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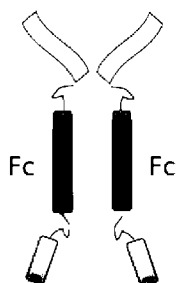
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(54) Title: BIFUNCTIONAL PROTEINS AND USES THEREOF

FIG. 1E

Notch Ligand ECD



Muscle-targeting scFv

(57) **Abstract:** Provided herein are compositions and methods of treating muscular dystrophies by administering an effective amount of a composition comprising a bifunctional protein comprising a first binding moiety that binds to muscle-specific molecules and a second functional domain that activates Notch signaling, thereby spatiotemporally activating Notch signaling in muscle tissues to boost satellite cell renewal in situ, and thus enhancing muscle repair/regeneration to improve muscle function as a treatment of various muscular dystrophies and sarcopenia. Also provided are engineered DLL4 extracellular domains and protein constructs comprising thereof.

BIFUNCTIONAL PROTEINS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This patent application claims priority benefits of U.S. Provisional Patent Application No. 63/639,356 filed on April 26, 2024, and U.S. Provisional Patent Application No. 63/537,382 filed on September 8, 2023, the contents of each of which are incorporated herein by reference in their entirety.

REFERENCE TO AN ELECTRONIC SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (340742000140SEQLIST.xml; Size: 457,221 bytes; and Date of Creation: September 5, 2024) is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0003] The present invention relates to bifunctional protein constructs comprising a first binding moiety that specifically binds to a muscle-specific molecule and a second binding moiety that specifically binds to a Notch receptor and activates the Notch receptor. The present invention also relates to methods for making such bifunctional protein constructs and the use of such bifunctional protein constructs for treating muscle-related diseases (*e.g.*, muscular dystrophies and sarcopenia). Also provided are engineered DLL4 extracellular domains (ECDs) and protein constructs comprising thereof.

BACKGROUND

[0004] Muscular dystrophy (MD) is a diverse group of muscle diseases of many subtypes that present with muscle weakness and degeneration at different levels of severity. An MD is commonly linked to a defect(s) in a gene encoding a protein that is important for muscle integrity or function. Degenerative MDs are typically caused by defects in structural proteins that are directly or indirectly associated with the dystrophin-associated glycoprotein complex (DGC), which is essential to maintaining muscle cell membrane integrity.

[0005] A direct link between MD and Notch signaling in human was established with limb-girdle muscular dystrophy (LGMD R21), which is caused by Protein O-glucosyltransferase 1 (POGLUT1) biallelic mutations, reduced Notch signaling, and satellite cell loss (Servián-Morilla et al., 2016, EMBO Mol Med. 8(11):1289-1309; Servián-Morilla et al., 2020, Acta Neuropathol. 139(3):565-582).

[0006] All references cited herein, including patent applications, patent publications, and Genbank Accession numbers are herein incorporated by reference, as if each individual reference were specifically and individually indicated to be incorporated by reference in its entirety.

BRIEF SUMMARY OF THE INVENTION

[0007] The present application in one aspect provides a bifunctional protein construct comprising a first binding moiety and a second binding moiety, wherein the first binding moiety specifically binds to a muscle-specific molecule, and wherein the second binding moiety specifically binds to a Notch receptor and activates the Notch receptor.

[0008] In some embodiments according to the bifunctional protein construct described above, the muscle-specific molecule is a target antigen on the sarcolemma, between the sarcolemma and the basal lamina, or in the basal lamina. In some embodiments, the target antigen is selected from the group consisting of laminin, agrin, nidogen, perlecan, and M-cadherin (CDH15). In some embodiments, the target antigen is a component of the dystrophin-associated glycoprotein complex (DGC). In some embodiments, the target antigen is selected from the group consisting of α -dystroglycan (α -DG), β -DG, laminin-211, perlecan, collagen, α -sarcoglycan, β -sarcoglycan, γ -sarcoglycan, δ -sarcoglycan, ϵ -sarcoglycan, ζ -sarcoglycan, biglycan, sarcospan, and matriglycan on α -DG. In some embodiments, the target antigen is a laminin subunit alpha-2 (LAMA2), CDH15, α -DG, or matriglycan on α -DG.

[0009] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises an antibody moiety specifically binding to the muscle-specific molecule. In some embodiments, the antibody moiety is selected from the group consisting of a full-length antibody, a Fab, a Fab', a F(ab')₂, an scFv, and an sdAb.

[0010] In some embodiments according to any of the bifunctional protein constructs described above, the antibody moiety specifically binds to LAMA2 (anti-LAMA2 antibody moiety). In some embodiments, the anti-LAMA2 antibody moiety comprises: (i) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 6; (ii) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 7, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 9, an LC-CDR1

comprising the amino acid sequence of SEQ ID NO: 10, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 12; (iii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (iv) comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (v) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (vi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (vii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (viii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (ix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (x) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (xi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (xii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (xiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (xiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (xv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL

comprising the amino acid sequence of SEQ ID NO: 69; (xvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (xvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (xviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (xix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (xx) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (xxi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (xxii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (xxiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (xxiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (xxv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (xxvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (xxvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (xxviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (xxix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid

sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (xxx) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (xxxi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (xxxii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (xxxiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (xxxiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (xxxv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (xxxvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (xxxvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (xxxviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (xxxix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (xl) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (xli) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (xlii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID

NO: 69; (xliii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (xliv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (xlv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (xlvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (xlvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (xlviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (xlix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (l) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (li) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (lii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (liii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (liv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (lv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (lvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-

CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (lvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (lviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (lix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (lx) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (lxi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (lxii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (lxiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (lxiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (lxv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (lxvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (lxvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (lxviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (lxix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (lxx) an HC-CDR1, HC-CDR2, and

HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (lxxi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (lxxii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (lxxiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (lxxiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (lxxv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (lxxvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (lxxvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (lxxviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (lxxix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (lxxx) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (lxxxii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (lxxxiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL

comprising the amino acid sequence of SEQ ID NO: 65; (lxxxiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (lxxxv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (lxxxvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (lxxxvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (lxxxviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (lxxxix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (xc) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; (xci) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 63, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73; (xcii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65; (xciii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66; (xciv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67; (xcv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68; (xcvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69; (xcvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid

sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70; (xcviii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71; (xcix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72; or (c) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 6. In some embodiments, the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 49, and a VL comprising the amino acid sequence of SEQ ID NO: 50.

[0011] In some embodiments according to any of the bifunctional protein constructs described above, the anti-LAMA2 antibody moiety is an anti-LAMA2 scFv. In some embodiments, the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 51. In some embodiments, the anti-LAMA2 antibody moiety is an anti-LAMA2 Fab. In some embodiments, the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 52, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 53.

[0012] In some embodiments according to any of the bifunctional protein constructs described above, the anti-LAMA2 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 7, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 9, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 10, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 12.

[0013] In some embodiments according to any of the bifunctional protein constructs described above, the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID

NO: 65. In some embodiments, the anti-LAMA2 antibody moiety comprises: (i) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 65; (ii) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 66; (iii) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 67; (iv) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 68; (v) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 69; (vi) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 70; (vii) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 71; (viii) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 72; (ix) a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 73; (x) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 65; (xi) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 66; (xii) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 67; (xiii) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 68; (xiv) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 69; (xv) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 70; (xvi) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 71; (xvii) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 72; (xviii) a VH comprising the amino acid sequence of SEQ ID NO: 55, and a VL comprising the amino acid sequence of SEQ ID NO: 73; (xix) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 65; (xx) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 66; (xxi) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 67; (xxii) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 68; (xxiii) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL

comprising the amino acid sequence of SEQ ID NO: 69; (xxiv) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 70; (xxv) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 71; (xxvi) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 72; (xxvii) a VH comprising the amino acid sequence of SEQ ID NO: 56, and a VL comprising the amino acid sequence of SEQ ID NO: 73; (xxviii) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 65; (xxix) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 66; (xxx) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 67; (xxxi) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 68; (xxxii) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 69; (xxxiii) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 70; (xxxiv) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 71; (xxxv) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 72; (xxxvi) a VH comprising the amino acid sequence of SEQ ID NO: 57, and a VL comprising the amino acid sequence of SEQ ID NO: 73; (xxxvii) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 65; (xxxviii) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 66; (xxxix) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 67; (xl) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 68; (xli) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 69; (xlii) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 70; (xliii) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 71; (xliv) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 72; (xlv) a VH comprising the amino acid sequence of SEQ ID NO: 58, and a VL comprising the amino acid sequence of SEQ ID NO: 73; (xlvi) a VH comprising the amino

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SEQ ID NO: 65; (xcii) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 66; (xciii) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 67; (xciv) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 68; (xcv) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 69; (xcvi) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 70; (xcvii) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 71; (xcviii) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 72; or (xcix) a VH comprising the amino acid sequence of SEQ ID NO: 64, and a VL comprising the amino acid sequence of SEQ ID NO: 73.

[0014] In some embodiments according to any of the bifunctional protein constructs described above, the anti-LAMA2 antibody moiety is an anti-LAMA2 scFv. In some embodiments, the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO:145.

[0015] In some embodiments according to any of the bifunctional protein constructs described above, the anti-LAMA2 antibody moiety is an anti-LAMA2 Fab. In some embodiments, the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166.

[0016] In some embodiments according to any of the bifunctional protein constructs described above, the antibody moiety specifically binds to matriglycan on α -DG (anti-matriglycan antibody moiety). In some embodiments, the anti-matriglycan antibody moiety comprises: (i) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 74, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 76, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 77, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 78, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 79; (ii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (iii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (iv) an HC-CDR1, HC-CDR2,

and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; (v) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98; (vi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (vii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (viii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; (ix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98; (x) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (xi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (xii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; (xiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98; (xiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (xv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (xvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; or (xvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL

comprising the amino acid sequence of SEQ ID NO: 98. In some embodiments, the anti-matriglycan antibody moiety comprises a VH comprising the amino acid sequence of any one of SEQ ID NOs: 89-93, and a VL comprising the amino acid sequence of any one of SEQ ID NOs: 94-98.

[0017] In some embodiments according to any of the bifunctional protein constructs described above, the anti-matriglycan antibody moiety comprises: (i) a VH comprising the amino acid sequence of SEQ ID NO: 89, and a VL comprising the amino acid sequence of SEQ ID NO: 94; (ii) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (iii) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (iv) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (v) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (vi) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (vii) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (viii) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (ix) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (x) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (xi) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (xii) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (xiii) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (xiv) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (xv) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (xxvi) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 97; or (xxvii) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 98.

[0018] In some embodiments according to any of the bifunctional protein constructs described above, the anti-matriglycan antibody moiety is an anti-matriglycan scFv. In some

embodiments, the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 99.

[0019] In some embodiments according to any of the bifunctional protein constructs described above, the anti-matriglycan antibody moiety is an anti-matriglycan Fab. In some embodiments, the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 100, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 101.

[0020] In some embodiments according to any of the bifunctional protein constructs described above, the antibody moiety specifically binds to CDH15 (anti-CDH15 antibody moiety). In some embodiments, the anti-CDH15 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 102, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 103, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 104, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 105, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 106, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 107.

[0021] In some embodiments according to any of the bifunctional protein constructs described above, the anti-CDH15 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 108, and a VL comprising the amino acid sequence of SEQ ID NO: 109.

[0022] In some embodiments according to any of the bifunctional protein constructs described above, the anti-CDH15 antibody moiety is an anti-CDH15 scFv. In some embodiments, the anti-CDH15 scFv comprises the amino acid sequence of SEQ ID NO: 110.

[0023] In some embodiments according to any of the bifunctional protein constructs described above, the anti-CDH15 antibody moiety is an anti-CDH15 Fab. In some embodiments, the anti-CDH15 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 111, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 112.

[0024] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises a non-antibody moiety specifically binding to the muscle-specific molecule. In some embodiments, the non-antibody moiety comprises a protein domain selected from the group consisting of a laminin G-like domain (LG domain) of laminin, an LG domain of agrin, an LG domain of nidogen, an LG domain of perlecan, the laminin coiled-coil binding domain of agrin, and the laminin γ binding domain of nidogen. In some embodiments, wherein the non-antibody moiety comprises an LG

domain of laminin. In some embodiments, the non-antibody moiety comprises an LG domain of laminin subunit α -1 (LAMA1), LAMA2, laminin subunit α -3 (LAMA3), laminin subunit α -4 (LAMA4), or laminin subunit α -5 (LAMA5). In some embodiments, the non-antibody moiety comprises the amino acid sequence of any of SEQ ID NOs: 113-117.

[0025] In some embodiments according to any of the bifunctional protein constructs described above, the non-antibody moiety comprises an LG domain of LAMA2. In some embodiments, the non-antibody moiety comprises LG4-5 domains of LAMA2 (LAMA2 LG4-5). In some embodiments, the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 118 or 119.

[0026] In some embodiments according to any of the bifunctional protein constructs described above, the non-antibody moiety comprises an LG domain of perlecan. In some embodiments, the non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 120.

[0027] In some embodiments according to any of the bifunctional protein constructs described above, the non-antibody moiety comprises an LG domain of agrin. In some embodiments, the non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 121.

[0028] In some embodiments according to any of the bifunctional protein constructs described above, the non-antibody moiety comprises a laminin coiled-coil binding domain of agrin. In some embodiments, the laminin coiled-coil binding domain of agrin comprises the amino acid sequence of SEQ ID NO: 122.

[0029] In some embodiments according to any of the bifunctional protein constructs described above, the non-antibody moiety comprises a laminin γ binding domain of nidogen. In some embodiments, the laminin γ binding domain of nidogen comprises the amino acid sequence of SEQ ID NO: 123 or 124.

[0030] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety comprises an extracellular domain (ECD) or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jagged1 (Jag1), and Jag2.

[0031] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety comprises a DLL4 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a DLL4 ECD, and wherein the DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 125. In some embodiments, wherein the second binding moiety comprises a variant DLL4 ECD, and wherein the variant

DLL4 ECD comprises MNNL domain, DSL domain, and EGF1-5 domains of DLL4, or a sequence having at least about 90% sequence identity to the sequence of MNNL domain, DSL domain, and EGF1-5 domains of DLL4. In some embodiments, the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267.

[0032] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety comprises a DLL1 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130.

[0033] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety comprises a DLL3 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131.

[0034] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety comprises a Jag1 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a Jag1 ECD, and wherein the Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 132. In some embodiments, wherein the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises MNNL domain, DSL domain, and EGF1-6 domains of Jag1, or a sequence having at least about 90% sequence identity to the sequence of MNNL domain, DSL domain, and EGF1-6 domains of Jag1. In some embodiments, the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134.

[0035] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety comprises a Jag2 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135.

[0036] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety is an anti-Notch antibody moiety that activates the Notch receptor. In some embodiments, the anti-Notch agonist antibody moiety is selected from the group consisting of a full-length antibody, a Fab, a Fab', a F(ab')₂, an scFv, and an sdAb.

[0037] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety is fused to the second binding moiety via an optional linker. In some embodiments, the first binding moiety is fused to the N-terminus of the second binding moiety. In some embodiments, the first binding moiety is fused to the C-

terminus of the second binding moiety. In some embodiments, the bifunctional protein construct comprises (i) the second binding moiety comprising an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2; and (ii) the first binding moiety comprising: (a) an antibody moiety, wherein the antibody moiety is an scFv, a Fab, or an sdAb specifically binding to a muscle-specific molecule; or (b) a non-antibody moiety, wherein the non-antibody moiety comprises a protein domain selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan. In some embodiments, the first binding moiety comprises two or more non-antibody moieties connected in tandem.

[0038] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises an LAMA2 LG4-5 comprising the amino acid sequence of SEQ ID NO: 118 or 119. In some embodiments, the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of any of SEQ ID NOs: 136-139. In some embodiments, the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 140. In some embodiments, the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 141. In some embodiments, the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 142 or 143. In some embodiments, the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 144.

[0039] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises an anti-LAMA2 scFv. In some embodiments, the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of any of SEQ ID NOs: 146-154.

[0040] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises an anti-matriglycan scFv. In some embodiments, the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of any of SEQ ID NOs: 156-164.

[0041] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises a Fab specifically binding to a muscle-specific molecule. In some embodiments, the second binding moiety is fused to the N-terminus of the VL of the Fab via an optional linker.

[0042] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises an anti-LAMA2 Fab. In some embodiments, the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, and wherein the fusion polypeptide comprises the amino acid sequence of any of SEQ ID NOs: 167-175.

[0043] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety comprises an anti-matriglycan Fab. In some embodiments, the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, and wherein the fusion polypeptide comprises the amino acid sequence of any of SEQ ID NOs: 178-186.

[0044] In some embodiments according to any of the bifunctional protein constructs described above, the first binding moiety is fused to the second binding moiety via a carrier protein. In some embodiments, the carrier protein is selected from the group consisting of an human serum albumin (HSA), an anti-HSA antibody moiety, and a subunit of an Fc domain. In some embodiments, the first binding moiety is fused to the N-terminus of the carrier protein via an optional first linker, and the second binding moiety is fused to the C-terminus of the carrier protein via an optional second linker. In some embodiments, the first binding

moiety is fused to the C-terminus of the carrier protein via an optional first linker, and the second binding moiety is fused to the N-terminus of the carrier protein via an optional second linker. In some embodiments, the bifunctional protein construct comprises (i) the second binding moiety comprising an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2; and (ii) the first binding moiety comprising: (a) an antibody moiety, wherein the antibody moiety is an scFv, a Fab, or an sdAb specifically binding to a muscle-specific molecule; or (b) a non-antibody moiety, wherein the non-antibody moiety comprises a protein domain selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan. In some embodiments, the first binding moiety comprises two or more non-antibody moieties connected in tandem.

[0045] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct further comprises an Fc domain comprising a first subunit and a second subunit. In some embodiments, the Fc domain is derived from human IgG1, human IgG2, or human IgG4. In some embodiments, the Fc domain is derived from human IgG1 comprising the amino acid sequence of SEQ ID NO: 187. In some embodiments, each subunit of the Fc domain comprises a mutation that reduces or abolishes the effector function. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A mutation (EU numbering).

[0046] In some embodiments according to any of the bifunctional protein constructs described above, either the first subunit of the Fc domain or the second subunit of the Fc domain comprises an H435R/Y436F mutation (EU numbering). In some embodiments, the Fc domain comprises knob-into-hole mutations, and wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, the Fc domain comprises charged-pair mutations, and wherein: i) an amino acid residue in the first subunit of the Fc domain is replaced with a positively charged residue, and an amino acid residue in the second subunit of the Fc domain is replaced with a negatively charged residue; or ii) an amino acid residue in the first subunit of the Fc domain is replaced with a negatively charged residue, and an amino acid residue in the second subunit of the Fc domain is replaced with a positively charged residue. In some embodiments, the Fc domain comprises i) an amino acid residue at D399 (EU numbering) in

the first subunit of the Fc domain is replaced with a positively charged residue, and an amino acid residue at K409 (EU numbering) in the second subunit of the Fc domain is replaced with a negatively charged residue; or ii) an amino acid residue at K409 (EU numbering) in the first subunit of the Fc domain is replaced with a negatively charged residue, and an amino acid residue at D399 (EU numbering) in the second subunit of the Fc domain is replaced with a positively charged residue.

[0047] In some embodiments according to any of the bifunctional protein constructs described above, each subunit of the Fc domain comprises a mutation that reduces half-life. In some embodiments, each subunit of the Fc domain comprises an H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188.

[0048] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises: i) a first unit of a second binding moiety specifically binding to a first Notch receptor, and ii) a second unit of a second binding moiety specifically binding to a second Notch receptor, and wherein the first unit of the second binding moiety and the second unit of the second binding moiety each independently comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL4 ECD, and wherein the DLL4 ECD comprises the amino acid sequence of any one of SEQ ID NO: 125-129. In some embodiments, the first unit of the second binding moiety and the second unit of the second binding moiety are the same. In some embodiments, the first unit of the second binding moiety and the second unit of the second binding moiety are different. In some embodiments, the bifunctional protein construct comprises: i) a first unit of a first binding moiety specifically binding to a first muscle-specific molecule, and ii) a second unit of a first binding moiety specifically binding to a second muscle-specific molecule. In some embodiments, the first unit of the first binding moiety and the second unit of the first binding moiety are the same. In some embodiments, the first unit of the first binding moiety and the second unit of the first binding moiety are different. In some embodiments, the first unit of the first binding moiety comprises a first antibody moiety specifically binding to the first muscle-specific molecule, the second unit of the first binding moiety comprises a second antibody moiety specifically binding to the second muscle-specific molecule, and wherein the first antibody moiety and the second antibody moiety are each independently selected from the group consisting of a Fab, an scFv, and an sdAb.

[0049] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – VH1-(H1-CH1); ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – VH2-(H2-CH1); iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

[0050] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, the anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. In some embodiments, wherein the third polypeptide and the fourth polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 165, and the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of any of SEQ ID NOs: 189-192. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second

binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. In some embodiments, the third polypeptide and the fourth polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 165, and the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 193. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. In some embodiments, the third polypeptide and the fourth polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 165, and the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 194. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. In some embodiments, the third polypeptide and the fourth polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 165, and the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 195 or 196. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. In some embodiments, the third polypeptide and the fourth polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 165, and the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 197.

[0051] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises Fab1 and Fab2 both specifically bind to matriglycan. In some embodiments, the anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the third polypeptide and the fourth polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 176, and wherein: (i) the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of any of SEQ ID NOs: 198-201; (ii) the first polypeptide and the second polypeptide of the bifunctional protein construct each

comprises the amino acid sequence of SEQ ID NO: 202; (iii) the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 203; (iv) the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 204 or 205; or (v) the first polypeptide and the second polypeptide of the bifunctional protein construct each comprises the amino acid sequence of SEQ ID NO: 206.

[0052] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first sdAb (sdAb1), and the second antibody moiety is a second sdAb (sdAb2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – sdAb1; and ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – sdAb2. In some embodiments, the first antibody moiety is a first scFv (scFv1), and the second antibody moiety is a second scFv (scFv2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – scFv1; and ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – scFv2.

[0053] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises scFv1 and scFv2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. In some embodiments, the linker comprises an amino acid sequence of any one of SEQ ID NOs: 207-222. In some embodiments, the first subunit of the Fc domain and the second subunit of the Fc domain each comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of any of SEQ ID NOs: 223-226. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding

moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 227. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 228. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 229 or 230. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 231.

[0054] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises scFv1 and scFv2 both specifically bind to matriglycan. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising: (i) the amino acid sequence of any one of SEQ ID NOs: 232-235; (ii) the amino acid sequence of SEQ ID NO: 236; (iii) the amino acid sequence of SEQ ID NO: 237; (iv) the amino acid sequence of SEQ ID NO: 238 or 239; or (v) the amino acid sequence of SEQ ID NO: 240.

[0055] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain – optional linker – a first unit of a second binding moiety specifically binding to a first Notch receptor; ii) a second polypeptide comprising from N' to C': VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain – optional linker – a second unit of a second binding moiety specifically binding to a second Notch receptor; iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and iv) a fourth polypeptide

comprising from N' to C': VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

[0056] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first sdAb (sdAb1), and the second antibody moiety is a second sdAb (sdAb2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': sdAb1 – optional linker – the first subunit of the Fc domain – optional linker – a first unit of a second binding moiety specifically binding to a first Notch receptor; and ii) a second polypeptide comprising from N' to C': sdAb2 – optional linker – the second subunit of the Fc domain – optional linker – a second unit of a second binding moiety specifically binding to a second Notch receptor.

[0057] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first scFv (scFv1), and the second antibody moiety is a second scFv (scFv2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': scFv1 – optional linker – the first subunit of the Fc domain – optional linker – a first unit of a second binding moiety specifically binding to a first Notch receptor; and ii) a second polypeptide comprising from N' to C': scFv2 – optional linker – the second subunit of the Fc domain – optional linker – a second unit of a second binding moiety specifically binding to a second Notch receptor.

[0058] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': VL1-(L1-CL) – optional linker – a first unit of a second binding moiety specifically binding to a first Notch receptor; and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL) – optional linker – a second unit of a second binding moiety specifically binding to a second Notch receptor; and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

[0059] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': VH2-(H2-CH1) – optional

linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

[0060] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

[0061] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct further comprises a third unit of a second binding moiety specifically binding to a third Notch receptor, and a fourth unit of a second binding moiety specifically binding to a fourth Notch receptor, and wherein the third unit of the second binding moiety and the fourth unit of the second binding moiety each independently comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2. In some embodiments, the third unit of the second binding moiety and the fourth unit of the second binding moiety each independently comprises an ECD or a variant thereof of DLL4. In some embodiments, the third unit of the second binding moiety and/or the fourth unit of the second binding moiety comprises a DLL4 ECD, and wherein the DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 125. In some embodiments, the third unit of the second binding moiety and/or the fourth unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises MNNL domain, DSL domain, and EGF1-5 domains of DLL4. In some embodiments, the variant DLL4 ECD comprises the amino acid sequence of any one of SEQ ID NO: 126-129 and 260-267. In some embodiments, all four units of the second

binding moiety are the same. In some embodiments, at least one of the four units of the second binding moiety is different from the others.

[0062] In some embodiments according to any of the bifunctional protein constructs described above, the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2); wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': a third unit of a second binding moiety specifically binding to a third Notch receptor – optional linker – VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': a fourth unit of a second binding moiety specifically binding to a fourth Notch receptor – optional linker – VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

[0063] In some embodiments according to any of the bifunctional protein constructs described above, the first unit of the first binding moiety comprises a first non-antibody moiety specifically binding to the first muscle-specific molecule, the second unit of the first binding moiety comprises a second non-antibody moiety specifically binding to the second muscle-specific molecule, and wherein the first non-antibody moiety and the second non-antibody moiety are each independently selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan. In some embodiments, the first unit of the first binding moiety comprises two or more first non-antibody moieties connected in tandem, and the second unit of the first binding moiety comprises two or more second non-antibody moieties connected in tandem. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises LAMA2 LG4-5 comprising the amino acid sequence of SEQ ID NO: 118 or 119.

[0064] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the first binding moiety – optional linker – the first subunit of the Fc domain – optional linker – a first unit of a second binding moiety specifically binding to a first Notch receptor; and ii) a second polypeptide comprising from N' to C': the second unit of the first binding moiety – optional linker – the second subunit of

the Fc domain – optional linker – a second unit of a second binding moiety specifically binding to a second Notch receptor.

