments can then be collected and concentrated by membrane filtration and the like. For further description of general techniques for the isolation of active fragments of antibodies, see
20 for example, Khaw, B. A. et al. J. Nucl. Med. 23:1011-1019 (1982); Rousseaux et al. Methods Enzymology, 121:663-69, Academic Press, 1986.

The term "antibody" is used in the broadest sense and specifically covers single monoclonal antibodies and/or recombinant antibodies (including agonist and antagonist antibodies), antibody compositions with polyepitopic specificity, as well as antibody fragments (e.g., Fab, $F(ab')_2$, and Fv), so long as they exhibit the desired biological activity. In some embodiments, the antibody may be monoclonal, polyclonal, chimeric, single chain, multi-specific or multi-effective, human and humanized antibodies, as well as active fragments thereof. Examples of active fragments of molecules that bind to known antigens include Fab, $F(ab')_2$, scFv and Fv fragments, including the products of a Fab immunoglobulin expression library and epitope-binding
30 fragments of any of the antibodies and fragments mentioned above.

The term "Fv" refers to the minimum antibody fragment which contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) can recognize and bind antigen, although at a lower affinity than the entire binding site.

In some embodiments, antibody may include immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e. molecules that contain a binding site and that immunospecifically bind an antigen. A typical antibody refers to heterotetrameric protein comprising typically of two heavy (H) chains and two light (L) chains. Each heavy chain is comprised of a heavy chain variable domain (abbreviated as VH) and a heavy chain constant domain. Each light chain is comprised of a light chain variable domain (abbreviated as VL) and a light chain constant domain. The light chains of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

10 The VH and VL regions can be further subdivided into domains of hypervariable complementarity determining regions (CDR), and more conserved regions called framework regions (FR). Each variable domain (either VH or VL) is typically composed of three CDRs and four FRs, arranged in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4 from amino-terminus to carboxy-terminus. Within the variable regions of the light and heavy chains there are binding regions that interacts with the antigen.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG-1, IgG-2, IgG-3, and IgG-4; IgA-1 and IgA-2. The heavy chain

20 constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to conventional (polyclonal) antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to

30 their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present disclosure may be made by the hybridoma method first described by Kohler & Milstein, Nature, 256:495 (1975) or may be made by recombinant DNA methods (see, e.g., U.S. Pat. No. 4,816,567). "Recombinant" means the antibodies are generated using recombinant nucleic acid techniques in exogeneous host cells.

Monoclonal antibodies can be produced using various methods, including without limitation, mouse hybridoma, phage display, recombinant DNA, molecular cloning of antibodies directly from primary B cells, and antibody discovery methods (see Siegel. *Transfus. Clin. Biol.* 2002; Tiller. *New Biotechnol.* 2011; Seeber et al. *PLOS One.* 2014). Monoclonal antibodies may include “chimeric” antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 [1984]).

The term “humanized antibody” refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one (or more) human immunoglobulin(s). In addition, framework support residues may be altered to preserve binding affinity. Methods to obtain “humanized antibodies” are well known to those skilled in the art. (see, e.g., Queen et al., *Proc. Natl Acad Sci USA*, 86:10029-10032 (1989), Hodgson et al., *Bio/Technology*, 9:421 (1991)). Humanization of antibodies discovered in non-human species is a common practice not only to decrease the immunogenicity, but also to increase stability and remove sequence liabilities.

The terms “isolated” or “purified” refers to a biological molecule free from at least some of the components with which it naturally occurs. Either “isolated” or “purified,” when used to describe the various polypeptides disclosed herein, means a polypeptide that has been identified and separated and/or recovered from a cell or cell culture from which it was expressed. Ordinarily, a purified polypeptide will be prepared by at least one purification step. An “isolated” or a “purified” antibody refers to an antibody which is substantially free of other antibodies having different antigenic a binding specificity.

The term “immunogenic” refers to substances which elicit or enhance the production of antibodies, T-cells or other reactive immune cells directed against an immunogenic agent and contribute to an immune response in humans or animals. An immune response occurs when an individual produces sufficient antibodies, T-cells and other reactive immune cells against administered immunogenic compositions of the present disclosure to moderate or alleviate the disorder to be treated. While the immunogenic response generally includes both cellular (T cell) and humoral (antibody) arms of the immune response, antibodies directed against therapeutic proteins (anti-drug antibodies, ADA) may consist of IgM, IgG, IgE, and/or IgA isotypes.

The terms “specific binding”, “specifically binds to”, or “is specific for a particular antigen or an epitope” means that the binding is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control molecule, which generally is a molecule of similar structure that does not

have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target.

The term “affinity” refers to a measure of the attraction between two polypeptides, such as antibody/antigen, receptor/ligand, etc. The intrinsic attraction between two polypeptides can be expressed as the binding affinity equilibrium dissociation constant (KD) of a particular interaction. A KD binding affinity constant can be measured, e.g., by Bio-Layer Interferometry, where KD is the ratio of kdis (the dissociation rate constant) to kon (the association rate constant), as $KD = kdis/kon$.

Specific binding for a particular antigen or an epitope can be exhibited, for example, by an antibody having a KD for an antigen or epitope of at least about 10^{-4} M, at least about 10^{-5} M, at least about 10^{-6} M, at least about 10^{-7} M, at least about 10^{-8} M, at least about 10^{-9} M, alternatively at least about 10^{-10} M, at least about 10^{-11} M, at least about 10^{-12} M, or greater, where KD refers to the equilibrium dissociation constant of a particular antibody-antigen interaction. Typically, an antibody that specifically binds an antigen will have a KD that is 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for a control molecule relative to the antigen or epitope.

Also, specific binding for a particular antigen or an epitope can be exhibited, for example, by an antibody having a KA or Ka for an antigen or epitope of at least 20-, 50-, 100-, 500-, 1000-, 5,000-, 10,000- or more times greater for the epitope relative to a control, where KA or Ka refers to an association rate of a particular antibody-antigen interaction.

The present disclosure may be understood more readily by reference to the following detailed description of specific embodiments and examples included herein. Although the present disclosure has been described with reference to specific details of certain embodiments thereof, it is not intended that such details should be regarded as limitations upon the scope of the disclosure.

EXAMPLES

Example 1. Generation of Anti-DLL3 Antibodies

Rabbit antibodies:

Immunizations:

For immunization, New Zealand white rabbits were split into two cohorts (see Table 1A and 1A). Cohort 1 received a prime immunization of 100ug DLL3-His protein purchased from Acro (cat #DL3-H52H4) in Complete Freund's adjuvant. Rabbits then received 4 boosts at 7-day intervals containing one 50ug and two 25ug immunizations in alternating Incomplete Freund's adjuvant and Alum CpG2007. After the 4th immunization, rabbits received 3 boosts at 21-day intervals at 25ug of protein in alternating Incomplete Freund's adjuvant and Alum CpG2007. At 28-days post third boost, rabbits began another round of boosts at 21-day intervals for three 25ug boosts and two 10ug boosts in alternating Incomplete Freund's adjuvant and Alum CpG2007. At 63 days after the last boost, rabbits began another round of boosts at 21-day increments. These

boosts followed the following immunization strategy: one 10ug and four 5ug immunizations in alternating Incomplete Freund's adjuvant and Alum CpG2007. The same immunization strategy was used for the second cohort, except rabbits received DLL3-Fc protein purchased from Acro (cat #DL3-H5255). For both cohorts, whole peripheral blood was collected on days 28 through 329 (no blood collected on days 98, 245, and 308), and PBMC were isolated and stored in liquid nitrogen for future sorting.

PBMC Isolation:

10 Diluted blood at a 1:1 ratio, with DPBS, was layered onto 15mL of Lympholyte Cell Separation Media (Cedarlane, Cat. CL5050) in a 50mL tube. To obtain a layer of PBMCs, tubes were centrifuged at 2500rpm for 30 minutes at room temperature with no break. The white layer of PBMCs was then carefully removed and placed into a clean 50mL tube and diluted with DPBS to 50mL. Cells were then pelleted by centrifugation at 2500rpm for 10 minutes at room temperature with break. Any remaining red blood cells, RBCs, were then lysed by RBC lysis buffer (Qiagen, Cat. No. 158904). Briefly, cells were resuspended in 10mL of RBC lysis buffer and incubated at room temperature for 5 minutes. Lysis was then neutralized with 40mL of DPBS. Cells were pelleted again by centrifugation at 2500rpm for 10 minutes at room temperature. PBMCs were then prepared for storage by resuspending in 10% DMSO in FBS at a final concentration of $\leq 5 \times 10^7$ cells per ml.

Isolation of Rabbit B-Cells by FACS:

20 Rabbit PBMCs were thawed in immune cell media (ICM). Once thawed, cells were stained in an antibody staining mix containing specific rabbit B-cell markers. B-cells were enriched from thawed PBMCs through magnetic-activated cell sorting (MACS) by a QuadroMACs Separator magnet (Miltenyi Biotec, Cat. No. 130-090-976). Following MACS separation, cells were stained with live/dead efluor780 viability dye (ebioscience, Cat. No. 65-0865-14), washed, resuspended in buffer, and kept at 4°C until cells were sorted by Fluorescence Activated Cell Sorting (FACS).

Prior to sorting B-cells, appropriate compensation was performed by sorter software and manual adjustments. To obtain live and IgG-positive rabbit B-cells, gates were adjusted through manual adjustments. Single B-cells were sorted from the final gate into 96-well plates which contained previously prepared B-cell culture media containing ICM, rabbit splenocyte conditioned media, and feeder cells. A total of 7 sorts were completed and up to 33 plates were sorted. Plates were incubated at 37°C with 5% CO₂ for 12 days prior to screening.

Antibody Screen by ELISA:

30 Prior to ELISA screening, B-cell culture supernatants were harvested from their respective culture plates and stored for screening at 4 °C. PBMCs remaining in the culture plates were stored in RNA Later (Invitrogen, Cat. No. AM7021) at -80 °C for later RT-PCR amplification of the antibody variable regions. IgG secretion and DLL3 binding of B-cell cultures were screened by direct sandwich ELISA. Flat bottom ELISA plates were coated with 1 ug/mL anti-rabbit IgG Fc fragment (Jackson ImmunoResearch, Cat. No. 111-005-046) or Human DLL3-His (Acro, Cat. No.

DL3-H52H4) and incubated at 4 °C overnight. Plates were then washed three times with 1X PBST and then blocked with 2% BSA in DPBS for 1 hour at room temperature. Once blocked, plates were then washed as described previously and then a 1:10 dilution, diluted in 2% BSA in DPBS, of B-cell supernatant was added to each plate and incubated for 1 hour at 4 °C. Following incubation with primary antibody, plates were again washed as described previously. Anti-Rabbit IgG secondary antibody conjugated to HRP (Jackson ImmunoResearch, Cat. No. 111-035-046) was then added at a 1:15,000 dilution, diluted in 2% BSA in DPBS, and incubated for 30 minutes at 4 °C. Plates were washed, and bound antibody was detected by TMB substrate (ThermoFisher Scientific, Cat. No. SS04). Plates were incubated for 10 minutes at room temperature and reactions were quenched by commercial stop solution (ThermoFisher Scientific, Cat. No. SS04). Plates were read by a spectrophotometer at 450nm. Detection of rabbit IgG antibodies specific to DLL3 were confirmed based on OD values which exceeded secondary only negative control.

