

ANTI-DLL3 CHIMERIC ANTIGEN RECEPTORS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to chimeric antigen receptors (CARs) targeting DLL3 and binding proteins specific for DLL3. The present invention also concerns nucleic acid sequences encoding the CARs or the binding proteins, modified immune cells expressing the CARs, as well as their uses for treating DLL3 associated disorders.

BACKGROUND

Advances in cellular immunotherapy have provided a promising approach for the treatment of various tumors. One such treatment involves genetic engineering of immune cells, particularly T cells, to express chimeric antigen receptors (CARs) on the cell surface. Chimeric antigen receptors are proteins which, in their usual format, graft the specificity of a monoclonal antibody (mAb) to the effector function of a T cell. Once the CARs are expressed in a T cell, the CAR modified T cell (CAR-T or CAR-T cell) acquires some properties, such as antigen specific recognition, antitumor reactivity and proliferation, and thus can act as “living drugs” to eradicate targeted tumor cells. In principal, any antigens (e.g., cell surface molecules) can be targeted by these CAR-T cells. CAR-T cell therapy can override tolerance to self-antigens and provide a treatment which is not reliant on the MHC status of a patient. Using T cells engineered to express chimeric antigen receptors targeting CD19, recent trials have demonstrated remarkable clinical responses in leukaemia and lymphoma patients.

CARs are expressed as transmembrane proteins, including an antigen-specific binding site, a transmembrane region, and a signaling cytoplasmic domain (e.g., a CD3 ζ chain). The antigen-specific binding site is usually a monoclonal antibody-derived single chain variable fragment (scFv) consisting of a heavy and light chain joined by a flexible linker. Recently CAR constructs have incorporated additional cytoplasmic domains from co-stimulatory molecules such as CD28 or 4-1 BB to enhance T cell survival *in vivo*. Other genetic modifications have also been made to CARs, e.g. the addition of cytokine genes or genes to avoid immunosuppressive mechanisms at the tumor site.

DLL3 (delta-like ligand 3) protein has been found to be clinically associated with various proliferative disorders, including tumors exhibiting neuroendocrine features, such as small-cell lung cancer (SCLC). SCLC, originating from neuroendocrine progenitor cells, comprises approximately 15% of all lung cancers, and has one of the lowest 5-year survival rates at 6% (Alvarado-Luna *et al.*, 2016, *Transl Lung Cancer Res* 5:26-38; Siegel *et al.*, 2017, *CA Cancer J Clin* 67:7-30). This is because it is highly aggressive, with about two-thirds of patients having metastatic diseases at diagnosis, and is highly refractory to conventional treatment (e.g., platinum-based chemotherapy).

There is a need for improved therapeutic approaches to treat SCLC and other DLL3-expressing cancers.

SUMMARY

In one aspect, the present disclosure provides a chimeric antigen receptor (CAR) targeting DLL3 (anti-DLL3 CAR). The anti-DLL3 CAR comprises a DLL3 binding domain, wherein the DLL3 binding domain comprises or is derived from a single domain antibody (sdAb) or a single chain variable fragment (scFv).

In some embodiments, the sdAb comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

In some embodiments, the sdAb comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243, or a variant of the polypeptide comprising up to about 3 amino acid substitutions in the CDR1, CDR2 and CDR3.

In some embodiments, the sdAb comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof comprising up to about 3 amino acid substitutions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about

3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof comprising up to about 3 amino acid substitutions;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof comprising up to about 3 amino acid substitutions; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171, or a variant thereof comprising up to about 3 amino acid substitutions.

In some embodiments, the sdAb comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 168;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 196;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 201;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88; and a CDR 3 comprising the

amino acid sequence of SEQ ID NO: 169;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 170; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 90; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 171.

In some embodiments, the sdAb is a camel sdAb raised against human or rhesus DLL3.

In some embodiments, the sdAb comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 274-354.

In some embodiments, the sdAb is humanized through CDR grafting.

In some embodiments, the humanized sdAb comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOs: 355-367.

In some embodiments, the scFv comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH domain of the scFv comprises a CDR1 set forth in SEQ ID NO: 498 or 504 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 499 or 505 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 500 or 506 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3, and the VL domain of the scFv comprises a CDR1 set forth in SEQ ID NO: 495 or 501 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 496 or 502 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 497 or 503 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

In some embodiments, the VH domain of the scFv comprises a CDR1 set forth in SEQ ID NO: 498, a CDR2 set forth in SEQ ID NO: 499, and a CDR3 set forth in SEQ ID NO: 500, and the VL domain of the scFv comprises a CDR1 set forth in SEQ ID NO: 495, a CDR2 set forth in SEQ ID NO: 496, and a CDR3 set forth in SEQ ID NO: 497; or the VH domain of the scFv comprises a CDR1 set forth in SEQ ID NO: 504, a CDR2 set forth in SEQ ID NO: 505, and a CDR3 set forth in SEQ ID NO: 506, and the VL domain of the scFv comprises a CDR1 set forth in SEQ ID NO: 501, a CDR2 set forth in SEQ ID NO: 502, and a CDR3 set forth in SEQ ID NO: 503.

In some embodiments, the VH domain of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 508, and the VL domain of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 507; or the VH domain of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 510, and the VL domain of the scFv comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set

forth in SEQ ID NO: 509.

In some embodiments, the scFv is obtained from a synthetic human Fab phage library.

In some embodiments, the DLL3 is human or rhesus DLL3.

In some embodiments, the anti-DLL3 CAR comprises, from N-terminus to C-terminus, a signal peptide, the DLL3 binding domain, a hinge domain, a transmembrane domain, and an intracellular signaling domain.

In some embodiments, the intracellular signaling domain is derived from CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b, or CD66d.

In some embodiments, the intracellular signaling domain further comprises an intracellular co-stimulatory sequence.

In some embodiments, the intracellular co-stimulatory sequence is derived from a co-stimulatory molecule selected from the group consisting of CD27, CD28, 4-1BB, OX40, CD40, PD-1, LFA-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, TNFRSF9, TNFRSF4, TNFRSF8, CD40LG, ITGB2, KLRC2, TNFRSF18, TNFRSF14, HAVCR1, LGALS9, DAP10, DAP12, CD83, ligands of CD83 and combinations thereof.

In some embodiments, the CAR comprises an amino acid sequence having at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 476-484, SEQ ID NOs: 485-494 or SEQ ID NOs: 515-516.

In some embodiments, the DLL3 binding domain comprises two sdAbs linked to each other.

In some embodiments, each of the sdAbs independently comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO:356 or SEQ ID NO:366.

In some embodiments, the CAR comprises an amino acid sequence having at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 518-520.

In some embodiments, the CAR comprises an amino acid sequence of SEQ ID NO: 520.

In another aspect, the present disclosure provides a DLL3 binding protein comprising a single domain antibody (sdAb) moiety that specifically binds to DLL3, wherein the sdAb moiety comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

In some embodiments, the sdAb moiety comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243, or a variant of the polypeptide comprising up to about 3 amino acid substitutions in the

CDR1, CDR2 and CDR3.

In some embodiments, the sdAb moiety comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 87, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof comprising up to about 3 amino acid substitutions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof comprising up to about 3 amino acid substitutions;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof comprising up to about 3 amino acid substitutions; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9, or a variant

thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 171, or a variant thereof comprising up to about 3 amino acid substitutions.

In some embodiments, the sdAb moiety comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 168;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 102; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 183;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 186;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 108; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 169;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171.

In some embodiments, the sdAb moiety is a camel sdAb raised against human or rhesus DLL3.

In some embodiments, the sdAb moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOS: 274-354.

In some embodiments, the sdAb moiety is humanized through CDR grafting.

In some embodiments, the humanized sdAb comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence of any one of SEQ ID NOS: 355-367.

In some embodiments, the DLL3 is human or rhesus DLL3.

In another aspect, the present disclosure provides a DLL3 binding protein

comprising a single chain variable fragment (scFv) moiety that specifically binds to DLL3, wherein the scFv moiety comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH domain of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 498 or 504 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 499 or 505 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 500 or 506 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3, and the VL domain of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 495 or 501 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 set forth in SEQ ID NO: 496 or 502 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 set forth in SEQ ID NO: 497 or 503 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

In some embodiments, the scFv moiety comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH domain of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 498, a CDR2 set forth in SEQ ID NO: 499, and a CDR3 set forth in SEQ ID NO: 500, and the VL domain of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 495, a CDR2 set forth in SEQ ID NO: 496, and a CDR3 set forth in SEQ ID NO: 497; or the VH domain of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 504, a CDR2 set forth in SEQ ID NO: 505, and a CDR3 set forth in SEQ ID NO: 506, and the VL domain of the scFv moiety comprises a CDR1 set forth in SEQ ID NO: 501, a CDR2 set forth in SEQ ID NO: 502, and a CDR3 set forth in SEQ ID NO: 503.

In some embodiments, the VH domain of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 508, and the VL domain of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 507; or the VH domain of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 510, and the VL domain of the scFv moiety comprises an amino acid sequence having at least about 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 509.

In some embodiments, the scFv moiety is obtained from a synthetic human Fab phage library.

In some embodiments, the DLL3 is human or rhesus DLL3.

In another aspect, the present disclosure provides an isolated nucleic acid molecule encoding an anti-DLL3 CAR or a DLL3 binding protein as described above.

In some embodiments, the isolated nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 368-448 which encodes a camel single domain antibody (sdAb).

In some embodiments, the isolated nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 449-461 which encodes a humanized camel sdAb.

In some embodiments, the isolated nucleic acid molecule comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 511-514 which encodes a VL or VH domain of a human scFv.

In some embodiments, the nucleic acid molecule further comprises a polynucleotide sequence encoding a Chimeric Switch Receptor (CSR) or a Dominant Negative Receptor (DNR).

In some embodiments, the nucleic acid molecule further comprises a polynucleotide sequence encoding a PD-1 Dominant Negative Receptor (PD-1 DNR), a PD-1 Chimeric Switch Receptor (PD-1 CSR), or a TGF- β Dominant Negative Receptor (TGF- β DNR).

In some embodiments, the PD-1 DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 523.

In some embodiments, the PD-1 CSR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 524.

In some embodiments, the TGF- β DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 529.

In some embodiments, the polynucleotide sequence encoding the PD-1 DNR, the PD-1 CSR or the TGF- β DNR is linked to the polynucleotide sequence encoding the CAR through a polynucleotide sequence encoding a 2A self-cleaving peptide.

In some embodiments, the 2A self-cleaving peptide is a T2A peptide or a P2A peptide.

In some embodiments, the nucleic acid molecule comprises, in the 5' to 3' direction, a polynucleotide sequence encoding the CAR, a polynucleotide sequence encoding the 2A self-cleaving peptide, and a polynucleotide sequence encoding the PD-1 DNR, the PD-1 CSR or the TGF- β DNR.

In some embodiments, the nucleic acid molecule encoding a peptide having at least about 95% sequence identity to SEQ ID NO: 521 or 522, or the nucleic acid molecule encoding a peptide having at least about 95% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NOs: 525-528.

In another aspect, the present disclosure provides an expression vector comprising an isolated nucleic acid molecule as described above.

In another aspect, the present disclosure provides an engineered immune cell comprising an isolated nucleic acid molecule as described above.

In some embodiments, the engineered immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer T cell, a $\gamma\delta$ T cell, a NKT cell and a Nature Killer cell.

In another aspect, the present disclosure provides an engineered immune cell expressing an anti-DLL3 CAR as described above.

In some embodiments, the engineered immune cell also expresses a CSR or a DNR.

In some embodiments, the CSR is a PD-1 CSR, the DNR is a PD-1 DNR or a TGF- β DNR.

In some embodiments, the PD-1 DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 523.

In some embodiments, the PD-1 CSR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 524.

In some embodiments, the TGF- β DNR comprises an amino acid sequence having at least about 95% sequence identity to SEQ ID NO: 529.

In some embodiments, the CAR and the CSR, or the CAR and the DNR, are co-expressed through a 2A self-cleaving peptide.

In some embodiments, the 2A self-cleaving peptide is a T2A peptide or a P2A peptide.

In some embodiments, the engineered immune cell expresses the CAR and the PD-1 DNR, and is stimulated by a cell expressing DLL3 and PD-L1.

In some embodiments, the engineered immune cell expresses the CAR and the PD-1 CSR, and is stimulated by a cell expressing DLL3 and PD-L1.

In some embodiments, the engineered immune cell expresses the CAR and the TGF- β DNR, and is stimulated by a cell expressing DLL3 in the present of TGF- β .

In some embodiments, the engineered immune cell is selected from the group consisting of a cytotoxic T cell, a helper T cell, a natural killer T cell, a $\gamma\delta$ T cell, a NKT cell and a Nature Killer cell.

In another aspect, the present disclosure provides a pharmaceutical composition comprising an anti-DLL3 CAR, an isolated DLL3 binding protein, an expression vector, or an engineered immune cell as described above, and a physiologically acceptable excipient.

In another aspect, the present disclosure provides a method for treating a DLL3 associated disorder in a subject, comprising administering to the subject a therapeutically effective amount of engineered immune cells as described above or a therapeutically effective amount of a pharmaceutical composition as described above.

In another aspect, the present disclosure provides the use of an anti-DLL3 CAR, an isolated DLL3 binding protein, an expression vector, or an engineered immune cell as described above for the preparation of a medicament for treating a DLL3 associated disorder.

In another aspect, the present disclosure provides a medicament for use in treating a DLL3 associated disorder comprising an anti-DLL3 CAR, a DLL3 binding protein, an expression vector, or an engineered immune cell as described above.

In some embodiments, the DLL3 associated disorder is a cancer selected from the group consisting of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma.

In some embodiments, the cancer expresses DLL3 and PD-L1.

In some embodiments, the cancer has a higher expression level of TGF- β compared to corresponding normal tissue.

In some embodiments, the DLL3 associated disorder is small cell lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows schematic representation of a V_HH based CAR construct. Sequences which can be used in the construct are listed in SEQ ID NOs: 462-472, 474 and 475.

FIG. 2 shows the results of an *in vitro* cytotoxicity assay of T cells expressing exemplary monospecific CARs comprising various camel anti-DLL3 sdAbs against small cell lung cancer cell line SHP-77 with an E:T of 2: 1 or 5:1. The results for the CARs are depicted in the order as in the legend shown on the right.

FIG. 3 shows the results of cytokine release levels of T cells expressing exemplary monospecific CARs comprising various camel anti-DLL3 sdAbs, after co-incubated with DLL3-expressing tumor cell line SHP-77. IFN- γ release levels and TNF- α release levels (with an E:T of 2: 1 or 5:1) are showed in FIG. 3A and FIG. 3B, respectively. In each figure, the results for the CARs are depicted in the order as in the legend shown on the right.

FIG. 4 shows fold expansions of T cells expressing exemplary monospecific CARs comprising various camel anti-DLL3 sdAbs, after long-term stimulation with small cell lung cancer cell line SHP-77.

FIG. 5 shows the results of *in vivo* anti-tumor efficacy of the CAR-T cells expressing CARs with camel anti-DLL3 sdAbs in a SHP-77 tumor model. In this model, each mouse was infused with a dose of 1.0 million CAR-T cells.

FIG. 6 shows the results of an *in vitro* cytotoxicity assay of T cells expressing exemplary monospecific CARs comprising various humanized camel anti-DLL3 sdAbs against small cell lung cancer cell line SHP-77 (FIG. 6A, 6B) and NCI-H82 (FIG. 6C, 6D).

FIG. 7 shows the results of cytokine release levels of T cells expressing exemplary monospecific CARs comprising various humanized camel anti-DLL3 sdAbs after stimulated by SHP-77. IFN- γ release levels and TNF- α release levels (with an E:T of 3: 1 or 10: 1) are showed in FIG. 7A and FIG. 7B, respectively. In each figure, the results for the CARs are depicted in the order as in the legend shown on the right.

FIG. 8 shows fold expansions of T cells expressing exemplary monospecific CARs comprising various humanized camel anti-DLL3 sdAbs, after long-term stimulation of with small cell lung cancer cell line SHP-77.

FIG. 9 shows the results of *in vivo* anti-tumor efficacy of the CAR-T cells expressing CARs with humanized camel anti-DLL3 sdAbs in a SHP-77 tumor model. In this model, each mouse was infused with a dose of 0.2 million CAR-T cells. The results of 9 groups are compared in FIG. 9A. The results of each mouse in each group are shown in FIG. 9B-9J, respectively.

FIG. 10 shows schematic representation of tandem CAR (FIG. 10A) and armored CAR constructs (FIG. 10B, C)

FIG. 11 shows comparison results of tandem CAR-T cells and monospecific CAR-T cells *in vitro* functional activities by measuring short-term cytotoxicity (FIG. 11A-E, V) and cytokine release (FIG. 11F-K, W-X), and by long-term stimulation assays (FIG. 11L-U, Y-Z).

FIG. 12 shows *in vitro* functional comparison results of PD-1 DNR or PD-1 CSR

armored CAR-T cells and T3 targeting SHP-77 cells (FIG. 12A, B) and SHP-77/PD-L1, respectively (FIG. 12C, D).

FIG. 13 shows that TGF- β -DNR enhances the *in vitro* and *in vivo* anti-tumor efficacy of DLL3 CAR-T cells. FIG. 13A shows schematic representation of the TGF- β -DNR armored CARs. FIG. 13B shows the positive ratio of CAR and TGF- β -DNR on respective CAR-T cells. *In vitro* anti-tumor efficacy was evaluated in short-term (FIG. 13C, D) and long-term stimulation assays (FIG. 13E-G). FIG. 13H shows *in vivo* anti-tumor efficacy. FIG. 13I shows the pharmacokinetics of CAR-T cells in the peripheral blood of SHP77 xenograft model after treatment.

DETAILED DESCRIPTION

Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art. Any methods, devices and materials similar or equivalent to those described herein can be used in the practice of this invention. The following definitions are provided to facilitate understanding of certain terms used frequently herein and are not meant to limit the scope of the present disclosure.

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “binding protein” as used herein refers to a molecule or a portion of a molecule which binds a target molecule (e.g., DLL3). In some embodiments, the binding protein comprises an antibody. In some embodiments, the binding protein comprises an antigen-binding fragment of an antibody. In some embodiments, the binding protein can further comprise a small molecular weight component, such as a small-molecule drug or toxin. The binding protein can also be an antibody or an antigen-binding fragment thereof. In some embodiments, the binding protein comprises the ligand-binding domain of a receptor. In some embodiments, the binding protein comprises the extracellular domain of a transmembrane receptor. The binding protein can also be the ligand-binding domain of a receptor, or the extracellular domain of a transmembrane receptor. In some embodiments, the binding protein comprises a single domain antibody (sdAb) or a single chain variable fragment (scFv). In some embodiments, the binding protein can be an sdAb or a scFv. A DLL3 binding protein can be a DLL3 binding domain. In some embodiment, the DLL3 binding protein comprises an antibody or an antigen-binding fragment of an antibody which binds DLL3. In some embodiments, the DLL3 binding protein can be an antibody or an antigen-binding fragment of an antibody. In some embodiments, the DLL3 binding protein comprises a single domain antibody (sdAb) or a single chain variable fragment (scFv) which binds DLL3. In some embodiments, the DLL3 binding protein can be an sdAb or a scFv.

The term “antibody” generally refers to any immunoglobulin (Ig) molecule comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains, or any functional fragment thereof, which retains the essential epitope binding features of the Ig molecule. In a full-length antibody, each heavy chain is comprised

of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG 1, IgG2, IgG 3, IgG4, IgA1 and IgA2) or subclass. In a broad meaning, the term “antibody” further refers to scFv or sdAb which is not derived from an immunoglobulin molecule with four polypeptide chains.

An antibody fragment is a portion of an antibody, for example as F(ab')₂, Fab, Fv, scFv, sdAb, and the like. Functional fragments of a full length antibody retain the target specificity of a full length antibody. Recombinant functional antibody fragments, such as scFv (single chain variable chain fragments), have therefore been used to develop therapeutics as an alternative to therapeutics based on mAbs. scFv fragments (~25kDa) consist of the two variable domains, VH and VL. Naturally, VH and VL domains are non-covalently associated via hydrophobic interaction and tend to dissociate. However, stable fragments can be engineered by linking the domains with a hydrophilic flexible linker to create a scFv.

As used herein, the term “single domain antibody” (sdAb) has its general meaning in the art and refers to the single heavy chain variable domain of antibodies of the type that can be found in Camelid mammals and are naturally devoid of light chains. Such single-domain antibody is also called V_HH or “Nanobody”. The amino acid sequence and structure of a single-domain antibody can be considered to be comprised of four framework regions (FR1, FR2, FR3, and FR4), and three complementary determining regions (CDR1, CDR2, and CDR3). Accordingly, the single-domain antibody can be defined as an amino acid sequence with the general structure: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4, which is similar to variable domain VH or VL. The use of sdAbs as single antigen-binding proteins or as an antigen-binding domain in larger proteins or polypeptides offer a number of significant advantages over the use of conventional antibodies or antibody fragments(e.g., scFv). The advantages of sdAbs include: only a single domain is required to bind an antigen with high affinity and with high selectivity; sdAbs are highly stable to denaturing agents or conditions including heat, pH, and proteases; and sdAbs can access targets and epitopes not accessible to conventional antibodies. Typically, sdAbs are produced in camelids such as llamas, but can also be synthetically generated using techniques that are well known in the art.

As used herein, the term “humanized sdAb” means an sdAb that has had one or more amino acid residues in the amino acid sequence of the naturally occurring V_HH sequence replaced by one or more of the amino acid residues that occur at the

corresponding position in a VH domain from a conventional 4-chain antibody from a human. This can be performed by methods that are well known in the art. For example, the FRs of the sdAbs can be replaced by human variable FRs. Humanized sdAbs thus have less antigenicity when administered into human bodies.

As used herein, the term “heavy chain-only antibody” or “HCAb” refers to a functional antibody, which comprises heavy chains, but lacks the light chains usually found in 4-chain antibodies. Camelid animals (such as camels, llamas, or alpacas) are known to produce HCAs.

“DLL3”, also known as “delta-like ligand 3”, is a transmembrane protein involved in Notch signaling pathway. The Notch signaling pathway, first identified in *C. elegans* and *Drosophila* and subsequently shown to be evolutionarily conserved from invertebrates to vertebrates, participates in a series of fundamental biological processes including normal embryonic development, adult tissue homeostasis, and stem cell maintenance. In *Drosophila*, Notch signaling is mediated primarily by one Notch receptor gene and two ligand genes, known as Serrate and Delta (Wharton *et al.*, 1985; Rebay *et al.*, 1991). In humans, there are four known Notch receptors and five DSL (Delta-Serrate LAG2) ligands--two homologs of Serrate, known as Jagged1 and Jagged 2, and three homologs of Delta, termed delta-like ligands or DLL1, DLL3 and DLL4. In humans, the DLL3 gene is located on chromosome 19q13, and consists of 8 exons spanning 9.5 kb. Alternate splicing within the last exon gives rise to two protein isoforms. Both share overall 100% identity across their extracellular domains and their transmembrane domains, differing only in that the longer isoform contains an extended cytoplasmic tail.

As used herein, the term “specifically bind” or “specific binding” or any synonym thereof refers to the ability of a polypeptide, such as a single domain antibody (sdAb), to specifically recognize and detectably bind, as assayed by standard *in vitro* assays, to a DLL3 molecule. For example, binding, as used herein, is measured by the capacity of an anti-DLL3 polypeptide of the invention to recognize a DLL3 molecule on the surface of a cell using well described antigen-antibody binding assays, flow cytometry, and other assays known to those of skill in the art.

As used herein, the term “expression vector” is a nucleic acid construct or sequence, generated recombinantly or synthetically, with specific nucleic acid elements that permit transcription and/or expression of another nucleic acid in a host cell. An expression vector can be part of a plasmid, virus, or nucleic acid fragment. In one example, an expression vector is a DNA vector, such as a plasmid, that comprises at least one promoter sequence and at least one terminator sequence (e.g., a polyadenylation sequence), and optionally an origin of replication (ori) sequence, and optionally a selection or selectable marker sequence. Optionally, the expression vector may further comprise at least one nucleotide coding sequence of interest that codes for at least one polypeptide, wherein the at least one promoter sequence is operably linked with the at least one coding sequence. The term “expression” includes any step involved in the production of the polypeptide including, but not limited to, transcription, post-transcriptional modification, translation, post-translational modification, and/or secretion.

The term “isolated” refers to a material that is substantially or essentially free from components that normally accompany it in its native state. The material can be a cell or a macromolecule such as a protein or nucleic acid. For example, an “isolated nucleic acid,” as used herein, refers to a polynucleotide, which has been purified from the sequences which flank it in a naturally-occurring state, e.g., a DNA fragment which has been removed from the sequences that are normally adjacent to the fragment. Alternatively, an “isolated antibody” or an “isolated polypeptide” and the like, as used herein, refer to *in vitro* isolation and/or purification of an antibody or polypeptide molecule from its natural cellular environment, and from association with other components of the cell.