[0065] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – the first unit of the first binding moiety; and ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the first binding moiety.

[0066] In some embodiments according to any of the bifunctional protein constructs described above, the first unit of the first binding moiety comprises two LAMA2 LG4-5 connected in tandem, and the second unit of the first binding moiety comprises two LAMA2 LG4-5 connected in tandem. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of any one of SEQ ID NOs: 241-244. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 245. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 246. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 247 or 248. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises

the amino acid sequence of SEQ ID NO: 135. In some embodiments, the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 249.

[0067] In some embodiments according to any of the bifunctional protein constructs described above, i) the first binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional first linker, and the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional second linker; or ii) the first binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional first linker, and the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional second linker. In some embodiments, the first binding moiety is a Fab specifically binding to the muscle-specific molecule, and wherein the C-terminus of the CH1 of the Fab is fused to the N-terminus of the first subunit of the Fc domain or the second subunit of the Fc domain via the optional first linker. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2.

[0068] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises: i) a first unit of a second binding moiety specifically binding to a first Notch receptor, and ii) a second unit of a second binding moiety specifically binding to a second Notch receptor; wherein the first unit of the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional first linker, and the second unit of the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional second linker; and wherein the first binding moiety is fused to the C-terminus of either the first subunit of the Fc domain or the second subunit of the Fc domain via an optional third linker. In some embodiments, the bifunctional protein construct comprises: i) a first unit of a first binding moiety specifically binding to a first muscle-specific molecule, and ii) a second unit of a first binding moiety specifically binding to a second muscle-specific molecule; and wherein the first unit of the first binding moiety is fused to the C-terminus of the first subunit of the Fc domain via an optional third linker, and the second unit of the first binding moiety is fused to the C-terminus of the second subunit of the Fc domain via an optional fourth linker.

[0069] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional linker; wherein the bifunctional protein construct comprises one or more units of the first binding moiety specifically binding to one or more muscle-

specific molecules; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the C-terminus of the first subunit of the Fc domain; ii) the N-terminus of the second subunit of the Fc domain; and iii) the C-terminus of the second subunit of the Fc domain.

[0070] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional linker; wherein the bifunctional protein construct comprises one or more units of the first binding moiety specifically binding to one or more muscle-specific molecules; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the N-terminus of the first subunit of the Fc domain; ii) the C-terminus of the first subunit of the Fc domain; and iii) the C-terminus of the second subunit of the Fc domain.

[0071] In some embodiments according to any of the bifunctional protein constructs described above, the bifunctional protein construct comprises: i) a first unit of a second binding moiety specifically binding to a first Notch receptor, and ii) a second unit of a second binding moiety specifically binding to a second Notch receptor; wherein the first unit of the second binding moiety is fused to the C-terminus of the first subunit of the Fc domain via an optional first linker, and the second unit of the second binding moiety is fused to the C-terminus of the second subunit of the Fc domain via an optional second linker; and wherein the first binding moiety is fused to the N-terminus of either the first subunit of the Fc domain or the second subunit of the Fc domain via an optional third linker. In some embodiments, the bifunctional protein construct comprises: i) a first unit of a first binding moiety specifically binding to a first muscle-specific molecule, and ii) a second unit of a first binding moiety specifically binding to a second muscle-specific molecule; and wherein the first unit of the first binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional third linker, and the second unit of the first binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional fourth linker.

[0072] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety is fused to the C-terminus of the first subunit of the Fc domain via an optional linker; wherein the bifunctional protein construct comprises one or more units of the first binding moiety specifically binding to one or more muscle-specific molecules; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the N-terminus of the first subunit of

the Fc domain; ii) the N-terminus of the second subunit of the Fc domain; and iii) the C-terminus of the second subunit of the Fc domain.

[0073] In some embodiments according to any of the bifunctional protein constructs described above, the second binding moiety is fused to the C-terminus of the second subunit of the Fc domain via an optional linker; wherein the bifunctional protein construct comprises one or more units of the first binding moiety specifically binding to one or more muscle-specific molecules; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the N-terminus of the first subunit of the Fc domain; ii) the C-terminus of the first subunit of the Fc domain; and iii) the N-terminus of the second subunit of the Fc domain.

[0074] In some embodiments according to any of the bifunctional protein constructs described above, i) the one or more units of the second binding moiety each independently comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2; and ii) the one or more units of the first binding moiety each independently comprises an antibody moiety specifically binding to a muscle-specific molecule, and wherein the antibody moiety is independently selected from the group consisting of an scFv, a Fab, and an sdAb. In some embodiments, i) the two units of the second binding moiety are the same; and/or ii) the two or more units of the first binding moiety are the same. In some embodiments, i) the two units of the second binding moiety are different; and/or ii) at least one of the two or more units of the first binding moiety is different from the other(s). In some embodiments, the Fc domain comprises knob-into-hole mutations and/or charged-pair mutations. In some embodiments, (i) the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 348, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 255; (ii) the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 255, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 348; (iii) the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 256, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 257; (iv) the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 257, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 256; (v) the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 258, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 259; or (vi) the first subunit of the Fc domain comprises the amino acid

sequence of SEQ ID NO: 259, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 258.

[0075] In another aspect, provided herein is one or more isolated nucleic acids encoding any of the bifunctional protein construct described above.

[0076] In another aspect, provided herein is one or more vectors comprising one or more isolated nucleic acids described above. In some embodiments, the one or more vectors is a viral vector. In some embodiments, the viral vector is an adeno-associated virus (AAV) vector or a lentiviral vector.

[0077] In another aspect, provided herein is a host cell expressing any of the bifunctional protein constructs described above, the one or more isolated nucleic acids described above, or the one or more vectors described above. In some embodiments, the host cell is a Chinese hamster ovary (CHO) cell or an HEK293 cell.

[0078] Also provided are pharmaceutical compositions comprising: i) any of the bifunctional protein constructs described above, the one or more isolated nucleic acids described above, or the one or more vectors described above; and ii) a pharmaceutically acceptable excipient.

[0079] In another aspect, provided herein is a method of producing a bifunctional protein construct, comprising: i) culturing a host cell comprising the one or more isolated nucleic acids described above or the one or more vectors described above, or the host cell described above, under a condition suitable for the expression of the bifunctional protein construct; and ii) recovering the expressed bifunctional protein construct from the cultured host cell. In some embodiments, the method further comprises introducing the one or more isolated nucleic acids or the one or more vectors into the host cell.

[0080] In another aspect, provided herein is a method of treating a muscle-related disease in an individual, comprising administering to the individual an effective amount of any of the bifunctional protein constructs described above or the pharmaceutical composition described above. In some embodiments, the muscle-related disease is selected from the group consisting of Pompe disease, centronuclear myopathy, fibrodysplasia ossificans progressive (FOP), Friedreich's ataxia (FRDA), familial hypertrophic cardiomyopathy, Laing distal myopathy, myofibrillar myopathy, and muscular dystrophy. In some embodiments, the muscle disease is muscular dystrophy. In some embodiments, the muscular dystrophy comprises one or more of: Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), limb-girdle muscular dystrophy (LGMD), congenital muscular dystrophy (CMD), facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy (DM),

oculopharyngeal muscular dystrophy (OPMD), distal muscular dystrophy (DD), congenital myopathy, Charcot-Marie-Tooth (CMT) disorder, and Emery-Dreifuss muscular dystrophy (EDMD). In some embodiments, the bifunctional protein construct or the pharmaceutical composition is administered intravenously, subcutaneously, or intramuscularly. In some embodiments, the individual is a human.

[0081] In another aspect, the present inventions provides an antibody construct comprising an antibody moiety specifically recognizing matriglycan on α -DG (anti-matriglycan antibody moiety), wherein the anti-matriglycan antibody moiety comprises: (i) an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 74, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 76, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 77, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 78, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 79; (ii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (iii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (iv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; (v) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98; (vi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (vii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (viii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; (ix) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98; (x) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-

CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (xi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (xii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; (xiii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98; (xiv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95; (xv) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96; (xvi) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97; or (xvii) an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98.

[0082] In some embodiments according to any of the antibody constructs described above, the anti-matriglycan antibody moiety comprises a VH comprising the amino acid sequence of any one of SEQ ID NOs: 89-93, and a VL comprising the amino acid sequence of any one of SEQ ID NOs: 94-98. In some embodiments, the anti-matriglycan antibody moiety comprises: (i) a VH comprising the amino acid sequence of SEQ ID NO: 89, and a VL comprising the amino acid sequence of SEQ ID NO: 94; (ii) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (iii) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (iv) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (v) a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (vi) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (vii) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (viii) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (ix) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (x) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 94; (xi) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (xii) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (xiii) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (xiv) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (xv) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 94; (xvi) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (xvii) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (xviii) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (xix) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 98.

NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (ix) a VH comprising the amino acid sequence of SEQ ID NO: 91, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (x) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (xi) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (xii) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 97; (xiii) a VH comprising the amino acid sequence of SEQ ID NO: 92, and a VL comprising the amino acid sequence of SEQ ID NO: 98; (xiv) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 95; (xv) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 96; (xvi) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 97; or (xvii) a VH comprising the amino acid sequence of SEQ ID NO: 93, and a VL comprising the amino acid sequence of SEQ ID NO: 98.

[0083] In some embodiments according to any of the antibody constructs described above, the anti-matriglycan antibody moiety is selected from the group consisting of a full-length antibody, a Fab, a Fab', a F(ab')₂, and an scFv. In some embodiments, the anti-matriglycan antibody moiety is an anti-matriglycan scFv. In some embodiments, the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 99.

[0084] In some embodiments according to any of the antibody constructs described above, the anti-matriglycan antibody moiety is an anti-matriglycan Fab. In some embodiments, the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 100, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 101.

[0085] In some embodiments according to any of the antibody constructs described above, the anti-matriglycan antibody moiety is an anti-matriglycan Fab. In some embodiments, the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 100, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 101.

[0086] In some embodiments according to any of the antibody constructs described above, the anti-matriglycan antibody moiety is an anti-matriglycan full-length antibody. In some embodiments, the anti-matriglycan full-length antibody comprises an Fc domain derived from human IgG1, human IgG2, or human IgG4. In some embodiments, the Fc

domain is derived from human IgG1 comprising the amino acid sequence of SEQ ID NO: 187. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A mutation (EU numbering). In some embodiments, each subunit of the Fc domain comprises an H435A mutation (EU numbering). In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277.

[0087] In some embodiments according to any of the antibody constructs described above, the antibody construct further comprises a second binding moiety specifically binding to a second target molecule. In some embodiments, the second binding moiety specifically binds to a Notch receptor and activates the Notch receptor. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2.

[0088] In another aspect, the present invention provides an engineered DLL4 extracellular domain (ECD), wherein the engineered DLL4 ECD comprises a mutation selected from the group consisting of T52N and T135N, and wherein the amino acid position is in reference to a reference DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the engineered DLL4 ECD further comprises a mutation at one or more amino acid positions selected from the group consisting of G2, E14, R66, P80, F81, H168, Q220, N231, and N260. In some embodiments, the further mutation is selected from the group consisting of G2S, E14H, R66S, R66T, P80L, F81L, H168Y, Q220H, N231D, and N260D. In some embodiments, the engineered DLL4 ECD comprises a mutation selected from the group consisting of: (i) T52N and T135N; (ii) T52N, R66S, and T135N; (iii) E14H, T52N, R66T, P80L, T135N, and N231D; (iv) T52N, R66T, P80L, T135N, Q220H, and N260D; (v) G2S, T52N, F81L, T135N, and H168Y; (vi) G2S, T52N, F81L, R66S, T135N, and H168Y; (vii) G2S, E14H, T52N, F81L, R66T, P80L, T135N, H168Y, and N231D; and (viii) G2S, T52N, R66T, P80L, F81L, T135N, H168Y, Q220H, and N260D. In some embodiments, the engineered DLL4 ECD comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NOs: 261-264.

[0089] In another aspect according to any of the engineered DLL4 ECD described above, the present invention provides a protein construct comprising the engineered DLL4 ECD. In

some embodiments, the protein construct further comprises a binding moiety that specifically binds to a muscle-specific molecule.

[0090] It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0091] FIGs. 1A-1M depict different configurations of bifunctional proteins comprising an anti-muscle target protein and a Notch ligand or agonist. FIG. 1A depicts a monovalent Notch ligand with an anti-muscle protein antibody (Ab) in “Knob-into-Hole” format. FIGs. 1B and 1C depict additional formats and configurations of bifunctional proteins, of which R1, R2, R3, and R4 can be an anti-muscle target protein or a Notch ligand/agonist. FIG. 1D depicts a bivalent fusion protein with Notch ligands fused to the N-terminus of the Fc and an anti-muscle protein antibody Fab fused to the C-terminus of the Fc. FIG. 1E depicts a bivalent fusion protein with Notch ligands fused to the N-terminus of the Fc and an anti-muscle protein antibody scFv fused to the C-terminus of the Fc. FIG. 1F depicts a bivalent fusion protein with Notch ligands fused to the N-terminus of the Fc and an anti-muscle target protein antibody single chain Ab (VHH or nanobody) fused to the C-terminus of the Fc. FIG. 1G depicts a bivalent fusion protein with Notch ligands fused to the C-terminus of the Fc and an anti-muscle protein antibody Fab fused to the N-terminus of the Fc. FIG. 1H depicts a bivalent fusion protein with Notch ligands fused to the C-terminus of the Fc and an anti-muscle protein scFv fused to the N-terminus of the Fc. FIG. 1I depicts a bivalent fusion protein with Notch ligands fused to the C-terminus of Fc and an anti-muscle protein VHH/nanobody fused to the N-terminus of Fc. FIG. 1J depicts a bivalent fusion protein with Notch ligands fused to the C-terminus of the antibody light chains. FIG. 1K depicts a bivalent fusion protein with Notch ligands fused to the N-terminus of the antibody light chains. FIG. 1L depicts a bivalent fusion protein with Notch ligands fused to the N-terminus of the antibody heavy chains. FIG. 1M depicts a tetravalent fusion protein with Notch ligands fused to the N-terminus of the antibody light and heavy chains.

[0092] FIGs. 2A-2J depict different configurations of bifunctional proteins comprising a non-antibody moiety (e.g., an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan) and a Notch ligand or agonist. FIG. 2A depicts a monovalent protein with a Notch ligand fused to the N-terminus of a laminin G-like domain (LG domain) monomer, or alternatively, a scFv, sdAb, or Fab to a muscle specific protein.

FIG. 2B depicts a monovalent protein with a Notch ligand fused to the N-terminus of an LG domain dimer, or alternatively, a scFv, sdAb, or Fab specifically recognizing a muscle specific protein. FIG. 2C depicts a monovalent protein with a Notch ligand fused to the N-terminus of an LG domain trimer or multimers in tandem, or alternatively, a scFv, sdAb, or Fab to a muscle specific protein. FIG. 2D depicts a monovalent protein from N'-to C' terminus: a Notch ligand – an albumin, anti-albumin scFv or sdAb, or a monomeric human Fc – an LG domain monomer. FIG. 2E depicts a monovalent protein from N'-to C' terminus: a Notch ligand – an albumin, anti-albumin scFv or sdAb, or a monomeric human Fc – an LG domain dimer. FIG. 2F depicts a monovalent protein from N'-to C' terminus: a Notch ligand – an albumin, anti-albumin scFv or sdAb, or a monomeric human Fc – an LG domain trimer or multimers in tandem. FIGs. 2G and 2H depict bivalent fusion proteins with Notch ligands fused to the N-terminus of the Fc and LG domain fused to the C-terminus of Fc as monomer, dimer, or multimers in tandem, respectively. FIGs. 2I and 2J depict bivalent fusion proteins with Notch ligands fused to the C-terminus of the Fc and LG domain fused to the N-terminus of Fc as monomer, dimer, or multimers in tandem, respectively.

[0093] FIG. 3A depicts an SDS-PAGE of the reduced and non-reduced DLL4v-Fc-LG4-5 construct. FIG. 3B depicts a size exclusion chromatography (SEC) profile for protein standards (upper profile) and the DLL4v-Fc-LG4-5 construct (lower profile).

[0094] FIG. 4A depicts an SDS-PAGE of the reduced and non-reduced DLL4wt-Fc-LG4-5 construct. FIG. 4B depicts a size exclusion chromatography (SEC) profile for protein standards (upper profile) and the DLL4wt-Fc-LG4-5 construct (lower profile).

[0095] FIG. 5A depicts an SDS-PAGE of the reduced and non-reduced DLL4v-Fc-LAMA2scFv construct. FIG. 5B depicts a size exclusion chromatography (SEC) profile for protein standards (upper profile) and the DLL4v-Fc-LAMA2scFv construct (lower profile).

[0096] FIG. 6 depicts binding of bifunctional proteins DLL4v-Fc-LG4-5, DLL4wt-Fc-LG4-5, and DLL4v-Fc-LAMA2scFv to Notch-1 using a sandwich ELISA. The DLL4v-Fc-LG4-5 and DLL4v-Fc-LAMA2scFv constructs have higher affinity (or avidity) to Notch 1, compared to the DLL4wt-Fc-LG4-5 construct.

[0097] FIG. 7A depicts a kinetic analysis of the DLL4v-Fc-LG4-5 construct binding to different concentrations of purified matriglycan using Biacore system. The y-axis represents the absolute response (RU), and the x-axis represents the time in seconds. The arrows indicate the injection points of purified matriglycan. FIG. 7B depicts Western blot results of a laminin-overlay assay that shows DLL4v-Fc-LG4-5 binds to matriglycan.

[0098] FIG. 8 depicts a kinetic analysis of the DLL4v-Fc-LAMA2scFv construct binding to different concentrations of recombinant human LG4-5 using Biacore system, confirming that LAMA2scFv binds to LG4-5. The arrows indicate the injection points of recombinant human LG4-5.

[0099] FIG. 9A depicts a study schema. Male D2.mdx mice at approximately 7-9 weeks of age were assessed for muscle function by forelimb grip strength. The mice were randomized into two groups (n=10/group). The control group was treated triweekly with 20 mg/kg of an isotype control antibody against an irrelevant antigen trinitrophenol (TNP). The experimental group was treated triweekly with 5 mg/kg of DLL4v-Fc-LAMA2scFv. The wildtype (WT) group received no treatment. Forelimb grip strength was assessed monthly over 7 months. FIG. 9B depicts the forelimb grip strength of WT, DLL4v-Fc-LAMA2scFv-treated, and isotype control-treated D2.mdx mice over 7 months. FIG. 9C depicts the bodyweight of WT, DLL4v-Fc-LAMA2scFv-treated, and isotype control-treated D2.mdx mice over 7 months.

[0100] FIG. 10A depicts a size exclusion chromatography (SEC) profile for protein standards (upper profile), huD4v11_2N-FcAAG-LG21DS, huD4v12_2N_A2-FcAAG-LG21DS, huD4v13_2N_-FcAAG-LG21DS, and huD4v14_2N_H2-FcAAG-LG21DS. FIG. 10B depicts a table outlining the yield and percentage of main peak as determined by analytical size exclusion chromatography (aSEC).

[0101] FIG. 11A depicts binding affinity of huD4v11_2N-FcAAG-LG21DS, huD4v12_2N_A2-FcAAG-LG21DS, huD4v13_2N_-FcAAG-LG21DS, and huD4v14_2N_H2-FcAAG-LG21DS to a murine Notch1 receptor, compared to that of the huD4v_G2S_F81L_H168Y-Fc(AAG)-LG21scFvDS (parental) and mud4v constructs as determined by an ELISA assay. FIG. 11B depicts a table outlining the binding affinity (K_D) of each construct measured in nM.

DETAILED DESCRIPTION

[0102] The present application provides bifunctional protein constructs that specifically target and delivered to muscle tissues with Notch activation in a spatiotemporally controlled manner. Binding of the bifunctional protein construct to muscle tissue, either via a protein on the muscle (cell) sarcolemma or a protein in the extracellular matrix (basal lamina), anchors the bifunctional protein construct and Notch activating moiety comprised therein (e.g., a Notch ligand or agonistic antibody specifically recognizing Notch 1-4), which is a

requirement for Notch signaling. Therefore, the bifunctional protein constructs disclosed in this disclosure fulfill the three requirements for specific Notch signaling in muscles: 1) muscle targeting to ensure tissue specificity; 2) Notch ligand anchoring required for trans-activation; and 3) timely control of Notch activation for satellite cells renewal while permitting myoblast differentiation during muscle repair.

[0103] The present application thus in one aspect provides a bifunctional protein construct comprising a first binding moiety and a second binding moiety, wherein the first binding moiety specifically binds to a muscle-specific molecule, and wherein the second binding moiety specifically binds to a Notch receptor and activates the Notch receptor.

[0104] In another aspect, there is provided a method of making the bifunctional protein constructs described herein. Isolated nucleic acids, vectors, and host cells encoding any of the bifunctional protein constructs are also provided. Also provided are methods of treating a muscle-related disease in an individual (e.g., human), by administering to the individual an effective amount of the bifunctional protein construct described herein or pharmaceutical composition thereof.

[0105] In another aspect, there is provided an engineered DLL4 extracellular domain (ECD) comprising a mutation selected from the group consisting of T52N and T135N, and wherein the amino acid position is in reference to a reference DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. Also provided are protein constructs comprising the DLL4 ECD described herein.

I. Definitions

[0106] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, exemplary methods and materials are described.

[0107] The term “antibody” herein is used in its broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), full-length antibodies and antigen-binding fragments thereof, so long as they exhibit the desired antigen-binding activity. The term “antibody moiety” refers to a full-length antibody or an antigen-binding fragment thereof.

[0108] An “antibody” may refer to an immunoglobulin molecule or a fragment thereof which is able to specifically bind to a specific epitope of an antigen (including the basic 4-chain antibody unit). Antibodies can be intact immunoglobulins derived from natural sources, or from recombinant sources and can be immunoreactive portions of intact immunoglobulins. The antibodies in the present invention may exist in a variety of forms including, for example, polyclonal antibodies, monoclonal antibodies, intracellular antibodies (“intrabodies”), antigen-binding fragments (such as Fv, Fab, Fab’, F(ab)₂ and F(ab’)₂), as well as single chain antibodies (scFv), heavy chain antibodies, such as camelid antibodies, and humanized antibodies (Harlow et al., 1999, *Using Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, NY; Harlow et al., 1989, *Antibodies: A Laboratory Manual*, Cold Spring Harbor, New York; Houston et al., 1988, *Proc. Natl. Acad. Sci. USA* 85:5879-5883; Bird et al., 1988, *Science* 242:423-426).

[0109] A full-length antibody comprises two heavy chains and two light chains. The variable regions of the light and heavy chains are responsible for antigen binding. The variable domains of the heavy chain and light chain may be referred to as “VH” and “VL”, respectively. The variable regions in both chains generally contain three highly variable loops called the complementarity determining regions (CDRs) (light chain (LC) CDRs including LC-CDR1, LC-CDR2, and LC-CDR3, heavy chain (HC) CDRs including HC-CDR1, HC-CDR2, and HC-CDR3). CDR boundaries for the antibodies and antigen-binding fragments disclosed herein may be defined or identified by the conventions of Kabat, Chothia, or Al-Lazikani (Al-Lazikani 1997; Chothia 1985; Chothia 1987; Chothia 1989; Kabat 1987; Kabat 1991). The three CDRs of the heavy or light chains are interposed between flanking stretches known as framework regions (FRs), which are more highly conserved than the CDRs and form a scaffold to support the hypervariable loops. The constant regions of the heavy and light chains are not involved in antigen binding, but exhibit various effector functions. Antibodies are assigned to classes based on the amino acid sequence of the constant region of their heavy chain. The five major classes or isotypes of antibodies are IgA, IgD, IgE, IgG, and IgM, which are characterized by the presence of α , δ , ϵ , γ , and μ heavy chains, respectively. Several of the major antibody classes are divided into subclasses such as IgG1 (γ 1 heavy chain), IgG2 (γ 2 heavy chain), IgG3 (γ 3 heavy chain), IgG4 (γ 4 heavy chain), IgA1 (α 1 heavy chain), or IgA2 (α 2 heavy chain).

[0110] The term “antigen-binding fragment” as used herein refers to an antibody fragment including, for example, a diabody, a Fab, a Fab’, a F(ab’)₂, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a bispecific dsFv (dsFv-dsFv’), a disulfide

stabilized diabody (ds diabody), a single-chain Fv (scFv), an scFv dimer (bivalent diabody), a multispecific antibody formed from a portion of an antibody comprising one or more CDRs, a single domain antibody (sdAb) (*e.g.*, a camelized single domain antibody), a nanobody, a domain antibody, a bivalent domain antibody, or any other antibody fragment that binds to an antigen but does not comprise a complete antibody structure. An antigen-binding fragment is capable of binding to the same antigen to which the parent antibody or a parent antibody fragment (*e.g.*, a parent scFv) binds. In some embodiments, an antigen-binding fragment may comprise one or more CDRs from a particular human antibody grafted to a framework region from one or more different human antibodies.

[0111] “Fv” is the minimum antibody fragment, which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the heavy and light chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0112] “Single-chain Fv,” also abbreviated as “sFv” or “scFv,” are antibody fragments that comprise the VH and VL antibody domains connected into a single polypeptide chain. In some embodiments, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding. For a review of scFv, *see* Plückthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994).

[0113] The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. An IgM antibody consists of 5 of the basic heterotetramer units along with an additional polypeptide called a J chain, and contains 10 antigen binding sites, while IgA antibodies comprise from 2-5 of the basic 4-chain units which can polymerize to form polyvalent assemblages in combination with the J chain. In the case of IgGs, the 4-chain unit is generally about 150,000 Daltons. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (VH) followed by three constant domains (CH) for each of the α

and γ chains and four CH domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (VL) followed by a constant domain at its other end. The VL is aligned with the VH and the CL is aligned with the first constant domain of the heavy chain (CH1).

Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a VH and VL together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see e.g., Basic and Clinical Immunology, 8th Edition, Daniel P. Sties, Abba I. Terr and Tristram G. Parslow (eds), Appleton & Lange, Norwalk, Conn., 1994, page 71 and Chapter 6. The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (CH), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, having heavy chains designated α , δ , ϵ , γ and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in the CH sequence and function, e.g., humans express the following subclasses: IgG1, IgG2A, IgG2B, IgG3, IgG4, IgA1 and IgA2.

[0114] The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, the region which is also recognized by Fc receptors (FcR) found on certain types of cells.