The results of direct sandwich ELISA for screening and identifying anti-DLL3 antibodies are shown in Figure 1. For Sort #1, 11.1% of B-cells sorted were IgG-positive. A total of 2 clones bound to DLL3-His. For Sort #2, 16.7% of B-cells sorted were IgG-positive. A total of 2 clones bound to DLL3-His. For Sort #3, a total of 4 clones bound to DLL3-His. For Sort #6, 10.1% of B-cells sorted were IgG-positive. A total of 6 clones bound to DLL3-His. All clones that bound to the DLL3-His protein were forwarded for amplification of antibody variable regions to identify heavy and light chain sequences.

Example 2. Rabbit/Human Chimeric Monoclonal Antibodies:

Amplification of Antibody Variable Regions:

B-cell clones selected through ELISA screening were thawed from storage at -80°C. Primers specific to the leader sequence and constant region of the rabbit IgG and rabbit kappa sequences were used to amplify heavy and light chain variable sequences by multiplex RT-PCR. In a secondary PCR, amplicons were further amplified using nested primers containing restriction sites. Heavy chain and light chain amplicons were cloned into an expression vector containing human IgG1 or human IgK, respectively. Sequence-verified expression plasmids were transiently co-transfected into 293 HEK cells for rabbit/human chimeric antibody production.

Characterization of Chimeric Anti-DLL3 Antibodies – Flow Cytometry:

The supernatants that contained recombinant antibodies were screened for binding to surface expressed DLL3 by flow cytometry. Under normal conditions, DLL3 is localized intracellularly at the Golgi apparatus. To facilitate surface expression in transfected cells, a DLL3-EpCAM fusion construct was utilized. The DLL3-EpCAM fusion construct contained the extracellular domain of DLL3; however, the DLL3 transmembrane domain was replaced with the EpCAM membrane domain. ExpiCHO cells were transiently transfected with eukaryotic expression vectors encoding human or cynomolgus monkey DLL3-EpCAM fusion constructs (SEQ ID NO: 33-34). ExpiCHO cells transfected with irrelevant DNA were used as a negative control. Two days after transfection, cells were collected, stained with cell tracker dye (ThermoFisher

Scientific, Cat. No. C34565), combined, and plated at $\sim 1.5 \times 10^5$ cells per well. Cells were stained with chimeric antibodies serially diluted from 10 $\mu\text{g/ml}$ to 40 ng/ml for 1 hour at 4°C . Cells were washed, then stained with PE-conjugated anti-rabbit IgG Fc secondary antibody (Jackson ImmunoResearch, Cat. No. 111-605-008) for 30 minutes at 4°C . Cells were washed, resuspended in FACS buffer, and binding was determined by flow cytometry using a BD Fortessa flow cytometer. Clones expressing antibodies that bound human and cynomolgus monkey DLL3 were selected for further screening. For instance, 5018A1 and 5029C10 are the exemplary antibodies capable of binding to both human and cynomolgus monkey DLL3-transfected CHO but not to the negative control (see Figure 2).

10 Characterization of Chimeric Anti-DLL3 Antibodies – OCTET Affinity:

The supernatants that contained recombinant antibodies were validated for binding to DLL3 by bio-layer interferometry (also referred to in the patent as OCTET) using a ForteBio Octet Red 384 instrument. Antibodies were diluted to 10 $\mu\text{g/ml}$ and captured onto anti-human Fc biosensors. Antibody-coated sensors were associated with a 1:3 dilution series of recombinant human DLL3 extracellular domain (Acro Biosystems, Cat. No. DL3-H52H4) starting at 300nM. Following baseline establishment in kinetics buffer, the dissociation of DLL3 from antibody was measured by bio-layer interferometry. Manufacturer-provided software was used to calculate curve fits and affinity. The results of bio-Layer interferometry affinity of disclosed antibodies indicated that chimeric antibodies bound recombinant human DLL3 at high affinity with KD values
20 in 0.1 to 1 nM range (Figure 3). And all antibodies bound recombinant both human and cynomolgus monkey DLL3.

Cross-Species Binding to Mouse and Rat DLL3:

Humanized anti-DLL3 clone 5018A1 GS was analyzed for cross-species binding to mouse and rat DLL3 by OCTET following methods described in earlier examples. As shown in Figure 4, humanized 5018A1 GS bound recombinant mouse and rat DLL3 by bio-layer interferometry at high affinity with KD values below 1 nM, although OCTET response and affinity decreased following affinity modulation.

Example 3. Humanized Anti-DLL3 Antibodies

Humanization of Heavy and Light Chain Variable Regions:

30 The heavy and light chain variable regions of antibodies selected as leads were humanized using the 'Predict Humanizing Mutations' algorithm in Discovery Studio. Methods chosen for humanization included best single mutation (BSM), frequent residue substitution (FRS), or germline graft (GS). For 5029C10, humanized sequences were also obtained using computationally-derived methods. DNA sequences encoding the humanized antibody VH and VL regions were cloned into mammalian expression vectors containing human IgG1/kappa constant regions using gene fragments (Genewiz). Sequence analysis revealed an NG motif within CDR-H3 of the heavy chain for clone 5018A1. To remove any liability for deamidation, a series of mutants at either the asparagine or glycine residues were generated with no significant effect on

expression, aggregation, or binding. Clone 5018A1 was further engineered to modulate affinity. Mutations were introduced into the heavy and/or light chain CDRs to obtain lower affinity. The profile of engineered clones, including ExpiCHO transfection titer and percent protein of interest (%POI) following purification, is shown in Table 2A.

Antibody Binning:

The epitopes of antibodies were binned by Bio-Layer Interferometry (i.e., OCTET) In-Tandem Assay using a ForteBio OCTET Red 384 instrument. Biotinylated recombinant human DLL3 full-length protein (Acro Biosystems, Cat. No. DL3-H82E4, 10 µg/ml) was captured onto streptavidin-conjugated biosensors, then associated with 10 µg/ml of antibody (i.e., 1st association). Sensors were then moved to wells containing a different antibody (i.e., 2nd association). Using the instrument software, antibodies were binned based off hierarchical clustering of the change in response from the 1st association to the 2nd association. To determine blocking or nonblocking antibody pairs, a threshold was set at the appropriate self-binding signal. Antibodies that blocked binding were clustered into the same bin and considered to have similar epitopes. Antibodies that did not block binding were clustered into separate bins and considered to have different epitopes.

OCTET Affinity:

Humanized antibody supernatants were used for characterizing OCTET and a summary for the engineered clone binding affinity is summarized in Table 2B. High affinity binding was detected for humanized clone supernatants by bio-layer interferometry, with affinities between 0.2 to 4 nM. The N99S mutation for 5018A1 did not significantly alter the affinity. Further mutations to 5018A1 for affinity modulation successfully decreased the binding affinity from 0.5 nM to 30 nM.

OCTET Avidity:

Bio-layer interferometry was also used to evaluate engineered antibody avidity to recombinant human DLL3. Biotinylated recombinant human DLL3 (10 µg/ml) was captured onto streptavidin biosensors, then associated with antibodies diluted 1:3 from 300 nM (Table 2C). Sensors were moved to wells containing kinetics buffer to analyze dissociation of the antibody/DLL3 complex. Curve fits and avidity calculations were analyzed using manufacturer-provided software.

OCTET Affinity and Avidity of Purified Antibodies:

Following Protein A purification, the disclosed humanized antibodies were characterized for binding affinity and avidity to human DLL3 by OCTET using methods described in previous examples. Purified, disclosed antibodies, SI-83M10 (also referred to within as 5018A1 GS VH-N99S) and SI-83M8 (also referred to within as 5029C10 FRS) bound human DLL3 with high affinity and avidity at KD values within picomolar range (Figure 5). Table 2D summarized that the avidity of lead clones to recombinant human DLL3 was within a range of 0.2 to 12 nM. The high avidity detected for 5018A1-GS-N99S was not calculated because the values had exceeded the limit of

the program software. However, further engineering for affinity modulation decreased the avidity to a detectable value of 0.5 nM. Mutations within both the heavy and light chains further decreased the avidity to 153 nM.

Flow Cytometry:

Using previously described flow cytometry methods, the on-cell binding of the disclosed humanized antibodies was detected (Figure 2). The humanized antibodies bound human and cynomolgus monkey DLL3-EpCAM on transiently transfected ExpiCHO. However, the N99S mutation for 5018A1 GS was not sufficient to alter on-cell binding activity, and additional mutations for affinity modulation were required to successfully decrease the binding. The binding was eliminated in 5018A1-N99S containing affinity modulation mutations in both the heavy and light chains as shown in Table 2D.

The binding of purified humanized antibodies to human cancer cells was characterized by using CORL279 (small cell lung cancer), NCI-H82 (lung carcinoma), MIA Paca-2 (pancreatic cancer), and ExpiCHO transiently transfected with a eukaryotic expression vector encoding human DLL3-EpCAM fusion construct (SEQ ID NO: 33) (Figure 6). Due to low surface expression and intracellular localization of DLL3, both surface and intracellular binding were analyzed (Figure 6, upper and lower panels, respectively). ExpiCHO cells transiently transfected with DLL3-EpCAM, as previously described, were included as a positive control.

Surface staining by flow cytometry utilized methods described in previous sections. For intracellular staining, cells were incubated with BD Fixation Buffer (BD, Cat. No. 554655) for 1 hour at 4°C. Cells were then washed 2 times in 1X BD Perm/Wash buffer (BD, Cat. No. 554723) and incubated in BD Perm/Wash (BD, Cat. No. 554723) buffer for 15 minutes at 4°C. Cells were then spun down and diluted to $\sim 1.5 \times 10^5$ cells per well and then stained with antibodies serially diluted from 10 µg/ml to 40 ng/ml for 1 hour at 4°C. Cells were washed, then stained with FITC-conjugated anti-human IgG Fc secondary antibody (Jackson ImmunoResearch, Cat. No. 10-096-003) for 30 minutes at 4°C. After incubation, cells were then washed, resuspended in FACS buffer, and binding was determined by flow cytometry using a BD Fortessa flow cytometer. As expected, binding was detected on the surface of transiently transfected ExpiCHO (Figure 6, upper panel).

Intracellular staining led to > 10-fold increase in binding (Figure 6, lower panel). For all three cell lines, minimal surface staining was detected. However, after intracellular staining, a detectable shift in binding was detected when compared to the unstained (i.e., secondary only) control (Figure 6B-6D). This is consistent with the low surface expression and high intracellular expression detected in DLL3-expressing cell lines. Binding was further detected with comparator clones, SI-83C1 and SI-83C2. The data demonstrate binding of the disclosed clones, SI-83M8 and SI-83M10 to cell models of neuroendocrine tumor origin.

Example 4. Comparative Advantages of Anti-DLL3 Antibodies as Candidates of Therapeutics

When targeting tumors with heterogenous antigen expression, antibody-dependent cellular cytotoxicity (ADCC) directed towards tumors with low density antigen expression is often more

efficient with high affinity antibodies. Conversely, high affinity antibodies, particularly those with slow dissociation rates, can lead to unwanted toxicity. For antibody drug conjugates, lowering the affinity of the antibody may lead to an improved therapeutic window. In addition, antibody internalization and downstream biological activities can be altered by the antibody binding site. Thus, antibodies targeting novel epitopes with different binding properties may improve therapeutic efficacy.