“Humanized” forms of non-human (e.g., camelid) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. In some embodiments, a humanized antibody is a human immunoglobulin (recipient antibody) in which residues from a hypervariable region (HVR) of the recipient are replaced by residues from an HVR of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired specificity, affinity, and/or capacity. In some instances, framework (“FR”) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications may be made to further refine antibody performance, such as binding affinity. In general, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin sequence, and all or substantially all of the FR regions are those of a human immunoglobulin sequence, although the FR regions may include one or more individual FR residue substitutions that improve antibody performance, such as binding affinity, isomerization, immunogenicity, etc. The number of these amino acid substitutions in the FR is typically no more than 6 in the H chain, and in the L chain, no more than 3. The humanized antibody optionally will also comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see, e.g., Jones *et al.*, Nature 321:522-525 (1986); Riechmann *et al.*, Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992). See also, for example, Vaswani and Hamilton, Ann. Allergy, Asthma & Immunol. 1:105-115 (1998); Harris, Biochem. Soc. Transactions 23:1035-1038 (1995); Hurle and Gross, Curr. Op. Biotech. 5:428-433 (1994); and U.S. Pat. Nos. 6,982,321 and 7,087,409.

“sequence identity” and “homology” with respect to a peptide, polypeptide or antibody sequence are defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer

software such as BLAST, BLAST-2, ALIGN or MEGALIGN™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

The dissociation constant (K_D or K_d) is used as an indicator showing affinity of antibodies to antigens. For example, easy analysis is possible by the Scatchard method using antibodies marked with a variety of marker agents, as well as by using BiacoreX (made by Amersham Biosciences), which is an over-the-counter, measuring kit, or similar kit, according to the user's manual and experiment operation method attached with the kit. The K_D value that can be derived using these methods is expressed in units of M (Mols).

“Chimeric Switch Receptor (CSR)” as used herein refers to a receptor which is created to reverse the outcomes of its original signaling pathway in order to confer an immune cell (e.g., a CAR T cell) with a desired activity, such as, the ability to overcome the immunosuppressive tumor microenvironment and to allow it to have greater *in vivo* persistence. In some embodiments, a CSR can exploit the inhibitory molecules expressed by a cancer cell to further stimulate the CAR T cell. In a non-limiting example, a CAR T cell can be engineered to express a CSR composed of the extracellular ligand binding domain of the human inhibitory receptor programmed cell death protein 1 (PD-1) fused to the transmembrane and cytoplasmic co-stimulatory signaling domains of CD28. When the CAR T cell is administrated into a subject with a cancer expressing DLL3 and programmed cell death ligand 1 (PD-L1), the expressed CAR can bind to the DLL3 and the expressed switch receptor can bind to PD-L1. The nature of the PD-1/CD28 chimeric switch receptor fusion protein prevents the normal PD1/PD-L1-mediated T-cell suppression and, instead, promotes signaling through the CD28 domain, which results in the stimulation of the CAR T cell. Thus, exchanging the transmembrane and intracellular domain of PD-1 with that of CD28 converts PD-L1 into a co-stimulation ligand of the CAR T cell. This will induce enhanced toxicity against PD-L1-expressing cancer cells. In other embodiments, a CSR can also be used to inhibit the effects of a CAR T cell on unintended target cells.

“Dominant Negative Receptor (DNR)” as used herein refers to a receptor which is able to bind its ligand but will not induce a signaling cascade inside the cell. A DNR usually has an intact ligand binding region but is missing an intracellular enzymatic region. It may be a mutated form of a full length receptor or a truncated form of the receptor. Following CAR T cell immunotherapy, some cancers, especially solid cancers may upregulate inhibitory ligands that bind to inhibitory receptors on CAR T cells. This adaptive resistance compromises the efficacy of chimeric CAR T cell therapies. Some cancers, particularly solid cancer, are known to secrete transforming growth factor β (TGF- β), creating an immunosuppressive milieu. TGF- β is known to induce or promote metastasis and to potentially suppress the immune system. Therefore, in some embodiments, we use a truncated version of the TGF- β receptor TGFBR2 as a TGF- β DNR to improve the antitumor performance of the CAR T cells disclosed herein. In some embodiments, the CAR and the TGF- β DNR are

co-expressed on a T cell's surface by using a 2A self-cleaving peptide. In some embodiments, the CAR and the TGF- β DNR are separately expressed on a T cell's surface by using two expression vectors. We find TGF- β DNR, when introduced into the anti-DLL3 CAR T cells disclosed herein, is able to enhance the cytotoxicity of the CAR T cells against some DLL3 positive cancer cells, such as SCLC cells. Similarly, in some embodiments, we use a truncated version of the PD-1 receptor as a PD-1 DNR to improve the antitumor performance of the CAR T cells disclosed herein.

As used herein, "treatment" or "treating," includes any beneficial or desirable effect on the symptoms or pathology of a disease or pathological condition, and may include even minimal reductions in one or more measurable markers of the disease or condition being treated, e.g., cancer, autoimmune disease, immune disorder, etc. Treatment can optionally involve delaying of the progression of the disease or condition. "Treatment" does not necessarily indicate complete eradication or cure of the disease or condition, or associated symptoms thereof.

Some aspects of the present invention relate to a DLL3 binding protein, which has binding specificity for human or rhesus DLL3 protein.

In some embodiments, the DLL3 binding protein comprising a single domain antibody ("sdAb") moiety that specifically binds to DLL3, wherein the sdAb moiety comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2, and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3.

In some embodiments, the sdAb comprises a polypeptide that comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81, a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162; and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243, or a variant of the polypeptide comprising up to about 3 amino acid substitutions in the CDR regions. In some embodiments, the anti-DLL3 antibody is or comprises a single domain antibody (sdAb), which is produced from camel after been immunized with human or rhesus DLL3 proteins. In some embodiments, the sdAb comprises a CDR set (i.e., a combination of CDR1, CDR2, and CDR3) as listed in each row of Table 1.

In some embodiments, the sdAb comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 87, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof comprising up to about 3 amino acid substitutions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to about

3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof comprising up to about 3 amino acid substitutions;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof comprising up to about 3 amino acid substitutions; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 171, or a variant thereof comprising up to about 3 amino acid substitutions.

In some embodiments, the sdAb comprises a polypeptide comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 168;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 102; and a CDR 3 comprising

the amino acid sequence of SEQ ID NO: 183;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 186;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 108; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 169;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171.

In some embodiments, the sdAb comprises an amino acid sequence having at least about 95% (e.g., about 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 274-354. In some embodiments, the sdAb comprises the amino acid sequence of any one of SEQ ID NOs: 274-354. In other embodiments, the sdAb is humanized, and comprises an amino acid sequence having at least about 95% (e.g., about 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 355-367. In some embodiments, the sdAb comprises the amino acid sequence of any one of SEQ ID NOs: 355-367. A humanized antibody can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (see, e.g., U.S. Pat. Nos. 5,225,539, 5,530,101, and 5,585,089), veneering or resurfacing (see, e.g., European Patent Nos. EP 592,106 and EP 519,596), and chain shuffling (see, e.g., U.S. Pat. No. 5,565,332). Generally, during humanization, the CDR residues of a receptor antibody (e.g., a human antibody) are replaced with CDR residues of a donor antibody (e.g., a rodent antibody), to retain the antigen-binding specificity while minimizing the *in vivo* immunogenicity. Often, framework residues in the framework regions will also be substituted with the corresponding residue from the donor antibody to alter, for example improve, antigen binding. These framework substitutions, e.g., conservative substitutions are identified by methods well-known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual

framework residues at particular positions. (See, e.g., Queen *et al.*, U.S. Pat. No. 5,585,089; and Riechmann *et al.*, 1988, Nature, 332:323).

In some cases, the sdAb can be fused with a human IgG hinge fragment and a Fc fragment to form a heavy chain antibody (HCAb). In some cases, the sdAb can be fused with another sdAb or scFv which is specific for an antigen other than DLL3 to form a bispecific antibody. In some cases, the sdAb can be fused with two or more sdAbs or scFvs which are specific for an antigen other than DLL3 to form a multispecific antibody. In other cases, the sdAb can be chemically modified to carry a drug molecule. Thus the anti-DLL3 sdAb can be used *in vivo* to lead the drug molecule to a DLL3-expressing cell.

In some embodiments, the DLL3 binding protein is or comprises a single chain variable fragment (scFv) that specifically bind DLL3. In some cases, the scFv is isolated from a synthetic human Fab or scFv phage library through repeated rounds of phage panning, with each round of panning involving the processes of binding, removal of nonspecific phages, and the elution and amplification of bound phages for the next round. In some embodiments, the DLL3 binding protein comprising a scFv moiety that specifically binds to DLL3, wherein the scFv comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH domain of the scFv comprises CDR1 set forth in SEQ ID NO: 498 or 504, CDR2 set forth in SEQ ID NO: 499 or 505, and CDR3 set forth in SEQ ID NO: 500 or 506, and the VL domain of the scFv comprises CDR1 set forth in SEQ ID NO: 495 or 501, CDR2 set forth in SEQ ID NO: 496 or 502, and CDR3 set forth in SEQ ID NO: 497 or 503. In some embodiments, the DLL3 binding protein comprising scFv moiety that specifically binds to DLL3, wherein the scFv comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH domain of the scFv comprises CDR1 set forth in SEQ ID NO: 498, CDR2 set forth in SEQ ID NO: 499, and CDR3 set forth in SEQ ID NO: 500, and the VL domain of the scFv comprises CDR1 set forth in SEQ ID NO: 495, CDR2 set forth in SEQ ID NO: 496, and CDR3 set forth in SEQ ID NO: 497; or the VH domain of the scFv comprises CDR1 set forth in SEQ ID NO: 504, CDR2 set forth in SEQ ID NO: 505, and CDR3 set forth in SEQ ID NO: 506, and the VL domain of the scFv comprises CDR1 set forth in SEQ ID NO: 501, CDR2 set forth in SEQ ID NO: 502, and CDR3 set forth in SEQ ID NO: 503.

In some cases, the scFv can be fused with another sdAb or scFv which is specific for an antigen other than DLL3 to form a bispecific antibody. In some cases, the scFv can be fused with two or more sdAbs or scFvs which are specific for an antigen other than DLL3 to form a multispecific antibody. In other cases, the scFv can be chemically modified to carry a drug molecule. Thus the anti-DLL3 scFv can be used *in vivo* to lead the drug molecule to a DLL3-expressing cell.

Some aspects of the present invention relate to a CAR or a CAR-T cell comprising a DLL3 binding domain (anti-DLL3 CAR or anti-DLL3 CAR-T cells).

A CAR of the present invention comprises an extracellular domain, a transmembrane domain and an intracellular domain. In some embodiments, the CAR further includes a signal peptide at N-terminus, and a hinge region between the

extracellular domain and the transmembrane domain. The extracellular domain includes a target-specific binding element (also referred to as an antigen recognition domain or antigen binding domain). The intracellular domain, or otherwise the cytoplasmic domain, often includes one or more co-stimulatory signaling domains and a CD3 ζ chain portion. The co-stimulatory signaling domain refers to a portion of the CAR including the intracellular domain of a co-stimulatory molecule.

Antigen recognition or antigen targeting by a CAR molecule most commonly involves the use of an antibody or antibody fragment. In accordance with the present invention, the antigen binding domain is an antibody or antibody fragment that specifically binds to DLL3. Preferably, the antigen binding domain of the CAR of the invention is an anti-DLL3 scFv or sdAb as mentioned above.

The transmembrane domain may be derived either from a natural or from a synthetic source. Where the source is natural, the domain may be derived from any membrane-bound or transmembrane protein. Transmembrane regions of particular use in this invention may be derived from (i.e. comprise at least the transmembrane region(s) of), for example, the alpha, beta or zeta chain of the T-cell receptor, CD8 α chain.

The intracellular signaling domain of the CAR of the invention is responsible for activation of at least one of the normal effector functions of an immune cell. The term "effector function" refers to a specialized function of a cell. Effector function of a T cell, for example, may be cytolytic activity or helper activity including the secretion of cytokines. Thus, the term "intracellular domain" refers to the portion of a protein which transduces the effector function signal and directs the cell to perform a specialized function. While usually the entire cytoplasmic domain can be employed, in many cases it is not necessary to use the entire chain. To the extent that a truncated portion of a cytoplasmic domain is used, such truncated portion may be used in place of an intact chain as long as it transduces the effector function signal. The term intracellular domain is thus meant to include any truncated portion of a cytoplasmic domain sufficient to transduce the effector function signal. Preferred examples of cytoplasmic domains for use in the CAR of the invention include the cytoplasmic sequences of the T cell receptor (TCR) and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any synthetic sequence that has the same functional capability. In some embodiments, the intracellular signaling domain is derived from CD3 ζ , FcR γ , FcR β , CD3 γ , CD3 δ , CD3 ϵ , CD5, CD22, CD79a, CD79b, or CD66d.

Often, signals generated through the TCR alone are insufficient for full activation of the T cell. Accordingly, a secondary or co-stimulatory signal is used. Thus, T cell activation can be said to be mediated by two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation through the TCR (primary cytoplasmic signaling sequences) and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal (secondary cytoplasmic signaling sequences). The co-stimulatory signaling sequence refers to a portion of the CAR including the intracellular domain of a co-stimulatory molecule. A co-stimulatory molecule is a cell surface molecule other than an antigen

receptor or their ligands that is required for an efficient response of lymphocytes to an antigen. Examples of such molecules include CD27, CD28, 4-1BB, OX40, CD40, PD-1, LFA-1, ICOS, CD2, CD7, LIGHT, NKG2C, B7-H3, TNFRSF9, TNFRSF4, TNFRSF8, CD40LG, ITGB2, KLRC2, TNFRSF18, TNFRSF14, HAVCR1, LGALS9, DAP10, DAP12, CD83, ligands of CD83 and combinations thereof..

The hinge region between the extracellular domain and the transmembrane domain of the CAR generally means any oligo- or polypeptide that functions to link the transmembrane domain to the extracellular domain in the polypeptide chain. The hinge region may be up to 300 amino acids, preferably 2 to 100 amino acids and most preferably 2 to 10 amino acids.

In addition to the antigen binding domain, transmembrane domain, cytoplasmic domain, and hinge region, the CAR of the present invention can also include a signal peptide sequence linked to the N-terminus of the CAR. Signal peptide sequences exist at the N-terminus of many secretory proteins and membrane proteins, and typically have a length of 15 to 30 amino acids. Since many of the protein molecules mentioned above have signal peptide sequences, these signal peptides can be used as a signal peptide for the CAR of this invention.

In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises or is derived from a single domain antibody (sdAb) or a single chain variable fragment (scFv).

In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises or is derived from a single domain antibody (sdAb), wherein the sdAb comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR1; a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR2; and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243 or a variant thereof comprising up to about 3 amino acid substitutions in the CDR3. In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises or is derived from a single domain antibody (sdAb), wherein the sdAb comprises a CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 1-81; a CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 82-162; and a CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 163-243.

In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises an sdAb comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 168, or a variant thereof comprising up to about 3 amino acid substitutions;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to about

3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 183, or a variant thereof comprising up to about 3 amino acid substitutions;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186, or a variant thereof comprising up to about 3 amino acid substitutions;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189, or a variant thereof comprising up to about 3 amino acid substitutions;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 115, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 196, or a variant thereof comprising up to about 3 amino acid substitutions;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 201, or a variant thereof comprising up to about 3 amino acid substitutions;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 169, or a variant thereof comprising up to about 3 amino acid substitutions;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 170, or a variant thereof comprising up to about 3 amino acid substitutions; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9, or a variant thereof comprising up to about 3 amino acid substitutions; a CDR2 comprising the amino acid sequence of SEQ ID NO: 90, or a variant thereof comprising up to about 3 amino acid substitutions; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 171, or a variant thereof comprising up to about 3 amino acid substitutions.

In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises an sdAb comprising any one of the following:

(1) a CDR1 comprising the amino acid sequence of SEQ ID NO: 6; a CDR2 comprising the amino acid sequence of SEQ ID NO: 87; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 168;

(2) a CDR1 comprising the amino acid sequence of SEQ ID NO: 21; a CDR2 comprising the amino acid sequence of SEQ ID NO: 102; and a CDR3 comprising the

amino acid sequence of SEQ ID NO: 183;

(3) a CDR1 comprising the amino acid sequence of SEQ ID NO: 24; a CDR2 comprising the amino acid sequence of SEQ ID NO: 105; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 186;

(4) a CDR1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR2 comprising the amino acid sequence of SEQ ID NO: 108; and a CDR3 comprising the amino acid sequence of SEQ ID NO: 189;

(5) a CDR1 comprising the amino acid sequence of SEQ ID NO: 34; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 115; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 196;

(6) a CDR1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR2 comprising the amino acid sequence of SEQ ID NO: 120; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 201;

(7) a CDR1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR2 comprising the amino acid sequence of SEQ ID NO: 88; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 169;

(8) a CDR1 comprising the amino acid sequence of SEQ ID NO: 8; a CDR2 comprising the amino acid sequence of SEQ ID NO: 89; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 170; or

(9) a CDR1 comprising the amino acid sequence of SEQ ID NO: 9; a CDR 2 comprising the amino acid sequence of SEQ ID NO: 90; and a CDR 3 comprising the amino acid sequence of SEQ ID NO: 171.

In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises a camel sdAb, wherein the sdAb comprises an amino acid sequence having at least about 95% (*e.g.* 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 274-354. In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises a camel sdAb comprising an amino acid of any one of SEQ ID NOs: 274-354. In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises a humanized sdAb, wherein the sdAb comprises an amino acid sequence having at least about 95% (*e.g.* 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 355-367. In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises a humanized sdAb comprising an amino acid sequence of any one of SEQ ID NOs: 355-367.

In some embodiments, the CAR comprising a DLL3 binding domain, wherein the DLL3 binding domain comprises or is derived from a single chain variable fragment (scFv), wherein the VH domain of the scFv comprises CDR1 set forth in SEQ ID NO: 498, CDR2 set forth in SEQ ID NO: 499, and CDR3 set forth in SEQ ID NO: 500, and the VL domain of the scFv comprises CDR1 set forth in SEQ ID NO: 495, CDR2 set forth in SEQ ID NO: 496, and CDR3 set forth in SEQ ID NO: 497; or the VH domain of the scFv comprises CDR1 set forth in SEQ ID NO: 504, CDR2 set forth in SEQ ID NO: 505, and CDR3 set forth in SEQ ID NO: 506, and the VL domain of the scFv comprises CDR1 set forth in SEQ ID NO: 501, CDR2 set forth in

SEQ ID NO: 502, and CDR3 set forth in SEQ ID NO: 503. In some embodiments, the VH domain of the scFv comprises an amino acid sequence set forth in SEQ ID NO: 508, and the VL domain of the scFv comprises an amino acid sequence set forth in SEQ ID NO: 507; or the VH domain of the scFv comprises an amino acid sequence set forth in SEQ ID NO: 510, and the VL domain of the scFv comprises an amino acid sequence set forth in SEQ ID NO: 509.

In some embodiments, the CAR of the present invention comprises a camel sdAb provided herein as the DLL3 binding domain and comprises an amino acid sequence having at least about 95% (*e.g.* 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 476-484. In some embodiments, the CAR of the present invention comprises a camel sdAb provided herein as the DLL3 binding domain and has an amino acid sequence selected from the group consisting of SEQ ID NOs: 476-484. In some embodiments, the CAR of the present invention comprises a humanized sdAb provided herein as the DLL3 binding domain and comprises an amino acid sequence having at least about 95% (*e.g.* 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 485-494. In other embodiments, the CAR of the present invention comprises a humanized sdAb provided herein as the DLL3 binding domain and has an amino acid sequence selected from the group consisting of SEQ ID NOs: 485-494.

In some embodiments, the CAR of the present invention comprises a human scFv provided herein as the DLL3 binding domain and comprises an amino acid sequence having at least about 95% (*e.g.* 96%, 97%, 98%, 99% or 100%) sequence identity to the amino acid sequence of any one of SEQ ID NOs: 515-516. In some embodiments, the CAR of the present invention comprises a human scFv provided herein as the DLL3 binding domain and has an amino acid sequence selected from the group consisting of SEQ ID NOs: 515-516.

In some embodiments, the CAR of the present invention comprises, from N-terminus to C-terminus, a signal peptide, the DLL3 binding domain, a hinge region, a transmembrane domain, and a cytoplasmic signaling domain. In particular embodiments, the CAR of the present invention comprises, from N-terminus to C-terminus, a CD8 α signal peptide as set forth in SEQ ID NO: 465, the DLL3 binding domain, a CD8 α hinge domain as set forth in SEQ ID NO: 466, a CD8 α transmembrane domain as set forth in SEQ ID NO: 467, a CD137 cytoplasmic domain as set forth in SEQ ID NO: 468, a CD28 cytoplasmic domain as set forth in SEQ ID NO: 469, and a CD3 ζ cytoplasmic domain as set forth in SEQ ID NO: 470.

Some aspects of the present invention relates to an isolated nucleic acid molecule which encodes the sdAb, scFv, or CAR of the present invention. In some embodiments, the nucleic acid molecule encodes a camel sdAb and comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 368-448. In some embodiments, the nucleic acid molecule encodes a humanized sdAb and comprises a polynucleotide sequence selected from the group consisting of SEQ ID NOs: 449-461. In some embodiments, the nucleic acid molecule encodes a VH and a VL domain of a scFv, wherein the VH domain encoding sequence comprises a polynucleotide sequence of SEQ ID NOs: 512 or 514, the VL domain encoding

sequence comprises a polynucleotide sequence of SEQ ID NOs: 511 or 513.

Some aspects of present application relates to an engineered immune cell, comprising any one of the CARs provided above, or any one of the isolated nucleic acids described above, or any one of the vectors described above. In some embodiments, the engineered immune cell is a cytotoxic T cell, a helper T cell, a natural killer T cell, a $\gamma\delta$ T cell, a NKT cell and a Nature Killer cell. In some embodiments, the cells comprise an expression vector which carries an isolated nucleic acid molecule of the present invention. Genetically modifying a cell with an expression vector to express a polypeptide encoded by a portion of the nucleic acid molecule is a genetic technique well known in the art.

Some aspects of the present invention relates to uses of the DLL3 binding proteins, anti-DLL3 CARs, nucleic acid molecules or CAR-T cells of the present invention. In some embodiments, the CAR-T cells of the present invention are formulated as a pharmaceutical composition with a physiologically acceptable excipient. As used herein, "physiologically acceptable excipient" includes without limitation any adjuvant, carrier, diluent, preservative, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, surfactant, or emulsifier as being acceptable for use in humans or domestic animals. In some embodiments, the CAR-T cells of the present invention or the pharmaceutical composition comprising the same is used to treat a DLL3-related disorder in a subject. Accordingly, a method for treating a DLL3-related disorder is provided, which comprises administering to a subject suffering from a DLL3 associated disorder a therapeutically effective amount of the CAR-T cells or the pharmaceutical composition of the present invention. A "therapeutically effective amount" of antibodies, CAR-T cells or a pharmaceutical composition may vary according to factors such as the disease state, age, sex, and weight of a subject (e.g., a patient). The term "therapeutically effective amount" may include an amount that is effective to "treat" a subject. When a therapeutic amount is indicated, the precise amount contemplated in particular embodiments, to be administered, can be determined by a physician in view of the condition of the subject. In some embodiments, the DLL3 associated disorder is a cancer expressing DLL3 as cell surface proteins, such as, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma. Preferably, the DLL3 associated disorder is a lung cancer, especially small cell lung cancer (SCLC).

EXAMPLES

The examples described herein are not intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (for example, amounts, temperature, etc.), but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Animal immunization and antibody library construction

This example demonstrated that the immunized camel showed good immune response towards human or rhesus DLL3 protein and the acquired immunized library showed superior quality.

Animal Immunization

Immunogens comprising extracellular domain of human DLL3 protein (aa27-466) having an N-terminal FLAG tag (AdipoGen, AG-40B-0151) or/and DLL3-expressing plasmid or DLL3-expressing cells (CHO-K1/DLL3 or/and CHO-K1/EGF4) were mixed with adjuvant or PBS and injected to camels. Typically, the camels were immunized for 2-4 times with 1-week to 2-week intervals. After multiple rounds of immunization, immune reactions against the target antigen DLL3 were assessed by serum titration through both enzyme-linked immune sorbent assay (ELISA) and flow cytometric assay.

Phage Display Library Construction

Total RNA was extracted from lymphocytes of immunized camel using TRIZOL® Reagent according to the manufacturer's protocol. cDNA was synthesized based on RNA template with an oligo(dT)20 primer using PRIMESCRIPT™ 1st Strand cDNA Synthesis Kit according to the manufacturer's protocol. V_HHs were amplified from camel cDNA for generation of V_HH phage library.

Example 2. Generation of anti-DLL3 antibodies

Anti-DLL3 antibodies provided herein include single domain antibodies (sdAbs) generated from an immunized camel or human Fab isolated from synthetic human Fab library.