[0115] The “variable region” or “variable domain” of an antibody refers to the amino-terminal domains of the heavy or light chain of the antibody. The variable domains of the heavy chain and light chain may be referred to as “VH” and “VL”, respectively. These domains are generally the most variable parts of the antibody (relative to other antibodies of the same class) and contain the antigen binding sites. Heavy-chain only antibodies from the *Camelidae* species have a single heavy chain variable region, which is referred to as “VHH”. VHH is thus a special type of VH.

[0116] The term “variable” refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines the specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the entire span of the variable domains. Instead, it is concentrated in three segments called hypervariable regions (HVRs) both in the light-chain and the heavy chain variable domains. The more highly conserved portions of variable domains are called the framework regions (FR). The variable domains of

native heavy and light chains each comprise four FR regions, largely adopting a beta-sheet configuration, connected by three HVRs, which form loops connecting, and in some cases forming part of, the beta-sheet structure. The HVRs in each chain are held together in close proximity by the FR regions and, with the HVRs from the other chain, contribute to the formation of the antigen binding site of antibodies (see Kabat et al., Sequences of Immunological Interest, Fifth Edition, National Institute of Health, Bethesda, Md. (1991)). The constant domains are not involved directly in the binding of antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

[0117] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations and/or post-translation modifications (*e.g.*, isomerizations, amidations) that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. In contrast to polyclonal antibody preparations which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier “monoclonal” indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present application may be made by a variety of techniques, including, for example, the hybridoma method (*e.g.*, Kohler and Milstein., *Nature*, 256:495-97 (1975); Hongo *et al.*, *Hybridoma*, 14 (3): 253-260 (1995), Harlow *et al.*, *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling *et al.*, in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981)), recombinant DNA methods (see, *e.g.*, U.S. Pat. No. 4,816,567), phage-display technologies (see, *e.g.*, Clackson *et al.*, *Nature*, 352: 624-628 (1991); Marks *et al.*, *J. Mol. Biol.* 222: 581-597 (1992); Sidhu *et al.*, *J. Mol. Biol.* 338(2): 299-310 (2004); Lee *et al.*, *J. Mol. Biol.* 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee *et al.*, *J. Immunol. Methods* 284(1-2): 119-132 (2004), and technologies for producing human or human-like antibodies in animals that have parts or all of the human immunoglobulin loci or genes encoding human immunoglobulin sequences (see, *e.g.*, WO 1998/24893; WO 1996/34096;

WO 1996/33735; WO 1991/10741; Jakobovits *et al.*, *Proc. Natl. Acad. Sci. USA* 90: 2551 (1993); Jakobovits *et al.*, *Nature* 362: 255-258 (1993); Bruggemann *et al.*, *Year in Immunol.* 7:33 (1993); U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016; Marks *et al.*, *Bio/Technology* 10: 779-783 (1992); Lonberg *et al.*, *Nature* 368: 856-859 (1994); Morrison, *Nature* 368: 812-813 (1994); Fishwild *et al.*, *Nature Biotechnol.* 14: 845-851 (1996); Neuberger, *Nature Biotechnol.* 14: 826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13: 65-93 (1995).

[0118] The terms “full-length antibody,” “intact antibody” or “whole antibody” are used interchangeably to refer to an antibody in its substantially intact form, as opposed to an antibody fragment. Specifically full-length 4-chain antibodies include those with heavy and light chains including an Fc region. The constant domains may be native sequence constant domains (*e.g.*, human native sequence constant domains) or amino acid sequence variants thereof. In some cases, the intact antibody may have one or more effector functions.

[0119] The term “diabodies” refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10) residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, thereby resulting in a bivalent fragment, *i.e.*, a fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two “crossover” sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described in greater detail in, for example, EP 404,097; WO 93/11161; Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993).

[0120] The monoclonal antibodies herein specifically include “chimeric” antibodies (immunoglobulins) in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is(are) identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Pat. No. 4,816,567; Morrison *et al.*, *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include PRIMATTZFACTOR D® antibodies wherein the antigen-binding region of the antibody is derived from an antibody produced by, *e.g.*, immunizing macaque monkeys with an antigen of interest. As used herein, “humanized antibody” is used as a subset of “chimeric antibodies.”

[0121] As used herein, the term “CDR” or “complementarity determining region” is intended to mean the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. These particular regions have been described by Kabat *et al.*, J. Biol. Chem. 252:6609-6616 (1977); Kabat *et al.*, U.S. Dept. of Health and Human Services, “Sequences of proteins of immunological interest” (1991); Chothia *et al.*, J. Mol. Biol. 196:901-917 (1987); Al-Lazikani B. *et al.*, J. Mol. Biol., 273: 927-948 (1997); MacCallum *et al.*, J. Mol. Biol. 262:732-745 (1996); Abhinandan and Martin, *Mol. Immunol.*, 45: 3832-3839 (2008); Lefranc M.P. *et al.*, *Dev. Comp. Immunol.*, 27: 55-77 (2003); and Honegger and Plückthun, *J. Mol. Biol.*, 309:657-670 (2001), where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or grafted antibodies or variants thereof is intended to be within the scope of the term as defined and used herein. The amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth below in Table 1 as a comparison. CDR prediction algorithms and interfaces are known in the art, including, for example, Abhinandan and Martin, *Mol. Immunol.*, 45: 3832-3839 (2008); Ehrenmann F. *et al.*, *Nucleic Acids Res.*, 38: D301-D307 (2010); and Adolf-Bryfogle J. *et al.*, *Nucleic Acids Res.*, 43: D432-D438 (2015). The contents of the references cited in this paragraph are incorporated herein by reference in their entireties for use in the present application and for possible inclusion in one or more claims herein.

Table 1: CDR Definitions

	Kabat¹	Chothia²	MacCallum³	IMGT⁴	Aho⁵
VH CDR1	31-35	26-32	30-35	27-38	25-40
VH CDR2	50-65	53-55	47-58	56-65	58-77
VH CDR3	95-102	96-101	93-101	105-117	109-137
VL CDR1	24-34	26-32	30-36	27-38	25-40
VL CDR2	50-56	50-52	46-55	56-65	58-77
VL CDR3	89-97	91-96	89-96	105-117	109-137

¹Residue numbering follows the nomenclature of Kabat *et al.*, *supra*

²Residue numbering follows the nomenclature of Chothia *et al.*, *supra*

³Residue numbering follows the nomenclature of MacCallum *et al.*, *supra*

⁴Residue numbering follows the nomenclature of Lefranc *et al.*, *supra*

⁵Residue numbering follows the nomenclature of Honegger and Plückthun, *supra*

[0122] The expression “variable-domain residue-numbering as in Kabat” or “amino-acid-position numbering as in Kabat,” and variations thereof, refers to the numbering system used

for heavy-chain variable domains or light-chain variable domains of the compilation of antibodies in Kabat *et al.*, supra. Using this numbering system, the actual linear amino acid sequence may contain fewer or additional amino acids corresponding to a shortening of, or insertion into, a FR or hypervariable region (HVR) of the variable domain. For example, a heavy-chain variable domain may include a single amino acid insert (residue 52a according to Kabat) after residue 52 of H2 and inserted residues (*e.g.* residues 82a, 82b, and 82c, *etc.* according to Kabat) after heavy-chain FR residue 82. The Kabat numbering of residues may be determined for a given antibody by alignment at regions of homology of the sequence of the antibody with a “standard” Kabat numbered sequence.

[0123] Unless indicated otherwise herein, the numbering of the residues in an immunoglobulin heavy chain is that of the EU index as in Kabat *et al.*, supra with minor modification. The “EU index as in Kabat” refers to the residue numbering of the human IgG1 EU antibody.

[0124] “Framework” or “FR” residues are those variable-domain residues other than the CDR residues as herein defined.

[0125] As used herein, an “immunoassay” refers to any binding assay that uses an antibody capable of binding specifically to a target molecule to detect and quantify the target molecule.

[0126] “Humanized” forms of non-human (*e.g.*, rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region (HVR) of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies can comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the 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 and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. A suitable human acceptor antibody may be one selected from a

conventional database, e.g., the KABAT database, Los Alamos database, the AbM, and Swiss Protein database, by homology to the nucleotide and amino acid sequences of the donor antibody. A human antibody characterized by a homology to the framework regions of the donor antibody (on an amino acid basis) may be suitable to provide a heavy chain constant region and/or a heavy chain variable framework region for insertion of the donor CDRs. A suitable acceptor antibody capable of donating light chain constant or variable framework regions may be selected in a similar manner. It should be noted that the acceptor antibody heavy and light chains are not required to originate from the same acceptor antibody. The prior art describes several ways of producing such humanized antibodies (see, for example, EP-A-0239400 and EP-A-054951). 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); Hurler and Gross, *Curr. Op. Biotech.* 5:428-433 (1994); and U.S. Pat. Nos. 6,982,321 and 7,087,409.

[0127] A “human antibody” is an antibody that possesses an amino-acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies as disclosed herein. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues. Human antibodies can be produced using various techniques known in the art, including phage-display libraries. Hoogenboom and Winter, *J. Mol. Biol.*, 227:381 (1991); Marks *et al.*, *J. Mol. Biol.*, 222:581 (1991). Also available for the preparation of human monoclonal antibodies are methods described in Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, p. 77 (1985); Boerner *et al.*, *J. Immunol.*, 147(1):86-95 (1991). See also van Dijk and van de Winkel, *Curr. Opin. Pharmacol.*, 5: 368-74 (2001). Human antibodies can be prepared by administering the antigen to a transgenic animal that has been modified to produce such antibodies in response to antigenic challenge, but whose endogenous loci have been disabled, e.g., immunized xenomice (see, e.g., U.S. Pat. Nos. 6,075,181 and 6,150,584 regarding XENOMOUSE™ technology). See also, for example, Li *et al.*, *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006) regarding human antibodies generated *via* a human B-cell hybridoma technology.

[0128] The term “donor antibody” refers to an antibody (monoclonal, and/or recombinant) which contributes the amino acid sequences of its variable regions, CDRs, or other functional fragments or analogs thereof to a first immunoglobulin partner, so as to

provide the altered immunoglobulin coding region and resulting expressed altered antibody with the antigenic specificity and neutralizing activity characteristic of the donor antibody.

[0129] The term “acceptor antibody” refers to an antibody (monoclonal and/or recombinant) heterologous to the donor antibody, which contributes all (or any portion, but in some embodiments all) of the amino acid sequences encoding its heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions to the first immunoglobulin partner. In certain embodiments a human antibody is the acceptor antibody.

[0130] The term “attach,” “attached,” “fuse,” or “fused” as used herein, refers to connecting or uniting by a bond, link, force or tie in order to keep two or more components together, which encompasses either direct or indirect attachment such that, for example, where a first polypeptide is directly bound to a second polypeptide or material, and, for example, where one or more intermediate compounds (e.g., amino acids, peptides, polypeptides, etc.) are disposed between the first polypeptide and the second polypeptide or material.

[0131] “Percent (%) amino acid sequence identity” or “homology” with respect to the polypeptide and antibody sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the polypeptide being compared, after aligning the sequences 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, Megalign (DNASTAR), or MUSCLE 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. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program MUSCLE (Edgar, R.C., *Nucleic Acids Research* 32(5):1792-1797, 2004; Edgar, R.C., *BMC Bioinformatics* 5(1):113, 2004).

[0132] “Homologous” refers to the sequence similarity or sequence identity between two polypeptides or between two nucleic acid molecules. When a position in both of the two compared sequences is occupied by the same base or amino acid monomer subunit, e.g., if a position in each of two DNA molecules is occupied by adenine, then the molecules are homologous at that position. The percent of homology between two sequences is a function of the number of matching or homologous positions shared by the two sequences divided by the number of positions compared times 100. For example, if 6 of 10 of the positions in two

sequences are matched or homologous then the two sequences are 60% homologous. By way of example, the DNA sequences ATTGCC and TATGGC share 50% homology. Generally, a comparison is made when two sequences are aligned to give maximum homology.

[0133] The term “constant domain” refers to the portion of an immunoglobulin molecule having a more conserved amino acid sequence relative to the other portion of the immunoglobulin, the variable domain, which contains the antigen-binding site. The constant domain contains the C_H1, C_H2 and C_H3 domains (collectively, C_H) of the heavy chain and the C_HL (or C_L) domain of the light chain.

[0134] The “light chains” of antibodies (immunoglobulins) from any mammalian species can be assigned to one of two clearly distinct types, called kappa (“κ”) and lambda (“λ”), based on the amino acid sequences of their constant domains.

[0135] The “CH1 domain” (also referred to as “C1” or “H1” domain) usually extends from about amino acid 118 to about amino acid 215 (EU numbering system).

[0136] “Hinge region” is generally defined as a region in IgG corresponding to Glu216 to Pro230 of human IgG1 (Burton, *Molec. Immunol.* 22:161-206 (1985)). Hinge regions of other IgG isotypes may be aligned with the IgG1 sequence by placing the first and last cysteine residues forming inter-heavy chain S-S bonds in the same positions.

[0137] The “CH2 domain” of a human IgG Fc domain (also referred to as “C2” domain) usually extends from about amino acid 231 to about amino acid 340. The CH2 domain is unique in that it is not closely paired with another domain. Rather, two N-linked branched carbohydrate chains are interposed between the two CH2 domains of an intact native IgG molecule. It has been speculated that the carbohydrate may provide a substitute for the domain-domain pairing and help stabilize the CH2 domain. Burton, *Molec Immunol.* 22:161-206 (1985).

[0138] The “CH3 domain” (also referred to as “C3” domain) comprises the stretch of residues C-terminal to a CH2 domain in an Fc domain (*i.e.* from about amino acid residue 341 to the C-terminal end of an antibody sequence, typically at amino acid residue 446 or 447 of an IgG).

[0139] The term “Fc domain” or “fragment crystallizable region” herein is used to define a C-terminal region of an immunoglobulin heavy chain, including native-sequence Fc domains and variant Fc domains. Although the boundaries of the Fc domain of an immunoglobulin heavy chain might vary, the human IgG heavy-chain Fc domain is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU

numbering system) of the Fc domain may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue. Suitable native-sequence Fc domains for use in the antibodies described herein include human IgG1, IgG2 (IgG2A, IgG2B), IgG3 and IgG4.

[0140] “Fc receptor” or “FcR” describes a receptor that binds the Fc domain of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors, FcγRII receptors include FcγRIIA (an “activating receptor”) and FcγRIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor FcγRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (See M. Daëron, *Annu. Rev. Immunol.* 15:203-234 (1997). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol.* 9: 457-92 (1991); Capel *et al.*, *Immunomethods* 4: 25-34 (1994); and de Haas *et al.*, *J. Lab. Clin. Med.* 126: 330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein.

[0141] The term “epitope” as used herein refers to the specific group of atoms or amino acids on an antigen to which an antibody or antibody moiety binds. Two antibodies or antibody moieties may bind the same epitope within an antigen if they exhibit competitive binding for the antigen.

[0142] As use herein, the terms “specifically binds,” “specifically recognizing,” and “is specific for” refer to measurable and reproducible interactions, such as binding between a target and an antibody or antibody moiety, which is determinative of the presence of the target in the presence of a heterogeneous population of molecules, including biological molecules. For example, an antibody or antibody moiety that specifically recognizes a target (which can be an epitope) is an antibody or antibody moiety that binds this target with greater affinity, avidity, more readily, and/or with greater duration than its bindings to other targets. In some embodiments, the extent of binding of an antibody to an unrelated target is less than about 10% of the binding of the antibody to the target as measured, *e.g.*, by a

radioimmunoassay (RIA). In some embodiments, an antibody that specifically binds a target has a dissociation constant (K_D) of $\leq 10^{-5}$ M, $\leq 10^{-6}$ M, $\leq 10^{-7}$ M, $\leq 10^{-8}$ M, $\leq 10^{-9}$ M, $\leq 10^{-10}$ M, $\leq 10^{-11}$ M, $\leq 10^{-12}$, $\leq 10^{-13}$, or $\leq 10^{-14}$ M. In some embodiments, an antibody specifically binds an epitope on a protein that is conserved among the protein from different species. In some embodiments, specific binding can include, but does not require exclusive binding. Binding specificity of the antibody or antigen-binding domain can be determined experimentally by methods known in the art. Such methods comprise, but are not limited to Western blots, ELISA-, RIA-, ECL-, IRMA-, EIA-, BIACORE™ -tests and peptide scans.

[0143] The term “specificity” refers to selective recognition of an antigen binding protein or antibody for a particular epitope of an antigen. Natural antibodies, for example, are monospecific. The term “multispecific” as used herein denotes that an antigen binding protein or an antibody has two or more antigen-binding sites of which at least two bind a different antigen or a different epitope of the same antigen. “Bispecific” as used herein denotes that an antigen binding protein or an antibody has two different antigen-binding specificities. The term “monospecific” antibody as used herein denotes an antibody that has one or more binding sites each of which bind the same epitope of the same antigen.

[0144] “Effector cells” are leukocytes which express one or more FcRs and perform effector functions. In one aspect, the effector cells express at least FcγRIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils. The effector cells may be isolated from a native source, e.g., blood. Effector cells generally are lymphocytes associated with the effector phase, and function to produce cytokines (helper T cells), killing cells in infected with pathogens (cytotoxic T cells) or secreting antibodies (differentiated B cells).

[0145] “Complement dependent cytotoxicity” or “CDC” refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202: 163 (1996), may be performed. Antibody variants with altered Fc region amino acid sequences and increased or decreased C1q binding capability are described in U.S. Pat. No. 6,194,551B1 and WO99/51642. The contents of those patent publications are specifically incorporated herein by reference. See, also, Idusogie *et al.* *J. Immunol.* 164: 4178-4184 (2000).

[0146] “Binding affinity” generally refers to the strength of the sum total of non-covalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen). Unless indicated otherwise, as used herein, “binding affinity” refers to intrinsic binding affinity that reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_d). Affinity can be measured by common methods known in the art, including those described herein. Low-affinity antibodies generally bind antigen slowly and tend to dissociate readily, whereas high-affinity antibodies generally bind antigen faster and tend to remain bound longer. A variety of methods of measuring binding affinity are known in the art, any of which can be used for purposes of the present application. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0147] An “on-rate,” “rate of association,” “association rate,” or “ k_{on} ” as used herein can also be determined as described above using methods such as biolayer interferometry and surface plasmon resonance (SPR).

[0148] An “isolated” polypeptide is one that has been identified, separated and/or recovered from a component of its production environment (e.g., natural or recombinant). Preferably, the isolated polypeptide is free of association with all other components from its production environment. Contaminant components of its production environment, such as that resulting from recombinant transfected cells, are materials that would typically interfere with research, diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified: (1) to greater than 95% by weight of antibody as determined by, for example, the Lowry method, and in some embodiments, to greater than 99% by weight; (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes the polypeptide in situ within recombinant cells since at least one component of the polypeptide’s natural environment will not be present. Ordinarily, however, an isolated polypeptide will be prepared by at least one purification step.

[0149] An “isolated” nucleic acid molecule encoding a construct, antibody, or antigen-binding fragment thereof described herein is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the environment in which it was produced. Preferably, the isolated nucleic acid

is free of association with all components associated with the production environment. The isolated nucleic acid molecules encoding the polypeptides and antibodies described herein is in a form other than in the form or setting in which it is found in nature. Isolated nucleic acid molecules therefore are distinguished from nucleic acid encoding the polypeptides and antibodies described herein existing naturally in cells. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0150] Nucleic acid is “operably linked” when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, “operably linked” means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

[0151] “Isolated” means altered or removed from the natural state. For example, a nucleic acid or a peptide naturally present in its normal context in a living subject is not “isolated,” but the same nucleic acid or peptide partially or completely separated from the coexisting materials of its natural context is “isolated.” An isolated nucleic acid or protein can exist in substantially purified form, or can exist in a non-native environment such as, for example, a host cell.

[0152] The term “hybridoma,” as used herein refers to a cell resulting from the fusion of a B-lymphocyte and a fusion partner such as a myeloma cell. A hybridoma can be cloned and maintained indefinitely in cell culture and is able to produce monoclonal antibodies. A hybridoma can also be considered to be a hybrid cell.

[0153] The terms “nucleic acid molecule”, “nucleic acid” and “polynucleotide” may be used interchangeably, and refer to a polymer of nucleotides. Such polymers of nucleotides may contain natural and/or unnatural nucleotides, and include, but are not limited to, DNA, RNA, and PNA. “Nucleic acid sequence” refers to the linear sequence of nucleotides that comprise the nucleic acid molecule or polynucleotide. An “isolated nucleic acid” refers to a

nucleic acid segment or fragment which has been separated from sequences which flank it in a naturally occurring state, i.e., a DNA fragment which has been removed from the sequences which are normally adjacent to the fragment, i.e., the sequences adjacent to the fragment in a genome in which it naturally occurs. The term also applies to nucleic acids which have been substantially purified from other components which naturally accompany the nucleic acid, i.e., RNA or DNA or proteins, which naturally accompany it in the cell. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote, or which exists as a separate molecule (i.e., as a cDNA or a genomic or cDNA fragment produced by PCR or restriction enzyme digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence.

[0154] “Complementary” as used herein to refer to a nucleic acid, refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds (“base pairing”) with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. In some embodiments, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and or at least about 75%, or at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. In some embodiments, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

[0155] The term “vector,” as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. A vector may be a viral vector, plasmid, bacteriophage, bacterial artificial chromosome or yeast artificial chromosome. A vector may

be an adeno-associated virus (AAV) vector or a lentiviral vector. A vector may be a DNA or RNA vector. A vector may be either a self-replicating extrachromosomal vector or a vector which integrates into a host genome. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as “expression vectors.”

[0156] “Encoding” refers to the inherent property of specific sequences of nucleotides in a polynucleotide, such as a gene, a cDNA, or an mRNA, to serve as templates for synthesis of other polymers and macromolecules in biological processes having either a defined sequence of nucleotides (i.e., rRNA, tRNA and mRNA) or a defined sequence of amino acids and the biological properties resulting there from. Thus, a gene encodes a protein if transcription and translation of mRNA corresponding to that gene produces the protein in a cell or other biological system. Both the coding strand, the nucleotide sequence of which is identical to the mRNA sequence and is usually provided in sequence listings, and the non-coding strand, used as the template for transcription of a gene or cDNA, can be referred to as encoding the protein or other product of that gene or cDNA.

[0157] The terms “polypeptide” and “peptide” are used interchangeably to refer to a polymer of amino acid residues, and are not limited to a minimum length. Such polymers of amino acid residues may contain natural or unnatural amino acid residues. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. Furthermore, a “polypeptide” includes modifications, such as deletions, additions, and substitutions (generally conservative in nature), to the native sequence, as long as the polypeptide maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

[0158] As used herein, “conjugated” refers to covalent attachment of one molecule to a second molecule.

[0159] “Variant” as the term is used herein, is a nucleic acid sequence or a peptide sequence that differs in sequence from a reference nucleic acid sequence or peptide sequence respectively, but retains essential biological properties of the reference molecule. Changes in the sequence of a nucleic acid variant may not alter the amino acid sequence of a peptide encoded by the reference nucleic acid, or may result in amino acid substitutions, additions, deletions, fusions and truncations. Changes in the sequence of peptide variants are typically

limited or conservative, so that the sequences of the reference peptide and the variant are closely similar overall and, in many regions, identical. A variant and reference peptide can differ in amino acid sequence by one or more substitutions, additions, deletions in any combination. A variant of a nucleic acid or peptide can be a naturally occurring such as an allelic variant, or can be a variant that is not known to occur naturally. Non-naturally occurring variants of nucleic acids and peptides may be made by mutagenesis techniques or by direct synthesis. In various embodiments, the variant sequence is at least 99%, at least 98%, at least 97%, at least 96%, at least 95%, at least 94%, at least 93%, at least 92%, at least 91%, at least 90%, at least 89%, at least 88%, at least 87%, at least 86%, at least 85% identical to the reference sequence.

[0160] The term “regulating” as used herein can mean any method of altering the level or activity of a substrate. Non-limiting examples of regulating with regard to a protein include affecting expression (including transcription and/or translation), affecting folding, affecting degradation or protein turnover, and affecting localization of a protein. Non-limiting examples of regulating with regard to an enzyme further include affecting the enzymatic activity. “Regulator” refers to a molecule whose activity includes affecting the level or activity of a substrate. A regulator can be direct or indirect. A regulator can function to activate or inhibit or otherwise modulate its substrate.

[0161] The term “control sequences” refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

[0162] A “pharmaceutically acceptable carrier” refers to a non-toxic solid, semisolid, or liquid filler, diluent, encapsulating material, formulation auxiliary, or carrier conventional in the art for use with a therapeutic agent that together comprise a “pharmaceutical composition” for administration to a subject. A pharmaceutically acceptable carrier is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. The pharmaceutically acceptable carrier is appropriate for the formulation employed.

[0163] The terms “pharmaceutical formulation” and “pharmaceutical composition” refer to a preparation which is in such form as to permit the biological activity of the active ingredient(s) to be effective, and which contains no additional components which are

unacceptably toxic to a subject to which the formulation would be administered. Such formulations may be sterile.

[0164] A “sterile” formulation is aseptic or essentially free from living microorganisms and their spores.

[0165] A “reconstituted” formulation is one which has been prepared by dissolving a lyophilized protein or antibody formulation in a diluent such that the protein is dispersed throughout. The reconstituted formulation is suitable for administration (*e.g.* subcutaneous administration) to a patient to be treated with the protein of interest and, in certain embodiments, may be one which is suitable for parenteral or intravenous administration.

[0166] An “isotonic” formulation is one which has essentially the same osmotic pressure as human blood. Isotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm. The term “hypotonic” describes a formulation with an osmotic pressure below that of human blood. Correspondingly, the term “hypertonic” is used to describe a formulation with an osmotic pressure above that of human blood. Isotonicity can be measured using a vapor pressure or ice-freezing type osmometer, for example. The formulations of the present application can be hypertonic as a result of the addition of salt and/or buffer.

[0167] The term “transfected” or “transformed” or “transduced” as used herein refers to a process by which exogenous nucleic acid is transferred or introduced into the host cell. A “transfected” or “transformed” or “transduced” cell is one which has been transfected, transformed or transduced with exogenous nucleic acid. The cell includes the primary subject cell and its progeny.