10 The disclosed antibodies (5018A1, 5029C10, and 5257C8) are humanized monoclonal antibodies that bind DLL3 with high affinity KD values ranging from 0.2 to 4 nM. Further disclosed are affinity modulated antibodies from parent clone, 5018A1. These include a low affinity variant with a relatively weaker KD of 30 nM. The binding affinity may greatly alter the efficacy and safety profile of a therapeutic antibody. When compared to clinical antibodies, Tarlatamab (Amgen, referred to within as SI-83C1) and Rovalpituzumab tesirine (Abbvie/StemCentRx, referred to within as SI-83C2), the affinities of the disclosed clones fall within an equivalent range (Table 2B).

20 The hierarchical clustering of the disclosed antibodies and positive control comparator antibodies SI-83C1 (Rovalpituzumab) and SI-83C2 (Tarlatamab) are shown in the binning matrix table (see Figure 7). One clone, 5257C8 was unidirectionally blocked by clone 5029C10, suggesting partial overlap of epitope (circled in Figure 7). None of the candidate antibodies blocked binding of or were blocked by the comparator antibodies, indicating binding of different epitopes than antibodies that are currently in development.

However, the binning result by bio-layer interferometry suggests that the disclosed clones bind DLL3 at a distinct epitope (see Clone 5018A1 in Figure 7).

Example 5. Antibody-Dependent Cell-Mediated Cytotoxicity

The Fc-mediated ADCC activity of antibody-based therapeutics can be compared in vitro to determine if there are any features of an antibody that enable a greater potential therapeutics mode of action. In this testing system, a low ADCC response may be due to the available antigen expression level over the duration of the assay. As a result, different binding properties, or antibody internalization may have an impact on the ADCC activity [17].

30 To test this, human primary NK (Natural Killer) cells were enriched from whole blood by negative selection, followed by density gradient centrifugation to become "effector" cells. Cells used for target cells were transduced to express Nuclear Red (NR) and included Daudi (Burkitt lymphoma B lymphoblast cell line), COR-L279 (lung small cell carcinoma line), CHO transduced to express DLL3, and non-transduced CHO. Target cells were treated with SI-83M10 (5018A1 GS VH N99S) and controls, including buffer alone, anti-DLL3 comparator Rovalpituzumab (SI-83C1), and experimental system controls Rituximab (anti-CD20) and Cetuximab (anti-EGFR), ranging from 33 nM to 0.04 nM in a 3-fold serial dilution. NK cells were added at a 5:1 E:T (effector : target) ratio to evaluate ADCC within the assay timeframe. ADCC was evaluated by loss of target cell NR signal using time-series fluorescent microscopy.

As shown in Figure 8A, the ADCC activity of CD20-specific Rituximab after 36 hours was detectable in the Daudi-NR target cell line, demonstrating efficacy in the assay system. As expected, no killing of 5018A1 GS or Rovalpituzumab was observed. Alternatively, ADCC activity from SI-83M10 was detected after 45 hours in the DLL3-expressing COR-L279-NR line (Figure 8B). This activity was significantly higher than Rovalpituzumab, which demonstrated no killing of the COR-L279 target cells. In transduced CHO, ADCC was not detected in CHO-NR, as expected (Figure 8C). However, both SI-83M10 and Rovalpituzumab showed substantial killing of CHO-NR-DLL3 after 60 hours. System controls Cetuximab and Rovalpituzumab were negative, as expected (Figure 8D). Taken together, the data demonstrate the enhanced ADCC activity of SI-83M10 in a lung small cell carcinoma line when compared to Rovalpituzumab.

Example 6. Internalization of Anti-DLL3 Antibodies and Lysosomal Trafficking

For many antibody-drug conjugate (ADC) drugs, a key step of the mechanism of action involves internalization [18]. Following antibody binding, internalization can facilitate the uptake of cytotoxic payload and trafficking to cancer cell lysosomes where lysosomes act as recycling centers within cells. Depending on the types of cytotoxic payload, cell lysis follows different mechanisms of action. Further, the mechanism of internalization and trafficking to lysosomes by anti-DLL3 antibodies may be the same, but the efficacy may depend on antibody binding.

The anti-DLL3 antibodies, SI-83M10 and comparator Rovalpituzumab, and experimental system control Rituximab, were labeled with FabFluor-pH red, an acid-sensitive fluorescent reagent that allows quantification of the trafficking of internalized proteins to acidic lysosomes. The fluorescent signal of FabFluor-pH red is dependent on the low pH environment of lysosomes. In this way, the accumulation of internalized antibodies into lysosomal compartments may be quantified over time using time-series fluorescent microscopy. Cell lines were thawed and cultured in RPMI media supplemented with Pen/Strep and 10% FBS. Cells were seeded at 10,000 cells/well in 50 μ l of culture in 96-well round bottom ULA plates (Corning). Culture media, anti-DLL3 antibodies, and controls were labeled with FabFluor-pH according to the manufacturer's instructions. Fifty microliters of FabFluor-pH labeled antibodies or control treatments were added to plated cells at 20 nM for 100 μ l final assay volume/well at a final concentration of 10 nM. Cells were cultured in an Incucyte S3 live imager (Sartorius) in a 37°C, 5% CO₂ humidified incubator for 20 hours.

Using time-series live-cell fluorescence microscopy, the internalization and trafficking signals were readily detectable for SI-83M10 at 10 nM concentration (Figure 9). The signals, Red Calibrated Unit (RCU), were automatically counted and plotted over time. In COR-L279 cells, a DLL3-expressing lung small cell carcinoma line, SI-83M10 was internalized more efficiently and trafficked more signals (indicative of cytotoxic payload in case of ADC) to lysosomes than Rovalpituzumab (Figure 9A). In SHP-77 cells, a DLL3-expressing epithelial cell line derived from a non-encapsulated primary lung tumor, internalization was similar between Rovalpituzumab and

SI-83M10 (Figure 9B). Finally, in the DLL3-negative gastric cancer cell line, NUGC-4, internalization of SI-83M10 and controls was not observed (Figure 9C).

Example 7. Sequence Alignment of Lead and Comparator Antibodies

To investigate the structural basis of unique binding characteristics, the coding sequences of disclosed (SI-83M10, SI-83M8, 5257C8 BSM) and comparator antibodies (see Table 3) were aligned in the Kabat numbering scheme using Geneious Prime bioinformatics software and shown in Figure 10. The complementarity-determining regions (CDRs) of heavy and light chains were aligned across all antibodies (boxed in upper and lower panels of Figure 10A, 10B). The percentage identity for all CDRs only, the framework regions (FRs) only, and the entire variable region (CDRs + FRs) were calculated for comparison in Figure 11A, 11B, and 11C, respectively. Of the aligned CDR sequences, SI-83M10 shared 13-46% identity with each comparator whereas each comparator shared 25-45% identity with another comparator. An exception to this comparison is Gocitamig and Obrixtamig, which shared only 5.6% identity. Similarly, SI-83M8 shared 24-45% identity with each comparator and 5257C8 BSM shared 14-67% identity. The wide range of sequence identities between the disclosed sequences and comparators demonstrates the variability of therapeutic antibodies within the competitive landscape.

Using a two-tailed, one-sample T-test, the percentage identity of SI-83M10, SI-83M8, or 5257C8 BSM to a given comparator was then compared to the average of percentage identities among the remaining comparators. While differences in sequence were observed between all antibodies, significant differences ($P < 0.05$) in % identity between comparators and disclosed clones were only observed when compared to a small number of clinical antibodies. For example, the percent identity of SI-83M10 to FZ-AD005 was significantly lower than the combined percent identities of the listed comparators ($P < 0.0001$ for CDR only). The same was also detected for SI-83M10 and Gocitamig ($P = 0.013$ for CDR only). The percent identity of SI-83M8 was significantly lower than the combined percent identities of the listed comparators when compared to Tarlatamab ($P = 0.05$ for CDR only). 5257C8 BSM demonstrated the most sequence diversity to comparators with percent identity significantly lower than FZ-AD005 ($P = 0.0093$ for CDR only), Gensun ($P = 0.0331$ for CDR only), and Rovalpituzumab ($P = 0.0046$ for CDR only). The differences detected in the amino acid sequences that encode the primary structure of CDRs, while not entirely significant, underlie the characteristic features of the disclosed antibodies, including epitope binning (Figure 7) and consequently, the biological activity.

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TABLES

Table 1A. Immunization Protocol for Anti-DLL3 Antibody Generation – Cohort 1

Day Post-Immunization	Immunogen	Dose (µg)	Adjuvant	Whole Bleed
0	DLL3-His	100	Complete Freund's	No
7	DLL3-His	50	Incomplete Freund's	No
14	DLL3-His	25	Alum CpG2007	No
21	DLL3-His	25	Incomplete Freund's	No
28	DLL3-His	25	Alum CpG2007	Yes
49	DLL3-His	25	Incomplete Freund's	Yes
70	DLL3-His	25	Alum CpG2007	Yes
98	DLL3-His	25	Incomplete Freund's	No
119	DLL3-His	25	Alum CpG2007	Yes
140	DLL3-His	25	Incomplete Freund's	Yes
161	DLL3-His	10	Alum CpG2007	Yes
182	DLL3-His	10	Incomplete Freund's	Yes
245	DLL3-His	10	Alum CpG2007	No
266	DLL3-His	5	Incomplete Freund's	Yes
287	DLL3-His	5	Alum CpG2007	Yes
308	DLL3-His	5	Incomplete Freund's	No
329	DLL3-His	5	Alum CpG2007	Yes

Table 1B. Immunization Protocol for Anti-DLL3 Antibody Generation – Cohort 2

Day Post-Immunization	Immunogen	Dose (µg)	Adjuvant	Whole Bleed
0	DLL3-Fc	100	Complete Freund's	No
7	DLL3-Fc	50	Incomplete Freund's	No
14	DLL3-Fc	25	Alum CpG2007	No
21	DLL3-Fc	25	Incomplete Freund's	No
28	DLL3-Fc	25	Alum CpG2007	Yes
49	DLL3-Fc	25	Incomplete Freund's	Yes
70	DLL3-Fc	25	Alum CpG2007	Yes
98	DLL3-Fc	25	Incomplete Freund's	No
119	DLL3-Fc	25	Alum CpG2007	Yes
140	DLL3-Fc	25	Incomplete Freund's	Yes
161	DLL3-Fc	10	Alum CpG2007	Yes
182	DLL3-Fc	10	Incomplete Freund's	Yes
245	DLL3-Fc	10	Alum CpG2007	No
266	DLL3-Fc	5	Incomplete Freund's	Yes
287	DLL3-Fc	5	Alum CpG2007	Yes
308	DLL3-Fc	5	Incomplete Freund's	No
329	DLL3-Fc	5	Alum CpG2007	Yes