Phage Display

A phage display library was constructed with the sdAbs obtained by immunization (Immunogens comprising extracellular domain of human DLL3 protein (aa27-466) having an N-terminal FLAG tag (AdipoGen, AG-40B-0151) or/and DLL3-expressing plasmid or DLL3-expressing cells (CHO-K1/DLL3 or/and CHO-K1/EGF4)). Another human Fab phage display library was synthesized. Both phage libraries were rescued and stored after filter sterilization at 4°C for further use. Bound phages were isolated with the above-mentioned two phage libraries using protein-based panning as well as cell-based panning. At least one round of panning was carried for both protein- and cell-based panning approaches using both libraries until the percentage of DLL3-specific phage clones reached 30%. Output phages of each round were assessed for the number of total output clones, percentage of DLL3 positive clones by ELISA and sequence diversity of DLL3-specific clones. Based on these results the best panning outputs were selected for high-throughput screening.

High-Throughput Screening

The selected output phages were used to infect exponentially growing *E. coli* cells. Double-strand DNA of the output phages was extracted. The sdAb/Fab insert were cut from the phagemid vector and inserted into an antibody fragment expression vector for high-throughput screening. The resulting plasmid was used to transform exponentially growing *E. coli* cells, which were subsequently plated and grown

overnight at 37°C. Thousands of colonies were picked individually and grown in 96 deep well plates containing 1 mL 2×YT medium. The expression of antibody fragment was induced by adding 1 mM IPTG.

The sdAb/Fab proteins in the supernatant were analyzed for their ability to bind DLL3 ECD protein by ELISA and DLL3 expressing SHP-77 cell lines (American Type Culture Collection (ATCC)® CRL-2195™) and CHO-K1/human DLL3 (in-house generation) by FACS. All binders were sequenced. The redundant sequences were removed. All together, 81 camel sdAbs and 2 human Fab binders that bound both human and rhesus DLL3 proteins and cell lines were obtained. All these binders have unique amino acid sequences.

Some of these unique binders were subjected to further characterization by surface plasmon resonance (SPR) on a BIAcore T200 instrument (GE Healthcare). The experiment was carried out as follows: the crude sdAb/Fab proteins were captured through an affinity tag onto the sensorchip. High-concentration (100 nM) of human DLL3 flowed over the sensorchip surface, and were allowed to bind the antibody fragments for 300 s followed by injection of running buffer to allow the dissociation of the complex formed. On-rate (k_a) and off-rate (k_d) were roughly calculated based on one association and dissociation curve, and were used to estimate the equilibrium dissociation constant (K_D). The binding affinities of some of these unique binders were shown in Table 7.

CDR sequences of anti-DLL3 camel sdAbs were listed in Table 1 and CDR sequences of anti-DLL3 human scFvs were listed in Table 2.

Table 1. Anti-DLL3 camel sdAb CDR sequences

sdAb	ID	CDR1 Sequence	ID	CDR2 Sequence	ID	CDR3 Sequence
AS63930	1	GYTYSGNYMA	82	VVYNIDGGGRFTTYAD SVKG	163	EVADPTWGSRDQRRYKY
AS63932	2	GYTYGSTFMG	83	VIYTGGSSTWYASSVK G	164	RYGSGNVNY
AS63951	3	RDIYGNNCMA	84	SIYPAGGRPPYADSVK G	165	RSFSIAVCATRSGITRSNF AY
AS63984	4	GYTYSSNFMG	85	TIVSGGGTTYADSVR G	166	GGPVTNAPRWYPLRPPG YNY
AS63987	5	GYRNCMA	86	VIYTPSGITDYASSVKG	167	DRPFVCNIANMRRSSN
AS63997	6	FSGYGVSTMA	87	AITVGSNGTYADSVK G	168	GYLSGGSWDVPGRYNY
AS64047	7	QYVYRWDLMG	88	AVYTG DGITYYADSVK G	169	GFVSGGRWNQSYRYKY
AS64052	8	GYTYRSNFMG	89	TIHSGVATTYADSVK G	170	GGPPANADRWYPLRPPG YNY
AS64062	9	RSPYSSRCMG	90	ALYTGGSSTSYADSVK G	171	VVPRGGSCRLDERGYH
AS64072	10	GYSYINLMA	91	AHGPGVSGTAYYTDSVK G	172	ETTMGWAHERGYRY
AS64097	11	GYTYSRNCMG	92	AINTGGSSTYADSLE	173	GPDLGGSWCRPVERAFT

				G		Y
AS64114	12	GNTYSTNYMG	93	VIYTRGGHTYYVDSVR G	174	ASRHRLRLNNPRDYDY
AS64123	13	GYTYTSNWL	94	IYTGSSTHYRSSVKG	175	RFSEYNY
AS64130	14	GYTYRSNFMG	95	TIDSRGTITYYADSVKG	176	GGPRTNDDRWWYPLRPPG YNY
AS64137	15	GSTYSTNFMG	96	TLVTWVERTAYADSVK G	177	AAASTDVRLDPGDFAY
AS64142	16	GFTFDRNAMR	97	CIDWTGANIAYADSVK G	178	DTTSGYCSGFWSTSRYS
AS64154	17	GYTYRYLYMG	98	CIYTGSGSTGYADSVK G	179	SSPRWGGTCRRWSQYNY
AS64160	18	VYTSSSYCMG	99	AMCFGGLVTHYADSV KG	180	DFGRDKNYLRPLLPHAY NY
AS64228	19	GVSYNRCSMG	100	RIQPGGNTYYADSVKG	181	LCWRENVNY
AS64300	20	GDIYNLMSMA	101	YINTIIGNTYTDSVKG	182	FNYGGAWYEERSYKY
AS64380	21	GNTYSSNYMG	102	VIYTRGGHTYYVDSVR G	183	SSRHRLGLNNPRDYDY
AS64395	22	GSTYSTNFMG	103	TLVTWAERTAYADSVK G	184	AASTAVRLDPGDFAY
AS64443	23	GYTDSVYIG	104	IYTGGESTHYRSSVKG	185	RFPVAVTY
AS64511	24	RATYSTNYIS	105	TITTDGGETAYADSVK G	186	NLRIGGDWFDGRDFRA
AS64536	25	RYTDNFVYMG	106	LIYPGGGSTYYASSVK G	187	KWGLGGGGLKSDTYMY
AS64597	26	GYTYRVNFMG	107	TIDSGVGTTYADSVK G	188	GGPPTDGDRWWYPLRPPG YNY
AS64617	27	GYTDRCMA	108	RISTSGFTNYAASVKG	189	IVGRTCSLNY
AS64634	28	GYSFRGDFMCM G	109	VFYPGGGSTNYADSAK G	190	RRWVSGTCYWDSDFHY
AS69498	29	GNTYSSNYMA	110	VIYTRGGHTYYIDSVR G	191	SSRHRLRLSDPRDYDY
AS69500	30	RYTYSSACMG	111	SIFTGTGGSTYYADSVK G	192	RAFQVGYCYLRTDVYNY
AS69527	31	RYTFSSTCMA	112	AIYTDDGSTWYADSVK G	193	RRWACPRVGSWHEFAY
AS68280	32	GSTYSSNYLG	113	AISTGDGATAYADSVK G	194	ARGRFIDWTKATQYDY
AS68355	33	GYTYSGVCMG	114	AIDSDGSTYADSVKG	195	AIVGGFNAYCSGGYVLD FGA
AS69443	34	GFTFDDSDMA	115	TISSDGSTYYADSVKG	196	DFLTGFYYSDSPHPAPCS ASDFGY
AS75376	35	GYTYSSHSMG	116	VIYTGDSSTYYADSVK	197	DPNPDYMLPFRSRRSW

				G		
AS75387	36	GYPYSSPCMA	117	VAYTGDDIQYLTDVSK G	198	DLRLPRAGGCAYS
AS75695	37	GYTVSAYCMG	118	FIDAGGATYADPVKG	199	DRRGRVRRCEYNA
AS76169	38	GYIYSSFCMG	119	YIRDNIMTSYTDSVKG	200	DRGGYANSCAVAARYDY
AS63931	39	FSGYGVSTMA	120	AITVGSGNTYYADSVT G	201	GWLSGGSWHVPGRYNY
AS63937	40	GSTISSRPMA	121	CIHTGLGRYYADSVK G	202	DSRRPCMVAAGYTY
AS63948	41	GYTYRYLYMG	122	CIYTGSGSTGYADSVK G	203	ASPRWGGTCRRWSEYNY
AS63956	42	GFTYSNCCMR	123	LINSSGGTTYADSVRG	204	YQAKYCSGPCAPPTD
AS63965	43	GYSSGSCRMG	124	KVISDGTTVYADSVKG	205	WCREYPGGILNNG
AS63993	44	GFTFDDLVMMA	125	LVATAGNSVYADSVKG	206	RTDSEHAFKF
AS63999	45	GYTYSSNWMG	126	IYTGISTHYRSSVKG	207	RYTDYNY
AS64006	46	GYTGDTTYIG	127	LIYTSGETSEYADSVKG	208	RSRTMMY
AS64057	47	GFTFDRNAMR	128	CISWTGANIAYADSVK G	209	DTTSGSCSGFWSTSRY
AS64060	48	GSTYCTYRMS	129	VIDSGGSTYADSVKG	210	DPTIGCPQTYRYNY
AS64071	49	GNTYRLNSMG	130	FIVMIRGTTYGASVK G	211	STKDQFYVFNPIGYDS
AS64093	50	RYIYGNNCMA	131	SIYPAGGRTYADSVK G	212	RSFSIGVCATQSGITWSNF AY
AS64118	51	GYTYSACRMA	132	FINSAGSTYYADSVKG	213	TWDSSCRFQY
AS64120	52	RYIYGNNCMA	133	SIYPAGGRPYADSVK G	214	RSFSIADCATQSGITRSNF AY
AS64124	53	TYTPSNNYMG	134	AIATIGGTTRYADSVKG	215	GRPYSLPLPLESGAYR Y
AS64135	54	TSTYCRYMR	135	AMQPDGTTSYSDSVKG	216	DPMGGSRTPTCTSA
AS64163	55	GYRYRWNCMA	136	AISTGSGSTYYAGSVK G	217	DPSVCPGGMWYSKEYRY
AS64182	56	GQTSRYLYMG	137	CIYTGSGSTGYADSVK G	218	SSPHWGGTCRRWSEYKY
AS64183	57	GHTYSANCMA	138	SVYTDDSTMYTDSV KG	219	DLSGGPAGCGYTH
AS64207	58	GYTYSSNFMG	139	TIVSGGGTTYADSVR G	220	GGPPTNGAKWYPLRPPG YNY
AS64276	59	GYTGSSRCMA	140	QIFTGRGTTGYADSVK G	221	SLGPGRGACGYNY
AS64336	60	GRTYSSCSMG	141	HIFSDGSRYADSVKG	222	RTGWAPRCAPVGY
AS64346	61	GYTYFMG	142	TIGTGDIENGAAYYVDS VKG	223	VQSKSSNYVLRDASTYN Y
AS64420	62	GDTSRSVWMG	143	TISTAGGSTWYTDSVK	224	RSRYATY

				G		
AS64473	63	GYTYRYLYMA	144	CIYTGSGTTGYADSVK G	225	SSPQWGGTCRRWSEYNY
AS64475	64	GYTWSRNWMG	145	TITISGGSTWYADSVKG	226	RDTARTY
AS64513	65	DYPYIDNCMG	146	AACTGGGSTYYADSVK G	227	GYYSGSGPGYLLPWRYN Y
AS64562	66	GYTARRDFMA	147	VIHTGGDTTYADSVK G	228	GFRPRGGGYTGDVLAQA AAYNY
AS64583	67	GFTIAVYTMG	148	CTSWAGGRITYADSVK G	229	KAHPDCSGDWSPSGYEY
AS64594	68	GYTYNSNYMG	149	LIYTGGGSTYYADSVK G	230	RTQTRNY
AS64605	69	RYPYSSICMG	150	RIYTGSTWYTDSVK G	231	RSNSYSYSSCDYGPLTRG GYNF
AS64606	70	GYTSRSNYMG	151	AFYLIYTRGGSTYYASS VKG	232	RLDEKMY
AS68121	71	GYTYSRNCMG	152	TDYIRFGRTYYADSVK G	233	DPGSRTDDSCGTSYNKG NFGY
AS68170	72	GYTYRSNCMG	153	TIYTGGGRNLYYADSV KG	234	ASDVAVGVNSCGGRTAG FDA
AS63964	73	GYTYSYNNMG	154	AISGGRFTAYADSVKG	235	EVVDPTWGSRDQRRYKY
AS64116	74	GYIYSCVG	155	GISTGGGGTVYADSVK G	236	DRWNSFANCGAWGRYT Y
AS68270	75	GYPSTYYMLS MA	156	AITSGTGSTYADSVKD	237	ASGWIVPSRSLTANLYRY
AS68320	76	GYTYNTNYMG	157	AIYRHSGNTAYADSVK G	238	GRAGPWALMRPTEFGY
AS68351	77	GDTFRAYYMN	158	GISASGGRTSYADSVK G	239	GAVRLSTSSVRDSS
AS75378	78	GNTRSTTYMG	159	IVYTGGGRDTYYAASVK G	240	RSYEYTY
AS75383	79	GYTFSSYCLG	160	TFNNRGVANYHDSVK G	241	DRRYGRQWYQPCEWNT
AS75751	80	GYFYNTYYFMG	161	AIDTDGRTSYADSVKG	242	GFGYMNVIQALNGMRQ NPDY
AS76422	81	GYTFAGNCLG	162	TYNNFGVANYADSVK G	243	DRRDGRRWSQPCEWNT

Table 2. Anti-DLL3 human scFv CDR sequences

Ab	ID	CDR1 Sequence	ID	CDR2 Sequence	ID	CDR3 Sequence
AS56704	495	VL: RASQSVSSAVA	496	VL: SASSLYS	497	VL: QQASWSPIT
	498	VH:	499	VH: YIYPSYGYTSY	500	VH: GGYYYHGMDY

		GFISSSYMH		ADSVKG		
AS56788	501	VL: RASQSVSSAVA	502	VL: SASSLYS	503	VL: QQHYAPSLIT
	504	VH: GFISSSYMH	505	VH: YISSYYGYTTY ADSVKG	506	VH: YSYYYGMDY

Anti-DLL3 sdAb amino acid sequences were listed in Table 3. CDRs of the sdAb were underlined. Nucleic acid sequences encoding the anti-DLL3 sdAbs were shown in SEQ ID NOs: 368-448.

Table 3. Anti-DLL3 camel sdAb amino acid sequences

SEQ ID	Camel sdAb	Amino Acid Sequence
274	AS63930	EVQLAESGGGSVQAGGSLRLSCAASGYTYSNGYMAWFRQAP GNREGVAVVYNIDGGGRFTTYADSVKGRFTISRNDKNTVYL QMNSLKPEDSGMYCAA <u>EVADPTWGSRDQRRYKYWGQGTQ</u> VTSS
275	AS63932	QVQLEESGGGSVQAGGSLRLSCVASGYTYGSTFMGWFRQNP KREGVAVIYTGGGSTWYASSVKGRFTISQDNAKNTVYLQMN SLKPEDTAMYYCAARYGSGNVNYWGQGTQVTSS
276	AS63951	QVHLMESGGGSVQAGGSLRLACETSRDIYGNNCMAWFRQAP GKREGVASIYPAGGRPYADSVKGRFTISQDNAKNTVYLQMD SLKPEDTAMYYCAARSFSIAVCATRSGITRSNFAYWGQGTQVT VSS
277	AS63984	QVKLVESGGGSVQAGGSLRLSCAASGYTYSSNFMGWFRQAPG KREGVATIVSGGGTTYADSVRGRFTISQDNAKNTVYLQMNS LKPEDTAMYYCAAGGPVTNAPRWYPLRPPGYNYWGQGTQVT VSS
278	AS63987	QVRLVESGGGSVQAGGSLRLSCEATGYRNCMAWFRQAPGKER EGVAVIYTPSGITDYASSVKGRFTISQNNARNTQYLQMNSLKPE DTAMYYCAADRPFCNIANMRRSSNWGRGTQVTSS
279	AS63997	QVRLVESGGGSVQAGGSLRLSCAGSFSGYGVSTMAWFRQAPG KREGVAITVGSGNTTYADSVKGRFTISRDNKRTVFLQMNS LKPEDTAMYYCAVGYLSGGSWDVPGRYNYWGQGTQVTSS
280	AS64047	QVHLMESGGGSVQAGGSLRLSCAASQYVYRWDLMGWFRQAP GKEREAVAAYTGDGITYYADSVKGRFSISQDNAKNTVYLQMN SLKPEDTGMFYCAAGFVSGGRWNQSYRYKYWGQGTQVTSS
281	AS64052	QVHLMESGGGSVQAGGSLRLSCAASGYTYRSNFMGWFRQAP GKREGIATIHSGVATTYYADSVKGRFTISQDNAKNTVYLQMN SLKPEDTAMYYCAAGGPPANADRWYPLRPPGYNYWGQGTQV TVSS
282	AS64062	QVRLVESGGGSVQVGGSLRLSCAASRSPYSSSRMCMGWFRQAP GKREGVAALYTGGGSTSYADSVKGRFTISQDNAKNTVYLQM NSLKPEDTAMYYCAAVVPRGGSCRLDERGYHHWGQGTQVT SS

283	AS64072	QVQLVESGGGSVQAGGFLRLSCALSGYSYYINLMAWFRQAPG KEREAVA <u>AHGPVSGTAYYTDSVKGRFTISRDPGKNTMYLQMFS</u> LQPEDTALYYCAA <u>ETTMGWAHERGYRYWGQGTQVTVSS</u>
284	AS64097	QVHLMESGGGSVQAGGSLRLSCEASGYTYSRNCMGWFRQAP GKEREGVA <u>INTGGGSTYYADSLEGRFTISQDNAKNTMYLQM</u> NSLKPEDTAMYYCAA <u>GPDLGGSWCRPVERAFTYWGQGTQVT</u> VSS
285	AS64114	QVQLQESGGGSVQAGGSLTLSCASGNTYSTNYMGWFRQAPG KEREVAVIYTRGGHTYYVDSVRGRFTISQDNAKNTVYLQMN SLKPEDTAMYYCAA <u>ASRHRLRLNNPRDYDYWGQGTQVTVSS</u>
286	AS64123	QVQLAESGGGSVQAGGSLRLSCAASGYTYTSNWLGWFRQAPG KEREVAVIYTGSGSTHYRSSVKGRFTISQDNAKNTVYLQMN SLKPEDTAMYYCAA <u>RFSEYNYWGQGTQVTVSS</u>
287	AS64130	EVQLAESGGGSVQAGGSLRLSCAASGYTYRSNFMGWFRQAPA KEREGVATIDSRGTITYYADSVKGRFTISQDNEKNTVYLQMN SLKPEDTAMYYCAA <u>GGPRTNDDRWYPLRPPGYNYWGQGTQVT</u> SS
288	AS64137	QVRLVESGGGSVQAGGSLRLSCAASGSTYSTNFMGWFRQAPG KEREGVATLVTWVERTAYADSVKGRFTISQDRAKNTVYLQMN SLKPEDTAMYYCAA <u>AAASTDVRLDLPDGFAYWGQGTQVTVSS</u>
289	AS64142	QVHLMESGGGLVQTGGSLRLSCTASGFTFDRNAMRWYRQAPG KEREGVSCIDWTGANIAYADSVKGRFTISRDNKNTLYLQMN SLKPEDTAMYYCAA <u>ADTTSGYCSGFWSTSRYSWGQGTQVTVSS</u>
290	AS64154	QVQLKESGGGSVQAGGSLRLSCTASGYTYRYLYMGWFRQTPG KEREGVACIYTGSGSTGYADSVKGRFTISQDNAKNTVYLQMN SLKPEDTAMYYCAA <u>ASSPRWGGTCRRWSQYNYWGQGTQVTVSS</u>
291	AS64160	EVQLVESGGGSVQAGGSLRLSCAASVYTSSSYCMGWFRQAPG KEREGVAA <u>MCFGGLVTHYADSVKGRFTISQDNAKNTVYLQMN</u> SLKPEDTAMYYCAA <u>DFGRDKNYLRPLLPHAYNYWGQGTQVT</u> VSS
292	AS64228	QVQLKESGGGSIQAGGSLRLSCAASGVSYNRCMGSWYRQAPG KGRVLSRIQPGGNTYYADSVKGRFTVSDNAKNTVSLQMN SLKPEDTAMYYCNA <u>LCWRENVNYWGQGTQVTVSS</u>
293	AS64300	QVHLMESGGGSVQTGGSLRLSCAVSGDIYNLMSMAWFRRAPG KEREGVAYINTIIGNTYYTDSVKGRFTISRDNKNTLYLQMN SLKPEDTAMYYCAA <u>FNYGGAWYEERSYKYWGQGTQVTVSS</u>
294	AS64380	EVQLVESGGGSVQAGGSLTLSCASGNTYSSNYMGWFRQAPG KEREVAVIYTRGGHTYYVDSVRGRFTISQDNAKNTVYLQMN SLKPEDTAMYYCAA <u>SSRHRLGLNNPRDYDYWGQGTQVTVSS</u>
295	AS64395	QVRLVESGGGSVQAGGSLRLSCAASGSTYSTNFMGWFRQAPG KEREGVATLVTTWAERTAYADSVKGRFTISQDRAKNTVYLQMN GLKPEDTAMYYCAA <u>AAASTAVRLDLPDGFAYWGQGTQVTVSS</u>
296	AS64443	QVHLMESGGGSVQAGGSLRLSCAASGYTDSSVYIGWFRQAPG KEREVAVIYTGGESTHYRSSVKGRFTVSDNAKNTLYLQMN

		LKPEDTAMYYCAAR <u>FPAVTY</u> WGQGTQVTVSS
297	AS64511	QVQLVESGGGSVQAGGSLRLSCAASRATYSTNYISWFRQAPGK EREAVATITTTGDGETAYADSVKGRFTISRDNKNTVYLQMNSL KPEDTAMYYCAANLRIIGGDWFDGRDFRAWGQGTQVTVSS
298	AS64536	QVQLVESGGGSVQAGGSLRLSCAASRYTDNFVYMGWFRQAPG KEREGVALIYPGGGSTYYASSVKGRFTISQDNAKGTVHLQMNN LKPEDTAMYYCAAKWGLGGGGLKSDTYMYWGQGTQVTVSS
299	AS64597	QVHLVESGGGSVQAGGSLRLSCAASGYTYRVNFMGWFRQTPG KEREGVATIDSGVGTTYADSVKGRFTISHNNAKNTIYLQMNS LKPEDTAMYYCAAGGPPTDGDWRWYPLRPPGYNYWGQGTQVT VSS
300	AS64617	QVQLVESGGGSVQAGGSLRLSCAASGYTDRCMAWYRQAPG KERELVSRISTSGFTNYAASVKGRFTISQDNAKNTVYLQMNSLN PGDTGMYCAIIVGRTCSLNYWNGILVTVSS
301	AS64634	QVRLVESGGGSVQAGGSLRLSCAASGYSFGRDFMCMGWFRQT PGKGREGVAVFYPGGGSTNYADSAKGRFTISQDNAKNTMYLQ MNTLKPEDTAMYYCAARRWVSGTCYWDSDFHYWGQGTQVT VSS
302	AS69498	QVQLQESGGGSVQAGGSLRLSCEASGNTYSSNYMAWFRQAPG KEREEVAIYTRGGHTYYIDSVRGRFTISQDNAKNTVYLQMNS LKPEDTAMYYCAASSRHRLRLSDPRDYDYWGQGTQVTVSS
303	AS69500	QVRLVESGGGSVQAGGSLRLSCAADRYTYSSACMGWFRQAPG KEREGVASIFTGTGGSTYYADSVKGRFTISQDNAKNTVYLQMN SLKPEDTAIYYCAARAFQVGYCYLRTDVYNYWGQGTQVTVSS
304	AS69527	EVQLAESGGGSVQAGGSLRLSCVASRYTFSSTCMAWFRQAPG KEREEVAIYTDGGSWTYADSVKGRFTISRDNKNTVYLQMN SLKPEDTAMYYCAARRWACPRVGSWHEFAYWGQGTQVTVSS
305	AS68280	QVQLVESGGGSVHPGGSLRLSCAASGSTYSSNYLGWFRQAPG KGRDWVAAISTGDGATAYADSVKGRFTISQDNAKNTVYLQMN SLKLEDSAMYYCAAARGRFIDWTKATQYDYWGQGTQVTVSS
306	AS68355	QMQLVESGGDSVQAGGSLRLSCAASGYTYSGVCMGWFRQAP GKEREGVAIDSDGSTSYADSVKGRFTISKDNAKNTLYLQMNS LKPEDTAMYYCAAIVGGFNAYCSGGYVLDFGAWGQGTQVT VSS
307	AS69443	EVQLAESGGGSVQAGGSLRLSCSASGFTFDDSDMAWYRQAPG DGCDLVSTISSDGSTYYADSVKGRFTISQDNAKNTVYLQMHSL KPEDTAVYYCAADFLTGFYYS DSPHPAPCSASDFGYWGQGTQV TVSS
308	AS75376	QVQLKESGGGSVQAGGSLRLSCAASGYTYSSHSMGWFRQAPG KEREGVAIYTGDSSTYYADSVKGRFTISQDNAKNTVYLQMNS LKPEDTAMYYCAADPNPDYMLPFRPSRRSWWGQGTQVTVSS
309	AS75387	QVHLVESGGGSVQAGGSLRLSCAASGYPYSSPCMAWFRQAPG KEREGVLVAYTGGDIQYLTDSVKGRFTISRDNKNTVYLQMNS