[0168] The terms “host cell,” “host cell line,” and “host cell culture” are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include “transformants” and “transformed cells,” which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, and may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0169] As used herein, “treatment” or “treating” is an approach for obtaining beneficial or desired results, including clinical results. For purposes of this application, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviating one or more symptoms resulting from the disease, diminishing the extent of the disease, stabilizing the disease (*e.g.*, preventing or delaying the worsening of the disease),

preventing or delaying the spread (*e.g.*, metastasis) of the disease, preventing or delaying the recurrence of the disease, delaying or slowing the progression of the disease, ameliorating the disease state, providing a remission (partial or total) of the disease, decreasing the dose of one or more other medications required to treat the disease, delaying the progression of the disease, increasing or improving the quality of life, increasing weight gain, and/or prolonging survival. The methods of the application contemplate any one or more of these aspects of treatment.

[0170] The terms “effective amount” and “pharmaceutically effective amount” as used herein refer to a sufficient amount of an agent to provide the desired biological result. That result can be reduction (*e.g.*, reducing at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100%) and/or alleviation of the signs, symptoms, or causes of a disease or disorder, or any other desired alteration of a biological system.

[0171] The terms “inhibition” or “inhibit” refer to a decrease or cessation of any phenotypic characteristic or to the decrease or cessation in the incidence, degree, or likelihood of that characteristic. To “reduce” or “inhibit” is to decrease, reduce or arrest an activity, function, and/or amount as compared to that of a reference. In certain embodiments, by “reduce” or “inhibit” is meant the ability to cause an overall decrease of 20% or greater (*e.g.*, at least about any of 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 100%). In another embodiment, by “reduce” or “inhibit” is meant the ability to cause an overall decrease of 50% or greater. In yet another embodiment, by “reduce” or “inhibit” is meant the ability to cause an overall decrease of 75%, 85%, 90%, 95%, or greater.

[0172] As used herein, to “suppress” a function or activity is to reduce the function or activity when compared to otherwise same conditions except for a condition or parameter of interest, or alternatively, as compared to another condition. For example, an antibody which suppresses tumor growth reduces the rate of growth of the tumor compared to the rate of growth of the tumor in the absence of the antibody.

[0173] As used herein, the terms “patient,” “subject,” “individual,” and the like are used interchangeably herein, and refer to any animal, in some embodiments a mammal, and in some embodiments a human, having a complement system, including a human in need of therapy for, or susceptible to, a condition or its sequelae. The individual may include, for example, dogs, cats, pigs, cows, sheep, goats, horses, rats, monkeys, mice, and humans. In some embodiments, the individual is a human.

[0174] An “affinity-matured” antibody is one with one or more alterations in one or more CDRs thereof that result in an improvement in the affinity of the antibody for antigen,

compared to a parent antibody that does not possess those alteration(s). In some embodiments, an affinity-matured antibody has nanomolar or even picomolar affinities for the target antigen. Affinity-matured antibodies are produced by procedures known in the art. For example, Marks et al., *Bio/Technology* 10:779-783 (1992) describes affinity maturation by VH- and VL-domain shuffling. Random mutagenesis of CDR and/or framework residues is described by, for example: Barbas et al. *Proc Nat. Acad. Sci. USA* 91:3809-3813 (1994); Schier et al. *Gene* 169:147-155 (1995); Yelton et al. *J. Immunol.* 155:1994-2004 (1995); Jackson et al., *J. Immunol.* 154(7):3310-9 (1995); and Hawkins et al, *J. Mol. Biol.* 226:889-896 (1992).

[0175] It is understood that embodiments of the application described herein include “consisting of” and/or “consisting essentially of” embodiments.

[0176] Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter *per se*. For example, description referring to “about X” includes description of “X”.

[0177] As used herein, reference to “not” a value or parameter generally means and describes “other than” a value or parameter. For example, the method is not used to treat disease of type X means the method is used to treat disease of types other than X.

[0178] The term “about X-Y” used herein has the same meaning as “about X to about Y.”

[0179] As used herein and in the appended claims, the singular forms “a,” “or,” and “the” include plural referents unless the context clearly dictates otherwise.

II. Bifunctional Protein Constructs

[0180] The present application in one aspect provides a bifunctional protein construct comprising a first binding moiety and a second binding moiety, wherein the first binding moiety specifically binds to a muscle-specific molecule, and wherein the second binding moiety specifically binds to a Notch receptor and activates the Notch receptor. It is to be understood that the term “bifunctional protein construct” used here refers to a protein construct which comprises binding functions to both a muscle-specific molecule and a Notch receptor, and can encompass constructs having additional functionalities. For example, in some embodiments, the bifunctional protein construct is multispecific. In some embodiments, the bifunctional protein construct comprises a first binding moiety and a second binding moiety, wherein the first binding moiety comprises a means for binding to a muscle-specific molecule, and wherein the second binding moiety comprises a means for binding to a Notch receptor and activates the Notch receptor.

[0181] In some embodiments, the first binding moiety comprising an antibody moiety, which includes, but is not limited to, full length antibody, scFv, Fab, or sdAb. In some embodiments, the first binding moiety comprises a non-antibody moiety. Exemplary first binding moieties include, but are not limited to, anti-LAMA2 antibody moieties (e.g., any of the anti-human LAMA2 antibody moieties described herein), anti-matriglycan antibody moieties (e.g., any of the anti-human ADG41 antibody moieties described herein), and anti-CDH15 antibodies (e.g., any of the anti-human CDH15 antibody moieties described herein). These antibody moieties are described in more details in sections below. Means for binding to a muscle-specific molecules described herein can be any of the antibody moieties described herein and functional equivalents thereof.

[0182] In some embodiments, the first binding moiety comprises a non-antibody binding moiety specifically binding to the muscle-specific molecule, for example, a protein domain (e.g., a laminin G-like domain (LG domain)) of an extracellular matrix (ECM) protein that can bind to matriglycan. In some embodiments, the non-antibody moiety comprises a protein domain selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan. In some embodiments, the first binding moiety comprises two or more non-antibody moieties connected in tandem. Means for binding to a muscle-specific molecule described herein can be any of the non-antibody binding moieties described herein and functional equivalents thereof.

[0183] The second binding moiety described herein specifically binds to a Notch receptor and activates the Notch receptor. In some embodiments, the second binding moiety comprises an extracellular domain (ECD) or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jagged1 (Jag1), and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises a DLL1 ECD comprising the amino acid sequence of SEQ ID NO: 130, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 130. In some embodiments, the second binding moiety comprises a DLL3 ECD comprising the amino acid sequence of SEQ ID NO: 131, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 131. In some embodiments, the second binding moiety comprises a DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 125, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 125. In some embodiments, the second binding moiety comprises a variant DLL4 ECD comprising

the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to any of SEQ ID NOs: 126-129 and 260-267. In some embodiments, the second binding moiety comprises a Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 132, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 132. In some embodiments, the second binding moiety comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133 or 134, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 133 or 134. In some embodiments, the second binding moiety comprises a Jag2 ECD comprising the amino acid sequence of SEQ ID NO: 135, or a variant thereof comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 135. Means for binding to a Notch receptor (and optionally activates the Notch receptor) described herein can be any of the non-antibody moieties described herein and functional equivalents thereof. In some embodiments, the second binding moiety is an anti-Notch antibody moiety that activates the Notch receptor. Means for binding to a Notch receptor (and optionally activates the Notch receptor) described herein can be any of the anti-Notch antibody moieties described herein and functional equivalents thereof.

[0184] The first binding moiety and the second binding moiety described herein may be directly or indirectly fused (i.e., covalently linked) to each other. In some embodiments, the first binding moiety is fused to the second binding moiety via a carrier protein (e.g., an albumin, an anti-human serum albumin antibody, or a monomeric Fc domain). In some embodiments, the first binding moiety is fused to the second binding moiety via an optional peptide linker (e.g., any of the peptide linkers described under the “Linkers” subsection), for example a peptide linker that is no more than about 30 (such as no more than about any one of 25, 20, or 15) amino acids long. In some embodiments, the bifunctional protein construct provided herein comprises an Fc domain comprising a first subunit and a second subunit.

[0185] The bifunctional protein constructs provided herein can be used with any one of a variety of bispecific or multispecific antibody construct formats known in the art. Numerous formats have been developed in the art to address therapeutic opportunities afforded by molecules with multiple binding specificities. Several approaches have been described to prepare bi-specific antibody constructs in which specific antibody light chains or fragment pair with specific antibody heavy chains or fragments.

[0186] For example, International Patent Application No. PCT/EP2011/056388 (WO2011/131746) describes an in vitro method for generating a heterodimeric protein in which asymmetrical mutations are introduced into the CH3 regions of two monospecific starting proteins in order to drive directional “Fab-arm” or “half-molecule” exchange between two monospecific IgG4 or IgG4-like antibodies upon incubation under reducing conditions.

[0187] Schaefer et al. (Roche Diagnostics GmbH), describe a method to assemble two heavy and two light chains, derived from two existing antibodies, into human bivalent bispecific IgG antibodies without use of artificial linkers (PNAS (2011) 108(27): 11187-11192 and US 2009/0232811). The method involves exchanging one or more heavy chain and light chain domains within the antigen-binding fragment (Fab) of one half of the bi-specific antibody (CrossMab). Based on the knobs-into-holes technology that enables heterodimerization of the heavy chains, correct association of the light chains and their cognate heavy chains is achieved by exchange of heavy-chain and light-chain domains within the antigen binding fragment (Fab) of one half of the bispecific antibody. This “crossover” retains the antigen-binding affinity but makes the two arms so different that light-chain mispairing can no longer occur. See WO2009/080251, WO2009/080252, WO2009/080253, and WO2009/080254, each incorporated herein by reference in its entirety.

1. Direct Fusions or Fusion via Carrier Proteins

[0188] The first binding moiety and the second binding moiety can be directly or indirectly linked (i.e., via a peptide linker or a carrier protein, such as a monomeric carrier protein) to each other. The first binding moiety can be fused to the second binding moiety via an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). The first binding moiety and the second binding moiety may also be fused directly to each other. The first binding moiety may be fused at the N-terminus or the C-terminus of the second binding moiety, such as at either the N-terminus or the C-terminus of any one of the polypeptide(s) of the second binding moiety.

[0189] In some embodiments, the first binding moiety and the second binding moiety are linked to each other via a carrier protein. In some embodiments, the carrier protein is selected from the group consisting of a human serum albumin (HSA), an anti-HSA antibody moiety, and a subunit of an Fc domain. Anti-HSA antibody moieties are known in the art, including, for example, Mandrup *et al.*, *Commun Biol.*, 4(1):310 (2021) and Benjamin *et al.*, *Hybridoma*, 6(2):183-90 (1987). In some embodiments, the first binding moiety is fused to

the N-terminus of the carrier protein via an optional first linker, and the second binding moiety is fused to the C-terminus of the carrier protein via an optional second linker. In some embodiments, the first binding moiety is fused to the C-terminus of the carrier protein via an optional first linker, and the second binding moiety is fused to the N-terminus of the carrier protein via an optional second linker. In some embodiments, the carrier protein (e.g., HSA) extends the half-life of the bifunctional protein construct (e.g., extending at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, or longer).

[0190] In some embodiments, the first binding moiety comprises an scFv comprising a VH and a VL specifically binding to a muscle-specific molecule, wherein the scFv is fused to a second binding moiety specifically binding to a Notch receptor. The second binding moiety can be fused to the N-terminus or C-terminus of the scFv specifically recognizing a muscle-specific molecule via an optional linker. In some embodiments, the optional linker between the second binding moiety and the scFv comprises a carrier protein, such as HSA, an anti-HSA antibody moiety, and a subunit of an Fc domain. In some embodiments, the optional linker between the second binding moiety and the scFv is a peptide linker. In some embodiments, the bifunctional protein construct comprises from the N' to the C': [VH – first optional linker (e.g., a peptide linker) – VL] forming the scFv – second optional linker (e.g., a peptide linker or a carrier protein) – a second binding moiety specifically binding to a Notch receptor. In some embodiments, the bifunctional protein construct comprises from the N' to the C': [VL – first optional linker (e.g., a peptide linker) – VH] forming the scFv – second optional linker (e.g., a peptide linker or a carrier protein) – a second binding moiety specifically binding to a Notch receptor. In some embodiments, the bifunctional protein construct comprises from the N' to the C': a second binding moiety specifically binding to a Notch receptor – first optional linker (e.g., a peptide linker or carrier protein) – [VH – second optional linker (e.g., a peptide linker) – VL] forming the scFv. In some embodiments, the bifunctional protein construct comprises from the N' to the C': a second binding moiety specifically binding to a Notch receptor – first optional linker (e.g., a peptide linker or carrier protein) – [VL – second optional linker (e.g., a peptide linker) – VH] forming the scFv. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the first binding moiety comprises an anti-matriglycan scFv (e.g., SEQ ID NO: 155). In some embodiments, the first binding moiety comprises an anti-LAMA2 scFv (e.g., SEQ ID NO: 145 or 268). In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1,

and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the first binding moiety comprises more than one (e.g., two or three) scFvs linked in tandem, optionally via a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0191] In some embodiments, the first binding moiety comprises a Fab comprising a first polypeptide chain comprising VH and CH1 and a second polypeptide chain comprising VL and CL, wherein the Fab specifically binds to a muscle-specific molecule and is fused to a second binding moiety specifically binding to a Notch receptor via an optional linker. In some embodiments, the second binding moiety is fused to the N-terminus of the first polypeptide chain of the Fab. In some embodiments, the second binding moiety is fused to the C-terminus of the first polypeptide chain of the Fab. In some embodiments, the second binding moiety is fused to the N-terminus of the second polypeptide chain of the Fab. In some embodiments, the second binding moiety is fused to the C-terminus of the second polypeptide chain of the Fab. In some embodiments, the bifunctional protein construct comprises: i) a fusion polypeptide comprising from N' to C': VH-CH1 – optional linker (e.g., a peptide linker or a carrier protein) – a second binding moiety specifically binding to a Notch receptor; and ii) a second polypeptide comprising from N' to C': VL-CL; wherein VH-CH1 and VL-CL form an Fab that specifically binds to a muscle-specific molecule. In some embodiments, the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH-CH1; and ii) a fusion polypeptide comprising from N' to C': VL-CL – optional linker (e.g., a peptide linker or a carrier protein) – a second binding moiety specifically binding to a Notch receptor; wherein VH-CH1 and VL-CL form an Fab that specially binds to a muscle-specific molecule. In some embodiments, the bifunctional protein construct comprises: i) a fusion polypeptide comprising from N' to C': a second binding moiety specifically binding to a Notch receptor – optional linker (e.g., a peptide linker or a carrier protein) – VH-CH1; ii) a second polypeptide comprising from N' to C': VL-CL; wherein VH-CH1 and VL-CL form an Fab that specifically binds to a muscle-specific molecule. In some embodiments, the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH-CH1; and ii) a fusion polypeptide comprising from N' to C': a second binding moiety specifically binding to a Notch receptor – optional linker (e.g., a peptide linker or a carrier protein) – VL-CL; wherein VH-CH1 and VL-CL form a Fab that specially binds to a muscle-specific molecule. In some embodiments, the optional linker between the second binding moiety and the Fab comprises a carrier protein,

such as HSA, an anti-HSA antibody moiety, and a subunit of an Fc domain. In some embodiments, the optional linker between the second binding moiety and the Fab is a peptide linker. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the first binding moiety comprises an anti-matriglycan Fab, such as an anti-matriglycan Fab comprising a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the first binding moiety comprises an anti-LAMA2 Fab, such as an anti-LAMA2 Fab comprising a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the first binding moiety comprises more than one (e.g., two or three) Fabs linked in tandem, optionally via a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0192] In some embodiments, the first binding moiety comprises an sdAb comprising a VHH domain specifically binding to a muscle-specific molecule, wherein the sdAb is fused to a second binding moiety specifically binding to a Notch receptor. The second binding moiety can be fused to the N-terminus or C-terminus of the sdAb. In some embodiments, the bifunctional protein construct comprises from N' to C': sdAb (e.g., VHH) specifically binding to a muscle-specific molecule – optional linker (e.g., a peptide linker or a carrier protein) – a second binding moiety specifically binding to a Notch receptor. In some embodiments, the bifunctional protein construct comprises from N' to C': a second binding moiety specifically binding to a Notch receptor – optional linker (e.g., a peptide linker or a carrier protein) – sdAb (e.g., VHH) specifically binding to a muscle-specific molecule. In some embodiments, the optional linker between the second binding moiety and the sdAb comprises a carrier protein, such as HSA, an anti-HSA antibody moiety, and a subunit of an Fc domain. In some embodiments, the optional linker between the second binding moiety and the sdAb is a peptide linker. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and

Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the first binding moiety comprises more than one (e.g., two or three) sdAbs linked in tandem, optionally via a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0193] In some embodiments, the first binding moiety comprises a non-antibody moiety specifically binding to a muscle-specific molecule, wherein the non-antibody moiety comprises an LG domain, e.g., selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan. In some embodiments, the bifunctional protein construct comprises from N' to C': a non-antibody moiety specifically binding to a muscle-specific molecule – optional linker (e.g., a peptide linker or a carrier protein) – a second binding moiety specifically binding to a Notch receptor. In some embodiments, the bifunctional protein construct comprises from N' to C': a second binding moiety specifically binding to a Notch receptor – optional linker (e.g., a peptide linker or a carrier protein) – a non-antibody moiety specifically binding to a muscle-specific molecule. In some embodiments, the optional linker between the second binding moiety and the non-antibody moiety comprises a carrier protein, such as HSA, an anti-HSA antibody moiety, and a subunit of an Fc domain. In some embodiments, the optional linker between the second binding moiety and the non-antibody moiety is a peptide linker. In some embodiments, the first binding moiety comprises an LAMA2 LG4-5 comprising the amino acid sequence of SEQ ID NO: 118 or 119. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the first binding moiety comprises more than one (e.g., 2, 3, 4, 5, 6, 7, 8, or 9) non-antibody moieties (such a LG domain) linked in tandem, optionally via a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

Exemplary Direct Fusions

[0194] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL4 ECD or a variant thereof (e.g., any of SEQ ID NOs: 126-135 and 260-267); an optional peptide linker (e.g.,

any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an LG domain of LAMA2 (e.g., LAMA2 LG4-5).

[0195] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 126; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 136 (hereinafter denoted as "DLL4wt-LG4-5").

[0196] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 127; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 137 (hereinafter denoted as "DLL4v-LG4-5").

[0197] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL4 variant ECD, wherein the DLL4 variant ECD comprises the amino acid sequence of SEQ ID NO: 128; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 138 (hereinafter denoted as "DLL4max-LG4-5").

[0198] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 129; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 139 (hereinafter denoted as "DLL4deimmune (DLL4di)-LG4-5").

[0199] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an LG domain of LAMA2 (e.g., LAMA2 LG4-5). In some embodiments, there is provided a bifunctional

protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD, wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 140 (hereinafter denoted as "DLL1wt-LG4-5").

[0200] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL3 ECD or a variant thereof; an optional peptide linker ; and a first binding moiety comprising an LG domain of LAMA2 (e.g., LAMA2 LG4-5). In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL3 ECD, wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 141 (hereinafter denoted as "DLL3wt-LG4-5").

[0201] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag1 ECD or a variant thereof (such as any of the Jag1 ECD described herein, e.g., any of SEQ ID NOs: 132-134); an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an LG domain of LAMA2 (e.g., LAMA2 LG4-5) (e.g., SEQ ID NO: 119).

[0202] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 142 (hereinafter denoted as "Jag1wt-LG4-5").

[0203] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 134; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119.

In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 143 (hereinafter denoted as “Jag1v-LG4-5”).

[0204] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an LG domain of LAMA2 (e.g., LAMA2 LG4-5). In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD, wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising a LAMA2 LG4-5, wherein the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 144 (hereinafter denoted as “Jag2wt-LG4-5”).

[0205] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL4 ECD or a variant thereof (such as any of the DLL4 ECD or engineered DLL4 ECDs described herein, e.g., any of SEQ ID NOs: 126-129 and 260-267); an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an anti-LAMA2 scFv (e.g., SEQ ID NO: 145 or 268).

[0206] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 126; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 146 (hereinafter denoted as “DLL4wt-LG21scFv”).

[0207] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 127; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 147 (hereinafter denoted as “DLL4v-LG21scFv”).

[0208] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD,

wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 128; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 148 (hereinafter denoted as “DLL4max-LG21scFv”).

[0209] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 129; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 149 (hereinafter denoted as “DLL4di-LG21scFv”).

[0210] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an anti-LAMA2 scFv. In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD, wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 150 (hereinafter denoted as “DLL1wt-LG21scFv”).

[0211] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL3 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an anti-LAMA2 scFv. In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL3 ECD, wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 151 (hereinafter denoted as “DLL3wt-LG21scFv”).

[0212] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag1 ECD or a variant

thereof (such as any of the Jag1 ECD described herein, e.g., any of SEQ ID NOs: 132-134); an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an anti-LAMA2 scFv (e.g., SEQ ID NO: 145 or 268).

[0213] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 152 (hereinafter denoted as "Jag1wt-LG21scFv").

[0214] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 134; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 153 (hereinafter denoted as "Jag1v-LG21scFv").

[0215] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an anti-LAMA2 scFv. In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD, wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-LAMA2 scFv, wherein the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 154 (hereinafter denoted as "Jag2wt-LG21scFv").

[0216] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL4 ECD or a variant thereof (such as any of the DLL4 ECD or engineered DLL4 ECDs described herein, e.g., any of SEQ ID NOs: 126-129 and 260-267); an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an anti-matriglycan scFv (e.g., SEQ ID NO: 155).

[0217] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 126; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 156 (hereinafter denoted as "DLL4wt-ADG41scFv").

[0218] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 127; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 157 (hereinafter denoted as "DLL4v-ADG41scFv").

[0219] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 128; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 158 (hereinafter denoted as "DLL4max-ADG41scFv").

[0220] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 129; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 159 (hereinafter denoted as "DLL4di-ADG41scFv").

[0221] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an anti-matriglycan scFv. In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD, wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130; an optional peptide linker (e.g., SEQ

ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 160 (hereinafter denoted as “DLL1wt-ADG41scFv”).

[0222] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL3 ECD or a variant thereof; an optional peptide linker; and a first binding moiety comprising an anti-matriglycan scFv. In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL3 ECD, wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 161 (hereinafter denoted as “DLL3wt-ADG41scFv”).

[0223] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag1 ECD or a variant thereof (such as any of the Jag1 ECD described herein, e.g., any of SEQ ID NOs: 132-134); an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an anti-matriglycan scFv (e.g., SEQ ID NO: 155).

[0224] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 162 (hereinafter denoted as “Jag1wt-ADG41scFv”).

[0225] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 134; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 163 (hereinafter denoted as “Jag1v-ADG41scFv”).

[0226] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD or a variant thereof; an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338); and a first binding moiety comprising an anti-matriglycan scFv. In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD, wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135; an optional peptide linker (e.g., SEQ ID NO: 211); and a first binding moiety comprising an anti-matriglycan scFv, wherein the anti-matriglycan scFv comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 164 (hereinafter denoted as "Jag2wt-ADG41scFv").

[0227] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab (e.g., SEQ ID NO: 165) and a second binding moiety comprising a DLL4 ECD or a variant thereof (such as any of the DLL4 ECD or engineered DLL4 ECDs described herein, e.g., any of SEQ ID NOs: 126-129 and 260-267), wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab (e.g., SEQ ID NO: 165) via an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0228] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 126, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 167 (hereinafter denoted as "DLL4wt-LG21-Fab").

[0229] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the

second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 127, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 168 (hereinafter denoted as “DLL4v-LG21-Fab”).

[0230] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 128, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 169 (hereinafter denoted as “DLL4max-LG21-Fab”).

[0231] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 129, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide

comprising the amino acid sequence of SEQ ID NO: 170 (hereinafter denoted as “DLL4di-LG21-Fab”).

[0232] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a DLL1 ECD or a variant thereof, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker. In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a DLL1 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 171 (hereinafter denoted as “DLL1wt-LG21-Fab”).

[0233] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a DLL3 ECD or a variant thereof, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker. In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a DLL3 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion

polypeptide comprising the amino acid sequence of SEQ ID NO: 172 (hereinafter denoted as “DLL3wt-LG21-Fab”).

[0234] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab (e.g., SEQ ID NO: 165) and a second binding moiety comprising a Jag1 ECD or a variant thereof (such as any of the Jag1 ECD described herein, e.g., any of SEQ ID NOs: 132-134), wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab (e.g., SEQ ID NO: 165) via an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0235] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a variant Jag1 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 173 (hereinafter denoted as “Jag1 wt-LG21-Fab”).

[0236] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a variant Jag1 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 134, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide

comprising the amino acid sequence of SEQ ID NO: 174 (hereinafter denoted as “Jag1v-LG21-Fab”).

[0237] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a Jag2 ECD or a variant thereof, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker. In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-LAMA2 Fab and a second binding moiety comprising a Jag2 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-LAMA2 Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135, and wherein the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-LAMA2 Fab, wherein the fusion polypeptide comprising the amino acid sequence of SEQ ID NO: 175 (hereinafter denoted as “Jag2wt-LG21-Fab”).

[0238] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab (e.g., SEQ ID NO: 176) and a second binding moiety comprising a DLL4 ECD or a variant thereof (such as any of the DLL4 ECD or engineered DLL4 ECDs described herein, e.g., any of SEQ ID NOs: 126-129 and 260-267), wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab (e.g., SEQ ID NO: 176) via an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0239] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 126, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a

second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 178 (hereinafter denoted as “DLL4wt-ADG41-Fab”).

[0240] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 127, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 179 (hereinafter denoted as “DLL4v-ADG41-Fab”).

[0241] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 128, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 180 (hereinafter denoted as “DLL4max-ADG41-Fab”).

[0242] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-

matriglycan Fab and a second binding moiety comprising a variant DLL4 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 129, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 181 (hereinafter denoted as “DLL4di-ADG41-Fab”).

[0243] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a DLL1 ECD or a variant thereof, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker. In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a DLL1 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 182 (hereinafter denoted as “DLL1wt-ADG41-Fab”).

[0244] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a DLL3 ECD or a variant thereof, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker. In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first

binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a DLL3 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 183 (hereinafter denoted as “DLL3wt-ADG41-Fab”).

[0245] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab (e.g., SEQ ID NO: 176) and a second binding moiety comprising a Jag1 ECD or a variant thereof (such as any of the Jag1 ECD described herein, e.g., any of SEQ ID NOs: 132-134), wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab (e.g., SEQ ID NO: 176) via an optional peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338).