Table 2A. Profile of Engineered Clones and Controls to DLL3

Clone	Antibody Type	CDR Engineering			Expression Titer (ug/ml)	% POI	Subclone
		HC NG Mutation	Affinity Modulation Mutation				
			VH	VL			
5018A1	Humanized – GS	-	-	-	-	-	5018A1-GS
5018A1	Humanized – GS	N99S	-	-	53	99.11	5018A1-GS-N99S
5018A1	Humanized – GS	N99S	Y33G	-	43.9	99.56	5018A1-GS-N99S-Y33G
5018A1	Humanized – GS	N99S	Y33G	Y93G	69.4	99.6	5018A1-GS-N99S-Y33G-Y93G
5018A1	Humanized – GS	N99S	-	Y93G	59.1	99.18	5018A1-GS-N99S-Y93G
5029C10	Humanized – FRS	-	-	-	216.6	99.47	5029C10-FRS
5257C8	Humanized – BSM	-	-	-	-	-	5257C8-BSM
SI-83C1	Control mAb	-	-	-	-	-	-
SI-83C2	Control mAb	-	-	-	-	-	-

Table 2B. Binding Affinity of Engineered Clones and Controls to DLL3

Clone	OCTET Affinity					
	Human DLL3			Cyno DLL3		
	KD (M)	kon (1/Ms)	kdiss(1/s)	KD (M)	kon (1/Ms)	kdiss(1/s)
5018A1-GS	2.16E-10	4.34E+05	9.36E-05	2.60E-10	1.91E+05	4.95E-05
5018A1-GS-N99S	5.18E-10	2.98E+05	1.54E-04	<1.0E-12	5.20E+05	<1.0E-07
5018A1-GS-N99S-Y33G	1.95E-09	3.08E+05	6.01E-04	-	-	-
5018A1-GS-N99S-Y33G-Y93G	3.01E-08	4.34E+05	1.30E-02	-	-	-
5018A1-GS-N99S-Y93G	5.64E-09	3.92E+05	2.21E-03	-	-	-
5029C10-FRS	4.49E-10	1.49E-05	6.71E-05	-	-	-
5257C8-BSM	3.87E-09	9.09E+04	3.52E-04	8.66E-08	2.81E+04	2.43E-03
SI-83C1 Control	1.16E-09	6.70E+05	7.77E-04	2.79E-09	3.72E+05	1.04E-03
SI-83C2 Control	6.95E-10	6.33E+05	4.40E-04	8.09E-10	3.61E+05	2.92E-04

Table 2C. Binding Avidity of Engineered Clones and Controls to DLL3

	OCTET Avidity		
	Human DLL3		
Clone	KD (M)	kon (1/Ms)	kdis(1/s)
5018A1-GS-N99S (SI-83M10)	<1.0E-12	5.20E+05	<1.0E-07
5018A1-GS-N99S-Y33G	5.91E-10	4.44E+05	2.62E-04
5018A1-GS-N99S-Y33G-Y93G	1.53E-07	1.75E+05	2.68E-02
5018A1-GS-N99S-Y93G	2.19E-09	5.01E+05	1.10E-03
5029C10-FRS (SI-83M8)	2.49E-10	6.22E+05	1.55E-04
5257C8-BSM	1.24E-08	1.28E+05	1.58E-03
SI-83C1 (control)	3.89E-10	1.66E+06	6.43E-04
SI-83C2 (control)	1.91E-10	5.44E+05	1.04E-04

Table 2D. On-Cell Binding of Engineered Clones and Controls to DLL3

Clone	Human DLL3-EpCAM*	Cyno DLL3-EpCAM*
5018A1-GS	9312	5279
5018A1-GS-N99S	9139	4639
5018A1-GS-N99S-Y33G	2430	1467
5018A1-GS-N99S-Y33G-Y93G	No Binding	No Binding
5018A1-GS-N99S-Y93G	1667	814
5029C10-FRS	9951	1207
5257C8-BSM	1734	730
SI-83C1 Control	10977	7136

*Transfected ExpiCHO (MFI at 1 ug/ml)

Table 3. Summary of Anti-DLL3 Antibodies

Antibody Code	Antibody Name	Company	Antibody Background
SI-83M10	5018A1-GS-N99S	Systimmune	Humanized Rabbit mAb
SI-83M8	5029C10-FRS	Systimmune	Humanized Rabbit mAb
	5257C8-BSM	Systimmune	Humanized Rabbit mAb
SI-83C1	Rovalpituzumab	Abbvie	Humanized Mouse mAb
SI-83C2	Tarlatamab	Imdelltra, Amgen	Origin Not Indicated, scFv
	FZ-AD005	Shanghai Fudan	Origin Not Indicated, mAb
	GenSun mAb	GenSun	Origin Not Indicated Humanized ScFv
	Gocatamig	Harpoon Therapeutics	Humanized Llama VHH
	Obrixtamig	Boehringer Ingelheim	Humanized Mouse mAb
	PT217	Phanes, Hoffmann-La Roche	Humanized Mouse mAb

SEQUENCE LISTING

Antibody	LC-VR nucleotide Seq ID	HC-VR nucleotide Seq ID	LC-VR amino acid Seq ID	HC-VR amino acid Seq ID
5018A1	1	2	16	17
5029C10	3	4	18	19
5257C8	5	6	20	21
5018A1-GS	7	8	22	23
5018A1-BSM	52	49	53	50
5018A1-FRS	58	55	59	56
5029C10-FRS	9	10	24	25
5029C10-BSM	64	61	65	62
5029C10-GS	70	67	71	68
5029C10-AP01	-	-	86	85
5029C10-OAS01	-	-	88	87
5029C10-OAS02	-	-	90	89
5029C10-OAS03	-	-	92	91
5257C8-BSM	11	12	26	27
5257C8-FRS	76	73	77	74
5257C8-GS	82	79	83	80
501A8-GS VH-N99S	7	13	22	28
5018A1-GS VH-N99S VH-Y33G	7	14	22	29
5018A1-GS VH-N99S VH-Y33G VL-Y93G	15	14	30	29
5018A1-GS VH-N99S VL-Y93G	15	13	30	28

Antibody	LC amino acid Seq ID	HC amino acid Seq ID
5018A1-GS	38	37
5018A1-BSM	54	51
5018A1-FRS	60	57
5029C10-FRS	40	39
5029C10-BSM	66	63
5029C10-GS	72	69
5257C8-BSM	42	41
5257C8-FRS	78	75
5257C8-GS	84	81

501A8-GS VH-N99S	44	43
5018A1-GS VH-N99S VH-Y33G	44	45
5018A1-GS VH-N99S VH-Y33G VL-Y93G	46	45
5018A1-GS VH-N99S VL-Y93G	46	43
5018A1-GS Null Fc	32	31

Plasmid/Domain	Seq ID
Human DLL3 ECD EpCAM Nucleic Acid	33
Cyno DLL3 ECD EpCAM Nucleic Acid	34
Human IgG1 Amino Acid	35
Human CK Amino Acid	36
Human IgG1 Null Amino Acid	47
Human CK with Insertion Amino Acid	48

Antibody	VH			VL		
	CDRL1	CDRL2	CDRL3	CDRH1	CDRH2	CDRH3
5018A1	101	102	103	104	105	106
5029C10	107	108	109	110	111	112
5257C8	113	114	115	116	117	118
5018A1-GS VH-N99S-28	-	-	-	-	-	119
5018A1-GS VH-Y33G-29	-	-	-	120	-	-
5018A1-GS VL- Y93G -30	-	-	121	-	-	-

*CDR regions in amino acid sequences are in **bold**

>Seq ID 1: 5018A1 light chain variable region nucleic acid sequence

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CAGGCCAGTGAGGATATTAGCGTTGGTTGGCCTGGTATCAGCAGAAACCAGGGCAGCCTCCCAAGCT
CCTCATCTACTGGGCATCCAATCTGGCATCTGGGGTCTCATCGCGTTCAAAGGCAGTAGATCTGGGAC
AGAGTTCATCTCACCATCAGCGACCTGGAGTGTGCCGATTCTGCCACTTACTACTGTCAATCTACTTTT
ATGGTACTAGTGATGTTGCTGCTTTCGGCGGAGGGACCGAGGTGGTGNTCAAA

>Seq ID 2: 5018A1 heavy chain variable region nucleic acid sequence

CAGTGTCAGTCGCTGGAGGAGTCCGGGGGTCGCCTGGTCACGCCTGGGACACCCCTGACACTCACCTGC
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GAATGGATCGGAGTCATTTATGCTAGTGGTGGCACATACTACGCGACCTGGGCGAAAGGCCGATTACAC
ATCTCCAAAACCTCGACCACGATGGATCTGAAAATCACCAGTCCGACAACCGAGGACACGGCCACCTAT
TTCTGTGCCAGAGCCTATCCTGATAATGGTATGGATTGGACATCTGGGGCCCAGGGACCCTCGTCACC
GTCTCGAGC

>Seq ID 3: 5029C10 light chain variable region nucleic acid sequence

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CCAGGCCAGTCAGAGCATTAGTAGTTACTTATCCTGGTATCAGCAGAAACCAGGGCAGCGTCCCAAGCT
CCTGATCTATCAGGCATCCACTCTGGCATCTGGGGTCCCATCGCGGTTCAAAGGCAGTGGATCTGGGAC
ACAGTTCACTCTACCATCAGCGACCTGGAGTGTGCCGATGCTGCCACTTACTACTGTCAAGGCTATGAT
TCTAATAGTGTTGAGAATGCTTTCGGCGGAGGGACCGAGGTGGAGTTCAAA

>Seq ID 4: 5029C10 heavy chain variable region nucleic acid sequence

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ATCTCCAAAACCTCGTCGACCACGGTGGATCTGAAAATGACCAGTCTGACACCCGAGGACACGGCCACC
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GC

>Seq ID 5: 5257C8 light chain variable region nucleic acid sequence

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>Seq ID 6: 5257C8 heavy chain variable region nucleic acid sequence

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GAGC

>Seq ID 7: 501A8-GS light chain variable region nucleic acid sequence

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>Seq ID 8: 501A8-GS heavy chain variable region nucleic acid sequence

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CTCCAAGTCCAAGAACACCATGTACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTGTACTA
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>Seq ID 9: 5029C10-FRS light chain variable region nucleic acid sequence

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>Seq ID 10: 5029C10-FRS heavy chain variable region nucleic acid sequence

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TCC

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>Seq ID 12: 5257C8-BSM heavy chain variable region nucleic acid sequence

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>Seq ID 15: 5018A1-GS VL-Y93G light chain variable region nucleic acid sequence

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 GCTGATCTACTGGGCCTCCAACCTGGCCTCCGGCGTGCCCTCCAGGTTCTCCGGCTCCGGCTCCGGCACC
 GACTTACCCTGACCATCTCCTCCCTGCAGCCGAGGACTTCGCCACCTACTACTGCCAGTCCACCTTCGG
 CGGCACCTCCGACGTGGCCGCCTTCGGCGGCGGCACCAAGGTGGAGATCAAG

>Seq ID 16: 5018A1 light chain variable region amino acid sequence

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 TLISDLECADSATYYC**QSTFYGTSDVAA**FGGGTEVVXK

>Seq ID 17: 5018A1 heavy chain variable region amino acid sequence

QSLEESGGRLVTPGTPLTLTCTASGDFDN**TYYMT**WVRQAPGKGLEWIG**VIYASGGTYATWAKGR**FTISKTS
 TTMDLKITSPTTEDTATYFCAR**AYPDNGDGLDI**WGPGLTVTVSS