		LKPEDTAMYYCAAD <u>LRLPRAGGCAYS</u> WGQGTQVTVSS
310	AS75695	QVRLVESGGGSVQAGGSLRLSCVASGYTVSAYCMGWFRQVLG KGRERIAFIDAGGATIYADPVKGRFTISKDNAKNTLYLQMNSLK PEDTAMYYCVADRRGRVRRCEYNAWGQGTQVTVSS
311	AS76169	QVHLMESGGGSVQAGGSLRLSCAASGYIYSSFCMGWFRQAPG KEREVVAIYRDNIMTSYTDSVKGRFTISKDNAKRTLYLQMNSL KPEDTGMYCYCAVDRGGYANSCAVAARYDYWGRGTQVTVSS
312	AS63931	EVQLAESGGGSVQAGGSLRLSCAGSFSGYGVSTMAWFRQAPG KEREVVAITVGSGNTTYADSVTGRFTISRDNKRTVYLQMNS LKPEDTAMYYCAAGWLSGGSWHVPGRYNYWGQGTQVTVSS
313	AS63937	QVKLVESGGGSVQAGGSLRLSCAASGSTISSRPMWFRQAPGK EREGVACIHTGLGRITYADSVKGRFTISQDNAKNTVYLQVNSL KPEDTAMYYCAADSRPCMVAAAGYTYWGQGTQVTVSS
314	AS63948	QVQLVESGGGSVQAGGSLRLSCTASGYTYRYLYMGWFRQTPG KEREVVAIYTGSGSTGYADSVKGRFTISQDNAENTVYLQMNS LKPEDTAMYYCAAASPRWGGTCRRWSEYNYWGQGTQVTVSS
315	AS63956	QVHLMESGGGLVQAGGSLRLSCAASGFTYSNCCMRWYRQAPG KARELVSLINSSGGTYADSVRGRFTISKDNAKNTLYLQMNSL KPEDTAMYYCAAYQAKYCSGPCAPPTDWGQGTQVTVSS
316	AS63965	QVQLVESGGGSVQAGGSLRLSCVASGYSSGSCRMGWYRQAPG KERELVSKVISDGTTVYADSVKGRFTLSQGNKNTVYLQMSSL LPEDTAMYYCNAWCREYPGGILNNGWGQGTQVTVSS
317	AS63993	QVKLVESGGGLVQAGGSLRLSCTVSGFTFDDLVMWFRQAPG KERQLVSLVATAGNSVYADSVKGRFTLSRDNAHSTAYLQMNSL KPEDTAMYYCAARTDSEHAFKFWGQGTQVTVSS
318	AS63999	EVQLVESGGGSVQAGGSLRLSCAASGYTYSSNWMGWFRQAP GKEREEVAIIYTGISTHYRSSVKGRFTISQDNAKNTVYLQMNS LKPEDTAMYYCAARYTDYNYWGQGTQVTVSS
319	AS64006	QVHLMESGGGSVQAGGSLRLSCEVSGYTGDTTYIGWFRQAPG KEREVVAIYTSYSGTSEYADSVKGRFIISRDNKNTVYLQMNSL KPEDTAMYYCGARSRTMMYWGQGTQVTVSS
320	AS64057	QVQLEESGGGLVQTGGSLRLSCTASGFTFDRNAMRWYRQAPG KEREVVAISWTGANIAYADSVKGRFTISRDNKNTLYLQMNS LKPEDTGMYCAADTTSGSCSGFWSTSRYYWGQGTQVTVSS
321	AS64060	QVKLVESGGGSVQAGGSLRLSCAASGSTYCTYRMSWFRQAPG KEREVVAVIDSGGSTSYADSVKGRFTISRDNKNTVYLQMNSL KPEDTAMYYCKTDPTIGCPQTYRYNYWGQGTQVTVSS
322	AS64071	QVHLMESGGGSVQAGGSLRLSCVASGNTYRLNSMGWFRQAP GKEREVVAFIVMIRGTTYGASVKGRFTISQDNAQTTVYLQMS SLKPEDTAMYYCAASTKDQFYVFNPIGYDSWGQGTQVTVSS
323	AS64093	QVHLMESGGGSVQAGGSLRLSCATSRYIYGNNCMAWFRQAPG KEREVVAIYPAGGRITYADSVKGRFTISQDNAKNTVYLQIDSL

		KPEDTAMYYCAAR <u>SFSIGVCATQSGITWSNFAYWGQGTQVTVS</u> S
324	AS64118	QVQLAESGGGSVQAGGSLRLSCAASGYTYSACRMAWYRQAP GKERELV <u>SFINSAGSTYYADSVKGRFAISR</u> DNAKTTVYLQMNA LKAEDTAIYYCNT <u>WDSSCRFQYWGQGTQVTVSS</u>
325	AS64120	QVRLVESGGGSVQAGGSLRLSCETSRYIYGNNCMAWFRQAPG KEREGVA <u>SIYPAGGRPYADSVKGRFTISQD</u> NAKNTVYLQMDS LKPEDTAMYYCAAR <u>SFSIADCATQSGITRSNFAYWGQGTQVTV</u> SS
326	AS64124	QVKLVESGGGSVQTGGSLRLSCAVSTYTPSNMYMGWFRQAPG KEREGVA <u>AIATIGGTTRYADSVKGRFTISQD</u> GAKNITVYLQMNGL KPEDTAMYYCAAGRPYSLPLPLESGAYRYWGQGTQVTVSS
327	AS64135	QVKLVESGGGSVQAGGSLRLSCVASTSTYCRYMRWYRQAPG KEREFV <u>SAMQPDGTTSYSDSVKGRFTMSQD</u> RANNMVLQMN LRPEDTAMYYCKRDPMGGSRTPTC <u>SAWGQGTQVTVSS</u>
328	AS64163	QVRLVESGGGSVQAGGSLRLSCAVSGYRWRWNCMAWFRQAP GKEREGVA <u>AISTGSGSTYYAGSVKGRFTISQD</u> NAKNMYLQMN LKPEDTAMYYCAADPSVCPGGMWYSKEYRYWGQGTQVTVSS
329	AS64182	QVHLMESGGGSVQAGGSLRLSCTASGQTSRYLYMGWFRQTPG KEREGVACIYTGSGSTGYADSVKGRFTISQDNAKNTVYLQTN LKPEDTAMYYCAASSPHWGGTCRRWSEYKYWGQGTQVTVSS
330	AS64183	QVHLMESGGGSVQAGGSLRLSCAASGHYTSANCMWFRQAPG KEREWVA <u>SVYTDDDSTMYTDSVKGRFTIFQD</u> NAKNTVYLQM NSLKPEDTGMYICAADLSGGPAGCGYTHWGQGTQVTVSS
331	AS64207	EVQLVESGGGSVQAGGSLRLSCAASGYTYSSNFMGWFRQAPG KEREGVATIVSGGGTTYADSVRGRFTISQDNAKNTVYLQMN LKPEDTAMYYCAAGGPPTNGAKWYPLRPPGYNYWGQGTQVT VSS
332	AS64276	QVHLMESGGGSVQAGGSLRLSCVVSQYTGSSRCMAWFRQAPG KEREAVAQIFTGRGTTGYADSVKGRFTISQDNAKNTVYLRMNS LRPEDTAIYYCAASLGPGRGACGYNYWGQGTQVTVSS
333	AS64336	QVQLVESGGGSVQAGGSLRLSCTTSGRTYSSCSMGWYRQAPG KERELVSHIFSDGSRYADSVKGRFTISQDNAKNTVYLQMN LKPEDTAMYYCNRRGTWAPRCAPGYWGQGTQVTVSS
334	AS64346	QVHLMESGGGSVQAGGSLRLSCAASGYTYFMGWFRQAPQKER EWVATIGTGDIENGAAAYVDSVKGRFAISQDNAKNTVYLQMN SLKPEDTAVYVCAAVQSKSSNYVLRDASTYNYWGQGTQVTVS S
335	AS64420	EVQLVESGGGSVQAEGLRLSCAASGDTSRVWMGWARQVPG KEREVVATISTAGGSTWYTDSVKGRFTISQDNAKNTVYLQMN LKPEDTAIYYCAARSRATYWGQGTQVTVSS
336	AS64473	QVRLVESGGGSVQAGGSLRLSCTASGYTYRYLYMAWFRQTPG KEREGVACIYTGSGTTGYADSVKGRFTISQDNAKNTVYLQMN LNAEDTAMYYCAASSPQWGGTCRRWSEYNYWGQGTQVTVSS

337	AS64475	QVQLQESGGGSVQAGGSLRLSCAASGYTWSRNWMGWFRQAP GKEREGFATITISGGSTWYADSVKGRFTISLDNAGNTVYLQMN SLKPEDTAMYYCAARDTARTYWGQGTQVTVSS
338	AS64513	EVQLVESGGGSVQAGGSLRLSCVASDYPYIDNCMGWFRQGPG KEREGVAAACTGGGSTYYADSVKGRFTISRDNKNTVYLQMN SLKPEDTDVYYCATGYYSGSGPGYLLPWRYNYWGQGTQVTVS S
339	AS64562	EVQLVESGGGSVQAGGSLRLSCAASGYTARRDFMAWFRQVPG KEREGVAVIHTGGDDTTYADSVKGRFTISRDNQNMNLQMNS LKPEDTAMYYCAAGFRPRGGGYTGDVLAQAAAYNYWGQGTQ VTVSS
340	AS64583	EVQLAESGGGLVQAGGSLRLSCTASGFTIAVYTMGWFRQAPGK EREGISCTSWAGGRITYADSVKGRFTISRDNKNTLYLQMN SLKPEDTAMYYCAAKAHPDCSGDWSPSGYEYWGQGTQVTVSS
341	AS64594	QVHLVESGGGSVQAGGSLRLSCAASGYTYNSNYMGWFRQAP GKEREGVALIYTGGGSTYYADSVKGRFTISRDNKNTVYLQMN SLKPEDTAMYYCSVRTQTRNYWGQGTQVTVSS
342	AS64605	QVKLVESGGGSVQAGGSLRLSCAVSRYPYSSICMGWFRQAPGK ESEGVARITYTGSTWYTDVSKGRFTIARDNAQNTVYLQMN SLKPEDTAMYYCAARSNSYSYSSCDYGPLTRGGYNFWGQGTQV TVSS
343	AS64606	EVQLAESGGGSVQAGGSLRLSCAVSGYTSRSNYMGWFRQAPG KEREGVALIYTRGGSTYYASSVKGRFTISQDSAKKTYLQMN SLKPEDTAMYYCALRLDEKMYWGQGTQVTVSS
344	AS68121	EVQLAESGGGSVQAGGSLRLSCDASGYTYSRNCMGWFRQAPG KEREGVAAFYTDYIRFGRTYYADSVKGRFTIFQDNKNTVYLQ MNSLKPEDTAMYYCAADPGSRTDDSCGTSYNKGNFGYWGQ GTQVTVSS
345	AS68170	QVQLVESGGGSVQAGGSLRLSCTASGYTYRSNMGWFRQAPG KEREGVATITYTGGGRNLYYADSVKGRFTISRDNKNTLYLQMN SLKPEDSARYYCAAASDVAVGVNSCGGRTAGFDAWGQGTQV TVSS
346	AS63964	QVRLVESGGGSVQAGGSLRLSCSASGYTYSYNNMGWFRQAPG NEREGVAAISGGRFTAYADSVKGRFTISRDNKNTLYLQMN SLKPEDTGMYYCAAEVVDPTWGSRDQRRYKYWGQGTQVTVSS
347	AS64116	QVKLVESGGGSVQAGGSLRLSCAASGYIYSCVWFRQAPGKE REGVAGISTGGGSTVYADSVKGRFTISRDNKNTVYLQMDSLK PEDTAMYYCAADRWNSFANCGAWGRYTYWGQGTQVTVSS
348	AS68270	QVQLAESGGGSVQAGGSLRLSCVASGYPSSTYYMLMAWFRQ APGKEREGVAAITSGTGSTYADSVKDRFTISKDYANNTLYLHI NNLKPEDTAMYYCAAASGWIVPSRSLTANLYRYWGQGTQVTV SS
349	AS68320	QVHLVESGGGSVQAGGSLRLSCAASGYTYNTNYMGWFRQAP GKEREGVAAIYRHSGNTAYADSVKGRFTISQDYAKNTVYLQMN

		SLKPEDTAMYYCAAG <u>RAGPWALMRPTEFGYWGQGTQVTVSS</u>
350	AS68351	QVQLEESGGGLVQPGGSLRLSCAASGDTFRAYYMNWVRQAPG KGF ~~EWV~~ SGISASGGRTSYADSVKGRFTISRDNAKNTLYLQNL STEDTGMYYCVKGA <u>VRLSTSSVRDSSWGQGTQVTVSS</u>
351	AS75378	QVQLEESGGGSVQAGGSLRLSCVVSNGNTRSTTYMGWFRQAPG KEREGVAIVYTGGRDITYAASVKGRFTISQDNAKTTIYLQMNS LEPEDTAMYYCAARSY <u>EYTYWGRGTQVTVSS</u>
352	AS75383	EVQLAESGGGSVQAGGSLRLSCVASGYTFSSYCLGWFRQAPGK QRQGVATFNNRGVANYHDSVKGRFTASVDNAKNTLLQMN EPDDTAMYYCAADRRYGRQWYQPC <u>EWNTWGQGTQVTVSS</u>
353	AS75751	QVRLVESGGGSVQAGGSLRLSCVASGYFYNTYYFMGWFRQAP GKEREGVAIDTDGRTSYADSVKGRFTISKDNAKNTLYLQMNS LKPEDTAMYYCAAGFGYMNVIQALNGMRQNP <u>DPYWGQGTQVTVSS</u>
354	AS76422	QVKLVESGGGSVQAGGSLRLSCAASGYTFAGNCLGWFRQAPG KGREGVVTYNNFGVANYADSVKGRFTVSQDNAKNTLLQMN SLEPEDTAMYYCAADRRDGRRWSP <u>CEWNTWGQGTQVTVSS</u>

Amino acid sequences of VH and VL domains of anti-DLL3 human scFvs were listed in Table 4. Nucleic acid sequences encoding VH or VL domain of anti-DLL3 human scFvs were shown in SEQ ID NOs: 511-514.

Table 4. Anti-DLL3 human scFv amino acid sequences

scFv	SEQ ID	Amino Acid Sequence
AS56704	507	VL: DIQMTQSPSSLSASVGDRVITICRASQSVSSAVAWYQQKPGKAP KLLIYSASSLYSGVPSRFSGSRSGTDFLTISLQPEDFATYYCQQ ASWSPITFGQGTKVEIK
	508	VH: EVQLVESGGGLVQPGGSLRLSCAASGFNISSSYMHWVRQAPGK GLEWVAYIYPSYGYTSYADSVKGRFTISADTSKNTAYLQMNSL RAEDTAVYYCARGGYYHGM DYWGQGTLVTVSS
AS56788	509	VL: DIQMTQSPSSLSASVGDRVITICRASQSVSSAVAWYQQKPGKAP KLLIYSASSLYSGVPSRFSGSRSGTDFLTISLQPEDFATYYCQQ HYAPSLITFGQGTKVEIK
	510	VH: EVQLVESGGGLVQPGGSLRLSCAASGFNISSSYMHWVRQAPGK GLEWVAYISSYGYTYYADSVKGRFTISADTSKNTAYLQMNSL RAEDTAVYYCARYSYYGMDYWGQGTLVTVSS

Example 3. Generation of monospecific camel CARs

The amino acid sequences of anti-DLL3 camel sdAb fragments were provided above in Table 3 and the nucleic acid sequences of anti-DLL3 camel sdAb fragments

were provided in SEQ ID NOs: 368-448. sdAb fragments of Table 3 and additional sequences were used to generate CAR constructs (SEQ ID NOs: 476-484). CAR3 scFv (SEQ ID NO: 473), which is a human anti-DLL3 scFv, was also used to generate a CAR construct as a reference (CAR3). A full length CAR contains from the N-terminus to the C-terminus: a CD8 α signal peptide (SEQ ID NO: 465), a DLL3 binding domain sdAb provided in Table 3, a CD8 α hinge domain (SEQ ID NO: 466), a CD8 α transmembrane domain (SEQ ID NO: 467), a CD137 intracellular domain (SEQ ID NO: 468) or a CD28 intracellular domain (SEQ ID NO: 469), and a CD3 ζ intracellular domain (SEQ ID NO: 470). Schematic representation of a CAR construct is shown in FIG. 1. Nucleic acid encoding the CAR fragment was then cloned into a lentiviral vector to create full length CAR construct in a single coding frame, using human EF1 α promoter for expression. The resulting CAR backbone vector was named “PLLV-hEF1 α -DLL3”.

Example 4. Generation of camel anti-DLL3 CAR-T cells

Preparation of lentivirus

The lentivirus packaging plasmid mixture including pCMV- Δ R-8.47 and pMD2.G (Addgene, Cat#12259) was pre-mixed with PLLV-hEF1 α -DLL3 vectors at a pre-optimized ratio (1:1:1:2) in the presence of polyethylenimine before added to the HEK293 cells. The supernatants were collected after overnight incubation. The virus-containing supernatants were filtered through a 0.45 μ m PES filter, and ultra-centrifuged to concentrate lentiviruses. The virus pellets were rinsed with pre-chilled DPBS. The viruses were aliquoted properly before stored at -80°C immediately. Virus titer was determined by measurement of transduction efficiency to supT1 cell line via flow cytometric assay.

Collection and transduction of T lymphocytes

Leukocytes were collected from healthy donors by apheresis. Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll-Paque™ PLUS Media according to manufacturer's protocol. Human T cells were purified from PMBCs using Pan T cell isolation kit (Miltenyi, Cat#130-096-535), following manufacturer's protocol. The purified T cells were subsequently pre-activated for 48 hours with human T cell activation/expansion kit (Miltenyi, Cat#130-091-441) according to manufacturer's protocol, in which anti-CD3/CD28 MACSiBead particles were added at a bead-to-cell ratio of 1:2. The pre-activated T cells were transduced with lentivirus stock in the presence of 7 μ g/mL polybrene. The transduced cells were then transferred to the cell culture incubator for transgene expression under suitable conditions.

Example 5. Evaluation of *in vitro* activity of camel anti-DLL3 CAR-T cells

***In vitro* cytotoxicity assay**

On day 6 post transduction, transduced T cells were harvested and co-incubated with DLL3-expressing tumor cell line SHP-77 at an effector (CAR-T) to target cell ratio of 2:1 and 5:1 for 20 hours. CAR3 CAR-T cells were used as a reference in all assays to compare assay variation and/or act as a control. Un-transduced T cells (UnT)

were used as a negative control.

The cytotoxicity of the transduced T cells was determined by a lactate dehydrogenase (LDH) assay. Results show that CAR3 CAR-T and some anti-DLL3 CAR-Ts exhibit strong anti-tumor activities *in vitro* against SHP-77 cells, while UnT has no target cell killing effect (FIG. 2).

IFN- γ and TNF- α release detection

Additionally, supernatants from the *in vitro* cytotoxicity assay were collected to assess CAR-induced cytokine release, e.g., interferon gamma (IFN- γ) and TNF- α release. As shown in FIG. 3A and FIG. 3B, CAR3 CAR-T and some anti-DLL3 CAR-Ts were stimulated by SHP-77 to produce IFN- γ and TNF- α , whereas UnT produced little IFN- γ and TNF- α . Protocols of IFN- γ and TNF- α release detection can be referred to CISBIO's human TNF- α kits and IFN- γ kits.

CAR-T expansion by long-term stimulation assay

On day 0, 1×10^5 SHP-77 cells were plated in 24 well plates to establish a monolayer. On day 1, transduced T cells were counted and 2×10^5 viable CAR⁺ T cells were plated on top of the SHP-77 cells in fresh media in the absence of cytokines. On day 3, a new 1×10^5 SHP-77 cells monolayer were plated on top of the CAR-T cells. On day 4, viable CAR-T cells were counted for each well. On the same day, 2×10^5 CAR⁺ T cells from wells that expanded (had at least this amount of cells) were re-plated to establish a new monolayer as on Day 1. The process was repeated to provide 3-4 rounds of stimulation. Fold expansion after each stimulation was calculated as [viable CAR⁺ T cells on day 4] / 2×10^5 , the amount of CAR T cells plated on day 1 of each stimulation. To normalize for cells discarded with each new stimulation, cumulative fold expansion was determined by [(fold expansion) x (fold expansion+1)...].

After 3 rounds of stimulation, the fold expansions of different CAR-T constructs were calculated. As it was showed in FIG. 4, most CAR-T constructs expanded more than CAR3 CAR-T with 3 rounds of stimulation by SHP-77 tumor cells.

Example 6. *In vivo* efficacy valuation of camel CARs by CAR-T cells mediated tumor growth inhibition

The anti-tumor activity of the camel CARs was evaluated in a SHP-77 tumor model. SHP-77 cells were implanted subcutaneously in NOD/SCID mice and randomized into 7 groups (4 mice per group, day 0). Group 1: vehicle (PBS only); Group 2: UnT (negative control); Group 3: CAR3; Group 4: CAS64380; Group 5: CAS64511; Group 6: CAS63931; Group 7: CAS63997. Treatment with CAR-T cells, UnT cells or vehicle (PBS only) began when tumors were palpable (100 mm^3) and mice were euthanized when their tumor volumes reached about 3000 mm^3 . Tumor volumes were measured 2 times per week. CAR-T cells were administered intravenously with 1×10^6 CAR positive T cells per mouse. Mice and tumors were monitored for about 21 days after tumor cell implantation.

As shown in FIG. 5, all selected camel CARs demonstrated anti-tumor activity in this animal tumor model.

Example 7. Humanization of camel sdAbs

Selected camel sdAbs (SEQ ID NOs: 279, 294, 297, 312) were humanized using CDR grafting technology (see, *e.g.*, U.S. Pat. No. 5,225,539). Briefly, the camel sdAb sequence was compared to those available in the Research Collaboratory for Structural Bioinformatics (RCSB) protein databank. A homology model of each camel sdAb was generated based on the nearest VH structures. From the model structure, residues that are in the proximity of CDRs or buried inside the molecule (*i.e.* with side chain solvent accessible surface area less than 15%) were identified.

Subsequently, each camel sdAb sequence was BLASTed against NCBI human germline V gene database to identify the human VH germline sequence (*i.e.* human acceptor) with highest identity to the sdAb (see, *e.g.*, Foote and Winter, *J. Mol. Biol.* 224:487-499 (1992); Morea V. *et al.*, *Methods* 20:267-279 (2000); Chothia C. *et al.*, *J. Mol. Biol.* 186:651-663 (1985).) In the CDR grafting approach, CDRs of the human acceptor were replaced by those of the camel sdAbs, which produced the straight-graft sequence. Straight-graft antibody usually lost binding activity, which needed to be restored by replacing the framework residues that were critical for the activity of the antibody with non-human residues. Amino acid residues that were in the proximity of CDRs or buried inside the molecule were usually important for the activity and structure of the antibody, and therefore should be potential back-mutation sites. A series of humanized variants were designed using this method. CDR amino acid sequences of the humanized variants were shown in Table 5. Full length amino acid sequences of the humanized variants were shown in Table 6. CDRs were underlined.