[0246] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a variant Jag1 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 184 (hereinafter denoted as “Jag1wt-ADG41-Fab”).

[0247] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a variant Jag1 ECD, wherein the

second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 134, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 185 (hereinafter denoted as “Jag1v-ADG41-Fab”).

[0248] In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a Jag2 ECD or a variant thereof, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker. In some embodiments, there is provided a bifunctional protein construct, wherein the bifunctional protein construct comprises a first binding moiety comprising an anti-matriglycan Fab and a second binding moiety comprising a Jag2 ECD, wherein the second binding moiety is fused to the N-terminus of the VL of the anti-matriglycan Fab via an optional peptide linker (e.g., SEQ ID NO: 211), wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135, and wherein the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the bifunctional protein construct comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a fusion polypeptide comprising the second binding moiety and the second polypeptide of the anti-matriglycan Fab, wherein the fusion polypeptide comprises the amino acid sequence of SEQ ID NO: 186 (hereinafter denoted as “Jag2wt-ADG41-Fab”).

[0249] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL4 ECD or a variant thereof (e.g., SEQ ID NO: 339); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0250] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD,

wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 339; an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 319 (hereinafter denoted as “DLL4(EGF1-6)-GSlinker-laminin-a2 LG4-5”).

[0251] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL4 ECD or a variant thereof (e.g., SEQ ID NO: 339); an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0252] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 339; an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 320 (hereinafter denoted as “DLL4(EGF1-6)-HSA-laminin-a2 LG4-5”).

[0253] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD or a variant thereof (e.g., SEQ ID NO: 340); an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0254] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL1 ECD, wherein the variant DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 340; an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 323 (hereinafter denoted as “DLL1(EGF1-6)-HSA-laminin-a2 LG4-5”).

[0255] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag1 ECD or a variant thereof (e.g., SEQ ID NO: 341); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0256] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 341; an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 325 (hereinafter denoted as "Jagged1(EGF1-6)-laminin-a2 LG4-5").

[0257] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag1 ECD or a variant thereof (e.g., SEQ ID NO: 341); an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0258] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag1 ECD, wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 341; an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 326 (hereinafter denoted as "Jagged1(EGF1-6)-HSA-laminin-a2 LG4-5").

[0259] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD or a variant thereof (e.g., SEQ ID NO: 342); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0260] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag2 ECD, wherein the variant Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 342; an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2

LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 328 (hereinafter denoted as “Jagged2(EGF1-6)-laminin-a2 LG4-5”).

[0261] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a Jag2 ECD or a variant thereof (e.g., SEQ ID NO: 342); an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0262] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant Jag2 ECD, wherein the variant Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 342; an optional peptide linker (e.g., SEQ ID NO: 337); a carrier protein (e.g., SEQ ID NO: 344); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 329 (hereinafter denoted as “Jagged2(EGF1-6)-HSA-laminin-a2 LG4-5”).

[0263] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a DLL1 ECD or a variant thereof (e.g., SEQ ID NO: 340); an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain (e.g., SEQ ID NO: 343).

[0264] In some embodiments, there is provided a bifunctional protein construct comprising from N' to C': a second binding moiety comprising a variant DLL1 ECD, wherein the variant DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 340; an optional peptide linker (e.g., SEQ ID NO: 337); and a first binding moiety comprising a laminin-a2 LG4-5 domain, wherein the laminin-a2 LG4-5 domain comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the bifunctional protein construct comprises the amino acid sequence of SEQ ID NO: 322 (hereinafter denoted as “DLL1(EGF1-6)-laminin-a2 LG4-5”).

2. Fc Domain Fusions

[0265] In some embodiments, the bifunctional protein construct comprises an Fc domain comprising a first subunit and a second subunit. The Fc domain can be a third moiety

connected to the first binding moiety and the second binding moiety. In some embodiments, when the first binding moiety or second binding moiety is a full-length antibody, the Fc domain can be part of the full-length antibody.

[0266] In some embodiments, the Fc domain is a variant Fc domain possessing minimal or no effector functions. In some embodiments, the variant Fc domain is derived from IgG1 Fc or IgG4 Fc.

[0267] One or more amino acid modifications may be introduced into the Fc domain, thereby generating an Fc domain variant. The Fc domain variant may comprise a human Fc domain sequence (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc domain) comprising an amino acid modification (e.g., a substitution) at one or more amino acid positions.

[0268] In some embodiments, the Fc domain possesses some but not all effector functions, which make it a desirable candidate for applications in which the half-life of the antibody moiety *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. In some embodiments, the Fc domain comprises one or more mutations that increase the half-life of the antibody moiety *in vivo*. In some embodiments, the variant Fc domain has increased FcRn binding at pH 6.0. In some embodiments, the variant Fc domain comprises an M252Y/S254T/T256E (“YTE”) mutation (EU numbering). *See, e.g., Dall’Acqua et al., J Immunol.*, 169:5171–5180 (2002) and Wang *et al., Protein & Cell*, 9(1):63-73 (2018). In some embodiments, the variant Fc domain comprises an M428L/N434S mutation. *See, e.g., Zalevsky et al., Nat Biotechnol.*, 28:157–159 (2010) and Wang *et al., Protein & Cell*, 9(1):63-73 (2018).

[0269] *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to analyze CDC and/or ADCC activities of the Fc domain. For example, Fc receptor (FcR) binding assays can be conducted to determine whether the antibody possesses FcγR binding (hence likely ADCC activity), and/or retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 2 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (*see, e.g. Hellstrom, I. et al. Proc. Nat’l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I. *Et al., Proc. Nat’l Acad. Sci. USA* 82:1499-1502 (1985); 5,821,337 (*see Bruggemann, M. Et al., J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (*see, for example, ACTITM* non-radioactive cytotoxicity assay for flow cytometry

(CellTechnology, Inc. Mountain View, CA; and CytoTox 96[®] non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in an animal model such as that disclosed in Clynes *et al. Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. *See, e.g.*, C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. FcRn binding and *in vivo* clearance/half-life determinations can also be performed using methods known in the art (*see, e.g.*, Petkova, S.B. *et al., Int'l. Immunol.* 18(12):1759-1769 (2006)).

[0270] Antibodies with reduced effector function include those with substitution of one or more of Fc domain residues 238, 265, 269, 270, 297, 327, and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include a variant Fc with substitutions at two or more of amino acid positions 265, 269, 270, 297, and 327, including the so-called “DANA” Fc variant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581). In some embodiments, the Fc domain of the bifunctional protein construct comprises one or more of these mutations. In some embodiments, the variant Fc domain comprises an N297A, N297Q, or N297G mutation. *See, e.g.*, Bolt *et al., Eur J Immunol.*, 23:403–411 (1993); Leabman *et al., Mabs*, 5:896–903 (2013); Tao and Morrison, *J Immunol.*, 143:2595–2601 (1989); Walker *et al., Biochem J.*, 259:347–353 (1989); and Wang *et al., Protein & Cell*, 9(1):63-73 (2018). In some embodiments, the variant Fc domain comprises a L235E mutation. *See, e.g.*, Alegre *et al., J Immunol.*, 148:3461–3468 (1992) and Wang *et al., Protein & Cell*, 9(1):63-73 (2018).

[0271] Certain antibody variants with improved or diminished binding to FcRs are described. *See, e.g.*, U.S. Patent No. 6,737,056; WO 2004/056312, and Shields *et al., J. Biol. Chem.* 9(2): 6591-6604 (2001).

[0272] In some embodiments, the Fc domain is derived from human IgG1, human IgG2, or human IgG4. In some embodiments, the Fc domain is derived from an IgG1 Fc domain (e.g., human IgG1 Fc domain). In some embodiments, the human IgG1 Fc comprises the amino acid sequence of SEQ ID NO: 187. In some embodiments, each subunit of the Fc domain comprises a mutation that reduces or abolishes the effector function. In some embodiments, effector function is eliminated through a mutation in the constant region that eliminated glycosylation, e.g., “effector-less mutation.” In one aspect, the effector-less mutation is an N297A or DANA mutation (D265A+N297A) in the CH2 region (EU

numbering). *See, e.g.,* Shields *et al.*, *J. Biol. Chem.* 276 (9): 6591-6604 (2001). Alternatively or additionally, effector function can be reduced or eliminated through production techniques, such as expression in host cells that do not glycosylate (e.g., *E. coli.*) or in which result in an altered glycosylation pattern that is ineffective or less effective at promoting effector function (e.g., Shinkawa *et al.*, *J. Biol. Chem.* 278(5): 3466-3473 (2003). In some embodiments, each subunit of the Fc domain comprises an L234A/L235A “LALA” mutation (EU numbering). In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the Fc domain comprises a mutation that reduces half-life of the bifunctional protein construct in blood circulation, such as an H435A mutation (EU numbering). In some embodiments, each subunit of the Fc domain (e.g., human IgG1 Fc) comprises L234A/L235A and H435A mutations. In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the Fc domain is an IgG4 (e.g., human IgG4) Fc domain. In some embodiments, the Fc domain comprises a mutation that reduces Fab exchange, such as an S228P mutation. In some embodiments, the IgG4 Fc domain comprises an F234A/L235A mutations. *See, e.g.,* Xu *et al.*, *Cell Immunol.*, 200:16–26 (2000) and Wang *et al.*, *Protein & Cell*, 9(1):63-73 (2018). *See also* Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc domain variants.

[0273] In some embodiments, when the bifunctional protein construct is a heterodimeric protein comprising two different polypeptide chains, the Fc domain can comprise one or more mutations that facilitate assembly of the heterodimeric protein. For example, knob-into-hole is a heterodimerization technology for the CH3 domain of an antibody. Previously, knobs-into-holes technology has been applied to the production of human full-length bispecific antibodies with a single common light chain (LC) (Merchant *et al.* “An efficient route to human bispecific IgG.” *Nat Biotechnol.* 1998;16:677–81; Jackman *et al.* “Development of a two-part strategy to identify a therapeutic human bispecific antibody that inhibits IgE receptor signaling.” *J Biol Chem.* 2010;285:20850–9.) *See also* WO1996027011, which is herein incorporated by reference in its entirety for all purposes. All these mutations can be incorporated into the bifunctional protein constructs described herein.

[0274] Thus, for example, in some embodiments, the bifunctional protein construct comprises an Fc domain comprising a first CH3 domain and a second CH3 domain

comprising knob-into-hole (KIH) residues. In some embodiments the first CH3 domain is altered so that within the CH3/CH3 interface, one or more amino acid residues are replaced with one or more amino acid residues having a larger side chain volume, thereby generating a protuberance on the surface of the first CH3 domain that interacts with the second CH3 domain; and the second CH3 domain is altered so that within the CH3/CH3 interface, one or more amino acid residues are replaced amino acid residues having a smaller side chain volume, thereby generating a cavity on the surface of the second CH3 domain that interacts with the first CH3 domain. In some embodiments, the protuberance is a knob. In some embodiments, the alteration to generate the knob is T366W. In some embodiments, the cavity is a hole. In some embodiments, the alterations to generate the hole are T366S/L368A/Y407V. Hence in some embodiments, the Fc domain described herein comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). Unless indicated otherwise, all amino acid positions within the Fc domain are numbered according to EU numbering system.

[0275] In some embodiments, the bifunctional protein construct comprises an Fc domain comprising a mutation allowing for purification of asymmetric Fc domains. In some embodiments, either the first subunit of the Fc domain or the second subunit of the Fc domain comprises an H435R/Y436F mutation (EU numbering). In some embodiments, each subunit of the Fc domain comprises an H435R/Y436F mutation (EU numbering).

[0276] Strop et al. (Rinat-Pfizer Inc.), describes a method of producing stable bi-specific antibodies by expressing and purifying two antibodies of interest separately, and then mixing them together under specified redox conditions (J. Mol. Biol. (2012) 420:204-19).

[0277] Other heterodimerization domains having a strong preference for forming heterodimers over homodimers can be incorporated into the instant bifunctional protein constructs. Illustrative examples include but are not limited to, for example, WO2007147901 (Kjærgaard et al.—Novo Nordisk: describing ionic interactions); WO2009/089004 (Kannan et al.—Amgen: describing electrostatic steering effects); WO2010/034605 (Christensen et al. —Genentech; describing coiled coils). See also, for example, Pack, P. & Plueckthun, A., Biochemistry 31, 1579-1584 (1992) describing leucine zipper or Pack et al., Bio/Technology 11, 1271-1277 (1993) describing the helix-turn-helix motif. The term “heterodimerization

domain” does not exclude additional units in addition to the two heterodimers in the bifunctional construct. In certain embodiments, the bifunctional protein construct comprises one or more heterodimerization domains.

[0278] In some embodiments, when the bifunctional protein construct is a heterodimeric protein comprising two different polypeptide chains, the Fc domain can comprise one or more charged-pair mutations that facilitate assembly of the heterodimeric protein. In some embodiments, an amino acid residue in the first subunit of the Fc domain is replaced with a positively charged residue (e.g., R, H, or K), and an amino acid residue in the second subunit of the Fc domain is replaced with a negatively charged residue (e.g., D or E). In some embodiments, an amino acid residue in the first subunit of the Fc domain is replaced with a negatively charged residue, and an amino acid residue in the second subunit of the Fc domain is replaced with a positively charged residue. In some embodiments, an amino acid residue at D399 (EU numbering) in the first subunit of the Fc domain is replaced with a positively charged residue, and an amino acid residue at K409 (EU numbering) in the second subunit of the Fc domain is replaced with a negatively charged residue. In some embodiments, an amino acid residue at K409 (EU numbering) in the first subunit of the Fc domain is replaced with a negatively charged residue, and an amino acid residue at D399 (EU numbering) in the second subunit of the Fc domain is replaced with a positively charged residue.

[0279] In some embodiments, the Fc domain used in the bifunctional protein construct described herein comprises the amino acid sequence of any one of SEQ ID NO: 188, 254, and 277.

[0280] In some embodiments, there is provided a bifunctional protein construct comprising: i) one or more units of a first binding moiety specifically binding to a muscle-specific molecule; ii) a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; iii) a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and iv) an Fc domain comprising a first subunit and a second subunit; optionally wherein the first unit of the second binding moiety and the second unit of the second binding moiety each independently comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the first unit of the second binding moiety and the second unit of the second binding moiety are the same. In some embodiments, the first unit of the second binding moiety and the second unit of the second binding moiety are different. The one or

more units of the first binding moiety can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, the bifunctional protein construct further comprises a third unit of a second binding moiety specifically binding to a third Notch receptor, and a fourth unit of a second binding moiety specifically binding to a fourth Notch receptor. In some embodiments, the third unit of the second binding moiety and the fourth unit of the second binding moiety each independently comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). The first, second, third, and/or fourth unit of the second binding moiety can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, all four units of the second binding moiety are the same. In some embodiments, at least one of the four units of the second binding moiety is different from the others. The one or more units of the first binding moiety can comprise antibody moiety or non-antibody moiety. The various binding moieties can independently fuse to the N and/or C terminus of the Fc domain. The bifunctional protein construct can be homodimeric or heterodimeric.

[0281] In some embodiments, there is provided a bifunctional protein construct comprising: i) a first unit of a first binding moiety specifically binding to a first muscle-specific molecule; ii) a second unit of a first binding moiety specifically binding to a second muscle-specific molecule; iii) one or more units of a second binding moiety specifically binding to a Notch receptor and activating the Notch receptor; and iv) an Fc domain comprising a first subunit and a second subunit. In some embodiments, there is provided a bifunctional protein construct comprising: i) a first unit of a first binding moiety comprising a first antibody moiety specifically binding to a first muscle-specific molecule, ii) a second unit of a first binding moiety comprising a second antibody moiety specifically binding to a second muscle-specific molecule, iii) one or more units of a second binding moiety specifically binding to a Notch receptor and activating the Notch receptor; and iv) an Fc domain comprising a first subunit and a second subunit; wherein the first antibody moiety and the second antibody moiety are each independently selected from the group consisting of a Fab, an scFv, and an sdAb. In some embodiments, there is provided a bifunctional protein construct comprising: i) a first unit of a first binding moiety comprising a first non-antibody moiety specifically binding to a first muscle-specific molecule, ii) a second unit of a first binding moiety comprising a second non-antibody moiety specifically binding to a second muscle-specific molecule, iii) one or more units of a second binding moiety specifically

binding to a Notch receptor and activating the Notch receptor; and iv) an Fc domain comprising a first subunit and a second subunit; wherein the first non-antibody moiety and the second non-antibody moiety are each independently selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises LAMA2 LG4-5 comprising the amino acid sequence of SEQ ID NO: 118 or 119. In some embodiments, the first unit of the first binding moiety comprises two or more first non-antibody moieties connected in tandem, and the second unit of the first binding moiety comprises two or more second non-antibody moieties connected in tandem. In some embodiments, the first unit of the first binding moiety and the second unit of the first binding moiety are the same. In some embodiments, the first unit of the first binding moiety and the second unit of the first binding moiety are different. The one or more units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. The various binding moieties can independently fuse to the N and/or C terminus of the Fc domain. The bifunctional protein construct can be homodimeric or heterodimeric.

[0282] In some embodiments, the one or more units of the first binding moiety in the bifunctional protein construct comprises (or is) a Fab, wherein the Fab can be connected to the C-terminus of a subunit of the Fc domain via VH or VL, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). For example, in some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VH1-(H1-CH1); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VH2-(H2-CH1); iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL); and wherein VL1-(L1-

CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. Fab1 and Fab2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, Fab1 and Fab2 both specifically bind to matriglycan Fab. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-

267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0283] In some embodiments, the one or more units of the first binding moiety comprises (or is) an scFv, wherein the scFv can be connected to the C-terminus of a subunit of the Fc domain via VH or VL, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). For example, in some embodiments, there is provided a bifunctional protein construct comprising: a first scFv (scFv1) specifically binding to a first muscle-specific molecule comprising VH (VH1) and VL (VL1); a second scFv (scFv2) specifically binding to a second muscle-specific molecule comprising a VH (VH2) and VL (VL2); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – scFv1 (VH1 – optional linker – VL1, or VL1 – optional linker – VH1); and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – scFv2 (VH2 – optional linker – VL2, or VL2 – optional linker – VH2). In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. scFv1 and scFv2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, scFv1 and scFv2 both specifically bind to matriglycan. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, scFv1 and scFv2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some

embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0284] In some embodiments, the one or more units of the first binding moieties comprises (or is) an sdAb, wherein the sdAb can be connected to the C-terminus of a subunit of the Fc domain, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). For example, in some embodiments, there is provided a bifunctional protein construct comprising: a first sdAb (sdAb1, e.g., VHH1) specifically binding to a first muscle-specific molecule; a second sdAb (sdAb2, e.g., VHH2) specifically binding to a second muscle-specific molecule; a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – sdAb1; ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – sdAb2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. sdAb1 and sdAb2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0285] In some embodiments, the one or more units of the first binding moieties comprises (or is) a Fab, wherein the Fab can be connected to the N-terminus of a subunit of the Fc domain via CH1 or CL, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific

molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain – optional linker – the first unit of the second binding moiety; ii) a second polypeptide comprising from N' to C': VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the second binding moiety; iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VL1-(L1-CL) – optional linker – the first subunit of the Fc domain – optional linker – the first unit of the second binding moiety; ii) a second polypeptide comprising from N' to C': VL2-(L2-CL) – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the second binding moiety specifically binding to a second Notch receptor; iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. Fab1 and Fab2 can be the same or different; and/or can bind to the

same or different muscle-specific molecules. In some embodiments, Fab1 and Fab2 both specifically bind to matriglycan Fab. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0286] In some embodiments, there is provided a bifunctional protein construct comprising: i) a first binding moiety comprising a full-length antibody specifically binding to a muscle-specific molecule, wherein the full-length antibody comprises an Fc domain comprising a first subunit and a second subunit; ii) a first unit of a second binding moiety fused (directly or via an optional linker) to the C-terminus of the first subunit of the Fc domain; and iii) a second unit of a second binding moiety fused (directly or via an optional linker) to the C-terminus of the second subunit of the Fc domain; wherein the first unit of the second binding moiety specifically binds to a first Notch receptor and activates the first Notch receptor, and the second unit of the second binding moiety specifically binds to a second Notch receptor and activates the second Notch receptor. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267).

In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0287] In some embodiments, the one or more units of the first binding moiety comprises (or is) an scFv, wherein the scFv can be connected to the N-terminus of a subunit of the Fc domain via VH or VL, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). In some embodiments, there is provided a bifunctional protein construct comprising: a first scFv (scFv1) specifically binding to a first muscle-specific molecule comprising VH (VH1) and VL (VL1); a second scFv (scFv2) specifically binding to a second muscle-specific molecule comprising a VH (VH2) and VL (VL2); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': scFv1 (VH1 -optional linker – VL1 or VL1 -optional linker – VH1) -optional linker– the first subunit of the Fc domain – optional linker – the first unit of the second binding moiety; and ii) a second polypeptide comprising from N' to C': scFv2 (VH2 – optional linker – VL2 or VL2 -optional linker – VH2) – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the second binding moiety. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. scFv1 and scFv2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, scFv1 and scFv2 both specifically bind to matriglycan. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, scFv1 and scFv2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some

embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0288] In some embodiments, the one or more units of the first binding moieties comprises (or is) an sdAb, wherein the sdAb can be connected to the N-terminus of a subunit of the Fc domain, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). In some embodiments, there is provided a bifunctional protein construct comprising: a first sdAb (sdAb1, e.g., VHH1) specifically binding to a first muscle-specific molecule; a second sdAb (sdAb2, e.g., VHH2) specifically binding to a second muscle-specific molecule; a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': sdAb1 – optional linker – the first subunit of the Fc domain – optional linker – the first unit of the second binding moiety; and ii) a second polypeptide comprising from N' to C': sdAb2 – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the second binding moiety. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. sdAb1 and sdAb2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0289] In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically

binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': VL1-(L1-CL) – optional linker – the first unit of the second binding moiety; and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL) – optional linker – the second unit of the second binding moiety; and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. Fab1 and Fab2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, Fab1 and Fab2 both specifically bind to matriglycan Fab. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0290] In some embodiments, there is provided a bifunctional protein construct comprising: i) a first binding moiety comprising a full-length antibody specifically binding to a muscle-specific molecule; ii) a first unit of a second binding moiety fused (directly or via an optional linker) to the C-terminus of a first light chain of the full-length antibody; and iii) a

second unit of a second binding moiety fused (directly or via an optional linker) to the C-terminus of a second light chain of the full-length antibody; wherein the first unit of the second binding moiety specifically binds to a first Notch receptor and activates the first Notch receptor, and the second unit of the second binding moiety specifically binds to a second Notch receptor and activates the second Notch receptor. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0291] In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-

specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. Fab1 and Fab2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, Fab1 and Fab2 both specifically bind to matriglycan Fab. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0292] In some embodiments, there is provided a bifunctional protein construct comprising: a first binding moiety comprising a full-length antibody specifically binding to a muscle-specific molecule, a first unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a first light chain of the full-length antibody, and a second unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a second light chain of the full-length antibody; wherein the first unit of the second binding moiety specifically binds to a first Notch receptor and activates the first Notch receptor, and the second unit of the second binding moiety specifically binds to a second Notch receptor and activates the second Notch receptor. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the

engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0293] In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. Fab1 and Fab2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, Fab1 and Fab2 both specifically bind to matriglycan Fab. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected

from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0294] In some embodiments, there is provided a bifunctional protein construct comprising: a first binding moiety comprising a full-length antibody specifically binding to a muscle-specific molecule, a first unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a first heavy chain of the full-length antibody, and a second unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a second heavy chain of the full-length antibody; wherein the first unit of the second binding moiety specifically binds to a first Notch receptor and activates the first Notch receptor, and the second unit of the second binding moiety specifically binds to a second Notch receptor and activates the second Notch receptor. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0295] In some embodiments, there is provided a bifunctional protein construct comprising: a first Fab (Fab1) specifically binding to a first muscle-specific molecule comprising VH (VH1), CH1 (H1-CH1), VL (VL1), and CL (L1-CL); a second Fab (Fab2) specifically binding to a second muscle-specific molecule comprising a VH (VH2), CH1 (H2-CH1), VL (VL2), and CL (L2-CL); a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor; a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor; a third unit of a second binding moiety specifically binding to a third Notch receptor and activating the third Notch receptor; a fourth unit of a second binding moiety specifically binding to a fourth Notch receptor and activating the fourth Notch

receptor; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain; ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain; iii) a third polypeptide comprising from N' to C': the third unit of the second binding moiety – optional linker – VL1-(L1-CL); and iv) a fourth polypeptide comprising from N' to C': the fourth unit of the second binding moiety – optional linker – VL2-(L2-CL); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the first and second muscle-specific molecules are independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. Fab1 and Fab2 can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, Fab1 and Fab2 both specifically bind to matriglycan Fab. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, Fab1 and Fab2 both specifically bind to LAMA2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. The first, second, third, and/or fourth units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, all four units of the second binding moiety are the same. In some embodiments, at least one of the four units of the second binding moiety is different from the others. In some embodiments, the second binding moiety (one or more units, or all units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or more units, or all units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0296] In some embodiments, there is provided a bifunctional protein construct comprising: a first binding moiety comprising a full-length antibody specifically binding to a

muscle-specific molecule, a first unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a first light chain of the full-length antibody, a second unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a second light chain of the full-length antibody, a third unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a first heavy chain of the full-length antibody, and a fourth unit of a second binding moiety fused (directly or via an optional linker) to the N-terminus of a second heavy chain of the full-length antibody; wherein the first unit of the second binding moiety specifically binds to a first Notch receptor and activates the first Notch receptor, the second unit of the second binding moiety specifically binds to a second Notch receptor and activates the second Notch receptor, the third unit of the second binding moiety specifically binds to a third Notch receptor and activates the third Notch receptor, and the fourth unit of the second binding moiety specifically binds to a fourth Notch receptor and activates the fourth Notch receptor. In some embodiments, the optional linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. The first, second, third, and/or fourth units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, all four units of the second binding moiety are the same. In some embodiments, at least one of the four units of the second binding moiety is different from the others. In some embodiments, the second binding moiety (one or more units, or all units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or more units, or all units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

[0297] In some embodiments, the one or more units of the first binding moiety comprises a non-antibody moiety specifically binding to a muscle-specific molecule, wherein the non-antibody moiety can be connected to the C-terminus or N-terminus of a subunit of an Fc domain, such as through an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). For example, in some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety specifically binding to a first muscle-specific molecule, a second non-antibody moiety specifically binding to a second muscle-specific molecule, a first unit of a second binding moiety specifically binding to a first Notch receptor

and activating the first Notch receptor, a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety specifically binding to a first muscle-specific molecule, a second non-antibody moiety specifically binding to a second muscle-specific molecule, a first unit of a second binding moiety specifically binding to a first Notch receptor and activating the first Notch receptor, a second unit of a second binding moiety specifically binding to a second Notch receptor and activating the second Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first non-antibody moiety -optional linker– the first subunit of the Fc domain – optional linker – the first unit of the second binding moiety; and ii) a second polypeptide comprising from N' to C': the second non-antibody moiety – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the second binding moiety. In some embodiments, the first and/or second non-antibody moiety comprises a protein domain independently selected from the group consisting of a laminin G-like domain (LG domain) of laminin, an LG domain of agrin, an LG domain of nidogen, an LG domain of perlecan, the laminin coiled-coil binding domain of agrin, and the laminin γ binding domain of nidogen. In some embodiments, the first and/or second non-antibody moiety comprises two or more protein domains (e.g., LG domain) connected in tandem, such as via an optional linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises LAMA2 LG4-5 comprising the amino acid sequence of SEQ ID NO: 118 or 119. In some embodiments, the first non-antibody moiety comprises two LAMA2 LG4-5 connected in tandem, and the second non-antibody moiety comprises two LAMA2 LG4-5 connected in tandem. In some embodiments, the non-antibody moiety comprises a laminin G-like domain (LG domain). In some embodiments, the bifunctional protein construct comprises more than one (e.g., two or three) non-antibody moieties (such as LG domains) linked in tandem, optionally via a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338). The first and second non-antibody

moieties can be the same or different; and/or can bind to the same or different muscle-specific molecules. In some embodiments, the optional peptide linker is a peptide linker (e.g., any of SEQ ID NOs: 211, 212, 337, and 338), which can be the same or different within the bifunctional protein construct. The first unit of the second binding moiety and the second unit of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptors. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267.