>Seq ID 18: 5029C10 light chain variable region amino acid sequence

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>Seq ID 19: 5029C10 heavy chain variable region amino acid sequence

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>Seq ID 20: 5257C8 light chain variable region amino acid sequence

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>Seq ID 21: 5257C8 heavy chain variable region amino acid sequence

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>Seq ID 22: 5018A1-GS light chain variable region amino acid sequence

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>Seq ID 23: 5018A1-GS heavy chain variable region amino acid sequence

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 SKSKNTMYLQMNSLRAEDTAVYYCARAYPDNGDGLDIWGQGLTVSS

>Seq ID 24: 5029C10-FRS light chain variable region amino acid sequence

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>Seq ID 25: 5029C10-FRS heavy chain variable region amino acid sequence

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>Seq ID 26: 5257C8-BSM light chain variable region amino acid sequence

DYQLTQSPSSVALTVGQRTINCQASQSIGGNLAWYQQKPGQRPKLLIYSASKLASGVPSRFSGSGSGTDFT
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>Seq ID 27: 5257C8-BSM heavy chain variable region amino acid sequence

QQQLQESGGRIKPGPEPLRLTCKTSGIDLSHYFNWVRQAPGKGLEWIGIVIYASGGTTYATWAKGRFTISKSTN
TVFLQMRLSRSEDATVYYCAGDRSVAYSNIWGQGTTLTVSS

>Seq ID 28: 5018A1-GS VH-N99S heavy chain variable region amino acid sequence

QVQLVESGGGLVQPGGSLRLSCAASGFDNFTYYMTWVRQAPGKGLEWVGVIYASGGTTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDATVYYCARAYPDSGDGLDIWGQGTTLTVSS

>Seq ID 29: 5018A1-GS VH-N99S VH-Y33G heavy chain variable region amino acid sequence

QVQLVESGGGLVQPGGSLRLSCAASGFDNFTYGMTWVRQAPGKGLEWVGVIYASGGTTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDATVYYCARAYPDSGDGLDIWGQGTTLTVSS

>Seq ID 30: 5018A1-GS VL-Y93G light chain variable region amino acid sequence

DVVMTQSPSSVSASVGDRVTITCQASEDISGWLAWYQQKPGQAPKLLIYWASNLASGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQSTFGGTSDVAAF¹GGGGTKVEIK

>Seq ID 31: 5018A1-GS null Fc heavy chain amino acid sequence

QVQLVESGGGLVQPGGSLRLSCAASGFDNFTYYMTWVRQAPGKGLEWVGVIYASGGTTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDATVYYCARAYPDSGDGLDIWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
RVEPKSCDKHTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMH
EALHNHYTQKSLSLSPG

>Seq ID 32: 5018A1-GS null Fc light chain amino acid sequence

DVVMTQSPSSVSASVGDRVTITCQASEDISGWLAWYQQKPGQAPKLLIYWASNLASGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQSTFYGTSDVAAF¹GGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVCTKSFNRC

>Seq ID 33: Nucleic acid sequence for human DLL3 ECD with EpCAM transmembrane and cytosolic domains

ATGGTGAGCCCTAGAATGAGCGGCCTGCTGTCTCAGACCGTGATCCTGGCCCTGATCTTCCTGCCTCAGA
CAAGACCCGCCGGCGTGTTTCGAGCTGCAAATCCATAGCTTCGGTCCCGGCCCGGCCCTGGTGACCTA
GAAGCCCTGCAGCGCTAGACTGCCCTGCAGACTGTTCTTCAGAGTATGCCTGAAACCCGGGCTGAGCG
AAGAGGCCGCCGAAAGTCCATGTGCCCTGGGAGCCGCCCTATCCGCGAGGGGGCCCGTGTATACCGAA
CAACCGGGCGCACCCGCCCGGACTTACCACTCCCCGACGGGTTGTTGCAAGTGCCCTTCAGAGACGCC
TGGCCCGGCACCTTCAGCTTCATCATCGAAACCTGGAGAGAAGAGCTGGGTGATCAGATCGGTGGCCC
GGCCTGGAGCCTTCTAGCACGGGTGGCCGGCAGAAGAAGACTGGCAGCCGGCGGCCCGTGGGCAAGA
GACATTCAGAGAGCCGGCGCCTGGGAGCTGAGATTAGCTACAGAGCTAGATGCGAACCCCGGCCGT
GGGCACCGCTGCACAAGACTGTGTAGACCTAGAAGCGCCCGTCCCGATGCGGCCCGGTCTTAGACC
CTGCGCCCCACTGGAAGACGAGTGTGAAGCCCCCTGGTTTGCCGTGCCGTTGCAGCCCCGAGCACGG
CTTCTGTGAACAGCCCCGGGAATGCAGATGCCTGGAAGGGTGGACTGGTCCCCTGTGCACCGTGCCCGT
GAGCACCTCGTCGTGCCTCTCTCCTAGAGGACCTAGCAGCGCAACGACCGGCTGCCTGGTGGCCGGCCC
CGGCCCTTGTGATGGCAACCCGTGCGCAAACGGCGGCTCATGCAGCGAGACCCCTAGAAGCTTCGAGT
GCACCTGCCCTAGAGGCTTCTACGGCCTGAGATGCGAGGTATCGGGGGTGACCTGTGCCGACGGCCCTT
GTTTTAATGGCGGGTTGTGCGTGGGAGGCGCGATCCCGACAGCGCCTACATCTGCCACTGTCCCCCG
GCTTCAAGGCAGCAACTGCGAGAAGAGAGTGACAGATGCAGCCTGCAGCCCTGCAGAAACGGCGGT
CTATGCCTCGACCTGGGCCACGCCCTGAGATGCAGATGCAGAGCGGGCTTCGCGGGCCCTAGATGTGA
ACATGATCTGGACGACTGTGCCGACGAGCATGCGCTAACGGAGGTACGTGTGTCGAAGGGGGAGGA
GCGCATCGATGCAGCTGCGCACTGGGCTTCGGAGGCAGAGACTGCAGAGAGAGAGCCGATCCGTGTGC
CGCACGGCCTTGTGCCACGGCGGCAGATGCTACGCCCACTTCAGCGGCCTGGTGTGCGCCTGTGCCCC
CGGCTACATGGGCGCGAGGTGCGAATTTCCCGTGCACCCGATGGAGCATCGGCATTGCCGCGAGCACC
TCCCGGCCTGCGGCCCGGTGACCCTCAGAGGTATTTATCTGGCGGAGGCGGCTCTGGCGCAGGCGTGA
TCGCCGTGATCGTGGTGGTGGTCATTGCCATCGTGGCTGGCATCGTGGTGTGCTGCTCATCTCCAGAAAGA
AGCGGATGGCCAAGTACGAGAAGGCCGAAATCAAAGAGATGGGCGAGATGCACAGAGAACTGAACGC
CTAG

>Seq ID 34: Nucleic acid sequence for cyno DLL3 ECD with EpCAM transmembrane and cytosolic domains

ATGGTGAGCCCTAGAATGAGCAGACTGCTGAGCCAAACCGTGATCCTGGCCCTGATCTTCATCCCCAA
GCTAGACCCGCCGGCGTATTGAACTTCAAATTCACAGCTTTGGCCCTGGTCCCGGCCCGGGCGCTCCAA
GAAGCCCTGCAGCGCTAGAGGCCCTGCCGACTGTTCTTTAGAGTGTGCCTGAAGCCCGGACTGAGCG
AGGAGGCGGCCGAGTCTCCCTGTGCGCTGGGCGCCGCATTGAGTGCGAGAGGCCCGTCTATACCGAA
CAACCTGAGGCTCTGCCCCGATCTGCCCCTGCCAACGGCCTGCTGCAAGTGCCCTTCAGAGACGCCT
GGCCCGGCACCTTCAGCCTGATCATCGAGACCTGGAGAGAGGAGCTGGGCGATCAGATCGGCGGCCCC
GCCTGGAGCCTGCTGGCTAGAGTGACAAGAAGAAGACTGGCCGCCGAGGCCCTGGGCTAGAG
ACATTCAGAGAGCCGGCGCCTGGGAGCTGAGATTAGCTACAGAGCTAGATGCGAACTTCGGGCCGTG
GGCACCGCCTGCACAAGATTATGCAGACCTAGAAGTGCTCCTAGCCGGTGTGGCCCTGGCTTGCGCCCC
TGCGCACCTTGGAAAGATGAGTGTGAAGCGCCCCCGGTGTGTAGGGCCGGCTGTAGCCTGGAGCACGG
CTTCTGCGAGCAGCCCGGCGAGTGCAGATGCCTGGAGGGCTGGACCGGCCCTGTGCATGGTGCCTG
TTTCCACAAGCAGCTGCCTGGGCCTGAGGGGGCTAGCTCAACTACGACCGGATGTCTGGTGGCCGGG

CCGGCCCATGCGACGGCAACCCATGTGCCAACGGCGGCTCATGCTCGGAGACCCCCGGCAGCTTCGAGT
 GCACCTGCCCTAGAGGCTTCTATGGTCTGAGATGCGAAGTGAGCGGCGTGACCTGCGCAGACGGCCCCCT
 GTTTAATGGCGGCTTGTGTGTGGGCGGCGCGGATCCCGATTGCGCCTACATCTGCCACTGCCCCCGG
 GCTTCAAGGCAGCAACTGCGAGAAGAGAGTGACAGATGCAGCCTGCAGCCCTGCAGAAACGGGGG
 GCTGTGCTGGACCTGGGCCACGCCCTGAGATGCAGATGCAGAGCCGGCTTCGCCGGCCCTAGATGCG
 AGCAGCAGCTGGACGATTGTGCCGGAAGGGCTTGCCTAACGGAGGTACTTGTGTTGAGGGCGGCGG
 GGCTCACAGATGCAGCTGCGCCCTGGGCTTCGGAGGGGAGAACTGCAGAGAAAGAGCTGACCCGTGC
 GCCGCGCGCCCTGCGCCACGGAGGCAGATGCTATGCCCATTTAGCGGCCTGGTTTGCCTGCGCC
 CCGGCTATATGGGTGCTAGATGCGAGTTCCCGTACACCCGGATGGCGTGTCTAGCTCTCCCGCAGCC
 CCACCTGGCCTGAGGCCCGGAGATCCCCAAAGATATCTG

>Seq ID 35: Human IgG1 amino acid sequence

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPS
 SLGTQTYICNVNHKPSNTKVDKRVKPSKDKHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVD
 VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
 KAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKL
 TVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPG

>Seq ID 36: Human CK amino acid sequence

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSSLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 37: 5018A1-GS heavy chain amino acid sequence

QVQLVESGGGLVQPGLSLRLSCAASGFDFT**TYMT**WVRQAPGKGLEWVG**VIYASGGTTYATWAKGR**FTI
 SKSKNTMYLQMNSLRAEDTAVYYCAR**AYPDNGDGLDI**WGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
 ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSLGTQTYICNVNHKPSNTKVDK
 RVEPKSCDKHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH
 NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
 TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH
 EALHNHYTQKSLSLSPG

>Seq ID 38: 5018A1-GS light chain amino acid sequence

DVVMQTSPSSVSASVGDRVTITC**QASEDISGWLAW**YQQKPGQAPKLLIY**WASNLAS**GVPSRFSGSGSGTD
 FTLTISLQPEDFATYYC**QSTFYGTSDVAA**FGGGTKVEIKVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
 KVQWKVDNALQSGNSQESVTEQDSKDYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 39: 5029C10-FRS heavy chain amino acid sequence