Table 5. Anti-DLL3 humanized sdAb CDR sequences

Ab	ID	CDR1 Sequence	ID	CDR2 Sequence	ID	CDR3 Sequence
AS64380VH 4	244	GNTYSSN YMG	254	VIYTRGGHTYYVD SVRG	264	SSRHRLGLNNPRD YDY
AS64380VH 5	245	GNTYSSN YMG	255	VIYTRGGHTYYVD SVRG	265	SSRHRLGLNNPRD YDY
AS64380VH 6	246	GNTYSSN YMG	256	VIYTRGGHTYYVD SVRG	266	SSRHRLGLNNPRD YDY
AS64380VH 7	247	GNTYSSN YMG	257	VIYTRGGHTYYVD SVRG	267	SSRHRLGLNNPRD YDY
AS64511VH 4	248	RATYSTN YIS	258	TITTGDGETAYADS VKG	268	NLRIGGDWFDGR DFRA
AS64511VH 5	249	RATYSTN YIS	259	TITTGDGETAYADS VKG	269	NLRIGGDWFDGR DFRA
AS64511VH 6	250	RATYSTN YIS	260	TITTGDGETAYADS VKG	270	NLRIGGDWFDGR DFRA
AS63997VH 4	251	FSGYGVS TMA	261	AITVGSGNTYYAD SVKG	271	GYLSGGSWDVP G RYNY
AS63997VH 5	252	FSGYGVS TMA	262	AITVGSGNTYYAD SVKG	272	GYLSGGSWDVP G RYNY

AS63997VH 6	253	FSGYGVS TMA	263	AITVGSGNTYYAD SVKG	273	GYLSGGSWDVP GRYNY
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Table 6. Anti-DLL3 humanized sdAb amino acid sequences

SEQ ID	Humanized sdAb	Amino Acid Sequence
355	AS64380VH4	EVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFRQAPG KGLLEVAVIYTRGGHTYYVDSVRGRFTISRDNKNSLYLQMNS LRAEDTAVYYCAASSRHRLGLNNPRDYDYWGQGLTVTVSS
356	AS64380VH5	EVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFRQAPG KGLLEVAVIYTRGGHTYYVDSVRGRFTISQDNKNSLYLQMNS LRAEDTAVYYCAASSRHRLGLNNPRDYDYWGQGLTVTVSS
357	AS64380VH6	EVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFRQAPG KGLLEVAVIYTRGGHTYYVDSVRGRFTISQDNKNSVYLQMN SLRAEDTAMYYCAASSRHRLGLNNPRDYDYWGQGLTVTVSS
358	AS64380VH7	EVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFRQAPG KGREEVAVIYTRGGHTYYVDSVRGRFTISQDNKNSVYLQMN SLRAEDTAMYYCAASSRHRLGLNNPRDYDYWGQGLTVTVSS
359	AS64511VH4	EVQLVESGGGLVQPGGSLRLSCAASRATYSTNYISWFRQAPGK GLEAVATITTTGDETAYADSVKGRFTISRDNKNSLYLQMNSLR AEDTAVYYCAANLRIGGDWFDGRDFRAWGQGLTVTVSS
360	AS64511VH5	EVQLVESGGGLVQPGGSLRLSCAASRATYSTNYISWFRQAPGK GLEAVATITTTGDETAYADSVKGRFTISRDNKNSVYLQMN SLRAEDTAMYYCAANLRIGGDWFDGRDFRAWGQGLTVTVSS
361	AS64511VH6	EVQLVESGGGLVQPGGSLRLSCAASRATYSTNYISWFRQAPGK GREAVATITTTGDETAYADSVKGRFTISRDNKNSVYLQMN SLRAEDTAMYYCAANLRIGGDWFDGRDFRAWGQGLTVTVSS
362	AS63931VH4	QVQLVESGGGVVQPGGSLRLSCAGSFSGYGVSTMAWFRQAPG KLEGVAAITVGSGNTYYADSVTGRFTISRDNKNTLYLQMNS LRAEDTAVYYCAAGWLSGGSWHVPGRYNYWGQGLTVTVSS
363	AS63931VH5	QVQLVESGGGVVQPGGSLRLSCAGSFSGYGVSTMAWFRQAPG KLEGVAAITVGSGNTYYADSVTGRFTISRDNKNTVYLQMN SLRAEDTAMYYCAAGWLSGGSWHVPGRYNYWGQGLTVTVSS
364	AS63931VH6	QVQLVESGGGVVQPGGSLRLSCAGSFSGYGVSTMAWFRQAPG KREGVAAITVGSGNTYYADSVTGRFTISRDNKNTVYLQMN SLRAEDTAMYYCAAGWLSGGSWHVPGRYNYWGQGLTVTVSS
365	AS63997VH4	QVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFRQAPG KLEGVAAITVGSGNTYYADSVKGRFTISRDNKNTLYLQMNS LRAEDTAVYYCAVGYSGGSWDVPGRYNYWGQGLTVTVSS
366	AS63997VH5	QVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFRQAPG KLEGVAAITVGSGNTYYADSVKGRFTISRDNKNTVYLQMN SLRAEDTAMYYCAVGYSGGSWDVPGRYNYWGQGLTVTVSS
367	AS63997VH6	QVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFRQAPG KREGVAAITVGSGNTYYADSVKGRFTISRDNKNTVYLQMN

		LRAEDTAMYYCAVGYLGGSDVPGRYNYWGQGLTVTVSS
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The camel and humanized sdAb sequences were fused with human IgG1 hinge and Fc, resulting the chimeric and humanized HCAb sequences. The DNAs encoding these HCAbs were synthesized and inserted into pTT5 vector. HCAb expression plasmids were used to transfect HEK293 cells. Crude HCAb proteins secreted to the medium were subjected to SPR affinity measurement as follows: briefly, capturing antibody anti-human Fc pAb (GE healthcare) was immobilized on a Biacore™ CM5 chip to approximately 6,000 RU using EDC-activated amine coupling chemistry. HCAb of interest was captured for 300 seconds onto the sensorchip surface. Human DLL3 (AdipoGen, AG-40B-0151) was flowed over the sensorchip surface at a series of increasing concentrations. Association and dissociation phases were monitored. Captured antibody and antigen were removed between cycles using 10 mM Glycine-HCl, pH 2.0 buffer in order to ensure a fresh binding surface for the antigen. The resulting sensorgrams were fit globally using a 1:1 binding model in order to calculate on- and off-rates (k_a and k_d , respectively), as well as affinities (K_D).

The binding affinities of some humanized sdAbs were measured and compared those of the original camel sdAbs (Table 7). Most of the humanized antibodies retained the binding affinities of the camel sdAbs. This example demonstrated that the humanization of sdAbs using our standard protocol was successful. Most of the sdAbs retained their binding affinities after humanization.

The scFvs have comparable K_D values (AS56788 and AS56704 in Table 7) when assayed with the same procedure as described above.

Table 7. Monovalent binding affinity of camel and humanized antibodies as well as scFvs.

Ligand	k_a (1/Ms)	k_d (1/s)	K_D (M)
AS64380	6.7E+05	5.6E-03	8.4E-09
AS64380VH4	3.1E+05	4.4E-03	1.4E-08
AS64380VH5	5.9E+04	1.5E-03	2.6E-08
AS64380VH6	8.8E+04	1.5E-03	1.7E-08
AS64380VH7	3.2E+04	1.5E-03	4.5E-08
AS64511	1.3E+05	4.0E-04	3.0E-09
AS64511VH4	1.6E+05	9.4E-04	6.0E-09
AS64511VH5	1.6E+05	4.7E-04	2.9E-09
AS64511VH6	1.4E+05	4.8E-04	3.4E-09
AS63997	3.9E+05	6.4E-03	1.6E-08
AS63997VH4	8.4E+05	1.8E-02	2.1E-08
AS63997VH5	5.8E+05	2.1E-02	3.7E-08
AS63997VH6	1.8E+06	6.0E-02	3.3E-08
AS64617	1.9E+05	3.8E-03	2.0E-08
AS69443	9.4E+04	9.0E-05	9.6E-10
AS63931	3.6E+06	1.7E-01	4.7E-08
AS64047	1.4E+05	9.6E-04	6.7E-09

AS64052	1.0E+05	4.1E-04	4.0E-09
AS64062	1.0E+05	7.1E-04	6.9E-09
AS56788	1.3E+05	3.0E-03	2.3E-08
AS56704	6.60E+04	5.59E-04	5.59E-09

Example 8. Generation of monospecific humanized CARs

The amino acid sequences of anti-DLL3 humanized sdAbs were provided above in Table 6 and the nucleic acid sequences of anti-DLL3 humanized sdAbs were listed in SEQ ID NOs: 449-461. Humanized sdAbs in Table 6 and additional sequences were used to generate full CAR constructs (SEQ ID NOs: 485-494). A full length CAR contains from the N-terminus to the C-terminus: a CD8 α signal peptide (SEQ ID NO: 465), a DLL3 binding domain (humanized sdAbs) provided in Table 6, a CD8 α hinge domain (SEQ ID NO: 466), a CD8 α transmembrane domain (SEQ ID NO: 467), a CD137 intracellular domain (SEQ ID NO: 468) or a CD28 intracellular domain (SEQ ID NO: 469), and a CD3 ζ cytoplasmic domain (SEQ ID NO: 470). Schematic representation of a CAR construct is shown in FIG. 1. Nucleic acid encoding the CAR fragment was then cloned into a lentiviral vector to create a full length CAR construct in a single coding frame, using human EF1 alpha promoter for expression. The resulting CAR backbone vector was named “PLLV-hEF1 α -DLL3”.

Example 9. Evaluation of *in vitro* activity of humanized anti-DLL3 CAR-T cells

Similar to the procedure described in Example 4, potency of humanized CARs was evaluated via CAR-T cell mediated killing of tumor cells, cytokine releasing and long-term stimulation assay.

In vitro cytotoxicity assay

The results were shown in FIG. 6A-6D. Our humanized CAR-Ts showed superior anti-tumor efficacy *in vitro*.

IFN- γ release assay

Additionally, supernatants from the *in vitro* cytotoxicity assay were collected to assess CAR-induced cytokine release, *e.g.*, interferon gamma (IFN- γ) and tumor necrosis factor α (TNF- α) release. As shown in FIG. 7A and FIG. 7B, CAR3 CAR-T and some anti-DLL3 CAR-Ts were stimulated by SHP-77 to produce IFN- γ and TNF- α , whereas UnT produced little IFN- γ or TNF- α .

CART expansion by long-term stimulation assay

On Day 0, 1×10^5 SHP-77 cells were plated in 24 well plates to establish a monolayer. On Day 1, CAR-T cells were counted and 2×10^5 viable CAR⁺ T cells were plated on top of the SHP-77 cells in fresh media in the absence of cytokines. On day 3, a new 1×10^5 NCI-H82 cells monolayer were plated on top of the CAR-T cells. On day 4, viable CAR-T cells were counted for each well. On the same day, 2×10^5 CAR⁺ T cells from wells that expanded (have at least this amount of cells) were re-plated to establish a new monolayer as on Day 1. The process was repeated for 3-4 rounds of stimulation. Fold expansion after each stimulation was calculated as [viable CAR⁺ T cells on day 4] / 2×10^5 , the amount of CAR-T cells plated on day 1 of each stimulation. To normalize for cells discarded with each new stimulation, cumulative fold

expansion was determined by [(fold expansion) x (fold expansion+1)...].

After 3 rounds of stimulation, the fold expansions of different CAR-T constructs were calculated. As it was showed in FIG. 8, most CAR-T constructs expanded more than CAR3 CAR-T with 3 rounds of stimulation by SHP-77 tumor cells.

Example 10. *In vivo* efficacy valuation of humanized CARs by CAR-T cells mediated tumor growth inhibition

The anti-tumor activity of the humanized CARs was evaluated in a SHP-77 tumor model. SHP-77 cells were implanted subcutaneously in NOD/SCID mice and randomized into 9 groups (4 mice per group, day 0): Vehicle (PBS only), UnT (negative control), CAR3, CAS64380, CAS64380VH5, CAS64511, CAS64511VH5, CAS63997, and CAS63997VH5. Treatment with CAR-T cells, UnT cells or vehicle (PBS only) began when tumors were palpable (100 mm³) and mice were euthanized when their tumor volumes reached about 3000 mm³. Tumor volumes were measured 2 times per week. CAR-T cells were administered intravenously with 0.2×10⁶ CAR positive T cells per mouse. Mice and tumors were monitored for about 21 days after tumor cell implantation.

As shown in FIG. 9A-9J, compared to benchmark CAR3, CAS64380VH5 and CAS63997VH5 showed superior anti-tumor activity in this animal model.

Anti-tumor activities of these humanized CARs were not observed to correlate with their potency of *in vitro* cell killing.

Listed below are some amino acid sequences and nucleic acid sequences mentioned herein.

Camel sdAb Nucleic Acid Sequences

SEQ ID NO: 368 (Camel sdAb AS63930 Nucleic Acid Sequence)

GAGGTGCAACTGGCGAGTCTGGGGGAGGATCGGTGCAGGCTGGAGGGTCTCTGAG
ACTCTCCTGTGTCAGCCTCTGGATACACCTACAGTGGCAACTATATGGCCTGGTTCCGC
CAGGCTCCAGGGAACGAGCGCGAGGGGGTTCGCAGTTGTTTATAATATTGACGGTGGC
GGTCGTTTCACTACCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGGCA
ACGACAAGAACACGGTGTATCTGCAATGAACAGCCTGAAACCTGAGGATAGTGGCA
TGTACTIONGTGCGGCAGAGGTAGCTGATCCGACCTGGGGGTTCGCGTGACCAAGAC
GATATAAGTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 369 (Camel sdAb AS63932 Nucleic Acid Sequence)

CAGGTGCAATTGGAGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGGATACACCTACGGTAGCACCTTCATGGGCTGGTTCCGCC
AGAATCCAGGGAAGGAGCGCGAGGGGGTTCGCAGTTATTTATACTGGTGGTGGTAGTA
CATGGTATGCCAGCTCCGTGAAGGGCCGATTACCATCTCCAGGACAACGCCAAGA
ACACGGTGTATCTGCAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGCGTTACGGGTCGGGAAACGTTAACTACTGGGGCCAGGGGACCCAGGTCA
CCGTCTCCTCA

SEQ ID NO: 370 (Camel sdAb AS63951 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCGCCTGTGAAACCTCTAGAGACATCTACGGTAACAACCTGCATGGCCTGGTTCCGCC

AGGCTCCAGGGAAGGAGCGCGAGGGAGTCGCGTCTATTTATCCTGCTGGTGGTCGCC
CGTACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGGACAGCCTGAAACCTGAGGACACGGCCATGTACTACT
GCGCGGCACGCTCTTTTCGATAGCAGTTTGCGCGACGCGCTCTGGTATTACCAGGTC
TAATTTTGCTTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 371 (Camel sdAb AS63984 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACAGTAGCAACTTCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAACTATTGTTTCTGGTGGTGGTACCA
CATACTATGCCGACTCCGTGAGGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGGGGCCCCGTTACGAACGCACCTAGATGGTACCCCCCTCCGACCTCCTG
GTTATACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 372 (Camel sdAb AS63987 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGAAGCCACTGGATATAGAACTGCATGGCCTGGTTCCGCCAAGCTCCAG
GGAAGGAACGCGAGGGGGTCGCAGTTATTTATACTCCTAGTGGTATCACGGACTATG
CAAGCTCCGTGAAGGGCCGATTACCATCTCCCCAAAACAACGCCAGGAACACGCAGT
ATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACTGTGCGGCAG
ATCGACCCTTTGTTTGTAAATATAGCGAATATGAGAAGGTCTCCAACCTGGGGCCGGG
GGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 373 (Camel sdAb AS63997 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGGCTCTTCTCTGGATACGGCGTCAGTACCATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAGCTATTACAGTTGGTAGTGGAAC
ACATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAAG
AGGACGGTGTTTTTCGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTAC
TGTGCGGTTCGGATACTTGTGCGGTGGTAGTTGGGACGTTCCCGGAAGGTATACTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 374 (Camel sdAb AS64047 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTCAGTACGTTTACAGGTGGGACCTCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGCGGTCTGCTGTTTATACTGGTGATGGTATTA
CATACTATGCCGACTCCGTGAAGGGCCGATTACGATTTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGGCATGTACTTCT
GTGCGGCAGGCTTCGTCTCTGGTGGTAGATGGAACCAGTCATATCGTTATAAATACTG
GGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 375 (Camel sdAb AS64052 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACCGCAGCAACTTCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGATCGCAACTATTCATTCTGGTGTGGCTACCA
CATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGGGGCCCCCTGCGAACGCTGATAGATGGTACCCCCCTCCGACCTCCTG

GTTATAACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 376 (Camel sdAb AS64062 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGTTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTAGATCTCCCTACAGTAGCAGTAGGTGCATGGGGTGGTTCC
GCCAGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAGCTCTTATACTGGTGGTGGTA
GCACATCCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCA
AGAATACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACT
ACTGTGCGGCAGTTGTCCCTAGGGGTGGTAGCTGCCGTCTTGATGAAAGAGGGTATT
ACCACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 377 (Camel sdAb AS64072 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCCGAGGGTTTCTGAGA
CTCTCCTGTGCACTCTCTGGATACAGCTACTATATTAAGTTGATGGCGTGGTTCCGTCA
GGCTCCAGGGAAGGAGCGCGAGGCAGTCGCAGCTCATGGTCTGTGAGTGGGACAGC
ATACTATACCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACCCCGGCAAGAA
CACGATGTATCTTCAAATGTTTAGCCTGCAACCGGAGGACACTGCCCTCTACTACTGT
GCGGCGGAAACGACTATGGGTTGGGCCCACGAACGCGGGTATAGGTACTGGGGCCA
GGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 378 (Camel sdAb AS64097 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGAAGCCTCTGGATACACCTACAGTCGCAACTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAGCTATTAACACTGGTGGTGGTAGC
ACATATTATGCCGACTCCCTTGAGGGCCGATTACCATCTCCCAAGACAACGCCAAG
AATACTATGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTAC
TGTGCGGCAGGTCCCGATCTCGGTGGTAGCTGGTGTGCGCCCGTTGAGCGGGCTTTTA
CGTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 379 (Camel sdAb AS64114 Nucleic Acid Sequence)

CAGGTGCAACTGCAGGAGTCTGGGGGGGGCTCGGTGCAGGCTGGAGGGTCTCTGACA
CTCTCCTGTGAAGCCTCTGGAAACACCTACAGTACTAATTACATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAAGAGGTCGCGGTTATTTACACTCGTGGTGGTCACA
CATACTATGTCGACTCCGTGAGGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGCTTCACGACATAGACTCCGTTTAAATAACCCACGGGACTATGACTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 380 (Camel sdAb AS64123 Nucleic Acid Sequence)

CAGGTGCAACTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACTTATACGAGCAACTGGCTGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGAGGTCGCAATTATTTATACTGGTAGTGGTAGTA
CACACTATCGCAGCTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGCGTTTCTCAGAGTATAATTACTGGGGCCAGGGGACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 381 (Camel sdAb AS64130 Nucleic Acid Sequence)

GAGGTGCAACTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACCGTAGCAACTTCATGGGCTGGTTCCGCC

AGGCTCCGGCGAAGGAGCGCGAGGGGGTCGCAACTATTGATTCTCGTGGTACTATCA
CATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGAGAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGGGGCCCCCGCACGAACGATGATAGATGGTACCCCTCCGACCTCCTG
GTTATACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 382 (Camel sdAb AS64137 Nucleic Acid Sequence)

CAGGTGAGGTTAGTGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCTGCCTCTGGATCCACCTACAGTACAACTTCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAACGCTGGTACTTGGGTTGAACGCA
CAGCCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACCGCGCCAAGA
ACACGGTGTATCTACAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGCCGCCGCTTCCACTGATGTACGTCTCCTCGACCCGGGGGACTTTGCTTA
CTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 383 (Camel sdAb AS64142 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTTGGTGCAGACAGGGGGTCTCTGAGA
CTCTCCTGTACAGCCTCTGGATTCACTTTTGATCGTAATGCCATGCGCTGGTACCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCTCATGTATTGATTGGACGGGTGCAAATA
TTGCCATATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGA
ACACGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGGCATGTATTACT
GTGCGGCAGATACGACGTCGGGGTATTGTTTCAGGCTTTTGGTCTACGAGCCGGTACTC
ATGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 384 (Camel sdAb AS64154 Nucleic Acid Sequence)

CAGGTGCAATTGAAGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTACAGCCTCTGGATACACCTACAGATACCTCTACATGGGCTGGTTCCGCC
AGACTCCAGGGAAGGAGCGCGAGGGGGTCGCATGTATTTATACTGGTAGTGGTAGCA
CAGGGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAACCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAAGTTCGCCCCGGTGGGGCGGTACCTGTGACGCTGGTCTCAGTATAACT
ACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 385 (Camel sdAb AS64160 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCGGCCTCTGTATACACCAGCAGTAGCTACTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAGCTATGTGTTTTGGTGGTCTTGTC
CACACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAATGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGATTTGCGCAGGGATAAAAACTATTACGACCGTTACTGCCCCATGCAT
ATACTACTGGGGCCAAGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 386 (Camel sdAb AS64228 Nucleic Acid Sequence)

CAGGTGCAATTGAAGGAGTCTGGGGGAGGTTTCGATCCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGAGTCTCCTACAATAGGTGCAGTATGGGCTGGTACCGCC
AGGCTCCAGGGAAGGGGCGCGAGTTGGTCTCACGTATTCAGCCGGGTGGTAATACAT
ACTATGCAGACTCCGTGAAGGGCCGATTACCGTCTCCCAAGACAACGCCAAGAACA
CAGTATCTCTACAAATGAACAGCCTGAAACCTGAGGACACGGCCATGTATTACTGTA
ACGCACTGTGCTGGCGGGAGAATGTTAACTACTGGGGCCAGGGGACCCAGGTCACCG

TCTCCTCA

SEQ ID NO: 387 (Camel sdAb AS64300 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGACTGGAGGATCTCTGAGA
CTCTCCTGTGCAGTCTCTGGAGACATCTATAACCTCATGTTCGATGGCCTGGTTCCGCC
GGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCATATATTAATACTATTATTGGTAACA
CATACTATACTGACTCCGTGAAGGGCCGATTACCATCTCCCGCGATAACTCCAAGAA
CACTTTGTATCTGCAAATGAACAACCTGAAACCTGAGGACACAGCCATGTACTACTGT
GCGGCGTTCAATTACGGAGGTGCCTGGTACGAGGAACGCAGCTATAAATACTGGGGC
CAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 388 (Camel sdAb AS64380 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCTGGGGGGGGCTCGGTGCAGGCTGGAGGGTCTCTGACA
CTCTCCTGTGAAGCCTCTGGAAACACCTACAGTAGTAATTACATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGAGGTGCGGTTATTTACTCTGGTGGTTCACA
CATACTATGTCGACTCCGTGAGGGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGTCTTCACGACATAGACTCGGTTTAAATAACCCACGGGACTATGACTACTG
GGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 389 (Camel sdAb AS64395 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCTGCCTCTGGATCCACCTACAGTACAACTTCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAACGCTTGTTACTTGGGCTGAACGCA
CAGCCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACCGCGCCAAGA
ACACGGTGTATCTACAAATGAACGGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGCCGCTTCCACTGCTGTACGCTCTCCTCGACCCGGGGGACTTTGCTTACTG
GGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 390 (Camel sdAb AS64443 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATATACCGACAGTAGCGTCTACATAGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGAGGTGCGGATTATTTATACTGGTGGTGAAAGCA
CACACTATCGCAGCTCCGTGAAGGGCCGATTACCGTCTCCCAAGACAACGCCAAGA
ACACGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCATGTATTACT
GTGCAGCACGATTCCCAGCTGTTACCTACTGGGGCCAGGGGACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 391 (Camel sdAb AS64511 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTAGAGCCACCTACAGTACCAACTACATAAGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGCGGTGCAACAATTACTACTGGTGATGGTGAG
ACAGCGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAAG
AACACGGTCTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTAC
TGTGCGGCGAACTTGCGAATCGGTGGCGACTGGTTCGACGGACGCGATTTTCGTGCCT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 392 (Camel sdAb AS64536 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTAGATACACCGACAATTTTCGTGTACATGGGCTGGTTCCGCC

AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCACTGATTTATCCTGGTGGTGGTAGCA
CCTACTATGCCTCCTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGG
GCACGGTGCATCTGCAAATGAACAACCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAAAATGGGGGCTGGGCGGGGGGGGCTGAAATCAGATACGTATATGTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 393 (Camel sdAb AS64597 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACCGTGTCAACTTCATGGGCTGGTTCCGCC
AGACTCCAGGGAAGGAGCGCGAGGGGGTCGCAACTATTGATTCTGGTGTGGGTACCA
CATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAATAACAACGCCAAGA
ACACGATTTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGGGGCCCCCTACGGACGGTGATAGATGGTACCCCTCCGACCTCCTG
GTTATACTATTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 394 (Camel sdAb AS64617 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACTGATAGATGCAGCATGGCCTGGTACCGCCAGG
CTCCAGGGAAGGAGCGCGAGTTGGTCTCGGTATTAGCACGAGCGGTTTCACAACT
ACGCAGCCTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGAACACGG
TGTATCTGCAAATGAACAGCCTGAACCCCGGGGACACGGGCATGTATTACTGTGCCA
TAATCGTAGGACGTACTTGTAGTTTGAAGTACTGGGGCAACGGCATCCTGGTCACCGT
CTCCTCA

SEQ ID NO: 395 (Camel sdAb AS64634 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCCGGATACAGTTTTAGAGGCGACTTTATGTGTATGGGCTGGT
TCCGCCAGACTCCAGGGAAGGGGCGCGAGGGGGTCGCAGTTTTTTATCCTGGTGGCG
GCAGCACAACACTATGCCGACTCCGCGAAGGGCCGATTACCATCTCCCAAGACAACG
CCAAGAACACGATGTATCTGCAAATGAACACCCTGAAACCTGAGGACACTGCCATGT
ACTACTGTGCGGCTCGACGGTGGGTGAGTGGTACCTGCTACTGGGATAGTGACTTTCA
TTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 396 (Camel sdAb AS69498 Nucleic Acid Sequence)

CAGATGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGAAACACCTACAGTACCAATTACATGGCGTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGAGGTCGCGGTTATTTACTCTGGTGGTCACA
CCTACTATATCGACTCCGTGAGGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATAAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGTCTTCACGAATTAGACTCCATTGAATCGACCCACGGGACTATCACGACTG
GGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 397 (Camel sdAb AS69500 Nucleic Acid Sequence)

CAGGTGAGGTTAGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCGACAGATACACCTACAGTAGCGCCTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCCTCTATTTTTACTGGTACTGGTGGTA
GCACATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCA
AGAACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATATACT
ACTGTGCGGCAAGGGCCTTCCAGGTCGGTTACTGCTACCTGCGAACCGATGTGTATAA

CTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 398 (Camel sdAb AS69527 Nucleic Acid Sequence)

GAGGTGCAGCTGGCGGAGTCTGGGGGAGGCTCGGTCCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTAGATACACCTTCAGTAGCACCTGCATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGGAGGAGGTCGCAGCTATTTATACTGATGATGGTAGCA
CATGGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCTATGTACTACT
GTGCGGCACGTAGGTGGGCGTGCCCCAGGGTTGGTAGCTGGCATGAGTTCGCCTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 399 (Camel sdAb AS68280 Nucleic Acid Sequence)

CAGGTGCAACTGGTGGAGTCTGGGGGAGGCTCGGTGCACCCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATCCACCTACAGTTCCAACCTCGGCTGGTTCCGCC
AGGCTCCAGGAAAGGGGCGGACTGGGTTGCGGCTATTAGCACTGGTGACGGTGCCA
CAGCCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCTTGAACTTGAGGACAGTGCCATGTACTACT
GTGCGGCGGCTCGCGGCAGATTTATCGATTGGACAAAGGCAACCCAGTATGACTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 400 (Camel sdAb AS68355 Nucleic Acid Sequence)

CAGATGCAGCTGGTGGAGTCTGGGGGAGACTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACAGCGGCGTCTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGGAGGGGGTTCGCAGCTATTGATAGTGATGGTAGCACA
AGCTACGCAGACTCCGTGAAGGGCCGATTACCATCTCCAAAGACAACGCCAAGAAC
ACTCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACTGTG
CGGCAGCCATTGTGCGGGGTTTAAATGCATATTGTAGTGGTGGTTATGTTCTGGACTT
TGGTGCCTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 401 (Camel sdAb AS69443 Nucleic Acid Sequence)

GAGGTGCAGCTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTTTCAGCCTCTGGTTTCACTTTTGATGATTCTGACATGGCCTGGTACCGCCA
GGCTCCAGGGGATGGGTGCGACTTGGTCTCAACTATTAGTAGTGATGGTAGCACATA
CTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGAACAC
GGTGTATCTGCAAATGCACAGCCTGAAACCTGAGGACACGGCCGTGTATTACTGTGC
GGCAGATTTCTCACCAGGCTTTTACTATAGCGACTCCCCCATCCGGCCCCCTGTTCTG
CATCCGACTTTGGTTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 402 (Camel sdAb AS75376 Nucleic Acid Sequence)

CAGGTGCAATTGAAGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACAGTAGCCACTCCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGGAGGGGGTTCGCAGTTATTTATACTGGTGATGGTAGCA
CATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGATCCGAACCCGATTATATGCTTCCGTTTCGGCCGTCCCGTAGGTCGTG
GTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 403 (Camel sdAb AS75387 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACCCCTACAGTAGCCCTGCATGGCCTGGTTTCGCC

AGGCTCCAGGGAAGGAGCGCGAGGGGGTTTTAGTTGCTTATACTGGTGGGGACATTC
AATACCTTACCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGGATCTGCGATTACCTCGTGCCGGCGGTTGTGCGTATAGCTACTGGGGCCA
GGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 404 (Camel sdAb AS75695 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGGATACACCGTCAGTGCCTACTGTATGGGCTGGTTCCGCC
AGGTTCTAGGGAAGGGGCGCGAGAGGATCGCATTTATCGATGCCGGGGGTGCTACGA
TTTACGCAGACCCCGTGAAGGGCCGATTACCATCTCCAAAGACAACGCCAAGAACA
CTCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACTGTGT
TGCAGATCGCCGGGGGCGGGTACGTCGGTGCAGTATAACGCCTGGGGCCAGGGGAC
CCAGGTCACCGTCTCCTCA

SEQ ID NO: 405 (Camel sdAb AS76169 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACATTTACAGTAGCTTCTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGTGGTTCGCGTATATTCGCGATAATATTATGACAA
GTTACACAGACTCCGTGAAGGGCCGATTACCATCTCCAAAGACAACGCCAAGAGAA
CTCTGTATCTACAAATGAACGGCCTGAAACCTGAAGATACTGGCATGTACTACTGTGC
GGTAGACCGGGGGGGATACGCTAATAGTTGCGCGGTAGCGGCCCGGTATGATTACTG
GGGCCGGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 406 (Camel sdAb AS63931 Nucleic Acid Sequence)

GAGGTGCAGCTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGGGGGTCTCTGAGA
CTCTCCTGTGCAGGCTCTTCTCTGGATACGGCGTCAGTACCATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGCGTATTAATGTTGGTAGTGAAACA
CATACTATGCCGACTCCGTGACGGGCCGATTACCATCTCCCGAGACAACGCCAAGA
GGACGGTGTATTTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCCGGATGGTTGTCGGGTGGTAGTTGGCACGTTCCCGGCAGGTATAACTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 407 (Camel sdAb AS63937 Nucleic Acid Sequence)

CAGGTGAAGTTAGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATCCACCATCAGTAGTCGCCCCGATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGCGTGTATACATACTGGTCTTGGTAGAA
CATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAGTGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGACTCGCGGCGGCCGTGTATGGTAGCCGCAGGGTATACCTACTGGGGCC
AGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 408 (Camel sdAb AS63948 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTACAGCCTCTGGATACACCTATAGATACCTCTACATGGGCTGGTTCCGCC
AGACTCCAGGGAAGGAGCGCGAGGGGGTTCGCGTGTATTTATACTGGTAGTGGTAGCA
CAGGGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCGAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGCTTCGCCCCGGTGGGGTGGTACCTGTGCGACGGTGGTCCGAGTATAACT

ACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 409 (Camel sdAb AS63956 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTTGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCCGGATTACCTACAGTAACTGCTGCATGAGGTGGTACCGCC
AGGCTCCAGGGAAGGCGCGAGTTGGTCTCATTAAATTAATAGTAGTGGTGGCACAT
ACTATGCAGACTCTGTGAGGGGCCGATTACCATCTCCAAAGACAACGCCAAGAACA
CGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCATGTATTACTGTG
CGGCTTACCAAGCCAAGTACTGTTTCAGGCCCTTGCGCCCCCCTAACTGACTGGGGCCA
GGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 410 (Camel sdAb AS63965 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGGATACAGCAGCGGTAGTTGTGCGATGGGCTGGTACCGCC
AGGCTCCAGGGAAGGAGCGCGAGTTGGTTTCAAAGGTTATTAGTGATGGTACTACAG
TCTATGCAGACTCCGTGAAGGGCCGATTACCCCTCTCCCAAGGAAACGCCAAGAACA
CGGTGTATCTGCAAATGAGTAGCCTGTTACCTGAGGACACGGCCATGTATTACTGTAA
TGCATGGTGTAGGGAGTATCCCGGGGGGATCCTGAATAACGGCTGGGGCCAGGGGAC
CCAGGTCACCGTCTCCTCA

SEQ ID NO: 411 (Camel sdAb AS63993 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGGGGCTTGGTGCAGGCAGGGGGTCTCTGAGA
CTCTCCTGTACAGTTTCTGGATTCACTTTTCGATGACCTCGTCATGGCCTGGTTCCGCCA
GGCTCCAGGGAAGGAGCGCCAACCTTGTTCTCGTTGGTTGCGACTGCTGGTAATAGCGT
CTATGCAGACTCCGTGAAGGGCCGATTACACTCTCCAGAGACAACGCCCACAGCAC
GGCGTATCTGCAAATGAACGGCCTGAAACCTGAGGACACGGCCATGTATTACTGTGC
GGCACGTACCGATTCTGAGCATGCGTTTAAGTTCTGGGGTCAGGGGACCCAGGTCAC
CGTCTCCTCA

SEQ ID NO: 412 (Camel sdAb AS63999 Nucleic Acid Sequence)

GAGGTGCAACTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACTTACAGTAGCAACTGGATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGAGGTCGCAATTATTTATACTGGTGGTATTAGTA
CACACTATCGCAGCTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGCGTTATACAGACTATACTACTGGGGCCAGGGGACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 413 (Camel sdAb AS64006 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGAAGTCTCTGGATACACCGGCGATACGACTTACATAGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCACTTATTTATACTAGTGGTACTAGCG
AGTACTACGCCGACTCCGTGAAGGGCCGATTATCATCTCCCGAGACAACGCCAAGA
ACACGGTGTATTTACAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGGCGCACGGAGCCGCACGATGATGTACTGGGGCCAGGGGACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 414 (Camel sdAb AS64057 Nucleic Acid Sequence)

CAGGTGCAATTGGAGGAGTCTGGGGGAGGCTTGGTGCAGACAGGGGGTCTCTGAGA
CTCTCCTGTACAGCCTCTGGATTCACTTTTGATCGTAATGCCATGCGCTGGTACCGCC

AGGCTCCAGGGAAGGAGCGCGAGGGGGTCTCATGTATTAGTTGGACGGGTGCAAATA
TTGCCTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGA
ACACGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGGCATGTATTACT
GTGCGGCAGATACGACGTCGGGGTCTTGTTTCAGGCTTTTGGTCTACGAGCCGGTACTA
CTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 415 (Camel sdAb AS64060 Nucleic Acid Sequence)

CAGGTGAAGTTAGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATCCACCTACTGTACCTACCGTATGAGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGTTCGTGCGAGTTATTGATAGTGGCGGTAGCACAA
GCTACGCAGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAAGAACA
CGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCATGTATTACTGTA
AAACAGATCCAACCATCGGCTGCCCCCAGACATATAGGTATAACTACTGGGGCCAGG
GGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 416 (Camel sdAb AS64071 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGGAACACTTACAGGCTCAACTCTATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGATTTATTGTTATGATTAGAGGTACCA
CATACTATGGCGCCTCCGTAAAGGGCCGATTACCATCTCCCAAGACAACGCCCAGA
CCACGGTGTATCTGCAAATGAGCAGCCTGAAACCGGAGGACACTGCCATGTACTACT
GTGCGGCATCCACTAAGGACCAGTTTTATGTATTTAATCCTATTGGGTATGACTCTTG
GGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 417 (Camel sdAb AS64093 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAACCTCTAGATACATCTACGGTAACAACCTGCATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGAGTCGCGTCTATTTATCCTGCTGGTGGTTCGCA
CGTACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATTGACAGCCTGAAACCTGAGGACACGGCCATGTACTACT
GCGCGGCACGCTCTTTTTCGATAGGAGTTTGC GCGACGCAGTCTGGTATTACCTGGTC
TAATTTTGCTTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 418 (Camel sdAb AS64118 Nucleic Acid Sequence)

CAGGTGCAACTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACAGTGCCTGTAGAATGGCCTGGTACCGCC
AGGCTCCCGGGAAGGAGCGCGAGTTGGTTTCATTTATTAATAGTGTGGTAGCACAT
ACTATGCCGACTCCGTGAAGGGCCGATTGCGCATCTCCCGAGACAACGCCAAGACAA
CGGTGTATCTACAAATGAACGCCCTGAAAGCTGAGGACACGGCCATATATTACTGTA
ACACATGGGATAGTAGCTGCCGCTTTCAGTACTGGGGCCAGGGGACCCAGGTCACCG
TCTCCTCA

SEQ ID NO: 419 (Camel sdAb AS64120 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGAAACCTCTAGATACATCTACGGTAACAACCTGCATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGAGTCGCGTCTATTTATCCTGCTGGTGGTTCGCC
CGTACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAG
AACACGGTGTATCTGCAAAATGGACAGCCCTGAAACCTGAGGACACGGCCCATGTA
CTACTGCGCGGGCACGCTCTTTTTTCGATAGCAAATTGCGCCAACGCAATCCTGGTA

TTAACCAGGGCCAAATTTTGGCTTACGGGGGCCAGGGGACCCAGGTCACCCCTTCTCCT
CA

SEQ ID NO: 420 (Camel sdAb AS64124 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGACTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGTCTCTACGTACACCCCCAGTAACAACCTACATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGCGTCGCGGCTATCGCTACTATTGGTGGTACCA
CACGTTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACGGCGCCAAGA
ACACGATATATCTGCAAATGAACGGCCTGAAACCGGAGGACACTGCCATGTACTACT
GTGCGGCCGGGCGGCCATACTCATTACCCTTACCCTTACCCTTGGAAGCGGTGCGTA
TCGCTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 421 (Camel sdAb AS64135 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTACATCAACCTACTGTAGGTACTACATGCGCTGGTACCGGC
AGGCTCCAGGGAAGGAGCGCGAGTTCGTCTCAGCGATGCAACCCGATGGTACGACAA
GCTACTCAGACTCCGTGAAGGGCCGATTACCATGTCCCAAGACAGAGCCAACAATA
TGTTGTATCTGCAAATGAACAGCCTGAGGCCTGAGGACACGGCCATGTATTACTGTA
AAAGAGATCCAATGGGGGGTTCAAGGACCCCGTGACCTCCGCTGGGGCCAGGGGA
CCCAGGTCACCGTCTCCTCA

SEQ ID NO: 422 (Camel sdAb AS64163 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGTCTCTGGATACAGATATAGATGGAAGTGCATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGACGCTATTTCTACTGGAAGCGGAAGC
ACATACTATGCCGGCTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAG
AACATGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACTGT
GCGGCAGATCCTTCGGTTTGCCCCGGTGGTATGTGGTACTCCAAAGAGTATAGGTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 423 (Camel sdAb AS64182 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGCACAGCCTCTGGACAGACCTCCAGATACCTCTACATGGGCTGGTTTCGCC
AGACTCCAGGGAAGGAGCGCGAGGGGGTTCGATGTATTTATACTGGTAGTGGTAGCA
CAGGGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAACGAATAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAAGTTCGCCCCATTGGGGCGGTACCTGTGACGCTGGTCCGAGTATAAGT
ACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 424 (Camel sdAb AS64183 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGACACACCTACAGTGCCAAGTGCATGGCCTGGTTCCGCC
GGGCCCCAGGGAAGGAGCGCGAGTGGGTCGCGTCCGTTTATACTGATGATGATAGCA
CAATGTATACCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGGCATGTACATCT
GTGCGGCAGATTTAAGCGGAGGACCGGCCGTTGTGGGTATACCCACTGGGGCCAGG
GGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 425 (Camel sdAb AS64207 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA

CTCTCCTGTGCAGCCTCTGGATACACCTACAGTAGCAACTTCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAACTATTGTTTCTGGTGGTGGTACCA
CATACTATGCCGACTCCGTGAGGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGGGGCCCCCTACGAACGGTGCTAAGTGGTACCCCCTCCGACCTCCTG
GTTATACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 426 (Camel sdAb AS64276 Nucleic Acid Sequence)

CAGGTGCACCTGATGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGC
CTCTCCTGTGTAGTCTCTGGATACACCGGCAGTAGCCGCTGTATGGCCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGCGGTGCGACAAATTTTTACTGGTCGTGGTACCA
CAGGCTATGCCGACTCCGTGAAGGGCCGATTCACTATTTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCGAATGAACAGTCTGAGACCTGAGGACACTGCCATTTACTACT
GTGCGGCGAGTCTCGGCCCGGGACGCGGAGCCTGTGGGTATACTACTGGGGCCAGG
GGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 427 (Camel sdAb AS64336 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTAAGA
CTCTCCTGTACAACCTCTGGACGCACCTACAGTAGCTGCAGCATGGGCTGGTACCGCC
AGGCTCCAGGGAAGGAGCGCGAGTTGGTCTCACATATTTTAGTGATGGTAGCAGAT
ACTATGCAGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGAACA
CGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCATGTATTACTGTA
ACCGCCGTACGGTTGGGCACCAAGGTGCGCTGTTCCCGGTTACTGGGGCCAGGGGA
CCCAGGTCACCGTCTCCTCA

SEQ ID NO: 428 (Camel sdAb AS64346 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTATTTTCATGGGCTGGTTCCGCCAGGCTCCAC
AGAAGGAGCGCGAATGGGTGCGGACTATTGGTACTGGTGATATTTTCAATGGCGCTG
CTTACTATGTGCGACTCCGTGAAGGGCCGATTGCGCATCTCCCAAGACAACGCCAAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAAGACACTGCCGTGTACGTCT
GTGCGGCAGTTCAATCGAAATCCTCAAACCTACGTGTTGAGAGACGCATCTACCTACA
ACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 429 (Camel sdAb AS64420 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGAAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGAGACACCAGTAGAAGCGTCTGGATGGGCTGGGCCCCGC
CAGGTTCCAGGGAAGAGCGCGAGGTGGTTCGCAACCATTAGTACTGCCGGTGGTAGT
ACATGGTATACCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAG
AACACGGTGTACCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATATACTAT
TGTGCGGCCAGAAGCAGATATGCTACCTACTGGGGCCAGGGGACCCAGGTCACCGTC
TCCTCA

SEQ ID NO: 430 (Camel sdAb AS64473 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTACAGCCTCTGGATACACCTACAGATACCTCTACATGGCCTGGTTCCGCC
AGACTCCAGGGAAGGAGCGCGAGGGGGTCGCATGTATTTATACTGGTAGTGGTACCA
CAGGGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
ATACGGTGTATCTGCAAATGAACAGCCTGAACGCTGAGGACACTGCCATGTACTACT

GTGCGGCAAGTTCGCCCCAGTGGGGCGGTACCTGTGACGCTGGTCCGAGTATAACT
ACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 431 (Camel sdAb AS64475 Nucleic Acid Sequence)

CAGGTGCAACTGCAGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTGGAGTCGCAACTGGATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGTTGCAACTATTACAATTAGTGGTGGTAGCA
CATGGTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCTAGACAACGCCGGGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGCGGGATACCGCGCGGACCTACTGGGGCCAGGCTACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 432 (Camel sdAb AS64513 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGAATCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGACTACCCCTACATAGACAAGTGCATGGGCTGGTTCCGCC
AGGGTCCAGGGAAGGAGCGCGAGGGGGTTCGCACTGCGTGTACTGGTGGTGGTAGC
ACATATTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAAG
AACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGACGTGTACTAC
TGTGCGACAGGCTACTATAGCGGCTCTGGTCCGGGGTATTTACTCCCATGGAGGTATA
ACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 433 (Camel sdAb AS64562 Nucleic Acid Sequence)

GAGGTGCAACTGGTGAATCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCGCTAGGCGCGACTTCATGGCCTGGTTCCGCC
AGGTTCCAGGGAAGGAGCGCGAGGGGGTTCGCACTCATTACTGGTGGTGACACCA
CATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGCGACAACGCCAAG
ACATAATGAATCTGCAAATGAACAGCCTTAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGTTTCCGTCCGCGTGGTGGAGGATACACGGGTGACGTCTTGCCCCAGG
CTGCGGCATACAAGTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 434 (Camel sdAb AS64583 Nucleic Acid Sequence)

GAGGTGCAGCTGGCGGAGTCTGGGGGAGGCTTGGTGCAGGCAGGGGGTCTCTGAG
ACTCTCCTGTACAGCCTCTGGATTCACTATTGCTGTTTATACCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGAATCTCATGTACTAGCTGGGCTGGTGGTCGCA
CATACACTGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAGA
ACACGCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACGGCCATGTATTACT
GTGCGGCAAAGGCACATCCCGACTGTTTCAGGGGATTGGTCCCCATCTGGGTATGAAT
ACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 435 (Camel sdAb AS64594 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACAATAGCAACTACATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGCACTTATTTATACTGGTGGTGGTAGCA
CATATTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCAAAA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTTTCGGTAAGAACGCAGACGCGTAAGTACTGGGGCCAGGGGACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 436 (Camel sdAb AS64605 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA

CTCTCCTGTGCAGTTTCTAGATATCCCTACAGCAGCATCTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGAGCGAGGGGTGTCGCACGTATTTATACTGGTACTGGTAGTA
CATGGTATACCGACTCCGTGAAGGGCCGATTACCATCGCCCCGAGACAACGCCCAGA
ACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCGCGTAGCAATTCATATTCATATTCAAGTTGTGATTACGGCCCCCTCACGAG
GGGGGGGTATAACTTCTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 437 (Camel sdAb AS64606 Nucleic Acid Sequence)

GAGGTGCAGCTGGCGGAGTCTGGGGGAGGATCGGTGCAGGCTGGAGGGTCTCTGAG
ACTCTCCTGTGCAGTCTCTGGATACACCAGCCGTAGCAATTACATGGGCTGGTTCCGC
CAGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGCGCTAATTTATACTCGTGGTGGTAGC
ACATACTATGCCTCCTCCGTGAAGGGCCGGTTACCATCTCCCAAGACAGTGCCAAG
AAAACGTATCTGCAAATGAACAGTGTGAAACCGGAGGACACTGCCATGTACTACTGT
GCTTTGCGCCTTGATGAGAAGATGTACTGGGGCCAGGGGACCCAGGTCACCGTCTCC
TCA

SEQ ID NO: 438 (Camel sdAb AS68121 Nucleic Acid Sequence)

GAGGTGCAGCTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGATGCCTCTGGATACACCTACAGCCGCAACTGCATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGCGAGCGTTCTATACTGATTATATTCGTT
TTGGGCGCACATATTATGCCGACTCCGTGAAGGGCCGATTACCATCTTCCAAGACAA
CGCCAAGAACACGGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCAT
GTACTACTGTGCGGCAGATCCTGGGAGTTCGTACAGACGATAGTTGTGGTACCTCATA
AACAAAGGGAATTTTGGTTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 439 (Camel sdAb AS68170 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTACAGCCTCTGGATACACCTACAGAAGCAACTGTATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGCAACAATCTATACTGGTGGTGGTCTGTA
ATCTATACTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCA
AGAACACCCTGTACCTGCAAATGAACAGCCTGAAGCCTGAGGACTCTGCCAGGTA
ACTGTGCGGCCGCGAGTGACGTGGCAGTTGGTGTAAATTCCTGCGGGGGAAGGACTG
CGGGGTTTGACGCCTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 440 (Camel sdAb AS63964 Nucleic Acid Sequence)

CAGGTGAGGTTAGTGGAGTCTGGGGGAGGATCGGTACAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTCTAGCCTCTGGATACACCTACAGTTACAACAATATGGGCTGGTTCCGCC
AGGCTCCAGGGAACGAGCGCGAGGGGGTTCGCGAGCTATTAGTGGTGGTCTGTTTACCG
CCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCGAGACAACGCCGAGAACA
CGCTGTATCTGCAAATGAACAACCTGAAACCTGAGGACACTGGGATGTACTACTGTG
CGGCAGAGGTAGTTGATCCGACCTGGGGGTTCGCGTGACCAAAGACGATATAAGTACT
GGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 441 (Camel sdAb AS64116 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCGTGTGCAGCCTCTGGATACATCTACAGTTGCGTGGGCTGGTTCCGCCAGGCTC
CAGGGAAGGAGCGCGAGGGGGTTCGCGAGGTATTAGTACTGGTGGTGGTGGCACAGTCT
ATGCCGACTCCGTGAAGGGCCAATTCACCATCTCCCGAGACAACGCCAAGAACACGG
TGTACCTGCAAATGGACAGCCTGAAACCTGAGGACACTGCCATGTACTACTGTGCGG

CAGATCGATGGAATTCATTCGCTAATTGCGGTGCCTGGGGAAGGTATACCTACTGGG
GCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 442 (Camel sdAb AS68270 Nucleic Acid Sequence)

CAGGTGCAACTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGGATAACCCCTCTTCCACCTACTACATGCTCAGCATGGCGTG
GTTCCGCCAGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCCGCTATTACTAGCGGTAC
TGGGAGCACAAGCTACGCAGACTCCGTGAAGGACCGATTACCATCTCCAAAGACTA
CGCCAACAACACTCTGTATCTGCACATAAACAACCTGAAACCTGAGGACACTGCCAT
GTACTACTGTGCGGCAGCCTCAGGTTGGATCGTTCCTAGTAGGTCCCTGACCGCCAAC
CTATATAGGTATTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 443 (Camel sdAb AS68320 Nucleic Acid Sequence)

CAGGTGCACCTGGTGGAGTCTGGGGGAGACTCGGTGCAGGCTGGAGGGTCCCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTACAATACCAACTACATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAGCTATTTATAGACATAGTGGTAACA
CAGCCTATGCCGACTCCGTGAAGGGCCGATTACCATCTCCCAAGACTACGCCAAGA
ACACCGTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACT
GTGCGGCAGGGCGCGCTGGTCCCTGGGCCCTGATGCGCCCGACTGAGTTTGGTTACTG
GGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 444 (Camel sdAb AS68351 Nucleic Acid Sequence)