Exemplary Fc Domain Fusions

[0298] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 Fab (anti-LAMA2 Fab1); a second anti-LAMA2 Fab (anti-LAMA2 Fab2); a first unit of second binding moiety comprising a DLL4 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-LAMA2 Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-LAMA2 Fab2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. Anti-LAMA2 Fab1 and anti-LAMA2 Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same

or different Notch receptor. In some embodiments, each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188 or 277.

[0299] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, there is provided a bifunctional protein construct comprising: a first polypeptide and a second polypeptide each comprising the amino acid sequence of any of SEQ ID NOs: 189, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “DLL4wt-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188.

[0300] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 127. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 190, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “DLL4v-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188.

[0301] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 128. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 191, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “DLL4max-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188.

[0302] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 129. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 192, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “DLL4di-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188.

[0303] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 Fab (anti-LAMA2 Fab1); a second anti-LAMA2 Fab (anti-LAMA2 Fab2); a first unit of second binding moiety comprising a DLL1 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-LAMA2 Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-LAMA2 Fab2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. Anti-LAMA2 Fab1 and anti-LAMA2 Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 193, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “DLL1wt-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0304] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 Fab (anti-LAMA2 Fab1); a second anti-LAMA2 Fab (anti-LAMA2 Fab2); a first unit of second binding moiety comprising a DLL3 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL3 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain –

optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-LAMA2 Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-LAMA2 Fab2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. Anti-LAMA2 Fab1 and anti-LAMA2 Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 194, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “DLL3wt-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0305] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 Fab (anti-LAMA2 Fab1); a second anti-LAMA2 Fab (anti-LAMA2 Fab2); a first unit of second binding moiety comprising a Jag1 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-LAMA2 Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-LAMA2 Fab2. In some embodiments, anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ

ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. Anti-LAMA2 Fab1 and anti-LAMA2 Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 195, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “Jag1wt-Fc-LG21-Fab”). In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 134. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 196, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “Jag1v-Fc-LG21-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0306] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 Fab (anti-LAMA2 Fab1); a second anti-LAMA2 Fab (anti-LAMA2 Fab2); a first unit of second binding moiety comprising a Jag2 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-LAMA2 Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-LAMA2 Fab2. In some embodiments, anti-LAMA2 Fab1 and/or

anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. Anti-LAMA2 Fab1 and anti-LAMA2 Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 197, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 165 (hereinafter denoted as “Jag2wt-Fc-LG21-Fab”).

[0307] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan Fab (anti-matriglycan Fab1); a second anti-matriglycan Fab (anti-matriglycan Fab2); a first unit of second binding moiety comprising a DLL4 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-matriglycan Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-matriglycan Fab2. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. Anti-matriglycan Fab1 and anti-matriglycan Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor.

[0308] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO:

126. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 198, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “DLL4wt-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0309] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 127. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 199, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “DLL4v-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0310] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 128. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 200, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “DLL4max-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0311] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 129. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 201, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “DLL4di-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0312] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan Fab (anti-matriglycan Fab1); a second anti-matriglycan Fab (anti-matriglycan Fab2); a first unit of second binding moiety comprising a DLL1 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-matriglycan Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-matriglycan Fab2. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. Anti-matriglycan Fab1 and anti-matriglycan Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 202, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “DLL1wt-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0313] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan Fab (anti-matriglycan Fab1); a second anti-matriglycan Fab (anti-matriglycan Fab2); a first unit of second binding moiety comprising a DLL3 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL3 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc

domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-matriglycan Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-matriglycan Fab2. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. Anti-matriglycan Fab1 and anti-matriglycan Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 203, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “DLL3wt-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0314] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan Fab (anti-matriglycan Fab1); a second anti-matriglycan Fab (anti-matriglycan Fab2); a first unit of second binding moiety comprising a Jag1 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-matriglycan Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-matriglycan Fab2. In some embodiments, anti-matriglycan Fab1 and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid

sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. Anti-matriglycan Fab1 and anti-matriglycan Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 204, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “Jag1 wt-Fc-ADG41-Fab”). In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 134. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 205, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “Jag1 v-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0315] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan Fab (anti-matriglycan Fab1); a second anti-matriglycan Fab (anti-matriglycan Fab2); a first unit of second binding moiety comprising a Jag2 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL); ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL); iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and wherein VL1-(L1-CL) and VH1-(H1-CH1) form anti-matriglycan Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form anti-matriglycan Fab2. In some embodiments, anti-matriglycan Fab1

and/or anti-matriglycan Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. Anti-matriglycan Fab1 and anti-matriglycan Fab2 can be the same or different. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 206, and a third polypeptide and a fourth polypeptide each comprising the amino acid sequence of SEQ ID NO: 176 (hereinafter denoted as “Jag2wt-Fc-ADG41-Fab”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0316] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 scFv (anti-LAMA2 scFv1); a second anti-LAMA2 scFv (anti-LAMA2 scFv2); a first unit of second binding moiety comprising a DLL4 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-LAMA2 scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-LAMA2 scFv2. Anti-LAMA2 scFv1 and anti-LAMA2 scFv2 can be the same or different. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, each subunit of the Fc domain comprises the amino acid sequence SEQ ID NOs: 188 or 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0317] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 223 (hereinafter denoted as “DLL4wt-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0318] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 127. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 224 (hereinafter denoted as “DLL4v-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0319] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 128. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 225 (hereinafter denoted as “DLL4max-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0320] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 129. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 226 (hereinafter denoted as “DLL4di-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0321] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO:

260. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 269 (hereinafter denoted as “huD4v_G2S_F81L_H168Y -Fc(AAG)-LG21scFvDS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0322] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 261. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 270 (hereinafter denoted as “huD4v11_G2S_T52N_F81L_T135N_H168Y-Fc(AAG)-LG21scFvDS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0323] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 262. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 271 (hereinafter denoted as “huD4v12_G2S_R66S_F81L_H168Y-Fc(AAG)-LG21scFvDS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0324] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 263. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 272 (hereinafter denoted as “huD4v13_G2S_E14H_T52N_R66T_P76L_F81L_T135N_H168Y_N231D-Fc(AAG)-LG21scFvDS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0325] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 264. In some embodiments, there is provided a bifunctional protein construct comprising a

first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 273 (hereinafter denoted as

“huD4v14_G2S_T52N_R66T_P76L_F81L_T135N_H168Y_Q220H_N260D-Fc(AAG)-LG21scFvDS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0326] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 265. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 274 (hereinafter denoted as “huD4v22_G2S_R66S_F81L_H168Y-Fc(AAG)-LG21scFvDS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0327] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 266. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 275 (hereinafter denoted as “huD4v23_G2S_E14H_R66T_P76L_F81L_H168Y_N231D-FcAAG-LG21DS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0328] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 267. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 276 (hereinafter denoted as “huD4v24_G2S_R66T_P76L_F81L_H168Y_Q220H_N260D-FcAAG-LG21DS”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0329] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 scFv (anti-LAMA2 scFv1); a second anti-LAMA2 scFv

(anti-LAMA2 scFv2); a first unit of second binding moiety comprising a DLL1 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-LAMA2 scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-LAMA2 scFv2. Anti-LAMA2 scFv1 and anti-LAMA2 scFv2 can be the same or different. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 227 (hereinafter denoted as “DLL1 wt-Fc-LG21 scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0330] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 scFv (anti-LAMA2 scFv1); a second anti-LAMA2 scFv (anti-LAMA2 scFv2); a first unit of second binding moiety comprising a DLL3 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL3 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-LAMA2 scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-LAMA2 scFv2. Anti-LAMA2 scFv1 and anti-LAMA2 scFv2 can be the same or different. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the

amino acid sequence of SEQ ID NO: 131. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 228 (hereinafter denoted as “DLL3wt-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0331] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 scFv (anti-LAMA2 scFv1); a second anti-LAMA2 scFv (anti-LAMA2 scFv2); a first unit of second binding moiety comprising a Jag1 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-LAMA2 scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-LAMA2 scFv2. Anti-LAMA2 scFv1 and anti-LAMA2 scFv2 can be the same or different. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 229 (hereinafter denoted as “Jag1wt-Fc-LG21scFv”). In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 134. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 230 (hereinafter denoted as “Jag1v-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain

comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0332] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-LAMA2 scFv (anti-LAMA2 scFv1); a second anti-LAMA2 scFv (anti-LAMA2 scFv2); a first unit of second binding moiety comprising a Jag2 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-LAMA2 scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-LAMA2 scFv2. Anti-LAMA2 scFv1 and anti-LAMA2 scFv2 can be the same or different. In some embodiments, anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 231 (hereinafter denoted as “Jag2wt-Fc-LG21scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0333] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan scFv (anti-matriglycan scFv1); a second anti-matriglycan scFv (anti-matriglycan scFv2); a first unit of second binding moiety comprising a DLL4 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-matriglycan scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second

subunit of the Fc domain – optional linker – anti-matriglycan scFv2. Anti-matriglycan scFv1 and anti-matriglycan scFv2 can be the same or different. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188 or 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0334] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 232 (hereinafter denoted as “DLL4wt-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0335] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 127. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 233 (hereinafter denoted as “DLL4v-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0336] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 128. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 234 (hereinafter denoted as “DLL4max-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some

embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0337] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 129. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 235 (hereinafter denoted as “DLL4di-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0338] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan scFv (anti-matriglycan scFv1); a second anti-matriglycan scFv (anti-matriglycan scFv2); a first unit of second binding moiety comprising a DLL1 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-matriglycan scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-matriglycan scFv2. Anti-matriglycan scFv1 and anti-matriglycan scFv2 can be the same or different. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 236 (hereinafter denoted as “DLL1wt-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0339] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan scFv (anti-matriglycan scFv1); a second anti-matriglycan

scFv (anti-matriglycan scFv2); a first unit of second binding moiety comprising a DLL3 ECD or a variant thereof; a second unit of a second binding moiety comprising a DLL3 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-matriglycan scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-matriglycan scFv2. Anti-matriglycan scFv1 and anti-matriglycan scFv2 can be the same or different. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 237 (hereinafter denoted as “DLL3wt-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0340] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan scFv (anti-matriglycan scFv1); a second anti-matriglycan scFv (anti-matriglycan scFv2); a first unit of second binding moiety comprising a Jag1 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-matriglycan scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-matriglycan scFv2. Anti-matriglycan scFv1 and anti-matriglycan scFv2 can be the same or different. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the

variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 238 (hereinafter denoted as “Jag1wt-Fc-ADG41scFv”). In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 134. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 239 (hereinafter denoted as “Jag1v-Fc-ADG41scFv”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0341] In some embodiments, there is provided a bifunctional protein construct comprising: a first anti-matriglycan scFv (anti-matriglycan scFv1); a second anti-matriglycan scFv (anti-matriglycan scFv2); a first unit of second binding moiety comprising a Jag2 ECD or a variant thereof; a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof; and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – anti-matriglycan scFv1; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – anti-matriglycan scFv2. Anti-matriglycan scFv1 and anti-matriglycan scFv2 can be the same or different. In some embodiments, anti-matriglycan scFv1 and/or anti-matriglycan scFv2 comprises the amino acid sequence of SEQ ID NO: 155. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 240 (hereinafter denoted as “Jag2wt-Fc-ADG41scFv”). In some

embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0342] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising LAMA2 LG4-5, a second non-antibody moiety comprising LAMA2 LG4-5, a first unit of a second binding moiety comprising a DLL4 ECD or a variant thereof, a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188 or 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0343] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 241 (hereinafter denoted as “DLL4wt-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0344] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 127. In some embodiments, there is provided a bifunctional protein construct comprising a

first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 242 (hereinafter denoted as “DLL4v-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0345] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 128. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 243 (hereinafter denoted as “DLL4max-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0346] In some embodiments, the first and second units of the second binding moiety each comprises a variant DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 129. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 244 (hereinafter denoted as “DLL4di-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0347] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising LAMA2 LG4-5, a second non-antibody moiety comprising LAMA2 LG4-5, a first unit of a second binding moiety comprising a DLL1 ECD or a variant thereof, a second unit of a second binding moiety comprising a DLL1 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the first unit

of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 245 (hereinafter denoted as “DLL1wt-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0348] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising LAMA2 LG4-5, a second non-antibody moiety comprising LAMA2 LG4-5, a first unit of a second binding moiety comprising a DLL3 ECD or a variant thereof, a second unit of a second binding moiety comprising a DLL3 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety– optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 246 (hereinafter denoted as “DLL3wt-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0349] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising LAMA2 LG4-5, a second non-antibody moiety comprising LAMA2 LG4-5, a first unit of a second binding moiety comprising a Jag1 ECD or a variant thereof, a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety– optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 247 (hereinafter denoted as “Jag1 wt-Fc-LG4-5”). In some embodiments, the first and second units of the second binding moiety each comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 134. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 248 (hereinafter denoted as “Jag1 v-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0350] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising LAMA2 LG4-5, a second non-antibody moiety comprising LAMA2 LG4-5, a first unit of a second binding moiety comprising a Jag2 ECD or a variant thereof, a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit;

wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety— optional linker — the first subunit of the Fc domain — optional linker — the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety — optional linker — the second subunit of the Fc domain — optional linker — the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 119. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 249 (hereinafter denoted as “Jag2wt-Fc-LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0351] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a DLL4 ECD or a variant thereof, a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety— optional linker — the first subunit of the Fc domain — optional linker — the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety — optional linker — the second subunit of the Fc domain — optional linker — the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL4 ECD or a variant thereof, and wherein the DLL4 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 339. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same

or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 321 (hereinafter denoted as “DLL4(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 345. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0352] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a DLL1 ECD or a variant thereof, a second unit of a second binding moiety comprising a DLL1 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety— optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD or a variant thereof, and wherein the DLL1 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 340. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 324 (hereinafter denoted as “DLL1(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 345. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0353] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a Jag1 ECD or a variant thereof, a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof, and an Fc domain comprising a first subunit and

a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety— optional linker — the first subunit of the Fc domain — optional linker — the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety — optional linker — the second subunit of the Fc domain — optional linker — the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag1 ECD or a variant thereof, and wherein the Jag1 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 341. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 327 (hereinafter denoted as “Jagged1(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 345. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0354] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a Jag2 ECD or a variant thereof, a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety— optional linker — the first subunit of the Fc domain — optional linker — the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety — optional linker — the second subunit of the Fc domain — optional linker — the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD or a variant thereof, and wherein the Jag2 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 342. The first and second units of the second binding

moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 330 (hereinafter denoted as “Jagged-2(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 345. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0355] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a DLL4 ECD or a variant thereof, a second unit of a second binding moiety comprising a DLL4 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety– optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL4 ECD or a variant thereof, and wherein the DLL4 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 339. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 331 (hereinafter denoted as “DLL4(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 346. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0356] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a DLL1 ECD or a variant thereof, a second unit of a second binding moiety

comprising a DLL1 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety– optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD or a variant thereof, and wherein the DLL1 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 340. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 332 (hereinafter denoted as “DLL1(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 346. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0357] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a Jag1 ECD or a variant thereof, a second unit of a second binding moiety comprising a Jag1 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety– optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag1 ECD or a variant thereof, and wherein the Jag1 ECD or a variant thereof comprises the

amino acid sequence of SEQ ID NO: 341. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 333 (hereinafter denoted as “Jagged1(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 346. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0358] In some embodiments, there is provided a bifunctional protein construct comprising: a first non-antibody moiety comprising laminin-a2 LG4-5, a second non-antibody moiety comprising laminin-a2 LG4-5, a first unit of a second binding moiety comprising a Jag2 ECD or a variant thereof, a second unit of a second binding moiety comprising a Jag2 ECD or a variant thereof, and an Fc domain comprising a first subunit and a second subunit; wherein the bifunctional protein construct comprises: i) a first polypeptide comprising from N' to C': the first unit of the second binding moiety – optional linker – the first subunit of the Fc domain – optional linker – the first non-antibody moiety; and ii) a second polypeptide comprising from N' to C': the second unit of the second binding moiety – optional linker – the second subunit of the Fc domain – optional linker – the second non-antibody moiety. The first and second non-antibody moieties can be the same or different. In some embodiments, the first non-antibody moiety and/or the second non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 343. In some embodiments, the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD or a variant thereof, and wherein the Jag2 ECD or a variant thereof comprises the amino acid sequence of SEQ ID NO: 342. The first and second units of the second binding moiety can be the same or different; and/or can bind to the same or different Notch receptor. In some embodiments, there is provided a bifunctional protein construct comprising a first polypeptide and a second polypeptide each comprising the amino acid sequence of SEQ ID NO: 334 (hereinafter denoted as “Jagged2(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5”). In some embodiments, each subunit of Fc domain comprises the amino acid sequence of SEQ ID NO: 346. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0359] In some embodiments, the bifunctional construct comprises the amino acid sequence of any one of SEQ ID NOs: 250-252.

[0360] In some embodiments, the bifunctional constructs provided herein can comprise a first unit of a first binding moiety comprising two or more LAMA2 LG4-5 connected in tandem, and a second unit of a first binding moiety comprising two or more LAMA2 LG4-5 connected in tandem. The first and second units of the first binding moiety can be the same or different.

Heterodimeric fusions

[0361] The bifunctional protein constructs described herein (e.g., comprising an Fc domain comprising a first subunit and a second subunit) may comprise two or more different polypeptide chains. In some embodiments, the bifunctional protein construct is heterodimeric. In some embodiments, there is provided a bifunctional protein construct comprising a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a muscle-specific molecule, a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a Notch receptor and activating the Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein: i) the first binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional first linker, and the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional second linker; or ii) the first binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional first linker, and the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional second linker. In some embodiments, the Fc domain comprises knob-into-hole mutations and/or charged-pair mutations. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional

linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0362] In some embodiments, the bifunctional protein construct comprises an Fc domain comprising a first subunit and a second subunit, wherein one subunit of the Fc domain is fused to a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a muscle-specific molecule (at N-terminus, C-terminus, or both), and the other subunit of the Fc domain is fused to a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a Notch receptor and activating the Notch receptor (at N-terminus, C-terminus, or both). The bifunctional protein construct can comprise two or more units of the first binding moiety, and/or two or more units of the second binding moiety. The two or more units of the first binding moiety can be the same or different. The two or more units of the second binding moiety can be the same or different. In some embodiments, there is provided a bifunctional protein constructs comprising: a first binding moiety comprising a Fab specifically binding to a muscle-specific molecule, a second binding moiety (e.g., comprising a Notch ligand ECD or variant thereof) specifically binding to a Notch receptor and activating the Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the Fab comprises a first polypeptide comprising VH-CH1 and a second polypeptide comprising VL-CL, wherein the C-terminus of the CH1 or CL of the Fab is fused to the N-terminus of the first subunit of the Fc domain via an optional first linker, and wherein the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional second linker. In some embodiments, the muscle-specific molecule is selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the first binding moiety comprises an anti-matriglycan Fab, such as an anti-matriglycan Fab comprising a first polypeptide comprising the amino acid sequence of SEQ ID NO: 176, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, the first binding moiety comprises an anti-LAMA2 Fab, such as an anti-LAMA2 Fab comprising a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-

hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0363] In some embodiments, there is provided a bifunctional protein construct comprising: i) a first unit of a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a first Notch receptor and activating the first Notch receptor, ii) a second unit of a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a second Notch receptor and activating the second Notch receptor; iii) a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a muscle-specific molecule; and iv) an Fc domain comprising a first subunit and a second subunit; wherein the first unit of the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional first linker, and the second unit of the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional second linker; and wherein the first binding moiety is fused to the C-terminus of either the first subunit of the Fc domain or the second subunit of the Fc domain via an optional third linker. In some embodiments, the bifunctional protein construct comprises: i) a first unit of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a first muscle-specific molecule, and ii) a second unit of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a second muscle-specific molecule; wherein the first unit of the first binding moiety is fused to the C-terminus of the first subunit of the Fc domain via an optional third linker, and the second unit of the first binding moiety is fused to the C-terminus of the second subunit of the Fc domain via an optional fourth linker. In some embodiments, the optional linker is a peptide linker, which can be the same or different within the bifunctional protein construct. In some embodiments,

the muscle-specific molecule is independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0364] In some embodiments, there is provided a bifunctional protein construct comprising: one or more units of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to one or more muscle-specific molecules, a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a Notch receptor and activating the Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional linker; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the C-terminus of the first subunit of the Fc domain; ii) the N-terminus of the second subunit of the Fc domain; and iii) the C-terminus of the second subunit of the Fc domain. In some embodiments, the optional linker is a peptide linker, which can be the same or different within the bifunctional protein construct. In some embodiments, the one or more muscle-specific molecules is independently selected from the group consisting of LAMA2, CDH15,

α -DG, and matriglycan on α -DG. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0365] In some embodiments, there is provided a bifunctional protein construct comprising: one or more units of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to one or more muscle-specific molecules, a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a Notch receptor and activating the Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional linker; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the N-terminus of the first subunit of the Fc domain; ii) the C-terminus of the first subunit of the Fc domain; and iii) the C-terminus of the second subunit of the Fc domain. In some embodiments, the optional linker is a peptide linker, which can be the same or different within the bifunctional protein construct. In some embodiments, the one or more muscle-specific molecules is independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting

of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0366] In some embodiments, there is provided a bifunctional protein construct comprising: i) a first unit of a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a first Notch receptor and activating the first Notch receptor, ii) a second unit of a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a second Notch receptor and activating the second Notch receptor; iii) a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a muscle-specific molecule; and iv) an Fc domain comprising a first subunit and a second subunit; wherein the first unit of the second binding moiety is fused to the C-terminus of the first subunit of the Fc domain via an optional first linker, and the second unit of the second binding moiety is fused to the C-terminus of the second subunit of the Fc domain via an optional second linker; and wherein the first binding moiety is fused to the N-terminus of either the first subunit of the Fc domain or the second subunit of the Fc domain via an optional third linker. In some embodiments, the bifunctional protein construct comprises: i) a first unit of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a first muscle-specific molecule, and ii) a second unit of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a second muscle-specific molecule; wherein the first unit of the first binding moiety is fused to the N-terminus

of the first subunit of the Fc domain via an optional third linker, and the second unit of the first binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional fourth linker. In some embodiments, the optional linker is a peptide linker, which can be the same or different within the bifunctional protein construct. In some embodiments, the muscle-specific molecule is independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the second binding moiety (one or both units) comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety (one or both units) comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0367] In some embodiments, there is provided a bifunctional protein construct comprising: one or more units of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to one or more muscle-specific molecules, a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a Notch receptor and activating the Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the second binding moiety is fused to the C-terminus of the first subunit of the Fc domain via an optional linker; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the N-terminus of the first subunit of the Fc domain; ii) the N-terminus of the second

subunit of the Fc domain; and iii) the C-terminus of the second subunit of the Fc domain. In some embodiments, the one or more muscle-specific molecules is independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0368] In some embodiments, there is provided a bifunctional protein construct comprising: one or more units of a first binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to one or more muscle-specific molecules, a second binding moiety (e.g., scFv, Fab, sdAb, or non-antibody moiety) specifically binding to a Notch receptor and activating the Notch receptor, and an Fc domain comprising a first subunit and a second subunit; wherein the second binding moiety is fused to the C-terminus of the second subunit of the Fc domain via an optional linker; and wherein each of the one or more units of the first binding moiety is independently fused via an optional linker to one of: i) the N-terminus of the first subunit of the Fc domain; ii) the C-terminus of the first subunit of the Fc domain; and iii) the N-terminus of the second subunit of the Fc domain. In some embodiments, the one or more muscle-specific molecules is independently selected from the group consisting of LAMA2, CDH15, α -DG, and matriglycan on α -DG. In some

embodiments, the second binding moiety comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). In some embodiments, the second binding moiety comprises the amino acid sequence of any of SEQ ID NOs: 126-135 and 260-267. In some embodiments, the Fc domain comprises knob-into-hole mutations, wherein: i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation. In some embodiments, the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering). In some embodiments, each subunit of the Fc domain further comprises an L234A/L235A/H435A mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188. In some embodiments, each subunit of the Fc domain comprises an L234A/L235A/P329G “LALALPG” mutation (EU numbering). In some embodiments, the Fc domain is derived from human IgG1, and wherein each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 277. In some embodiments, the optional linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

[0369] In some embodiments, the bifunctional protein constructs provided herein comprises i) one or more units of a second binding moiety each independently comprising an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267); and ii) one or more units of a first binding moiety each independently comprising an antibody moiety specifically binding to a muscle-specific molecule, optionally wherein the antibody moiety is independently selected from the group consisting of an scFv, a Fab, and an sdAb. In some embodiments, i) the two or more units of the second binding moiety are the same; and/or ii) the two or more units of the first binding moiety are the same. In some embodiments, i) the two or more units of the second binding moiety are different; and/or ii) at least one of the two or more units of the first binding moiety is different from the other(s).