QVQLVESGGGLVKPGGSLRLSCAASGIDFSRNVINWVRQAPGKGLEWVGIIATAGDTYYANWAKGRFTISK
TSKNTVYLQMNSLRAEDTAVYYCAGKYGDTFDLWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEK
SCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPG

>Seq ID 40: 5029C10-FRS light chain amino acid sequence

DVVMTQSPSSLSASVGDRVTISCQASQSISSYLSWYQQKPGQAPKLLIYQASTLASGVPSRFSGSGSGTDFTL
TISLEPEDFATYYCQGYDSNSVENAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 41: 5257C8-BSM heavy chain amino acid sequence

QQLQESGGRLIKPGEPLRLTCKTSGIDLSHYFNWVRQAPGKGLEWIGIVYASGSTYYASWAKGRFTISKSTN
TVFLQMRLSRSED TAVYYCAGDRSVAYSNIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD
YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKSCD
KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE
EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT
CLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPG

>Seq ID 42: 5257C8-BSM light chain amino acid sequence

DYQLTQSPSSVALTVGQRTVINCQASQSIGGNLAWYQQKPGQRPKLLIYSASKLASGVPSRFSGSGSGTDFT
LTISLQSEDFATYYCQQAWSYSNVDNTFGGGTRVDIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 43: 5018A1-GS VH-N99S heavy chain amino acid sequence

QVQLVESGGGLVQPGGSLRLSCAASGFDFNTYYMTWVRQAPGKGLEWVGVIYASGGTTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDTAVYYCARAYPDSGDGLDIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
RVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH
EALHNHYTQKSLSLSPG

>Seq ID 44: 5018A1-GS VH-N99S light chain amino acid sequence

DVVMTQSPSSVSASVGDRVITTCQASEDISGWLAWYQQKPGQAPKLLIYWASNLAGVPSRFSGSGSGTD
FTLTISLQPEDFATYYCQSTFYGTSDVAAFGGGKTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 45: 5018A1-GS VH-N99S VH-Y33G heavy chain amino acid sequence

QVQLVESGGGLVQPGGSLRLSCAASGFDFTYGMTWVRQAPGKGLEWVGVIYASGGTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDTAVYYCARAYPDSGDGLDIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDK
RVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH
EALHNHYTQKSLSLSPG

>Seq ID 46: 5018A1-GS VH-N99S VL-Y93G light chain amino acid sequence

DVVMTQSPSSVSASVGDRVITTCQASEDISGWLAWYQQKPGQAPKLLIYWASNLAGVPSRFSGSGSGTD
FTLTISLQPEDFATYYCQSTFGGTSADVAAFGGGKTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 47: Human IgG1 null amino acid sequence

APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCAVSNKALPAPIEKTISKAK

>Seq ID 48: Human CK with insertion amino acid sequence

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVCTKSFNRGEC

>Seq ID 49: 5018A1 BSM heavy chain variable nucleic acid sequence

CAGGTGCAGCTGCAGGAGTCCGGCGGCAGGCTGATCAAGCCCCGGCGCCCCCTGAGGCTGTCCTGCAA
GGCCTCCGGCTTCGACTTCAACACCTACTACATGACCTGGGTGAGGCAGGCCCCCGCAAGGGCCTGGA
GTGGATCGGCGTGATCTACGCCTCCGGCGGCACCTACTACGCCACCTGGGCCAAGGGCAGGTTACCAT
CTCCAAGTCCACCAACACCATGTACCTGCAGATCAGGTCCCCCAGGTCCGAGGACACCGCCATCTACTAC
TGCGCCAGGGCCTACCCCGACAACGGCGACGGCCTGGACATCTGGGGCCAGGGCACCCCTGGTGACCGT
GTCCTCC

>Seq ID 50: 5018A1 BSM heavy chain variable amino acid sequence

QVQLQESGGRLIKPGAPLRLSCKASGFDFTYYMTWVRQAPGKGLEWIGVIYASGGTTYATWAKGRFTISK
STNTMYLQIRSPREDAIYYCARAYPDNGDGLDIWGQGLTVTVSS

>Seq ID 51: 5018A1 BSM heavy chain amino acid sequence

QVQLQESGGRLIKPGAPLRLSCKASGFDFTYYMTWVRQAPGKGLEWIGVIYASGGTTYATWAKGRFTISK
STNTMYLQIRSPREDAIYYCARAYPDNGDGLDIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGC
LVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEP
KSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKT
KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALH
NHYTQKSLSLSPG

>Seq ID 52: 5018A1 BSM light chain variable nucleic acid sequence

GACGTGCAGATGACCCAGTCCCCCTCCTCCGTGTCCGCCACCGTGGGCCAGAGGGTGACCATCAAGTGC
CAGGCCTCCGAGGACATCTCCGGCTGGCTGGCTGGTACCAGCAGAAGCCCGGCAAGCCCCCAAGCT
GCTGATCTACTGGGCTCCAACTGGCCTCCGGCGTGCCCTCCAGGTTCTCCGGCTCCGGCTCCGGCACC
GACTTCACCTGACCATCTCCTCCCTGCACTGCGACGACTTCGCCACCTACTACTGCCAGTCCACCTTCTA
CGGCACCTCCGACGTGGCCGCCTTCGGCGGCGGCACCAAGGTGGACGTGAAG

>Seq ID 53: 5018A1 BSM light chain variable amino acid sequence

DVQMTQSPSSVSATVGQRVTIKCQASEDISGWLAWYQQKPGKPPKLLIYWASNLASGVPSRFSGSGSGTD
FTLTISLQCDDFATYYCQSTFYGTSDVAAFGGGTKVDVK

>Seq ID 54: 5018A1 BSM light chain amino acid sequence

DVQMTQSPSSVSATVGQRVTIKCQASEDISGWLAWYQQKPGKPPKLLIYWASNLASGVPSRFSGSGSGTD
FTLTISLQCDDFATYYCQSTFYGTSDVAAFGGGTKVDVKVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE
AKVQWKVDNALQSGNSQESVTEQDSKDSSTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 55: 5018A1 FRS heavy chain variable nucleic acid sequence

CAGGTGCAGCTGGTGGAGTCCGGCGGCGGCCTGGTGAAGCCCGGCGGCTCCCTGAGGCTGTCCTGCGC
CGCCTCCGGCTTCGACTTCAACACCTACTACATGACCTGGGTGAGGCAGGCCCCCGCAAGGGCCTGGA
GTGGGTGGGCGTGATCTACGCCTCCGGCGGCACCTACTACGCCACCTGGGCCAAGGGCAGGTTACCAT
CTCCAAGTCCAAGAACACCATGTACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTGTACTA
CTGCGCCAGGGCCTACCCGACAACGGCGACGGCCTGGACATCTGGGGCCAGGGCACCTGGTGACCG
TGTCTCC

>Seq ID 56: 5018A1 FRS heavy chain variable amino acid sequence

QVQLVESGGGLVKPGGSLRLSCAASGFDFTYYMTWVRQAPGKGLEWVGVIYASGGTTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDTAVYYCARAYPDNGDGLDIWGQGLTVTVSS

>Seq ID 57: 5018A1 FRS heavy chain amino acid sequence

QVQLVESGGGLVKPGGSLRLSCAASGFDFTYYMTWVRQAPGKGLEWVGVIYASGGTTYATWAKGRFTI
SKSKNTMYLQMNSLRAEDTAVYYCARAYPDNGDGLDIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTA
ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDK
RVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL
TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMH
EALHNHYTQKSLSLSPG

>Seq ID 58: 5018A1 FRS light chain variable nucleic acid sequence

GACGTGGTGATGACCCAGTCCCCCTCCTCCGTGTCCGCCTCCGTGGGCGACAGGGTGACCATCTCCTGCC
AGGCCTCCGAGGACATCTCCGGCTGGCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCAAGCTG
CTGATCTACTGGGCCTCCAACCTGGCCTCCGGCGTGCCCTCCAGGTTCTCCGGCTCCGGCTCCGGCACCG
ACTTCACCCTGACCATCTCCTCCCTGGAGCCCGAGGACTTCGCCACCTACTACTGCCAGTCCACCTTCTAC
GGCACCTCCGACGTGGCCGCCTTCGGCGGGCCACCAAGGTGGAGATCAAG

>Seq ID 59: 5018A1 FRS light chain variable amino acid sequence

DVVMTQSPSSVSASVGDRVTISCSASEDISGWLAWYQQKPGQAPKLLIYWASNLASGVPSRFSGSGSGTDF
TLTISSLEPEDFATYYCSSTFYGTSDVAAFGGGTKVEIK

>Seq ID 60: 5018A1 FRS light chain amino acid sequence

DVVMTQSPSSVSASVGDRVTISCSASEDISGWLAWYQQKPGQAPKLLIYWASNLASGVPSRFSGSGSGTDF
TLTISSLEPEDFATYYCSSTFYGTSDVAAFGGGTKVEIKVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 61: 5029C10 BSM heavy chain variable nucleic acid sequence

CAGGTGCAGCTGGTGGAGTCCGGCGGCAGGCTGGTGAAGCCCGCGGCTCCCTGAAGCTGACCTGCAA
GACCTCCGGCATCGACTTCTCCAGGAACGTGATCAACTGGGTGAGGCAGGCCCCCGCAAGGGCCTGG
AGTGGATCGGCATCATCGCCACCGCCGGCGACACCTACTACGCCAACTGGGCCAAGGGCAGGTTACCA
TCTCCAAGACCTCCACCAACACCGTGTTCTCTGCAGATGAGGTCCCTGAAGTCCGAGGACACCGCATCTA
CTACTGCGCCGGCAAGTACGGCGACACCTTCGACCTGTGGGGCCCCGGCACCTGGTGACCGTGTCTC
C

>Seq ID 62: 5029C10 BSM heavy chain variable amino acid sequence

QVQLVESGGRLVKPGGSLKLTCKTSGIDFSSRNVINWVRQAPGKGLEWIGIIATAGDTYYANWAKGRFTISK
STNTVFLQMRLKSEDTAIYYCAGKYGDTFDLWGPGLTVTVSS

>Seq ID 63: 5029C10 BSM heavy chain amino acid sequence

QVQLVESGGRLVKPGGSLKLTCKTSGIDFSSRNVINWVRQAPGKGLEWIGIIATAGDTYYANWAKGRFTISK
STNTVFLQMRLKSEDTAIYYCAGKYGDTFDLWGPGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVK
DYFPEPVTWSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVKSC
DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPR
EEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSL
TCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHY
TQKSLSLSPG

>Seq ID 64: 5029C10 BSM light chain variable nucleic acid sequence

GACGTGCAGATGACCCAGTCCCCCTCCTCCCTGGCCGCTCCGTGGGCCAGAGGGTGACCATCAACTGC
CAGGCCTCCAGTCCATCTCCTCCTACCTGTCTGGTACCAGCAGAAGCCCGGCCAGAGGCCCAAGCTGC
TGATCTACCAGGCCTCCACCCTGGCCTCCGGCGTGCCCTCCAGGTTCAAGGGCTCCGGCTCCGGCACCCA
GTTACCCCTGACCATCTCCTCCCTGCAGTGCACGACTTCGCCACCTACTACTGCCAGGGCTACGACTCC
AACTCCGTGGAGAACGCCTTCGGCGGCGGCACAGGGTGGAGATCAAG