CAGGTGCAATTGGAGGAGTCTGGGGGAGGCTTGGTGCAGCCTGGGGGGTCTCTGAGA
CTCTCCTGTGCGGCCTCTGGAGACACATTTCTGTCCTATTACATGAACTGGGTCCGCC
AGGCTCCAGGGAAGGGATTCTGAGTGGGTCTCAGGTATTAGCGCCAGTGGCGGCCGTA
CGTCATACGCAGACTCCGTGAAGGGCCGATTACCATCTCCAGAGACAACGCCAAAA
ACACGCTGTATCTGCAATTGAACAGCCTGAGCACTGAGGACACGGGCATGTATTATT
GTGTAAAGGGAGCTGTCCGTCTCTCGACATCGTCAGTACGGGATTCTGCTCTGGGGCCA
GGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 445 (Camel sdAb AS75378 Nucleic Acid Sequence)

CAGGTGCAATTGGAGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGTCTCTGGAAACACCCGCAGTACCACGTACATGGGCTGGTTCCGCC
AGGCTCCAGGGAAGGAGCGCGAGGGGGTCGCAATAGTTTATACTGGTGGTCTGTGACA
CATACTATGCCGCCTCCGTGAAGGGCCGATTACCATCTCCCAAGACAACGCCAAGA
CAACGATCTATCTGCAAATGAACAGTCTGGAACCTGAGGACACTGCCATGTACTACT
GTGCGGCACGCTCATATGAGTATACCTACTGGGGTCGGGGGACCCAGGTCACCGTCT
CCTCA

SEQ ID NO: 446 (Camel sdAb AS75383 Nucleic Acid Sequence)

GAGGTGCAACTGGCGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGTAGCCTCTGGATACACCTTCAGTAGCTACTGCTTGGGCTGGTTCCGCC
AGGCTCCAGGGAAGCAGCGCCAGGGGGTCGCAACGTTTAATAATAGAGGTGTGCGAA
ACTACCACGATTCCGTGAAGGGCCGATTACCGCCTCCGTAGACAACGCCAAGAACA
CTCTGCTTCTGCAAATGAACAGCCTGGAACCTGACGACACGGCCATGTACTACTGTGC
GGCGGATCGCCGGTACGGTCGTCACTGGTATCAGCCTTGCGAGTGGAACACCTGGGG
CCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 447 (Camel sdAb AS75751 Nucleic Acid Sequence)

CAGGTGAGGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA

CTCTCCTGTGTAGCCTCTGGATACTTCTACAATACCTACTACTTTATGGGCTGGTTCCG
CCAGGCTCCAGGGAAGGAGCGCGAGGGGGTTCGAGCTATTGATACTGATGGTAGAAC
AAGTTACGCAGACTCCGTGAAGGGCCGATTACCATCTCCAAAGACAACGCCAAGAA
CACTCTGTATCTGCAAATGAACAGCCTGAAACCTGAGGACACTGCCATGTACTACTGT
GCGGCAGGTTTTGGCTATATGAATGTTATTTCAGGCTCTTAATGGCATGAGACAGAATC
CCGACTACTGGGGCCAGGGGACCCAGGTCACCGTCTCCTCA

SEQ ID NO: 448 (Camel sdAb AS76422 Nucleic Acid Sequence)

CAGGTGAAGTTGGTGGAGTCTGGGGGAGGCTCGGTGCAGGCTGGAGGGTCTCTGAGA
CTCTCCTGTGCAGCCTCTGGATACACCTTCGCTGGCAACTGCTTGGGCTGGTTTCGCC
AGGCTCCAGGGAAGGGGCGCGAGGGGGTTCGTAACGTACAATAACTTCGGTGTGCCA
ACTACGCCGATTCCGTGAAGGGCCGATTACCGTCTCCCAAGACAACGCCAAGAACA
CTCTGCTTCTGCAAATGAACAGCCTGGAACCTGAGGACACTGCCATGTACTACTGTGC
GGCGGACCGCCGGGACGGTCGTCGCTGGTCTCAGCCTTGCGAGTGGAATACCTGGGG
CCAGGGGACCCAGGTCACCGTCTCCTCA

Humanized Camel sdAb Nucleic Acid Sequences

SEQ ID NO: 449 (Humanized sdAb AS64380VH4 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCATCTGGAAACACCTACAGCTCCAATTATATGGGATGGTTTCAGGC
AGGCACCTGGCAAGGGACTGGAGGAGGTGGCCGTGATCTACACCAGGGGAGGACAC
ACATACTATGTGGACTCCGTGCGGGGACGGTTCACCATCAGCAGGGATAACGCCAAGA
ACAGCCTGTATCTGCAGATGAACTCTCTGAGAGCCGAGGACACAGCCGTGTACTATTG
TGCAGCATCTAGCAGGCACAGGCTGGGCCTGAACAATCCAAGGGACTACGATTATTGG
GGCCAGGGCACCCCTGGTGACAGTGTCTCT

SEQ ID NO: 450 (Humanized sdAb AS64380VH5 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCATCTGGAAACACCTACAGCTCCAATTATATGGGATGGTTTCAGGC
AGGCACCTGGCAAGGGCCTGGAGGAGGTGGCCGTGATCTACACCAGAGGCGGCCACA
CATACTATGTGGACTCCGTGCGGGGACGGTTCACCATCAGCCAGGATAACGCCAAGAA
CAGCCTGTATCTGCAGATGAACTCTCTGAGGGCCGAGGACACAGCCGTGTACTATTGT
GCAGCATCTAGCAGGCACAGGCTGGGCCTGAACAATCCAAGGGACTACGATTATTGGG
GCCAGGGCACCCCTGGTGACAGTGTCTCT

SEQ ID NO: 451 (Humanized sdAb AS64380VH6 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCATCTGGAAACACCTACAGCTCCAATTATATGGGATGGTTTCAGGC
AGGCACCTGGCAAGGGCCTGGAGGAGGTGGCCGTGATCTACACCAGAGGCGGCCACA
CATACTATGTGGACTCCGTGCGGGGACGGTTCACCATCAGCCAGGATAACGCCAAGAA
CAGCGTGTATCTGCAGATGAACTCTCTGAGGGCCGAGGACACAGCCATGTACTATTGT
GCAGCATCTAGCAGGCACAGGCTGGGCCTGAACAATCCAAGGGACTACGATTATTGGG
GCCAGGGCACCCCTGGTGACAGTGTCTCT

SEQ ID NO: 452 (Humanized sdAb AS64380VH7 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGAGCGGAGGAGGACTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCATCTGGAAACACCTACAGCTCCAATTATATGGGATGGTTTCAGGC
AGGCACCTGGCAAGGGAAGAGAGGAGGTGGCCGTGATCTACACCAGGGGAGGACAC

ACATACTATGTGGACTCCGTGCGGGGACGGTTCACCATCAGCCAGGATAACGCCAAGA
ACAGCGTGTATCTGCAGATGAACTCTCTGAGGGCCGAGGACACAGCCATGTACTATTG
TGCAGCATCTAGCAGGCACAGGCTGGGCCTGAACAATCCAAGGGACTACGATTATTGG
GGCCAGGGCACCCCTGGTGACAGTGTCTCT

SEQ ID NO: 453 (Humanized sdAb AS64511VH4 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCCGGAGGAGGACTGGTGCAGCCAGGAGGCTCTCTGAG
GCTGAGCTGCGCAGCATCCAGAGCAACCTACTCTACAACTATATCAGCTGGTTCAGG
CAGGCACCTGGCAAGGGACTGGAGGCAGTGGCAACCATCACACAGGCGATGGCGAG
ACAGCCTACGCCGACTCTGTGAAGGGCAGGTTTACCATCTCCCGCGATAACGCCAAGA
ACAGCCTGTATCTGCAGATGAACAGCCTGAGGGCCGAGGACACAGCCGTGTACTATTG
TGCAGCAAATCTGAGGATCGGAGGCGACTGGTTCGATGGAAGGGACTTTAGAGCATGG
GGACAGGGAACCCTGGTGACAGTGAGCTCC

SEQ ID NO: 454 (Humanized sdAb AS64511VH5 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCCGGAGGAGGACTGGTGCAGCCAGGAGGCTCTCTGAG
GCTGAGCTGCGCAGCATCCAGAGCAACCTACTCTACAACTATATCAGCTGGTTCAGG
CAGGCACCTGGCAAGGGACTGGAGGCAGTGGCAACCATCACACAGGCGATGGCGAG
ACAGCCTACGCCGACTCTGTGAAGGGCAGGTTTACCATCTCCCGCGATAACGCCAAGA
ACAGCGTGTATCTGCAGATGAACAGCCTGAGGGCCGAGGACACAGCCATGTACTATTG
TGCAGCAAATCTGAGGATCGGAGGCGACTGGTTCGATGGAAGGGACTTTAGAGCATGG
GGACAGGGAACCCTGGTGACAGTGAGCTCC

SEQ ID NO: 455 (Humanized sdAb AS64511VH6 Nucleic Acid Sequence)

GAGGTGCAGCTGGTGGAGTCCGGAGGAGGACTGGTGCAGCCAGGAGGCTCTCTGAG
GCTGAGCTGCGCAGCATCCAGAGCAACCTACTCTACAACTATATCAGCTGGTTCAGG
CAGGCACCTGGCAAGGGAAGGGAGGAGTGGCCACCATCACACAGGCGATGGCGA
GACAGCCTACGCCGACTCTGTGAAGGGCAGGTTTACCATCTCCCGCGATAACGCCAAG
AACAGCGTGTATCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCATGTACTATT
GTGCAGCAAATCTGAGGATCGGAGGCGACTGGTTCGATGGAAGGGACTTTAGAGCATG
GGGACAGGGAACCCTGGTGACAGTGAGCTCC

SEQ ID NO: 456 (Humanized sdAb AS63931VH4 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGAGCGGAGGAGGAGTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCTGCGCAGGCTCTTTCAGCGGATACGGCGTGTCCACCATGGCATGGTTTAGG
CAGGCACCTGGCAAGGGACTGGAGGGAGTGGCAGCAATCACCGTGGGATCCGGAAA
CACATACTATGCCGACTCTGTGACCGGCCGGTTCACAATCTCTAGAGATAACAGCAA
GAATACCCTGTATCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCGTGTACTA
TTGTGCAGCAGGATGGCTGTCCGGAGGATCTTGGCACGTGCCCCGGCAGGTACAATA
TTGGGGCCAGGGCACCCCTGGTGACAGTGAGCTCC

SEQ ID NO: 457 (Humanized sdAb AS63931VH5 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGAGCGGAGGAGGAGTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCTGCGCAGGCTCTTTCAGCGGATACGGCGTGTCCACCATGGCATGGTTTAGG
CAGGCACCTGGCAAGGGACTGGAGGGAGTGGCAGCAATCACCGTGGGATCCGGAAA
CACATACTATGCCGACTCTGTGACCGGCCGGTTCACAATCTCTAGAGATAACAGCAA
GAATACCGTGTATCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCATGTACTA
TTGTGCAGCAGGATGGCTGTCCGGAGGATCTTGGCACGTGCCCCGGCAGGTACAATA
TTGGGGCCAGGGCACCCCTGGTGACAGTGAGCTCC

SEQ ID NO: 458 (Humanized sdAb AS63931VH6 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGAGCGGAGGAGGAGTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGGCTCTTTCAGCGGATACGGCGTGTCCACCATGGCCTGGTTTAGG
CAGGCACCTGGCAAGGGAAGGGAGGGAGTGGCAGCAATCACCGTGGGATCCGGA
CACATACTATGCCGACTCTGTGACCGGCCGGTTCACAATCTCTAGAGATAACAGCAAG
AATACCGTGTATCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCATGTACTATT
GTGCAGCAGGATGGCTGTCCGGAGGATCTTGGCAGCTGCCCCGGCAGGTACAACCTATTG
GGGCCAGGGCACCCCTGGTGACAGTGAGCTCC

SEQ ID NO: 459 (Humanized sdAb AS63997VH4 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGAGCGGAGGAGGAGTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCCTCTTTCAGCGGATACGGCGTGTCCACCATGGCATGGTTTAGG
CAGGCACCTGGCAAGGGAAGGGAGTGGCAGCAATCACCGTGGGATCCGGA
CACATACTATGCCGACTCTGTGAAGGGCCGGTTCACCATCTCTAGAGATAACAGCAA
GAATACACTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCGTGTACTA
TTGTGCCGTGGGCTATCTGTCCGGAGGATCTTGGGATGTGCCAGGAAGGTACAACCTAT
TGGGGCCAGGGCACCCCTGGTGACAGTGAGCTCC

SEQ ID NO: 460 (Humanized sdAb AS63997VH5 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGAGCGGAGGAGGAGTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCCTCTTTCAGCGGATACGGCGTGTCCACCATGGCATGGTTTAGG
CAGGCACCTGGCAAGGGAAGGGAGTGGCAGCAATCACCGTGGGATCCGGA
CACATACTATGCCGACTCTGTGAAGGGCCGGTTCACCATCTCTAGAGATAACAGCAA
GAATACAGTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCATGTACTA
TTGTGCCGTGGGCTATCTGTCCGGAGGATCTTGGGATGTGCCAGGAAGGTACAACCTAT
TGGGGCCAGGGCACCCCTGGTGACAGTGAGCTCC

SEQ ID NO: 461 (Humanized sdAb AS63997VH6 Nucleic Acid Sequence)

CAGGTGCAGCTGGTGGAGAGCGGAGGAGGAGTGGTGCAGCCAGGAGGCAGCCTGAG
GCTGTCCTGCGCAGCCTCTTTCAGCGGATACGGCGTGTCCACCATGGCCTGGTTTAGG
AGGCACCTGGCAAGGGAAGGGAGGGAGTGGCAGCAATCACCGTGGGATCCGGA
ACATACTATGCCGACTCTGTGAAGGGCCGGTTCACCATCTCTAGAGATAACAGCAAGA
ATACAGTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACAGCCATGTACTATTG
TGCCGTGGGCTATCTGTCCGGAGGATCTTGGGATGTGCCAGGAAGGTACAACCTATTG
GGCCAGGGCACCCCTGGTGACAGTGAGCTCC

SEQ ID NO: 462 (Linker amino acid sequence)

GGGSGGGSGGGGS

SEQ ID NO: 463 (Linker amino acid sequence)

GGGSGGGGS

SEQ ID NO: 464 (Linker amino acid sequence)

GGGGS

SEQ ID NO: 465 (CD8 α signal peptide amino acid sequence)

MALPVTALLPLALLHAARP

SEQ ID NO: 466 (CD8 α hinge amino acid sequence)

TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSL
VITLYC

SEQ ID NO: 467 (CD8 α transmembrane domain amino acid sequence)

IYIWAPLAGTCGVLLLSLVITLYC

SEQ ID NO: 468 (4-1BB intracellular domain amino acid sequence)

KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFEEEEGGCEL

SEQ ID NO: 469 (CD28 intracellular domain amino acid sequence)

RSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS

SEQ ID NO: 470 (CD3 ζ intracellular domain amino acid sequence)

RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY
NELQKDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO: 471 (F2A element amino acid sequence)

GSQVQTLNFDLLKLAGDVESNPGP

SEQ ID NO: 472 (P2A element amino acid sequence)

GSQATNFSLLKQAGDVEENPGP

SEQ ID NO: 473 (CAR3 anti-DLL3 scFv amino acid sequence)

MALPVTALLLPLALLHAARPAIQLTQSPSSLSASVGDRTTICRASENIYYNLAWYQQKP
GKAPKLLIYTANSLEDVPSRFSGSGSGTDFTLTISSLQPEDFATYFCKQAYDVPPTFGGGTK
LEIKGGGGSGGGSGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTRYWIHWIRQ
APGQGLEWMGYINPTVYTEFNQNFKDRVTMTDSTSTVYMESSLRSEDTAVYYCARG
GSNFFDYWQGTTVTVSS

SEQ ID NO: 474 (CD28 transmembrane domain amino acid sequence)

FWVLVVGGVLACYSLLVTVAFIIFWV

SEQ ID NO: 475 (CD28 hinge)

IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPFPGPSKP

Camel anti-DLL3 CAR sequences

SEQ ID NO: 476 (CAS63997)

MALPVTALLLPLALLHAARPQVRLVESGGGSVQAGGSLRLSCAGSFGYGVSTMAWFR
QAPGKEREGVAAITVSGGNTYYADSVKGRFTISRDNKRTVFLQMNSLKPEDTAMYYCA
VGYLGGSWDVPGRYNYWGQGTQVTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE
EDGCSCRFEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR
DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKD
TYDALHMQALPPR

SEQ ID NO: 477 (CAS64380)

MALPVTALLLPLALLHAARPEVQLVESGGGSVQAGGSLTSCASGNTYSSNYMGWFR
QAPGKEREEVAVIYTRGGHTYYVDSVRGRFTISQDNKNTVYLQMNSLKPEDTAMYYCA
ASSRHLGLNPNRDYDYWGQGTQVTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE
DGCSCRFEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKDT
YDALHMQALPPR

SEQ ID NO: 478 (CAS64511)

MALPVTALLLPLALLHAARPQVQLVESGGGSVQAGGSLRLSCAASRATYSTNYISWFRQ
APGKEREAATITTDGETAYADSVKGRFTISRDNKNTVYLQMNSLKPEDTAMYYCAAN

LRIGGDWFDGRDFRAWGQGTQVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDG
CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE
MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD
ALHMQALPPR

SEQ ID NO: 479 (CAS64617)

MALPVTALLPLALLHAARPQVQLVESGGGSVQAGGSLRLSCAASGYTDRCSMAWYRQ
APGKERELVSRISTSGFTNYAASVKGRFTISQDNAKNTVYLMNSLNPGDTGMYCAIIV
GRTCSLNYWNGILVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFA
CDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEE
EGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK
NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP
PR

SEQ ID NO: 480 (CAS69443)

MALPVTALLPLALLHAARPEVQLAESGGGSVQAGGSLRLSCASGFTFDDSDMAWYR
QAPGDGCDLVSTISSDSTYYADSVKGRFTISQDNAKNTVYLMHSLKPEDTAVYYCAAD
FLTGFYYSDSPHPAPCSASDFGYWGQGTQVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRP
AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT
TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR
GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT
KDTYDALHMQALPPR

SEQ ID NO: 481 (CAS63931)

MALPVTALLPLALLHAARPEVQLAESGGGSVQAGGSLRLSCAGSFSGYGVSTMAWFR
QAPGKEREGVAAITVSGGNTYYADSVTGRFTISRDNKRTVYLMNSLKPEDTAMYYCA
AGWLSGGSWHVPGRYNYWGQGTQVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE
EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR
DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD
TYDALHMQALPPR

SEQ ID NO: 482 (CAS64047)

MALPVTALLPLALLHAARPQVHLVESGGGSVQAGGSLRLSCAASQYVYRWDLMGWF
RQAPGKEREAAVYTGDGITYYADSVKGRFSISQDNAKNTVYLMNSLKPEDTGMFYFC
AAGFVSGGRWNQSYRYKYWGQGTQVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRPA
GGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQ
EEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR
DPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKD
TYDALHMQALPPR

SEQ ID NO: 483 (CAS64052)

MALPVTALLPLALLHAARPQVHLMESGGGSVQAGGSLRLSCAASGYTYRSNFMGWF
RQAPGKEREGIAIHSGVATTYYADSVKGRFTISQDNAKNTVYLMNSLKPEDTAMYYCA
AGGPPANADRWYPLRPPGYNYWGQGTQVTVSSTTTPAPRPPTPAPTIASQPLSLRPEACRP
AAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQT
TQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRR
GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTAT

KDTYDALHMQALPPR

SEQ ID NO: 484 (CAS64062)

MALPVTALLPLALLHAARPQVRLVESGGGSVQVGGSRLRLSCAASRSPYSSSRMGWFR
QAPGKEREGVAALYTGGGSTSYADSVKGRFTISQDNAKNTVYLQMNSLKPEDTAMYYCA
AVVPRGGSCRLDERGYHGWGQGTQVTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAG
GAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQE
EDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGR
DPEMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKD
TYDALHMQALPPR

Humanized anti-DLL3 CAR sequences

SEQ ID NO: 485 (CAS64380VH4)

MALPVTALLPLALLHAARPEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFR
QAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISRDNKNSLYLQMNSLRAEDTAVYYCA
ASSRHLGLNNPRDYDYWGQGTTLTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE
DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDT
YDALHMQALPPR

SEQ ID NO: 486 (CAS64380VH5)

MALPVTALLPLALLHAARPEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFR
QAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISRDNKNSLYLQMNSLRAEDTAVYYCA
ASSRHLGLNNPRDYDYWGQGTTLTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE
DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDT
YDALHMQALPPR

SEQ ID NO: 487 (CAS64380VH6)

MALPVTALLPLALLHAARPEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFR
QAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISRDNKNSVYLQMNSLRAEDTAMYYCA
ASSRHLGLNNPRDYDYWGQGTTLTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE
DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDT
YDALHMQALPPR

SEQ ID NO: 488 (CAS64380VH7)

MALPVTALLPLALLHAARPEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFR
QAPGKGREEVAVIYTRGGHTYYVDSVRGRFTISRDNKNSVYLQMNSLRAEDTAMYYCA
ASSRHLGLNNPRDYDYWGQGTTLTVSSTTTPAPRPPTPAPTASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE
DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDT
YDALHMQALPPR

SEQ ID NO: 489(CAS64511VH4)

MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASRATYSTNYISWFRQ
APGKGLEAVATITTDGETAYADSVKGRFTISRDNKNSLYLQMNSLRAEDTAVYYCAAN
LRIGGDWFDGRDFRAWGQGTTLTVSSTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAV
HTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDG
CSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE
MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD
ALHMQALPPR

SEQ ID NO: 490 (CAS64511VH5)

MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASRATYSTNYISWFRQ
APGKGLEAVATITTDGETAYADSVKGRFTISRDNKNSVYLQMNSLRAEDTAMYYCAA
NLRIGGDWFDGRDFRAWGQGTTLTVSSTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED
GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE
MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD
ALHMQALPPR

SEQ ID NO: 491 (CAS64511VH6)

MALPVTALLLPLALLLHAARPEVQLVESGGGLVQPGGSLRLSCAASRATYSTNYISWFRQ
APGKGREAVATITTDGETAYADSVKGRFTISRDNKNSVYLQMNSLRAEDTAMYYCAA
NLRIGGDWFDGRDFRAWGQGTTLTVSSTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED
GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE
MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD
ALHMQALPPR

SEQ ID NO: 492 (CAS63997VH4)

MALPVTALLLPLALLLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGLEGVAAITVSGGNTYYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCAV
GYLSGGSWDVPGRYNYWGQGTTLTVSSTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGA
VHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEED
GCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPE
MGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYD
ALHMQALPPR

SEQ ID NO: 493 (CAS63997VH5)

MALPVTALLLPLALLLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGLEGVAAITVSGGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYCA
VGYSGGSWDVPGRYNYWGQGTTLTVSSTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE
DGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDT
YDALHMQALPPR

SEQ ID NO: 494 (CAS63997VH6)

MALPVTALLLPLALLLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGREGVAAITVSGGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYCA
VGYSGGSWDVPGRYNYWGQGTTLTVSSTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGG
AVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEE

DGCSRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRD
PEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHGGLYQGLSTATKDT
YDALHMQALPPR

Anti-DLL3 Human scFv VL and VH Domain Nucleic Acid Sequences

SEQ ID NO: 511 (Nucleic Acid Sequence for VL domain of anti-DLL3 human scFv AS56704)
GACATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTTGGTGACCGTGTT
ACCATTACCTGCCGTGCGAGCCAGAGCGTTAGCAGCGCGGTGGCGTGGTACCAGCAA
AAGCCGGGTAAAGCGCCGAAGCTGCTGATCTATAGCGCGAGCAGCCTGTATAGCGGCG
TTCCGAGCCGTTTCAGCGGTAGCCGTAGCGGCACCGACTTTACCCTGACCATTAGCAG
CCTGCAGCCGGAAGATTTGCAACTTATTACTGTCAGCAAGCTTCTTGGTCTCCGATCA
CGTTCGGACAGGGCACCAAAGTTGAGATTAAA

SEQ ID NO: 512 (Nucleic Acid Sequence for VH domain of anti-DLL3 human scFv AS56704)
GAGGTTCAACTGGTGGAGAGCGGTGGTGGTCTGGTTCAGCCGGGTGGTAGCCTGCGT
CTGAGCTGCGCAGCTTCTGGCTTCAACATCTCTTCTTATATGCACTGGGTGCGTCA
GGCGCCGGGTAAAGGCCTGGAATGGGTTGCATATATTTATCCTTCTTATGGCTATACTTC
TTATGCCGATAGCGTCAAGGGCCGTTTACCATCAGCGCGGATACCAGCAAAAACACC
GCATACCTGCAAATGAACAGCCTGCGTGCGGAAGATACCGCCGTCTATTATTGTGCTCG
CGGTGGTTACTACTACCATGGTATGGACTACTGGGGTCAAGGCACCCTGGTTACCGTGA
GCAGC