[0370] For Fc-containing bifunctional protein constructs comprising two or more different polypeptide chains (e.g., heterodimeric bifunctional protein constructs), the Fc domain comprising knob-into-hole mutations and/or charged-pair mutations may be used. In

some embodiments, the Fc domain comprises charged-pair mutations, wherein an amino acid residue in the first subunit of the Fc domain is replaced with a positively charged residue, and an amino acid residue in the second subunit of the Fc domain is replaced with a negatively charged residue. In some embodiments, the Fc domain comprises charged-pair mutations, wherein an amino acid residue in the first subunit of the Fc domain is replaced with a negatively charged residue, and an amino acid residue in the second subunit of the Fc domain is replaced with a positively charged residue. In some embodiments, the Fc domain comprises charged-pair mutations, wherein an amino acid residue at D399 (EU numbering) in the first subunit of the Fc domain is replaced with a positively charged residue, and an amino acid residue at K409 (EU numbering) in the second subunit of the Fc domain is replaced with a negatively charged residue. In some embodiments, the Fc domain comprises charged-pair mutations, wherein an amino acid residue at K409 (EU numbering) in the first subunit of the Fc domain is replaced with a negatively charged residue, and an amino acid residue at D399 (EU numbering) in the second subunit of the Fc domain is replaced with a positively charged residue. In some embodiments, the bifunctional protein construct comprises the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 348, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 255. In some embodiments, the bifunctional protein construct comprises the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 255, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 348. In some embodiments, the bifunctional protein construct comprises the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 256, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 257. In some embodiments, the bifunctional protein construct comprises the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 257, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 256. In some embodiments, the bifunctional protein construct comprises the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 258, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 259. In some embodiments, the bifunctional protein construct comprises the first subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 259, and the second subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 258.

A. First Binding Moiety Specifically Binding to Muscle-specific Molecules

Muscle-specific Molecules

[0371] The muscle-specific molecules allow the bifunctional protein construct to be preferentially delivered and anchored to muscle tissues. The first binding moiety of the bifunctional protein constructs described herein specifically bind to a muscle-specific molecule. In some embodiments, the muscle-specific molecule is expressed only in muscle cells or tissue. In some embodiments, the muscle-specific molecule is a molecule primarily expressed in muscle cells or tissue, compared to cells or tissues of organs that are not muscle. In some embodiments, the muscle-specific molecule is also expressed in a cells or tissues of organs that are not muscle. In some embodiments, the muscle-specific molecule is a target antigen on the sarcolemma, between the sarcolemma and the basal lamina, or in the basal lamina. In some embodiments, the target antigen is selected from the group consisting of laminin, agrin, nidogen, perlecan, and M-cadherin (CDH15).

[0372] In some embodiments, the target antigen is a component of the dystrophin-associated glycoprotein complex (DGC). In some embodiments, the target antigen is selected from the group consisting of α -dystroglycan (α -DG), β -DG, laminin, perlecan, collagen (e.g., Type IV collagen), α -sarcoglycan, β -sarcoglycan, γ -sarcoglycan, δ -sarcoglycan, ϵ -sarcoglycan, ζ -sarcoglycan, biglycan, sarcospan, and matriglycan on α -DG. In some embodiments, the target antigen is a laminin subunit alpha-2 (LAMA2), ADG41, CDH15, α -DG, or matriglycan on α -DG.

[0373] The first binding moiety can comprise an antibody moiety or a non-antibody moiety that specifically binds to the muscle-specific molecule. In some embodiments, the antibody moiety is selected from the group consisting of a full-length antibody, a Fab, a Fab', a F(ab')₂, an scFv, and an sdAb. A list of antibody moieties that specifically binding to muscle-specific molecules is presented in **Table 8**.

Table 8: Antibody or Non-antibody Moieties that Bind Muscle-Specific Molecules

Muscle-targeting antibody	Muscle specific proteins	Epitope or epitope region
Laminin-211 antibody	Laminin-211 alpha-2 chain	alpha-2 chain
Anti-laminin a-2 from Abnova, clone 2D4	Laminin-211 alpha-2 chain	amino acid sequence 3013 ~ 3122 of human laminin-alpha-2
LAMA2 monoclonal antibody (M02), clone 1A7	Laminin-211 alpha-2 chain	amino acid sequence 3013 ~ 3122 of human laminin-alpha-2
LAMA2 mAb, clone CL3450	Laminin-211 alpha-2 chain	in LG1 domain

Laminin-alpha-2 mAbs in US patent publication US2018/0237511	Laminin-211 alpha-2 chain	LG-4-5 domain
alpha-Dystroglycan antibody	alpha-dystroglycan	alpha-dystroglycan
Matriglycan antibody IIH6	O-glycans on alpha-dystroglycan	O-glycans on alpha-dystroglycan
Matriglycan antibody VIA-4	O-glycans on alpha-dystroglycan	O-glycans on alpha-dystroglycan
beta-Dystroglycan antibody	beta-dystroglycan	Extracellular region
beta-Dystroglycan mAbs in US patent publication US2018/0237511	beta-Dystroglycan	Extracellular region of beta-Dystroglycan
α -sarcoglycan antibody	α -sarcoglycan	Extracellular region
β -sarcoglycan antibody	β -sarcoglycan	Extracellular region
γ -sarcoglycan antibody	γ -sarcoglycan	Extracellular region
δ -sarcoglycan antibody	δ -sarcoglycan	Extracellular region
ϵ -sarcoglycan antibody	ϵ -sarcoglycan	Extracellular region
ζ -sarcoglycan antibody	ζ -sarcoglycan	Extracellular region
Sarcospan antibody	Sarcospan	Extracellular region
Biglycan antibody	Biglycan	Biglycan
Muscle-targeting alternative	Functional domain(s)	Binding Partner
Laminin-111 alpha-1 chain	LG domain 1-5	O-glycans on alpha-dystroglycan
Laminin-211 alpha-2 chain	LG domain 1-5	O-glycans on alpha-dystroglycan
Laminin-411 alpha-4 chain	LG domain 1-5	O-glycans on alpha-dystroglycan
Laminin-511 alpha-5 chain	LG domain 1-5	O-glycans on alpha-dystroglycan
Perlecan	LG domains	O-glycans on alpha-dystroglycan
Agrin	LG domain	O-glycans on alpha-dystroglycan
Agrin	N-terminal domain	Laminin coiled-coil region
Nidogens	Laminin gamma-ear binding domain	Laminin gamma ear

Anti-LAMA2 Antibody Moiety

[0374] In some embodiments, the first binding moiety comprises an anti-LAMA2 antibody moiety which specifically binds to LAMA2. Any of the anti-LAMA2 antibody moieties described herein can be used in the bifunctional protein constructs described herein. Means for binding to LAMA2 described herein can be any of the anti-LAMA2 antibody moieties described herein and functional equivalents thereof. The present application also provides novel anti-LAMA2 antibody moieties which can be used for purposes beyond being a component of the bifunctional protein constructs described herein.

[0375] In some embodiments, there is provided an anti- LAMA2 antibody construct comprising (or consisting essentially of, or consisting of) any of the anti- LAMA2 antibody moieties described herein. In some embodiments, the antibody is monospecific. In some embodiments, the antibody is multispecific (such as bispecific). Multispecific antibodies have

binding specificities for at least two different antigens or epitopes. In some embodiments, the antibody is monoclonal. In some embodiments, the antibody is polyclonal. In some embodiments, the antibody is ChIP-grade, or at least IP grade or western blot grade. The antibody can react with protein of interest from any organism, such as human, mouse, rabbit, rat, monkey, fruit fly, zebrafish, chicken, worms, bacteria, etc. In some embodiments, the antibody is chimeric, mouse, rabbit, rat, sheep, human, partially humanized, fully humanized, semi-synthetic, or fully-synthetic antibody.

[0376] Laminins are glycoproteins of the mammalian extracellular matrix. Laminins are heterotrimeric proteins made up of alpha, beta, and gamma chains. They are major constituents of the basal lamina and function in cell differentiation, migration, and adhesion. LAMA2 is the alpha 2 chain of laminin-2.

[0377] The anti-LAMA2 antibody moiety described herein can specifically bind to LAMA2 derived from any source, including but not limited to, dogs, cats, pigs, cows, sheep, goats, horses, rats, rabbits, hamsters, guinea pigs, monkeys, mice, and humans. In some embodiments, the LAMA2 is human LAMA2.

[0378] In some embodiments, the anti-LAMA2 antibody moiety binds to human LAMA2 only and does not bind to LAMA2 derived from another species. In some embodiments, the anti-LAMA2 antibody moiety has cross-species reactivity to LAMA2 other than human LAMA2, such as mouse or cynomolgus monkey LAMA2. Antibody moieties with cross-species reactivity can help extrapolate animal data to human clinical trials.

[0379] The anti-LAMA2 antibody moiety can be of any antibody format. In some embodiments, the anti-LAMA2 antibody moiety comprises a VH and a VL.

[0380] In some embodiments, there is provided an anti-LAMA2 antibody moiety comprising: i) a VH comprising an H-CDR1, an H-CDR2, and an H-CDR3, respectively comprising the amino acid sequence of an H-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an H-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an H-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VH having the amino acid sequence set forth in SEQ ID NO: 49, and ii) a VL comprising an L-CDR1, an L-CDR2, and an L-CDR3, respectively comprising the amino acid sequence of an L-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as

conserved substitutions)), an L-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an L-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VL having the amino acid sequence set forth in SEQ ID NO: 50.

[0381] In some embodiments, there is provided an anti-LAMA2 antibody moiety comprising a VH and a VL, wherein: (i) the VH comprises an H-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an H-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an H-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and (ii) the VL comprises an L-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an L-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an L-CDR3 comprising the amino acid sequence of SEQ ID NO: 6, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions).

[0382] In some embodiments (independent of or in addition to the CDR sequences described above), there is provided an anti-LAMA2 antibody moiety comprising a VH comprising the amino acid sequence of SEQ ID NO: 49, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more) amino acid sequence homology to SEQ ID NO: 49; and a VL comprising the amino acid sequence of SEQ ID NO: 50, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) amino acid sequence homology to SEQ ID NO: 50. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the CDRs. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more

of the framework regions (FRs). In some embodiments, the two or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in both CDRs and FRs.

[0383] In some embodiments, there is provided an anti-LAMA2 antibody moiety comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 6. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 49, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 50. In some embodiments, the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 49, and a VL comprising the amino acid sequence of SEQ ID NO: 50.

[0384] In some embodiments, there is provided an anti-LAMA2 antibody moiety comprising: i) a VH comprising an H-CDR1, an H-CDR2, and an H-CDR3, respectively comprising the amino acid sequence of an H-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an H-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an H-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VH having the amino acid sequence set forth in any one of SEQ ID NOs: 54-64, and ii) a VL comprising an L-CDR1, an L-CDR2, and an L-CDR3, respectively comprising the amino acid sequence of an L-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an L-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an L-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VL having the amino acid sequence set forth in any one of SEQ ID NOs: 65-73.

[0385] In some embodiments, there is provided an anti-LAMA2 antibody moiety comprising a VH and a VL, wherein: (i) the VH comprises an H-CDR1 comprising the amino acid sequence of any one of SEQ ID NO: 7, 13, 16, 19, 22, 25, 28, 31, and 34, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an H-CDR2 comprising the amino acid sequence of any one of SEQ ID NO: 8, 14, 17, 20, 23, 26, 29, 32, and 35, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an H-CDR3 comprising the amino acid sequence of any one of SEQ ID NO: 9, 15, 18, 21, 24, 27, 30, 33, and 36, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and (ii) the VL comprises an L-CDR1 comprising the amino acid sequence of any one of SEQ ID NO: 10, 37, 40, 43, and 46, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an L-CDR2 comprising the amino acid sequence of any one of SEQ ID NO: 11, 38, 41, 44, and 47, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an L-CDR3 comprising the amino acid sequence of any one of SEQ ID NO: 12, 39, 42, 45, and 48, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions).

[0386] In some embodiments (independent of or in addition to the CDR sequences described above), there is provided an anti-LAMA2 antibody moiety comprising a VH comprising the amino acid sequence of any one of SEQ ID NOs: 54-64, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more) amino acid sequence homology to any one of SEQ ID NOs: 54-64; and a VL comprising the amino acid sequence of any one of SEQ ID NOs: 65-73, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) amino acid sequence homology to any one of SEQ ID NOs: 65-73. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the CDRs. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the framework regions (FRs). In some embodiments, the two or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in both CDRs and FRs.

[0387] In some embodiments, there is provided an anti-LAMA2 antibody moiety comprising an HC-CDR1 comprising the amino acid sequence of any one of SEQ ID NO: 7, 13, 16, 19, 22, 25, 28, 31, and 34, an HC-CDR2 comprising the amino acid sequence of any one of SEQ ID NO: 8, 14, 17, 20, 23, 26, 29, 32, and 35, an HC-CDR3 comprising the amino acid sequence of any one of SEQ ID NO: 9, 15, 18, 21, 24, 27, 30, 33, and 36, an LC-CDR1 comprising the amino acid sequence of any one of SEQ ID NO: 10, 37, 40, 43, and 46, an LC-CDR2 comprising the amino acid sequence of any one of SEQ ID NO: 11, 38, 41, 44, and 47, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NO: 12, 39, 42, 45, and 48. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of any one of SEQ ID NOs: 54-64, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of any one of SEQ ID NOs: 65-73. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID

NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 54, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 55, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56,

and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 56, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 57, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2,

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HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 58, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1 (SEQ ID NO: 7), HC-CDR2 (SEQ ID NO: 26), and HC-CDR3 (SEQ ID NO: 9) of a VH comprising the amino acid sequence of SEQ ID NO: 59, and LC-CDR1 (SEQ ID NO: 10), LC-CDR2 (SEQ ID NO: 11), and LC-CDR3 (SEQ ID NO: 12) of a VL comprising the amino acid sequence of SEQ ID NO: 65. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 59, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL

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CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 60, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 65. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 66. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 68. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 61, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 62, and LC-

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sequence of SEQ ID NO: 64, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 69. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 70. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 71. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 72. In some embodiments, the anti-LAMA2 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 64, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 73. In some embodiments, the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of any one of SEQ ID NOs: 54-64, and a VL comprising the amino acid sequence of any one of SEQ ID NOs: 65-73. In some embodiments, the anti-LAMA2 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 7, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 9, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 10, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 12.

[0388] In some embodiments, the anti-LAMA2 antibody moiety comprises a VH selected from any of the exemplary VHs in Table 2 and a VL selected from any of the exemplary VLs in Table 3.

Table 2: Exemplary anti-LAMA2 VH

Notes	SEQ ID NO
anti-lama2 LG21 huVHpar	54
anti-lama2 LG21 huVH1	55
anti-lama2 LG21 huVH2	56
anti-lama2 LG21 huVH3	57
anti-lama2 LG21 huVH4	58
anti-lama2 LG21 huVH5	59
anti-lama2 LG21 huVH6	60
anti-lama2 LG21 huVH7	61
anti-lama2 LG21 huVH8	62
anti-lama2 LG21 huVH9	63

Notes	SEQ ID NO
anti-lama2 LG21 huVH10	64

Table 3: Exemplary anti-LAMA2 VL

Notes	SEQ ID NO
anti-lama2 LG21 huVLpar	65
anti-lama2 LG21 huVL1	66
anti-lama2 LG21 huVL2	67
anti-lama2 LG21 huVL3	68
anti-lama2 LG21 huVL4	69
anti-lama2 LG21 huVL5	70
anti-lama2 LG21 huVL6	71
anti-lama2 LG21 huVL7	72
anti-lama2 LG21 huVL8	73

[0389] In some embodiments, the anti-LAMA2 antibody moiety comprises a VH paired with a VL set forth in **Table 4**. In some embodiments, the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 65.

Table 4: Exemplary VH/VL combinations for an anti-LAMA2 antibody moiety

pair	VH	VL
1	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
2	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
3	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
4	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
5	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
6	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
7	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
8	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
9	anti-lama2 LG21 huVHpar (SEQ ID NO: 54)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
10	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
11	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
12	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
13	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
14	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
15	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)

pair	VH	VL
16	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
17	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
18	anti-lama2 LG21 huVH1 (SEQ ID NO: 55)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
19	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
20	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
21	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
22	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
23	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
24	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
25	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
26	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
27	anti-lama2 LG21 huVH2 (SEQ ID NO: 56)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
28	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
29	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
30	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
31	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
32	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
33	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
34	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
35	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
36	anti-lama2 LG21 huVH3 (SEQ ID NO: 57)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
37	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
38	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
39	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
40	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
41	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
42	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
43	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
44	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)

pair	VH	VL
45	anti-lama2 LG21 huVH4 (SEQ ID NO: 58)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
46	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
47	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
48	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
49	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
50	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
51	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
52	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
53	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
54	anti-lama2 LG21 huVH5 (SEQ ID NO: 59)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
55	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
56	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
57	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
58	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
59	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
60	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
61	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
62	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
63	anti-lama2 LG21 huVH6 (SEQ ID NO: 60)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
64	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
65	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
66	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
67	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
68	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
69	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
70	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
71	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
72	anti-lama2 LG21 huVH7 (SEQ ID NO: 61)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
73	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)

pair	VH	VL
74	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
75	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
76	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
77	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
78	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
79	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
80	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
81	anti-lama2 LG21 huVH8 (SEQ ID NO: 62)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
82	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
83	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
84	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
85	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
86	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
87	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
88	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
89	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
90	anti-lama2 LG21 huVH9 (SEQ ID NO: 63)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)
91	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVLpar (SEQ ID NO: 65)
92	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL1 (SEQ ID NO: 66)
93	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL2 (SEQ ID NO: 67)
94	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL3 (SEQ ID NO: 68)
95	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL4 (SEQ ID NO: 69)
96	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL5 (SEQ ID NO: 70)
97	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL6 (SEQ ID NO: 71)
98	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL7 (SEQ ID NO: 72)
99	anti-lama2 LG21 huVH10 (SEQ ID NO: 64)	anti-lama2 LG21 huVL8 (SEQ ID NO: 73)

[0390] In some embodiments, the anti-LAMA2 antibody moiety is an anti-LAMA2 scFv. In some embodiments, the anti-LAMA2 scFv comprises from N' to C': VH-optional linker-VL. In some embodiments, the anti-LAMA2 scFv comprises from N' to C': VL-optional

linker-VH. Any suitable linker (e.g., see “Linker” subsection below) can be used herein, including but are not limited to SEQ ID NO: 212. In some embodiments, the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 51. In some embodiments, the anti-LAMA2 scFv comprises the amino acid sequence of SEQ ID NO: 145 or 268.

[0391] In some embodiments, the anti-LAMA2 antibody moiety is an anti-LAMA2 Fab. In some embodiments, the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 52, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 53. In some embodiments, the anti-LAMA2 Fab comprises a first polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 55-64, and a second polypeptide comprising the amino acid sequence of any one of SEQ ID NOs: 65-73.

Anti-Matriglycan Antibody Moiety

[0392] In some embodiments, the first binding moiety comprises an anti-matriglycan antibody moiety which specifically binds to matriglycan on α -dystroglycan (α -DG). Any of the anti- α -DG antibody moieties described herein can be used in the bifunctional protein constructs described herein. Means for binding to matriglycan described herein can be any of the anti-matriglycan antibody moieties described herein and functional equivalents thereof. The present application also provides novel anti-matriglycan antibody moieties which can be used for purposes beyond being a component of the bifunctional protein constructs described herein.

[0393] In some embodiments, there is provided an anti-matriglycan antibody construct comprising (or consisting essentially of, or consisting of) any of the anti-matriglycan antibody moieties described herein. In some embodiments, the antibody is monospecific. In some embodiments, the antibody is multispecific (such as bispecific). Multispecific antibodies have binding specificities for at least two different antigens or epitopes. In some embodiments, the antibody is monoclonal. In some embodiments, the antibody is polyclonal. In some embodiments, the antibody is ChIP-grade, or at least IP grade or western blot grade. The antibody can react with protein of interest from any organism, such as human, mouse, rabbit, rat, monkey, fruit fly, zebrafish, chicken, worms, bacteria, etc. In some embodiments, the antibody is chimeric, mouse, rabbit, rat, sheep, human, partially humanized, fully humanized, semi-synthetic, or fully-synthetic antibody.

[0394] α -dystroglycan (α -DG), a laminin-binding protein and a component of the dystrophin associated glycoprotein complex (DGC), is uniquely modified on O-mannose sites by alternating xylose and glucuronic acid subunits, called matriglycan. Matriglycan is a

receptor for laminin-G domain-containing proteins. Matriglycan links α -DG to the basement membrane.

[0395] The anti-matriglycan antibody moiety described herein can specifically bind to matriglycan derived from any source, including but not limited to, dogs, cats, pigs, cows, sheep, goats, horses, rats, rabbits, hamsters, guinea pigs, monkeys, mice, and humans. In some embodiments, the matriglycan is human matriglycan.

[0396] In some embodiments, the anti-matriglycan antibody moiety binds to human matriglycan only and does not bind to matriglycan derived from another species. In some embodiments, the anti-matriglycan antibody moiety has cross-species reactivity to matriglycan other than human matriglycan, such as mouse or cynomolgus monkey matriglycan. Antibody moieties with cross-species reactivity can help extrapolate animal data to human clinical trials.

[0397] The anti-matriglycan antibody moiety can be of any antibody format. In some embodiments, the anti-matriglycan antibody moiety comprises a VH and a VL.

[0398] In some embodiments, the anti-matriglycan antibody moiety comprises: i) a VH comprising an H-CDR1, an H-CDR2, and an H-CDR3, respectively comprising the amino acid sequence of an H-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an H-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an H-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VH having the amino acid sequence set forth in any one of SEQ ID NOs: 89-93, and ii) a VL comprising an L-CDR1, an L-CDR2, and an L-CDR3, respectively comprising the amino acid sequence of an L-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an L-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an L-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VL having the amino acid sequence set forth in any one of SEQ ID NOs: 94-98.

[0399] In some embodiments, the anti-matriglycan antibody moiety comprising a VH and a VL, wherein: (i) the VH comprises an H-CDR1 comprising the amino acid sequence of

SEQ ID NO: 74 or 80, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an H-CDR2 comprising the amino acid sequence of SEQ ID NO: 75 or 81, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an H-CDR3 comprising the amino acid sequence of SEQ ID NO: 76 or 82, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and (ii) the VL comprises an L-CDR1 comprising the amino acid sequence of any one of SEQ ID NOs: 79, 83, and 86, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an L-CDR2 comprising the amino acid sequence of any one of SEQ ID NOs: 78, 84, and 87, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an L-CDR3 comprising the amino acid sequence of any one of SEQ ID NOs: 79, 85, and 88, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions).

[0400] In some embodiments (independent of or in addition to the CDR sequences described above), the anti-matriglycan antibody moiety comprises a VH comprising the amino acid sequence of any one of SEQ ID NOs: 89-93, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more) amino acid sequence homology to any one of SEQ ID NOs: 89-93; and a VL comprising the amino acid sequence of SEQ ID NO: 94-98, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) amino acid sequence homology to any one of SEQ ID NOs: 94-98. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the CDRs. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the framework regions (FRs). In some embodiments, the two or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in both CDRs and FRs.

[0401] In some embodiments, the anti-matriglycan antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 74 or 80, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75 or 81, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 76 or 82, an LC-CDR1 comprising the amino acid

sequence of any one of SEQ ID NO: 79, 83, and 86, an LC-CDR2 comprising the amino acid sequence of any one of SEQ ID NO: 78, 84, and 87, and an LC-CDR3 comprising the amino acid sequence of any one of SEQ ID NO: 79, 85, and 88. In some embodiments, the anti-matriglycan antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of any one of SEQ ID NOs: 89-93, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of any one of SEQ ID NOs: 94-98. In some embodiments, the anti-matriglycan antibody moiety comprises an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 89, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 94. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 90, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-

CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 91, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 92, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 95. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 96. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 93, and an LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 98. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising a VH comprising the amino acid sequence of any one of SEQ ID NOs: 89-93, and a VL comprising the amino acid sequence of any one of SEQ ID NOs: 94-98. In some embodiments, the anti-matriglycan antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 74, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising

the amino acid sequence of SEQ ID NO: 76, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 77, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 78, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 79. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 74, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 76, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 83, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 84, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 85.

[0402] In some embodiments, the anti-matriglycan antibody moiety comprises a VH selected from any of the exemplary VHs in Table 5 and a VL selected from any of the exemplary VLs in Table 6.

Table 5: Exemplary anti-ADG41 VH

Notes	SEQ ID NO
anti-ADG41 huVH1	90
anti-ADG41 huVH2	91
anti-ADG41 huVH3	92
anti-ADG41 huVH4	93

Table 6: Exemplary anti-ADG4 VL

Notes	SEQ ID NO
anti-ADG41 huVL1	95
anti-ADG41 huVL2	96
anti-ADG41 huVL3	97
anti-ADG41 huVL4	98

[0403] In some embodiments, there is provided an anti-matriglycan antibody moiety comprising a VH paired with a VL set forth in **Table 7**. In some embodiments, there is provided an anti-matriglycan antibody moiety comprising a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 95.