>Seq ID 65: 5029C10 BSM light chain variable amino acid sequence

DVQMTQSPSSLAASVGQRVTINCQASQSISSYLSWYQQKPGQRPKLLIYQASTLASGVPSRFGSGSGTQFT
LTISSLQDDFATYYCQGYDSNSVENAFGGGTRVEIK

>Seq ID 66: 5029C10 BSM light chain amino acid sequence

DVQMTQSPSSLAASVGQRVTINCQASQSISSYLSWYQQKPGQRPKLLIYQASTLASGVPSRFGSGSGTQFT
LTISSLQDDFATYYCQGYDSNSVENAFGGGTRVEIKVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

>Seq ID 67: 5029C10 GS heavy chain variable nucleic acid sequence

CAGGTGCAGCTGCTGGAGTCCGGCGGCGGCCTGGTGCAGCCCGGCGGCTCCCTGAGGCTGTCCTGCGC
CGCCTCCGGCATCGACTTCTCCAGGAACGTGATCAACTGGGTGAGGCAGGCCCCCGGCAAGGGCCTGG
AGTGGGTGGGCATCATCGCCACCGCGGCGACACCTACTACGCCAACTGGGCCAAGGGCAGGTTACCC
ATCTCCAAGACCTCCAAGAACACCGTGACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTG

TACTACTGCGCCGGCAAGTACGGCGACACCTTCGACCTGTGGGGCCAGGGCACCTGGTGACCGTGTCC
TCC

>Seq ID 68: 5029C10 GS heavy chain variable amino acid sequence

QVQLLESGGGLVQPGGSLRLSCAASGIDFSRNVINWVRQAPGKGLEWVGIIATAGDTYYANWAKGRFTISK
TSKNTVYLQMNSLRAEDTAVYYCAGKYGDTFDLWGQGLTVTVSS

>Seq ID 69: 5029C10 GS heavy chain amino acid sequence

QVQLLESGGGLVQPGGSLRLSCAASGIDFSRNVINWVRQAPGKGLEWVGIIATAGDTYYANWAKGRFTISK
TSKNTVYLQMNSLRAEDTAVYYCAGKYGDTFDLWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL
VKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSVTVPSSSLGTQYICNVNHKPSNTKVDKRVEPK
SCDKTHTCPPCPAPPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTK
PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV
SLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN
HYTQKSLSLSPG

>Seq ID 70: 5029C10 GS light chain variable nucleic acid sequence

GACGTGGTGATGACCCAGTCCCCCTCCTCCTGTCCGCTCCGTGGGCGACAGGGTGACCATCACCTGCC
AGGCCTCCCAGTCCATCTCCTCCTACCTGTCTGGTACCAGCAGAAGCCCGGCCAGGTGCCAAGCTGCT
GATCTACCAGGCCTCCACCCTGGCCTCCGGCGTGCCCTCCAGGTTCTCCGGCTCCGGCTCCGGCACCGAC
TTCACCCTGACCATCTCCTCCTGCAGCCCGAGGACGTGGCCACCTACTACTGCCAGGGCTACGACTCCA
ACTCCGTGGAGAACGCCTTCGGCGGCGGCACCAAGGTGGAGATCAAG

>Seq ID 71: 5029C10 GS light chain variable amino acid sequence

DVVMTQSPSSLSASVGDRVTITCQASQSISSYLSWYQQKPGQVPKLLIYQASTLASGVPSRFSGSGSGTDFTL
TISSLQPEDVATYYCQGYDSNSVENAFGGGTKEIK

>Seq ID 72: 5029C10 GS light chain amino acid sequence

DVVMTQSPSSLSASVGDRVTITCQASQSISSYLSWYQQKPGQVPKLLIYQASTLASGVPSRFSGSGSGTDFTL
TISSLQPEDVATYYCQGYDSNSVENAFGGGTKEIKVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC

>Seq ID 73: 5257C8 FRS heavy chain variable region nucleic acid

CAGCAGCTGGTGGAGTCCGGCGGCGGCCTGGTGAAGCCCGGCGGCTCCCTGAGGCTGTCCTGCGCCGC
CTCCGGCATCGACCTGTCCTCCCACTACTTCAACTGGGTGAGGCAGGCCCCGGCAAGGGCCTGGAGTG
GGTGGGCATCGTGACGCCTCCGGCTCCACCTACTACGCCTCCTGGGCCAAGGGCAGGTTACCATCTCC
AAGTCCAAGAACACCGTGTACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTGTACTACTGC
GCCGGCGACAGGTCCGTGGCCTACTCCAACATCTGGGGCCAGGGCACCTGGTGACCGTGTCTCTCC

>Seq ID 74: 5257C8 FRS heavy chain variable region amino acid

QQLVESGGGLVKPGGSLRLSCAASGIDLSSHYFNWVRQAPGKGLEWVGIVYASGSTYYASWAKGRFTISK
KNTVYLQMNSLRAEDTAVYYCAGDRSVAYSNIWGQGLTVTVSS

>Seq ID 75: 5257C8 FRS heavy chain amino acid sequence

QQLVESGGGLVKPGGSLRLSCAASGIDLSSHYFNWVRQAPGKGLEWVGIVYASGSTYYASWAKGRFTISK
KNTVYLQMNSLRAEDTAVYYCAGDRSVAYSNIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTPVSSSLGTQTYICNVNHKPSNTKVDKRVPEKS
CDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKP
REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH
YTQKSLSLSPG

>Seq ID 76: 5257C8 FRS light chain variable region nucleic acid sequence

GACTACGTGCTGACCCAGTCCCCCTCCTCCGTGTCCGTGTCCGTGGGCGACAGGGTGACCATCTCCTGCC
AGGCCTCCCAGTCCATCGGCGGCAACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAAGCTG
CTGATCTACTCCGCCTCCAAGCTGGCCTCCGGCGTGCCCTCCAGGTTCTCCGGCTCCGGCTCCGGCACCG
ACTTCACCCTGACCATCTCCTCCCTGGAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGCCTGGTC
CTACTCCAACGTGGACAACACCTTCGGCGGCGGCACCAAGGTGGAGATCAAG

>Seq ID 77: 5257C8 FRS light chain variable region amino acid sequence

DYVLTSPPSSVSVSGDRVTISCQASQSIGGNLAWYQKPGQAPKLLIYSASKLASGVPSRFSGSGSGTDFTL
TISSLEPEDFATYYCQQAWSYSNVDNTFGGGTKVEIK

>Seq ID 78: 5257C8 FRS light chain amino acid sequence

DYVLTQSPSSVSIVSGDRVTISCCQASQSIGGNLAWYQQKPGQAPKLLIYSASKLASGVPSRFSGSGSGTDFTL
 TISLEPEDFATYYCQQAWSYSNVDNTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREA
 KVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 79: 5257C8 GS heavy chain variable nucleic acid sequence

CAGCAGCTGGTGGAGTCCGGCGGCGGCTGGTGCAGCCCGGCGGCTCCCTGAGGCTGTCCTGCGCCGC
 CTCCGGCATCGACCTGTCCTCCCACTACTTCAACTGGGTGAGGCAGGCCCCGGCAAGGGCCTGGAGTG
 GGTGGGCATCGTGTACGCCTCCGGCTCCACCTACTACGCCTCCTGGGCCAAGGGCAGGTTACCATCTCC
 AAGTCCAAGAACACCGTGTACCTGCAGATGAACTCCCTGAGGGCCGAGGACACCGCCGTGTACTACTGC
 GCCGGCGACAGGTCCGTGGCCTACTCCAACATCTGGGGCCAGGGCACCTGGTGACCGTGTCTCTCC

>Seq ID 80: 5257C8 GS heavy chain variable amino acid sequence

QQLVESGGGLVQPGGSLRLSCAASGIDLSSHYFNWVRQAPGKGLEWVGIVYASGSTYYASWAKGRRFTISKS
 KNTVYLQMNSLRAEDTAVYYCAGDRSVAYSNIWGQGLTVTVSS

>Seq ID 81: 5257C8 GS heavy chain amino acid sequence

QQLVESGGGLVQPGGSLRLSCAASGIDLSSHYFNWVRQAPGKGLEWVGIVYASGSTYYASWAKGRRFTISKS
 KNTVYLQMNSLRAEDTAVYYCAGDRSVAYSNIWGQGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAAAGCLV
 KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEKS
 CDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTP
 REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVS
 LTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNH
 YTQKSLSLSPG

>Seq ID 82: 5257C8 GS light chain variable nucleic acid sequence

GACTACCAGCTGACCCAGTCCCCCTCCTCCGTGTCCGCCTCCGTGGGCGACAGGGTGACCATCACCTGCC
 AGGCCTCCCAGTCCATCGGCGGCAACCTGGCCTGGTACCAGCAGAAGCCCGGCCAGGCCCCCAAGCTG
 CTGATCTACTCCGCCTCCAAGCTGGCCTCCGGCGTGCCCTCCAGGTTCTCCGGCTCCGGCTCCGGCACCG
 ACTTCACCCTGACCATCTCCTCCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGCAGGCCTGGTC
 CTACTCCAACGTGGACAACACCTTCGGCGGCGGCACCAAGGTGGAGATCAAG

>Seq ID 83: 5257C8 GS light chain variable amino acid sequence

DYQLTQSPSSVSASVGDRVTITCQASQSIGGNLAWYQQKPGQAPKLLIYSASKLASGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQAWSYSNVDNTFGGGTKVEIK

>Seq ID 84: 5257C8 GS light chain amino acid sequence

DYQLTQSPSSVSASVGDRVTITCQASQSIGGNLAWYQQKPGQAPKLLIYSASKLASGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQAWSYSNVDNTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE
AKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

>Seq ID 85: 5029C10 AP01 heavy chain variable amino acid sequence

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNVINWVRQAPGKGLEWVGIIATAGDTYYANWAKGRFTISK
DSSKNTVYLQMNSLRAEDTAVYYCARKKYGDTFDLWGQGTLLTVSS