SEQ ID NO: 513 (Nucleic Acid Sequence for VL domain of anti-DLL3 human scFv AS56788)
GACATCCAGATGACCCAGAGCCCGAGCAGCCTGAGCGCGAGCGTTGGTGACCGTGTT
ACCATTACCTGCCGTGCGAGCCAGAGCGTTAGCAGCGCGGTGGCGTGGTACCAGCAA
AAGCCGGGTAAAGCGCCGAAGCTGCTGATCTATAGCGCGAGCAGCCTGTATAGCGGC
GTCCGAGCCGTTTCAGCGGTAGCCGTAGCGGCACCGACTTTACCCTGACCATTAGCA
GCCTGCAGCCGGAAGATTTGCAACTTATTACTGTCAGCAACATTACGCTCCGTCTCT
GATCACGTTTCGGACAGGGCACCAAAGTTGAGATTAAA

SEQ ID NO: 514 (Nucleic Acid Sequence for VH domain of anti-DLL3 human scFv AS56788)
GAGGTTCAACTGGTGGAGAGCGGTGGTGGTCTGGTTCAGCCGGGTGGTAGCCTGCGT
CTGAGCTGCGCAGCTTCTGGCTTCAACATCTCTTCTTATTCTATGCACTGGGTGCGTCA
GGCGCCGGGTAAAGGCCTGGAATGGGTTGCATATATTTCTTCTTATTATGGCTATACT
TATTATGCCGATAGCGTCAAGGGCCGTTTACCATCAGCGCGGATACCAGCAAAAAC
ACCGCATACCTGCAAATGAACAGCCTGCGTGCGGAAGATACCGCCGTCTATTATTGT
GCTCGCTACTCTTACTACTACGGTATGGACTACTGGGGTCAAGGCACCCTGGTTACCG
TGAGCAGC

Human anti-DLL3 scFv CAR sequences

SEQ ID NO: 515 (CAS56704)
MALPVTALLPLALLHAARPDIQMTQSPSSLSASVGDRTITCRASQSVSSAVAWYQQK
PGKAPKLLIYSASSLYSGVPSRFSRSGTDFLTITSLQPEDFATYCYCQASWSPITFGQG
TKVEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNISSSYMHWVR
QAPGKGLEWVAYIYPSYGYTSYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCA
RGYYHHGMDYWQGTLVTVSSTTPAPRPPTPAPTASQPLSLRPEACRPAAGGAVHTR
GLDFACDIYWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSC

RFEEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG
 GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDAL
 HMQALPPR
 SEQ ID NO: 516 (CAS56788)
 MALPVTALLPLALLHAARPDQMTQSPSSLSASVGDRTITCRASQSVSSAVAWYQQK
 PGKAPKLLIYSASSLYSGVPSRFSRSGTDFTLTISLQPEDFATYYCQQHYAPSLITFGQG
 TKVEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFNISSYSMHVVR
 QAPGKGLEWVAYISSYYGYTTYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYC
 ARYSYYYGMDYWGGQTLVTVSSTTPAPRPPTPAPTASQPLSLRPEACRPAAGGAVHTR
 GLDFACDIYWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSC
 RFEEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMG
 GKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDAL
 HMQALPPR

Anti-DLL3 benchmark CAR

SEQ ID NO: 517 (1H2.1 amino acid sequence)

MALPVTALLPLALLHAARPQVQLQESGPGLVKPSSETLSLTCTVSGDSISSYYWTWIRQP
 PGKGLEWIGYIYYSGTTNYPNPSLKSRTISVDTSKSKFSLKLSVTAADTAVYYCASIAGR
 GFFFDYWGGQTLVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATLSCRASQS
 VSSSYLAWYQQKPGQAPRLLIYGASTRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC
 QQYGTSPITFGGGTKVEIKRAAALDNEKSNGTIIHVKGKHLCPSPLPFGPSKPFVVLVVV
 GGVLCYSLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAY
 RSRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQE
 GLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR

Example 11. Evaluation of *in vitro* activity of humanized anti-DLL3 tandem CAR-T cells

To improve anti-tumor efficacy of CAR-Ts, we constructed three tandem CARs (T1, T2 and T3). The amino acid sequences of the tandem CARs were provided in SEQ ID: 518-520. The amino acid sequences of anti-DLL3 humanized sdAb fragments were provided in SEQ ID NO:356 (AS64380VH5) and SEQ ID NO: 366 (AS63997VH5). 1H2.1 (SEQ ID NO: 517, e.g., see, WO2019200007), which is an anti-DLL3 CAR, was also used to generate a CAR construct as a reference. A full length CAR contains from the N-terminus to the C-terminus: a CD8 α signal peptide (SEQ ID NO: 465), DLL3 binding domain sdAbs provided in SEQ ID NO: 356 (AS64380VH5) and SEQ ID NO: 366 (AS63997VH5), a CD8 α hinge domain (SEQ ID NO: 466), a CD8 α transmembrane domain (SEQ ID NO: 467), a CD137 intracellular domain (SEQ ID NO: 468) or a CD28 intracellular domain (SEQ ID NO: 469), and a CD3 ζ intracellular domain (SEQ ID NO: 470). Schematic representation of a CAR construct is shown in FIG. 10A. For T1, both of sdAb 1 and sdAb 2 were AS64380VH5. For T2, both of sdAb 1 and sdAb 2 were AS63997VH5. For T3, sdAb 1 and sdAb 2 were AS63997VH5 and AS64380VH5, respectively. Nucleic acid encoding the CAR fragment was then cloned into a lentiviral vector to create full length CAR construct in a single coding frame, using human EF1 α promoter for

expression.

SEQ ID NO: 518 (T1 amino acid sequence)

MALPVTALLLPLALLHAARPEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGWFR
QAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQDNAKNSLYLQMNSLRAEDTAVYYCA
ASSRHLGLNNPRDYDYWGQGLTVTVSSGGGGSGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGNTYSSNYMGWFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQDN
AKNSLYLQMNSLRAEDTAVYYCAASSRHLGLNNPRDYDYWGQGLTVTVSSTTTPAPR
PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYC
KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQN
QLYNELNLGRREEYDVLDKRRGRDPGEGKPRRKNPQEGLYNELQKDKMAEAYSEIGM
KGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO: 519 (T2 amino acid sequence)

MALPVTALLLPLALLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKLEGVAAITVSGGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYC
AVGYLSGGSWDVPGRYNYWGQGLTVTVSSGGGGSGGGSGGGGSQVQLVESGGGVVQ
PGGSLRLSCAASFSGYGVSTMAWFRQAPGKLEGVAAITVSGGNTYYADSVKGRFTISR
DNKNTVYLQMNSLRAEDTAMYYCAVGYLSGGSWDVPGRYNYWGQGLTVTVSSTTTP
APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVIT
LYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQ
GQNQLYNELNLGRREEYDVLDKRRGRDPGEGKPRRKNPQEGLYNELQKDKMAEAYS
EIGMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR

SEQ ID NO: 520 (T3 amino acid sequence)

MALPVTALLLPLALLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKLEGVAAITVSGGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYC
AVGYLSGGSWDVPGRYNYWGQGLTVTVSSGGGGSGGGSGGGGSEVQLVESGGGLVQ
PGGSLRLSCAASGNTYSSNYMGWFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQ
DNAKNSLYLQMNSLRAEDTAVYYCAASSRHLGLNNPRDYDYWGQGLTVTVSSTTTPA
PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITL
YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG
QNQLYNELNLGRREEYDVLDKRRGRDPGEGKPRRKNPQEGLYNELQKDKMAEAYSEI
GMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPR

***In vitro* cytotoxicity assay**

On day 9 post transduction, transduced T cells were harvested and co-incubated with DLL3-expressing tumor cell lines (SHP-77 with DLL3 high expression, NCI-H82 with DLL3 medium expression and NCI-H2171 with DLL3 low expression) and DLL3 negative expressing cell lines (NCI-H460 and HEK293) at an effector (CAR-T) to target cell ratio of 0.5:1 and 2:1 for 22 hours. CAR3 CAR-T cells were used as a reference in all assays to compare assay variation and/or act as a control. Un-transduced T cells (UnT) were used as a negative control.

The cytotoxicity of the transduced T cells was determined by a lactate

dehydrogenase (LDH) assay. Results show that CAR3 CAR-T and some anti-DLL3 tandem CAR-Ts exhibit strong anti-tumor activities *in vitro* against SHP-77 cells, while UnT has no target cell killing effect (FIG. 11A-C) and DLL3 negative expression cells (NCI-H460 and HEK293) did not induce cytotoxicity (FIG. 11D-E). Besides CAR3, We also compared *in vitro* cytotoxicity of SHP-77 cells of T3 and 1H2.1. Result shows that T3 had a comparable or less potent cell killing activity in short-term stimulation (FIG. 11V).

IFN- γ and TNF- α release detection

Additionally, supernatants from the *in vitro* cytotoxicity assay were collected to assess CAR-induced cytokine release, e.g., interferon gamma (IFN- γ) and TNF- α release. As shown in FIG. 11F-K, CAR3 CAR-T and some anti-DLL3 tandem CAR-Ts were stimulated by DLL3 expressing cell lines to produce IFN- γ and TNF- α , whereas UnT produced little IFN- γ and TNF- α . DLL3 negative expressing cell lines did not reduce specific release of IFN- γ and TNF- α (data not shown). Protocols of IFN- γ and TNF- α release detection can be referred to CISBIO's human TNF- α kits and IFN- γ kits.

Compared with 1H2.1, T3 released more IFN- γ and TNF- α (after co-incubation for 22 hours)(FIG. 11W-X).

Tandem CAR-T cytotoxicity and expansion by long-term stimulation assay

The DLL3 CAR-T cells were evaluated by repetitive antigen stimulation assay. Upon repetitive stimulation by the SCLC cell lines and control cell lines, the tandem CAR-T cell T3 showed more potent cytotoxicity to SCLC cells, especially to SHP-77 and NCI-H82 cells (FIG. 11L-P). In addition to cytotoxicity activity, tandem CAR-T cell T3 also showed higher proliferation capacity than other CARTs, especially when stimulated by SHP-77 and NCI-H82 cells (FIG. 11Q-U).

Besides CAR3, We also compared *in vitro* cytotoxicity of SHP-77 cells of T3 and 1H2.1. Result shows that T3 had a superior cytotoxicity and expansion in long-term stimulation (FIG. 11Y-Z).

The repetitive stimulation were carried out as follows.

Round 1: CAR-T cells and 3×10^5 target cells (e.g, SHP-77) were added to a 24-well plate at an effector to target cell ratio of 1: 5, and co-incubated in a carbon dioxide incubator in 37°C, 5% CO₂ for 3 days. 200 μ L of the cell culture supernatant was pipetted for cytokine detection, and the co-incubated cells were harvested to assess %CD3 and CAR positive rate by flow cytometry;

Round 2: Based on the CAR-T positive rate of the harvested cells in Round 1, the harvested cells were continued to co-incubate with the same volume of fresh target cells (SHP-77) at an effector to target cell ratio of 1: 2 for another 3 days. 200 μ L of the cell culture supernatant was pipetted for cytokine detection, and the co-incubated cells were harvested to assess %CD3 and CAR positive rate by flow cytometry;

Based on the CAR-T positive rate of each previous Round, Round 3 and next Rounds were performed in a similar manner to that of Round 2.

Example 12. Evaluation of *in vitro* activity of humanized anti-DLL3 PD-1 DNR or CSR armed CAR-T cells

To improve persistence of CAR-Ts, we constructed PD-1 Dominant Negative Receptor (PD-1DNR) or PD-1 Chimeric Switch Receptor (PD-1CSR) armored DLL3 CARs. The amino acid sequences of the two CARs were provided in SEQ ID: 521-522. PD-1DNR and PD-1CSR sequences were linked to T3 C terminal via P2A. The amino acid sequences of PD-1DNR and PD-1CSR were provided in SEQ ID: 523-524. Schematic representation of the CAR construct were shown in FIG. 10B.

SEQ ID NO: 521 (T3-PD-1DNR amino acid sequence)

MALPVTALLLPLALLLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGLEGVAAITVGSGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYC
AVGYLSGGSWDVPGRYNYWGQGLTVTVSSGGGGSGGGSGGGGSEVQLVESGGGLVQ
PGGSLRLSCAASGNTYSSNYMGWFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQ
DNAKNSLYLQMNSLRAEDTAVYYCAASSRHLGLNNPRDYDYWGQGLTVTVSSTTPA
PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLSLVITL
YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG
QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI
GMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPRGSGATNFSLLKQAGDVEENP
GPMQIPQAPWPVWAVLQLGWRPGWFLDSPDRPWNPTTFSPALLVVTEGDNATFTCSFS
NTSESVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRN
DSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRAGQAAAPTTTPAPRPP
TPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLSLVITLYCN
HRRIQ

SEQ ID NO: 522 (T3-PD-1CSR amino acid sequence)

MALPVTALLLPLALLLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGLEGVAAITVGSGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYC
AVGYLSGGSWDVPGRYNYWGQGLTVTVSSGGGGSGGGSGGGGSEVQLVESGGGLVQ
PGGSLRLSCAASGNTYSSNYMGWFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQ
DNAKNSLYLQMNSLRAEDTAVYYCAASSRHLGLNNPRDYDYWGQGLTVTVSSTTPA
PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLSLVITL
YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG
QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI
GMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPRGSGATNFSLLKQAGDVEENP
GPMQIPQAPWPVWAVLQLGWRPGWFLDSPDRPWNPTTFSPALLVVTEGDNATFTCSFS
NTSESVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRN
DSGTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHCPSPLFPGPSKPFVVLVVGGV
LACYSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS

SEQ ID NO: 523 (PD-1DNR amino acid sequence)

MQIPQAPWPVWAVLQLGWRPGWFLDSPDRPWNPTTFSPALLVVTEGDNATFTCSFSNT
SESVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRNDS
GTYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHPSPSPRAGQAAAPTTTPAPRPPPT

APTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCNHR
RIQ

SEQ ID NO: 524 (PD-1CSR amino acid sequence)

MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVTEGDNATFTCSFSNTS
ESFVLNWYRMSPSNQTDKLAAPEDRSQPGQDCRFRVTQLPNGRDFHMSVVRARRND SG
TYLCGAISLAPKAQIKESLRAELRVTERRAEVPTAHCPSPLPFGPSKPFWVLVVVGGVLAC
YSLLVTVAFIIFWVRSKRSRLHSDYMNMTPRRPGPTRKHYPYAPPRDFAAYRS

The PD-1DNR or PD-1CSR armored DLL3 CAR-T cells were evaluated by repetitive antigen stimulation assay. Upon repetitive stimulation by the SHP-77 cells, the armored CAR-T cells did not increase cytotoxicity potency and did not improve expansion capability compared with conventional CARTs (FIG. 12A-B). Upon repetitive stimulation by the SHP-77/PD-L1 cells (overexpressing human PD-L1 in SHP-77 cells), the PD-1 CSR armored CAR-T cells showed a superior cytotoxicity potency and expansion capability (FIG. 12C-D).

Example13. TGF- β -DNR enhances the anti-tumor efficacy of DLL3 CAR-T cells **Construction of TGF- β -DNR armored DLL3 CAR-T cells**

To improve the antitumor performance of the DLL3 CAR-T cells in tumor microenvironment, a TGF- β -DNR sequence was incorporated into the DLL3 CAR as shown in FIG. 13A. The TGF- β -DNR is a truncated version of TGFBR2, which consist of the extracellular and transmembrane domain of the TGFBR2. The constructs T3-P2A-TGF- β -DNR, T3-T2A-TGF- β -DNR comprise a T3-BBZ sequence in the N terminal, a P2A or T2A peptide as indicated, a TGF- β -DNR in the C terminal; the constructs TGF- β -DNR-P2A-T3 and TGF- β -DNR-T2A-T3 comprise a TGF- β -DNR sequence in the N terminal, a P2A or T2A peptide as indicated, and a T3-BBZ sequence in the C terminal. The detailed sequences of the TGF- β -DNR and armored DLL3 CARs were provided in SEQ ID: 525-529.

SEQ ID NO: 525 (T3-P2A-TGF- β -DNR amino acid sequence)

MALPVTALLLPLALLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGLEGVAAITVSGGNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYC
AVGYLSGGSWDVPGRYNYWGQGLTVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQ
PGGSLRLSCAASGNTYSSNYMGWFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQ
DNAKNSLYLQMNSLRAEDTAVYYCAASSRHLGLNNPRDYDYWGQGLTVTVSSTTPA
PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITL
YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG
QNQLYNELNLGRREEYDVLDKRRGRDPENGGKPRRKNPQEGLYNELQKDKMAEAYSEI
GMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPRGSGATNFSLLKQAGDVEENP
GPMGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCFCDVR
FSTCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAAS
PKCIMKEKKKPGETFFMCSSSDECNDNIIFSEEYNTSNPDLLLIVFQVTGISLLPPLGVAIS

VIIIFYCYRVNRQQKLSS

SEQ ID NO: 526 (TGF- β -DNR-P2A-T3 amino acid sequence)

MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDFRST
CDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAAPK
CIMKEKKKPGETFFMCSSDECNDNIIFSEEYNTSNPDLLLVIQVTGISLLPPLGVAISVIII
FYCYRVNRQQKLSSGSGATNFSLLKQAGDVEENPGPMALPVTALLPLALLLHAARPQV
QLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFRQAPGKGLEGVAAITVSGSNTYY
ADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYCAVGYLSSGSDVPGRYNYWGQ
GTLVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMG
WFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQDNAKNSLYLQMNSLRAEDTAV
YYCAASSRHLGLNNPRDYDYWGQGTTLVTVSSTTPAPRPPTPAPTIASQPLSLRPEACRP
AAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQ
TTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDR
RRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLST
ATKDTYDALHMQALPPR

SEQ ID NO: 527 (T3-T2A-TGF- β -DNR amino acid sequence)

MALPVTALLPLALLLHAARPQVQLVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFR
QAPGKGLEGVAAITVSGSNTYYADSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYC
AVGYLSSGSDVPGRYNYWGQGTTLVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQ
PGGSLRLSCAASGNTYSSNYMGWFRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQ
DNAKNSLYLQMNSLRAEDTAVYYCAASSRHLGLNNPRDYDYWGQGTTLVTVSSTTPA
PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITL
YCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQG
QNQLYNELNLGRREEYDVLDRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEI
GMKGERRRGKGGHDGLYQGLSTATKDTYDALHMQALPPRGSGEGRGSLLTCGDVEENPG
PMGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDFRST
TCDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAAPK
CIMKEKKKPGETFFMCSSDECNDNIIFSEEYNTSNPDLLLVIQVTGISLLPPLGVAISVIII
FYCYRVNRQQKLSS

SEQ ID NO: 528 (TGF- β -DNR-T2A-T3 amino acid sequence)

MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDFRST
CDNQKSCMSNCSITSICEKPQEVCAVWRKNDENITLETVCHDPKLPYHDFILEDAAAPK
CIMKEKKKPGETFFMCSSDECNDNIIFSEEYNTSNPDLLLVIQVTGISLLPPLGVAISVIII
FYCYRVNRQQKLSSGSGEGRGSLLTCGDVEENPGPMALPVTALLPLALLLHAARPQVQ
LVESGGGVVQPGGSLRLSCAASFSGYGVSTMAWFRQAPGKGLEGVAAITVSGSNTYYA
DSVKGRFTISRDNKNTVYLQMNSLRAEDTAMYYCAVGYLSSGSDVPGRYNYWGQ
TLVTVSSGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGNTYSSNYMGW
FRQAPGKGLEEVAVIYTRGGHTYYVDSVRGRFTISQDNAKNSLYLQMNSLRAEDTAVYY
CAASSRHLGLNNPRDYDYWGQGTTLVTVSSTTPAPRPPTPAPTIASQPLSLRPEACRPA
AGGAVHTRGLDFACDIYWAPLAGTCGVLLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTT
QEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDR

GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGGHDGLYQGLSTAT
KDTYDALHMQALPPR

SEQ ID NO: 529 (TGF- β -DNR amino acid sequence)

MGRGLLRGLWPLHIVLWTRIASTIPPHVQKSVNNDMIVTDNNGAVKFPQLCKFCDVRFST
CDNQKSCMSNCSITSICEKPQEVCAVVRKNDENITLETVCHDPKLPYHDFILEDAAAPK
CIMKEKKKPGETFFMCSSDECNDNIIFSEEYNTSNPDLLLVIQVTGISLLPPLGVAISVIII
FYCYRVNRQQKLSS

All the constructs were packaged into lentiviruses based on the second generation lentiviral system. Then primary T cells isolated from the PBMC of healthy donors were transduced with the lentiviruses. 4 days after transduction, the positive ratios of sdAb and TGF- β -DNR were detected by FACS (FIG. 13B). Results showed that the sdAb positive ratios of T3-P2A- TGF- β -DNR, T3-T2A- TGF- β -DNR, TGF- β -DNR -P2A-T3 and TGF- β -DNR-T2A-T3 CAR-T cells were comparable. However, the positive ratio of TGF- β -DNR were higher in constructs T3-P2A-TGF- β -DNR and T3-T2A- TGF- β -DNR than in TGF- β -DNR-P2A-T3 and TGF- β -DNR-T2A-T3. These results indicated the expression of TGF- β -DNR was higher when it conjugates to the C terminal of CAR.

***In vitro* cytotoxicity assays**

Then the cytotoxicity of these CAR-T cells was evaluated by LDH or IFN- γ releasing assays. 5 days after transduction, the CAR-T cells were adjusted to same sdAb positive ratios by untransduced T cells (UnT). Then the CAR-T cells or UnT cells were co-incubated with SHP77 for 48 h in the presence of 5 ng/mL TGF- β , and the LDH and IFN- γ releasing were measured (FIG. 13C-D). The results showed that the TGF- β -DNR armored CAR-T cells induced more specific lysis of target cell than the unarmored CAR-T cells. Accordingly, the TGF- β -DNR armored CAR-T cells showed a higher capacity of IFN- γ release upon antigen activation. In consistent with the TGF- β -DNR expression levels of the different CAR-T cells, the T3-P2A-TGF- β -DNR, T3-T2A-TGF- β -DNR showed higher levels of IFN- γ secretion than TGF- β -DNR-P2A-T3 and TGF- β -DNR-T2A-T3 CAR-T cells. Collectively these results demonstrated that the TGF- β -DNR was able to enhance the cytotoxicity of DLL3 CAR-T cells against the DLL3 positive SCLC cells.

Long-term stimulation assay

To determine whether the TGF- β -DNR could resist the inhibitory effects of TGF- β on CAR-T cells, a long-term stimulation assay was performed. Briefly, the T3-P2A-TGF- β -DNR and T3 CAR-T cells were repetitively challenged with SHP77 cells every 3 days in the presence or absence of 5 ng/mL of TGF- β . At the end of each round stimulation, the percentages of T cells in total viable cells were analyzed by FACS, and the expansion of CAR-T cells were calculated. As shown in FIG. 13E and FIG. 13F, the persistence and expansion of T3 CAR-T cells was inhibited by TGF- β .

In contrast, the persistence and expansion of T3-P2A-TGF- β -DNR was well maintained even in the presence of TGF- β . T cell exhaustion markers were analyzed by FACS after 2 rounds stimulation with SHP77 cells. As shown in FIG. 13G, treatment with TGF- β upregulated the expression of exhaustion markers in T3 cells, but not in T3-P2A-TGF- β -DNR CAR-T cells. Collectively, these results demonstrated that TGF- β -DNR protects DLL3 CAR-T cells from the inhibition by TGF- β . Because the expression level of TGF- β is usually elevated in the microenvironment of solid tumors, our results indicate that the addition of TGF- β -DNR improves the anti-tumor efficacy of DLL3 CAR-T cells in solid tumors.

***In vivo* anti-tumor efficacy study**

To further investigate whether the TGF- β -DNR could enhance the anti-tumor efficacy of DLL3 CAR-T cells *in vivo*, the T3-T2A-TGF- β -DNR CAR-T cells or the parental CAR-T cells were evaluated in xenograft model. Briefly, 1×10^7 SHP77 cells were subcutaneously implanted into NCG mice. After 7~10 days, when tumor volume reached 100~200 mm³, 2.5×10^5 CAR-T cells were injected intravenously into the mice. Then tumor volume was measured twice a week, and percentage of CAR-T in peripheral blood was measured once a week. As shown in FIG. 13H, at a suboptimal dose, the T3-T2A-TGF- β -DNR CAR-T cells could potently suppress tumor growth, while the parental T3 CAR-T could not. As shown in FIG 13I, the percentage of T3-T2A-TGF- β -DNR CAR-T in peripheral blood leukocytes was higher than T3. Collectively, these results demonstrate that the TGF- β -DNR could enhance the anti-tumor efficacy of DLL3 CAR-T cells *in vivo*.