>Seq ID 86: 5029C10 AP01 light chain variable amino acid sequence

DIQMTQSPSSLSASVGDRVTITCQASQSISSYLSWYQQKPGKAPKLLIYQASTLASGVPSRFSGSGSGTEFTLI
SSLQPDDFATYYCQGYDSNSVENAFGQGTKVEIK

>Seq ID 87: 5029C10 OAS01 heavy chain variable amino acid sequence

QVHLVESGGGVVQPGKSLRLSCAASGIDFSRNVINWVRQAPGKGLEWIGIIATAGDTYYANWAKGRFTISK
DSSRNTVYLQMDSLRAEDTAMYYCAGKYGDTFDLWGQGTLLTVSS

>Seq ID 88: 5029C10 OAS01 light chain variable amino acid sequence

DVQMTQSPSTLSASVGDSTITCQASQSISSYLSWYQQKPGKAPKLLIYQASTLASGVPSRFSGSGSGTEFTL
AISNLQPDDFATYYCQGYDSNSVENAFGQGTEVEIK

>Seq ID 89: 5029C10 OAS02 heavy chain variable amino acid sequence

EVQLVESGGGLVQPGRSLTVSCTSGIDFSRNVINWVRQAPGKGLEWIGIIATAGDTYYANWAKGRFTISKD
SSKNTVYLQMNSLTNEDTAVYFCAGKYGDTFDLWGQGTLLTVSS

>Seq ID 90: 5029C10 OAS02 light chain variable amino acid sequence

DVQMTQSPSSLSASVGDRVITTCQASQSISSYLSWYQQKPGKRPKLLIYQASTLASGVPSRFSGSGSGTDFTL
TISSLQPEDVATYYCQGYDSNSVENAFGGGTKVEIK

>Seq ID 91: 5029C10 OAS03 heavy chain variable amino acid sequence

EVQLVESGGGLVQPGGSLRLSCEASGIDFSRNVINWVRQAPGKGLEWVGIIATAGDTYYANWAKGRFTISK
TSKNTVYLQMNSLKTEDTAVYYCARKKYGDTFDLWGKGTTTVSS

>Seq ID 92: 5029C10 OAS03 light chain variable amino acid sequence

DIQMTQSPSSLSASVGDRVITTCQASQSISSYLSWYQQKPGKAPKLLIYQASTLASGVPSRFSGSGSGTDFTLT
ISSLQPEDFATYYCQGYDSNSVENAFGGGTKVEIK

>Seq ID 101: 5018A1 CDR L1

QASEDISGWLA

>Seq ID 102: 5018A1 CDR L2

WASNLAS

>Seq ID 103: 5018A1 CDR L3

QSTFYGTSDVAA

>Seq ID 104: 5018A1 CDR H1

TYYMT

>Seq ID 105: 5018A1 CDR H2

VIYASGGTYATWAKG

>Seq ID 106: 5018A1 CDR H3

AYPDNGDGLDI

>Seq ID 107: 5029C10 CDR L1

QASQSISSYLS

>Seq ID 108: 5029C10 CDR L2

QASTLAS

>Seq ID 109: 5029C10 CDR L3

QGYDSNSVENA

>Seq ID 110: 5029C10 CDR H1

RNVIN

>Seq ID 111: 5029C10 CDR H2

IIATAGDTYYANWAKG

>Seq ID 112: 5029C10 CDR H3

KYGDTFDL

>Seq ID 113: 5257C8 CDR L1

QASQSIGGNLA

>Seq ID 114: 5257C8 CDR L2

SASKLAS

>Seq ID 115: 5257C8 CDR L3

QQAWSYSNVDNT

>Seq ID 116: 5257C8 CDR H1

SHYFN

>Seq ID 117: 5257C8 CDR H2

IVYASGSTYYASWAKG

>Seq ID 118: 5257C8 CDR H3

DRSVAYSNI

>Seq ID 119: 5018A1-GS VH-N99S CDR H3

AYPDSGDGLDI

>Seq ID 120: 5018A1-GS VH-Y33G CDR H1

TYGMT

>Seq ID 121: 5018A1-GS VL-Y93G CDR L1

QSTFGGTSDVAA

ANTI-DLL3 ANTIBODY AND METHOD OF MAKING AND USING THEREOF**CLAIMS**

What is claimed is:

1. A Delta-Like Ligand 3 (DLL3) binding peptide having a binding specificity to human DLL3, comprising a variable heavy (VH) chain and a variable light (VL) chain,

wherein the VH chain comprises:

CDR H1 having an amino acid sequence of SEQ ID: 104, CDR H2 having an amino acid sequence of SEQ ID: 105, CDR H3 having an amino acid sequence of SEQ ID: 106,

CDR H1 having an amino acid sequence of SEQ ID: 110, CDR H2 having an amino acid sequence of SEQ ID: 111, CDR H3 having an amino acid sequence of SEQ ID: 112,

CDR H1 having an amino acid sequence of SEQ ID: 116, CDR H2 having an amino acid sequence of SEQ ID: 117, CDR H3 having an amino acid sequence of SEQ ID: 118, or

CDR H1 having an amino acid sequence of SEQ ID: 120, CDR H2 having an amino acid sequence of SEQ ID: 105, CDR H3 having an amino acid sequence of SEQ ID: 119, and

wherein the VL chain comprises:

CDR L1 having an amino acid sequence of SEQ ID: 101, CDR L2 having an amino acid sequence of SEQ ID: 102, and CDR L3 having an amino acid sequence of SEQ ID: 103,

CDR L1 having an amino acid sequence of SEQ ID: 107, CDR L2 having an amino acid sequence of SEQ ID: 108, and CDR L3 having an amino acid sequence of SEQ ID: 109,

CDR L1 having an amino acid sequence of SEQ ID: 113, CDR L2 having an amino acid sequence of SEQ ID: 114, and CDR L3 having an amino acid sequence of SEQ ID: 115, or

CDR L1 having an amino acid sequence of SEQ ID: 101, CDR L2 having an amino acid sequence of SEQ ID: 102, and CDR L3 having an amino acid sequence of SEQ ID: 121.

2. The DLL3 binding peptide of Claim 1, wherein the VH chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 17, 19, 21, 23, 25, 27, 28, or 29; and wherein the VL chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 18, 20, 22, 24, 26, or 30.

3. The DLL3 binding peptide of Claim 1, wherein the VH chain and the VL chain have an amino acid sequence selected from SEQ ID NO: 17 and 16; 19 and 18; 21 and 20; 23 and 22; 25 and 24; 27 and 26; 28 and 22; 29 and 22; 29 and 30; or 28 and 30.

4. The DLL3 binding peptide of Claim 1, comprising

a scFv domain, wherein the scFv domain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, or 32, and

a Fab domain, wherein the Fc domain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 31, 32, 35, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, or 47.

5. The DLL3 binding peptide of Claim 4, comprising a histidine residue linked to at least one end of the scFv domain.

6. The DLL3 binding peptide of Claim 4, further comprising a Fc domain linked to the Fab domain to provide a Fab-monoFc fusion protein.

7. The DLL3 binding peptide of Claim 1, comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 37, 38, 39, 40, 41, 42, 43, 44, 45, or 46.

8. A scFv domain, comprising the DLL3 binding peptide of Claim 1.

9. A Fab domain, comprising the DLL3 binding peptide of Claim 1.

10. An antibody having a binding specificity to human DLL3, comprising the DLL3 binding peptide of Claim 1.

11. The antibody of Claim 10, wherein the VH chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 17, 19, 21, 23, 25, 27, 28, or 29, and wherein the VL chain comprises an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 18, 20, 22, 24, 26, or 30.

12. The antibody of Claim 10, comprising a heavy chain (HC) and a light chain (LC),

wherein the HC comprises an amino acid sequence having at least 98% of sequence identity to SEQ ID NO: 37, 39, 41, 43, 45, or 31; and

wherein the LC comprises an amino acid sequence having at least 98% of sequence identity to SEQ ID NO: 32, 38, 40, 42, 44, or 46.

13. The antibody of Claim 10, comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, or a combination thereof.

14. The antibody of Claim 10, wherein the antibody comprises a mono-, bi- or multi-specific antibody, a purified antibody, a humanized antibody, an IgG, or a combination thereof.

15. An isolated nucleic acid sequence encoding the antibody of Claim 10.

16. An expression vector or a host cell comprising the isolated nucleic acid sequences of Claim 15.

17. An immunoconjugate, comprising the antibody of Claim 10 conjugated to a drug unit through a linker, wherein the linker comprises a covalent bond selected from an ester bond, an ether bond, an amine bond, an amide bond, a disulfide bond, an imide bond, a sulfone bond, a phosphate bond, a phosphorus ester bond, a peptide bond, a hydrazone bond or a combination thereof.

18. The immunoconjugate of Claim 17, wherein the drug unit comprises a unit derived from a therapeutic agent, an imaging agent, a diagnostic agent, a radioisotope, or a combination thereof.

19. The immunoconjugate of Claim 18, wherein the therapeutic agent comprises a cytotoxic agent, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof.

20. The immunoconjugate of Claim 18, wherein the therapeutic agent comprises capecitabine, cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide, epirubicin, pemetrexed, folinic acid, gemcitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lapatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopanib, lapatinib, sunitinib, nilotinib, sorafenib, nab-paclitaxel, everolimus, temsirolimus, dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof.

21. The immunoconjugate of Claim 18, wherein the radioisotope comprises deuterium, ¹³¹I, ³²P, ⁹⁰Sr, ⁹⁰Y, ⁸⁹Zr, ¹⁷⁷Lu, or a combination thereof.

22. A pharmaceutical composition, comprising the antibody of Claim 10 or the immunoconjugate of Claim 17 and a pharmaceutically acceptable carrier.

23. A method for producing the antibody of Claim 10, comprising culturing a host cell such that the DNA sequence encoding the antibody of Claim 10 is expressed, and purifying said antibody.

24. A method for producing the immunoconjugate of Claim 17, comprising conjugating the antibody of Claim 7 with the drug unit.

25. A method for treating or preventing a cancer, an autoimmune disease, or an infectious disease in a subject, comprising administering to the subject an effective amount of the antibody of Claim 10 or the immunoconjugate of Claim 17.

26. The method of Claim 25, wherein the cancer comprises lung cancer, small cell lung cancer (SCLC), large cell neuroendocrine carcinomas (LCNECs), medullary thyroid carcinomas (MTCs), cervical neuroendocrine carcinomas (CNECs), gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), bladder cancer, bladder NENs (BMENs), prostate cancer, NE prostate cancer (NEPC), merkel cell carcinoma (MCC), breast cancer, liver cancer, hepatocellular carcinoma (HCC), glioma, pancreatic cancer, or a combination thereof.

27. The method of Claim 25, further comprising co-administering an effective amount of a therapeutic agent, wherein the therapeutic agent comprises an antibody, a chemotherapy agent, an enzyme, an anti-estrogen agent, a receptor tyrosine kinase inhibitor, a kinase inhibitor, a cell cycle inhibitor, a DNA, RNA or protein synthesis inhibitor, a RAS inhibitor, or a combination thereof.

28. The method of Claim 27, wherein the therapeutic agent comprises capecitabine, cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil, Doxorubicin, cyclophosphamide, mustine, vincristine, procarbazine, prednisolone, bleomycin, vinblastine, dacarbazine, etoposide,

epirubicin, pemetrexed, folinic acid, gemcitabine, oxaliplatin, irinotecan, topotecan, camptothecin, docetaxel, paclitaxel, , fulvestrant, tamoxifen, letrozole, exemestane, anastrozole, aminoglutethimide, testolactone, vorozole, formestane, fadrozole, erlotinib, lapatinib, dasatinib, gefitinib, osimertinib, vandertanib, afatinib, imatinib, pazopinib, lapatinib, sunitinib, nilotinib, sorafenib, nab-paclitaxel, everolimus, temsirolimus, Dabrafenib, vemurafenib, trametinib, vintafolide, apatinib, crizotinib, periforsine, olaparib, Bortezomib, tofacitinib, trastuzumab, or a derivative or a combination thereof.

28. The method of Claim 25, wherein the subject is a human.

29. A solution comprising an effective concentration of the antibody of Claim 10 or the immunoconjugate of Claim 17, wherein the solution is blood plasma in a subject.