Table 7: Exemplary VH/VL combinations for an anti-ADG41 antibody moiety

pair	VH	VL
1	anti-ADG41 huVH1 (SEQ ID NO: 90)	anti-ADG41 huVL1 (SEQ ID NO: 95)
2	anti-ADG41 huVH1 (SEQ ID NO: 90)	anti-ADG41 huVL2 (SEQ ID NO: 96)
3	anti-ADG41 huVH1 (SEQ ID NO: 90)	anti-ADG41 huVL3 (SEQ ID NO: 97)

pair	VH	VL
4	anti-ADG41 huVH1 (SEQ ID NO: 90)	anti-ADG41 huVL4 (SEQ ID NO: 98)
5	anti-ADG41 huVH2 (SEQ ID NO: 91)	anti-ADG41 huVL1 (SEQ ID NO: 95)
6	anti-ADG41 huVH2 (SEQ ID NO: 91)	anti-ADG41 huVL2 (SEQ ID NO: 96)
7	anti-ADG41 huVH2 (SEQ ID NO: 91)	anti-ADG41 huVL3 (SEQ ID NO: 97)
8	anti-ADG41 huVH2 (SEQ ID NO: 91)	anti-ADG41 huVL4 (SEQ ID NO: 98)
9	anti-ADG41 huVH3 (SEQ ID NO: 92)	anti-ADG41 huVL1 (SEQ ID NO: 95)
10	anti-ADG41 huVH3 (SEQ ID NO: 92)	anti-ADG41 huVL2 (SEQ ID NO: 96)
11	anti-ADG41 huVH3 (SEQ ID NO: 92)	anti-ADG41 huVL3 (SEQ ID NO: 97)
12	anti-ADG41 huVH3 (SEQ ID NO: 92)	anti-ADG41 huVL4 (SEQ ID NO: 98)
13	anti-ADG41 huVH4 (SEQ ID NO: 93)	anti-ADG41 huVL1 (SEQ ID NO: 95)
14	anti-ADG41 huVH4 (SEQ ID NO: 93)	anti-ADG41 huVL2 (SEQ ID NO: 96)
15	anti-ADG41 huVH4 (SEQ ID NO: 93)	anti-ADG41 huVL3 (SEQ ID NO: 97)
16	anti-ADG41 huVH4 (SEQ ID NO: 93)	anti-ADG41 huVL4 (SEQ ID NO: 98)

[0404] In some embodiments, the anti-matriglycan antibody moiety is an anti-matriglycan scFv. In some embodiments, the anti-matriglycan scFv comprises from N' to C': VH-optional linker-VL. In some embodiments, the anti-matriglycan scFv comprises from N' to C': VL-optional linker-VH. Any suitable linker (e.g., see “Linker” subsection below) can be used herein, including but are not limited to SEQ ID NO: 212. In some embodiments, the anti-matriglycan antibody moiety comprises the amino acid sequence of SEQ ID NO: 99.

[0405] In some embodiments, the anti-matriglycan antibody moiety is an anti-matriglycan Fab. In some embodiments, the anti-matriglycan Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 100, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 101.

Anti-CDH15 Antibody Moiety

[0406] In some embodiments, the first binding moiety comprises an anti-CDH15 antibody moiety which specifically binds to CDH15. Any of the anti-CDH15 antibody moieties described herein can be used in the bifunctional protein constructs described herein. Means for binding to CDH15 described herein can be any of the anti-CDH15 antibody moieties described herein and functional equivalents thereof. The present application also

provides novel anti-CDH15 antibody moieties which can be used for purposes beyond being a component of the bifunctional protein constructs described herein.

[0407] Cadherin-15 (CDH15) is a member of the cadherin superfamily. Cadherins consist of an extracellular domain containing five cadherin domains, a transmembrane region, and a conserved cytoplasmic domain. CDH15 may be essential for myogenesis and may serve as a trigger for terminal muscle cell differentiation.

[0408] The anti-CDH15 antibody moiety described herein can specifically bind to CDH15 derived from any source, including but not limited to, dogs, cats, pigs, cows, sheep, goats, horses, rats, rabbits, hamsters, guinea pigs, monkeys, mice, and humans. In some embodiments, the CDH15 is human CDH15.

[0409] In some embodiments, the anti-CDH15 antibody moiety binds to human CDH15 only and does not bind to CDH15 derived from another species. In some embodiments, the anti-CDH15 antibody moiety has cross-species reactivity to CDH15 other than human CDH15, such as mouse or cynomolgus monkey CDH15. Antibody moieties with cross-species reactivity can help extrapolate animal data to human clinical trials.

[0410] The anti-CDH15 antibody moiety can be of any antibody format. In some embodiments, the anti-CDH15 antibody moiety comprises a VH and a VL.

[0411] In some embodiments, the anti-CDH15 antibody moiety comprises: i) a VH comprising an H-CDR1, an H-CDR2, and an H-CDR3, respectively comprising the amino acid sequence of an H-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an H-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an H-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)) within a reference VH having the amino acid sequence set forth in SEQ ID NO: 108, and ii) a VL comprising an L-CDR1, an L-CDR2, and an L-CDR3, respectively comprising the amino acid sequence of an L-CDR1 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), an L-CDR2 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions)), and an L-CDR3 (or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved

substitutions)) within a reference VL having the amino acid sequence set forth in SEQ ID NO: 109.

[0412] In some embodiments, the anti-CDH15 antibody moiety comprising a VH and a VL, wherein: (i) the VH comprises an H-CDR1 comprising the amino acid sequence of SEQ ID NO: 102, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an H-CDR2 comprising the amino acid sequence of SEQ ID NO: 103, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an H-CDR3 comprising the amino acid sequence of SEQ ID NO: 104, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and (ii) the VL comprises an L-CDR1 comprising the amino acid sequence of SEQ ID NO: 105, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); an L-CDR2 comprising the amino acid sequence of SEQ ID NO: 106, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions); and an L-CDR3 comprising the amino acid sequence of SEQ ID NO: 107, or a variant thereof comprising up to 3 (e.g., 3, 2, or 1) amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions).

[0413] In some embodiments (independent of or in addition to the CDR sequences described above), the anti-CDH15 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 108, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99%, or more) amino acid sequence homology to SEQ ID NO: 108; and a VL comprising the amino acid sequence of SEQ ID NO: 109, or a variant thereof having at least about 80% (e.g., at least about any of 85%, 90%, 95%, 96%, 97%, 98%, 99% or more) amino acid sequence homology to SEQ ID NO: 109. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the CDRs. In some embodiments, the one or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in one or more of the framework regions (FRs). In some embodiments, the two or more amino acid variations (e.g., insertions, deletions, and/or substitutions, such as conserved substitutions) are in both CDRs and FRs.

[0414] In some embodiments, the anti-CDH15 antibody moiety comprising an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 102, an HC-CDR2 comprising the

amino acid sequence of SEQ ID NO: 103, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 104, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 105, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 106, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 107. In some embodiments, the anti-CDH15 antibody moiety comprises HC-CDR1, HC-CDR2, and HC-CDR3 of a VH comprising the amino acid sequence of SEQ ID NO: 108, and LC-CDR1, LC-CDR2, and LC-CDR3 of a VL comprising the amino acid sequence of SEQ ID NO: 109. In some embodiments, the anti-CDH15 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 108, and a VL comprising the amino acid sequence of SEQ ID NO: 109.

[0415] In some embodiments, the anti-CDH15 antibody moiety is an anti-CDH15 scFv. In some embodiments, the anti-CDH15 scFv comprises from N' to C': VH-optional linker-VL. In some embodiments, the anti-CDH15 scFv comprises from N' to C': VL-optional linker-VH. Any suitable linker (e.g., see "Linker" subsection below) can be used herein, including but are not limited to SEQ ID NO: 212. In some embodiments, the anti-CDH15 scFv comprises the amino acid sequence of SEQ ID NO: 110.

[0416] In some embodiments, the anti-CDH15 antibody moiety is an anti-CDH15 Fab. In some embodiments, the anti-CDH15 Fab comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 111, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 112.

Non-Antibody Moiety

[0417] In some embodiments, the first binding moiety is a non-antibody binding moiety specifically binding to the muscle-specific molecule, for example a protein domain (e.g., a laminin G-like domain (LG domain)) of an extracellular matrix (ECM) protein that can bind to matriglycan. Means for binding to a muscle-tissue specific molecule described herein can be any of the non-antibody binding moieties described herein and functional equivalents thereof. A list of non-antibody moieties that specifically binding to muscle-specific molecules is presented in **Table 8**.

[0418] In some embodiments, the non-antibody moiety comprises a protein domain selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, an LG domain of perlecan, the laminin coiled-coil binding domain of agrin, and the laminin γ binding domain of nidogen.

[0419] In some embodiments, the non-antibody moiety provided herein comprises an LG domain of laminin. In some embodiments, the non-antibody moiety comprises an LG domain of any one of laminin subunit α -1 (LAMA1), LAMA2, laminin subunit α -3 (LAMA3), laminin subunit α -4 (LAMA4), or laminin subunit α -5 (LAMA5). In some embodiments, the non-antibody moiety comprises the amino acid sequence of any of SEQ ID NOs: 118-124. In some embodiments, the non-antibody moiety is a variant comprising a sequence having at least about 90% (e.g., at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) sequence identity to SEQ ID NOs: 118-124. In some embodiments, the non-antibody moiety comprises an LG domain of LAMA2. In some embodiments, the non-antibody moiety comprises LG4-5 domains of LAMA2 (LAMA2 LG4-5). In some embodiments, the LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 118 or 119.

[0420] In some embodiments, the non-antibody moiety comprises an LG domain of perlecan. In some embodiments, the non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 120.

[0421] In some embodiments, the non-antibody moiety comprises an LG domain of agrin. In some embodiments, the non-antibody moiety comprises the amino acid sequence of SEQ ID NO: 121.

[0422] In some embodiments, the non-antibody moiety comprises a laminin coiled-coil binding domain of agrin. In some embodiments, the laminin coiled-coil binding domain of agrin comprises the amino acid sequence of SEQ ID NO: 122. In some embodiments, the non-antibody moiety comprises a laminin α , β , and/or γ binding domain of agrin. In some embodiments, the non-antibody moiety comprises amino acids 1-271 of human agrin.

[0423] In some embodiments, the non-antibody moiety comprises a laminin γ binding domain of nidogen. In some embodiments, the laminin γ binding domain of nidogen comprises the amino acid sequence of SEQ ID NO: 123 or 124. In some embodiments, the non-antibody moiety comprises a C-terminal domain of human nidogen-1. In some embodiments, the C-terminal domain of human nidogen-1 comprises amino acids 390-1247 of human nidogen-1. In some embodiments, the non-antibody moiety comprises a C-terminal domain of human nidogen-2. In some embodiments, the C-terminal domain of human nidogen-2 comprises amino acids 515-1372 of human nidogen-2.

B. Second Binding Moiety Specifically Binding to a Notch Receptor and Activating the Notch Receptor

[0424] Notch signaling pathways play critical roles in cell-fate decision and differentiation in many tissues during embryonic and postnatal development. Satellite cells are muscle-resident stem cells responsible for the repair and regeneration of damaged muscles. One pathological feature of Duchenne muscular dystrophy (DMD) is the progressive depletion of satellite cells, leading to the failure of muscle repair. Satellite cells from mdx mice, a DMD mouse model, were found to have reduced activation of Notch signaling, which has been shown to be necessary to maintain satellite cell quiescence and self-renewal (*see, e.g., Bjornson, et al., Stem Cells. 2012, 30(2):232-42; Mourikis, et al., Stem Cells. 2012, 30(2):243-52*). More importantly and therapeutically relevant, they show in a mouse model that constitutive activation of Notch is sufficient to rescue the self-renewal deficiencies of mdx satellite cells, suggesting enhanced Notch signaling in muscles may be a therapeutic strategy to explore for treating muscular dystrophies (*see, e.g., Bjornson, et al., Stem Cells. 2012, 30(2):232-42; Mourikis, et al., Stem Cells. 2012, 30(2):243-52*). Nonetheless, constitutive activation of Notch signaling in transgenic mice with Notch intracellular C-terminal domain (NICD) inhibits myoblast differentiation and muscle injury repair (*see, e.g., Wen, et al., Mol Cell Biol. 2012, 32(12):2300-11*). Thus, to manipulate Notch signaling to enhance satellite cell renewal while maintaining myoblast differentiation for muscle regeneration and repair as a therapeutic approach for treating muscular dystrophy, a spatiotemporal control in the right place at the right time is required.

[0425] Four mammalian Notch receptor have been identified (Notch1, Notch2, Notch3, and Notch4). Notch receptors are activated by single-pass transmembrane ligands of the Delta, Serrate, Lag-2 (DSL) family, including Delta-like 1 (DLL1; *e.g., GenBank Accession No. NP005609*), Delta-like 3 (DLL3; *e.g., GenBank Accession Nos. NP_982353.1 or NP_058637.1*), Delta-like 4 (DLL4; *e.g., GenBank Accession No. NP_061947.1*), Jagged-1 (Jag1; *e.g., GenBank Accession No. AAC51731*), and Jagged-2 (Jag2; *e.g., GenBank Accession No. AAD15562*). The ligands are characterized by an N-terminus of Notch ligand (MNNL) region, a Delta/Serrate/LAG-2 (DSL) domain, and tandem epidermal growth factor (EGF)-like repeats within the extracellular domain. The extracellular domains of the Notch receptor and ligands interact leading to cleavage of Notch by furin-like convertase, ADAM (a disintegrin and metalloproteinase) metalloprotease, and/or a gamma secretase. The gamma-secretase-mediated cleavage generates and releases the Notch intracellular domain (NICD),

which translocates into the nucleus, where NICD binds to the transcription factor CSL (CBF1, Suppressor of Hairless, Lag-1) to induce expression of downstream target genes. *See, e.g., Chillakuri et al., Semin Cell Dev Biol., 2012, 23(4):421-8; Sekine et al., Arthritis Res Ther., 2012, 14(2):R45.*

[0426] DLL1, DLL3, and DLL4 are members of the Delta family of Notch ligands. DLL1 is a type I cell surface protein composed of an MNNL domain, DSL domain, and eight EGF-like repeats within the extracellular domain. The first two EGF-like domains of DLL1 are unusual in that they have very short loop sequences that resemble a motif seen in the OSM-11 protein in *C. elegans*. Further, DLL1 contains a PDZ-ligand domain on the cytosolic side of the ligand. The MNNL domain is amino acids 18-176, the DSL domain is amino acids 177-221, EGF-like repeat 1 is amino acids 226-254, EGF-like repeat 2 is amino acids 257-285, EGF-like repeat 3 is amino acids 292-325, EGF-like repeat 4 is amino acids 332-363, EGF-like repeat 5 is amino acids 370-402, EGF-like repeat 6 is amino acids 409-440, EGF-like repeat 7 is amino acids 447-478, and EGF-like repeat 8 is amino acids 485-516 of human DLL1. *See, e.g., Hirano et al., eLife, 2020, 9:e50979 and Chillakuri et al., Semin Cell Dev Biol., 2012, 23(4):421-8.*

[0427] DLL3 is the shortest of the mammalian Delta-like ligands, containing an MNNL domain, DSL domain, and six EGF-like repeats within the extracellular domain. The MNNL domain is amino acids 27-175, the DSL domain is amino acids 176-215, EGF-like repeat 1 is amino acids 216-249, EGF-like repeat 2 is amino acids 274-310, EGF-like repeat 3 is amino acids 312-351, EGF-like repeat 4 is amino acids 353-389, EGF-like repeat 5 is amino acids 391-427, and EGF-like repeat 6 is amino acids 429-465 of human DLL3. *See, e.g., Ladi et al., J Cell Biol., 2005, 170(6): 983-992.*

[0428] DLL4 is a type I cell surface protein composed of an MNNL domain, DSL domain, and eight EGF-like repeats within the extracellular domain. DLL4 contains a PDZ-ligand domain on the cytosolic side of the ligand. The MNNL domain is amino acids 27-172, the DSL domain is amino acids 173-217, EGF-like repeat 1 is amino acids 218-251, EGF-like repeat 2 is amino acids 252-282, EGF-like repeat 3 is amino acids 284-322, EGF-like repeat 4 is amino acids 324-360, EGF-like repeat 5 is amino acids 362-400, EGF-like repeat 6 is amino acids 402-438, EGF-like repeat 7 is amino acids 440-476, and EGF-like repeat 8 is amino acids 480-518 of human DLL4. *See, e.g., Hirano et al., eLife, 2020, 9:e50979 and Chillakuri et al., Semin Cell Dev Biol., 2012, 23(4):421-8;*

[0429] Jag1 and Jag2 are members of the Serrate family of Notch ligands. The Serrate family differs from the Delta family in that the Serrate family contain a cysteine-rich domain

(CRD) following the EGF-like repeats. Both Jag1 and Jag2 are composed of an MNL domain, DSL domain, 16 EGF-like repeats, and a CRD domain within the extracellular domain. The first two EGF-like domains of Jag1 and Jag2 are unusual in that they have very short loop sequences that resemble a motif seen in the OSM-11 protein in *C. elegans*. Further, Jag1 contains a PDZ-ligand domain on the cytosolic side of the ligand. *See, e.g., Chillakuri et al., Semin Cell Dev Biol.*, 2012, 23(4):421-8 and Kume, *J Angiogenesis Res.*, 2009, 1:8.

[0430] For human Jag1, the MNL domain is amino acids 34-184, the DSL domain is amino acids 185-229, EGF-like repeat 1 is amino acids 230-263, EGF-like repeat 2 is amino acids 264-294, EGF-like repeat 3 is amino acids 296-334, EGF-like repeat 4 is amino acids 336-372, EGF-like repeat 5 is amino acids 374-410, EGF-like repeat 6 is amino acids 412-448, EGF-like repeat 7 is amino acids 450-485, EGF-like repeat 8 is amino acids 487-523, EGF-like repeat 9 is amino acids 525-561, EGF-like repeat 10 is amino acids 586-627, EGF-like repeat 11 is amino acids 629-665, EGF-like repeat 12 is amino acids 667-703, EGF-like repeat 13 is amino acids 705-741, EGF-like repeat 14 is amino acids 744-780, EGF-like repeat 15 is amino acids 782-818. EGF-like repeat 16 is amino acids 820-856, and the CRD domain is amino acids 857-1067.

[0431] For human Jag 2, the MNL domain is amino acids 27-195, the DSL domain is amino acids 196-240, EGF-like repeat 1 is amino acids 241-274, EGF-like repeat 2 is amino acids 275-305, EGF-like repeat 3 is amino acids 307-345, EGF-like repeat 4 is amino acids 347-383, EGF-like repeat 5 is amino acids 385-421, EGF-like repeat 6 is amino acids 423-459, EGF-like repeat 7 is amino acids 461-496, EGF-like repeat 8 is amino acids 498-534, EGF-like repeat 9 is amino acids 536-572, EGF-like repeat 10 is amino acids 574-634, EGF-like repeat 11 is amino acids 636-672, EGF-like repeat 12 is amino acids 674-710, EGF-like repeat 13 is amino acids 712-748, EGF-like repeat 14 is amino acids 751-787, EGF-like repeat 15 is amino acids 789-825. EGF-like repeat 16 is amino acids 827-863, and the CRD domain is amino acids 864-1080.

Non-antibody Moiety

[0432] In some embodiments, the second binding moiety of any of the bifunctional protein construct provided herein comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2, such as any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NOs: 126-129 and 260-267). Means for binding to a Notch receptor described herein can be any of the Notch ligand ECD or variant described herein and functional equivalents thereof. In some embodiments, the

ECD or a variant thereof of a Notch ligand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 EGF-like domains. In some embodiments, the DLL1 ECD comprises EGF1-8 domains. In some embodiments, the DLL3 ECD comprises EGF1-6 domains. In some embodiments, the DLL4 ECD comprises EGF1-8 domains. In some embodiments, the Jag1 ECD comprises EGF1-16 domains. In some embodiments, the Jag2 ECD comprises EGF1-16 domains. In some embodiments, the ECD or variant thereof of a Notch ligand comprises a C2(MNNL) domain. In some embodiments, the ECD or variant thereof of a Notch ligand comprises a DSL domain. In some embodiments, the ECD or variant thereof of a Notch ligand comprises EGF1-3 domains, EGF1-4 domains, EGF1-4 domains, EGF1-5 domains, or EGF- 1-6 domains. In some embodiments, the ECD or a variant thereof of a Notch ligand comprises EGF1-5 domains. In some embodiments, the ECD or variant thereof of a Notch ligand comprises a C2(MNNL)-DSL-EGF1-3, C2(MNNL)-DSL-EGF1-4, C2(MNNL)-DSL-EGF1-5, or C2(MNNL)-DSL-EGF1-6 domain.

[0433] In some embodiments, the non-antibody moiety binds to a human Notch receptor described herein can be any of the Notch ligand ECD or variant described herein and functional equivalents thereof. In some embodiments, the non-antibody moiety has cross-species reactivity to a Notch receptor described herein can be any of the Notch ligand ECD or variant described herein and functional equivalents thereof, such as a mouse, rat, or cynomolgus monkey non-antibody moiety. Antibody moieties with cross-species reactivity can help extrapolate animal data to human clinical trials.

[0434] The present application provides engineered DLL ECDs, which can be incorporated into the bifunctional proteins described here. In some embodiments, there is provided an engineered DLL4 ECD, wherein the engineered DLL4 ECD comprises a mutation selected from the group consisting of T52N and T135N, and wherein the amino acid position is in reference to a reference DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the engineered DLL4 ECD further comprises a mutation at one or more amino acid positions selected from the group consisting of G2, E14, R66, P80, F81, H168, Q220, N231, and N26. In some embodiments, the further mutation is selected from the group consisting of G2S, E14H, R66S, R66T, P80L, F81L, H168Y, Q220H, N231D, and N260D. In some embodiments, the engineered DLL4 ECD comprises a mutation selected from the group consisting of: (i) T52N and T135N; (ii) T52N, R66S, and T135N; (iii) E14H, T52N, R66T, P80L, T135N, and N231D; (iv) T52N, R66T, P80L, T135N, Q220H, and N260D; (v) G2S, T52N, F81L, T135N, and H168Y; (vi) G2S, T52N, F81L, R66S, T135N, and H168Y; (vii) G2S,

E14H, T52N, F81L, R66T, P80L, T135N, H168Y, and N231D; and (viii) G2S, T52N, R66T, P80L, F81L, T135N, H168Y, Q220H, and N260D. In some embodiments, the engineered DLL4 ECD comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NOs: 261-264.

[0435] In some embodiments, there is provided an engineered DLL4 ECD, wherein the engineered DLL4 ECD comprises a mutation selected from the group consisting of G2, E14, T52, R66, P80, F81, T135, H168, Q220, N231, and N260, and wherein the amino acid position is in reference to a reference DLL4 ECD comprising the amino acid sequence of SEQ ID NO. In some embodiments, the mutation is selected from the group consisting of G2S, E14H, T52N, R66S, R66T, P80L, F81L, T135N, H168Y, Q220H, N231D, and N260D, and wherein the amino acid position is in reference to a reference DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126. In some embodiments, the engineered DLL4 ECD comprises a mutation selected from the group consisting of: (i) T52N and T135N; (ii) T52N, R66S, and T135N; (iii) E14H, T52N, R66T, P80L, T135N, and N231D; (iv) T52N, R66T, P80L, T135N, Q220H, and N260D; (v) G2S, T52N, F81L, T135N, and H168Y; (vi) G2S, T52N, F81L, R66S, T135N, and H168Y; (vii) G2S, E14H, T52N, F81L, R66T, P80L, T135N, H168Y, and N231D; and (viii) G2S, T52N, R66T, P80L, F81L, T135N, H168Y, Q220H, and N260D.

[0436] In some embodiments, the second binding moiety comprises a DLL4 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a DLL4 ECD, and optionally wherein the DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 125. In some embodiments, the second binding moiety comprises a variant DLL4 ECD, and optionally wherein the variant DLL4 ECD comprises an MNNL domain, a DSL domain, and/or an EGF1-5 domains of DLL4. In some embodiments, the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267, or a sequence having at least about 90% (e.g., at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) sequence identity to SEQ ID NOs: 126-129 and 260-267. In some embodiments, the variant DLL4 ECD comprises no more any of 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions in reference to SEQ ID NO: 126-129 and 260-267.

[0437] In some embodiments, the present invention also provides a protein construct comprising any of the engineered DLL4 ECDs described herein (e.g., any of SEQ ID NO: 126-129 and 260-267). In some embodiments, the protein construct is a bifunctional protein construct, such as any of the bifunctional protein constructs described herein comprising an engineered DLL4 ECD. In some embodiments, the protein construct further comprises a

binding moiety that specifically binds to a muscle-specific molecule. In some embodiments, the binding moiety that specifically binds to a muscle-specific molecule. In some embodiments, the muscle-specific molecule is a target antigen on the sarcolemma, between the sarcolemma and the basal lamina, or in the basal lamina. In some embodiments, the target antigen is selected from the group consisting of laminin, agrin, nidogen, perlecan, and M-cadherin (CDH15).

[0438] In some embodiments, the second binding moiety comprises a DLL1 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD of DLL1 comprises the amino acid sequence of SEQ ID NO: 130. In some embodiments, the second binding moiety comprises a variant DLL1 ECD, and optionally wherein the variant DLL1 ECD comprises a sequence having at least about 90% (e.g., at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) sequence identity to SEQ ID NOs: 130. In some embodiments, the variant DLL1 ECD comprises no more any of 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions in reference to SEQ ID NO: 130.

[0439] In some embodiments, the second binding moiety comprises a DLL3 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131. In some embodiments, the second binding moiety comprises a variant DLL3 ECD, and optionally wherein the variant DLL3 ECD comprises a sequence having at least about 90% (e.g., at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) sequence identity to SEQ ID NO: 131. In some embodiments, the variant DLL3 ECD comprises no more any of 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions in reference to SEQ ID NO: 131.

[0440] In some embodiments, the second binding moiety comprises a Jag1 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a Jag1 ECD, and wherein the Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 132. In some embodiments, the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises MNNL domain, DSL domain, and EGF1-6 domains of Jag1, or a sequence having at least about 90% (e.g., at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) sequence identity to the sequence of MNNL domain, DSL domain, and EGF1-6 domains of Jag1. In some embodiments, the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134.

[0441] In some embodiments, the second binding moiety comprises a Jag2 ECD or a variant thereof. In some embodiments, the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135. In some embodiments, the second binding moiety comprises a variant of Jag2 ECD, and optionally wherein the Jag2 ECD variant comprises a sequence having at least about 90% (e.g., at least about any of 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more) sequence identity to SEQ ID NO: 135. In some embodiments, the Jag2 ECD variant comprises no more any of 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 amino acid substitutions in reference to SEQ ID NO: 135.

[0442] In some embodiments, the non-antibody moiety further comprises an aptamer, a SOMAmer, a DARpin, or other engineered binding molecules or scaffolds. In some embodiments, the Notch activating moiety is conjugated to the 5' or 3' end of the aptamer or SOMAmer by chemical crosslinking.

Anti-Notch Antibody Moiety

[0443] In some embodiments, the second binding moiety is an anti-Notch antibody moiety that activates the Notch receptor. Anti-Notch antibodies capable of activating the Notch receptor (such as, e.g., Notch1, Notch2, Notch3, and Notch4) are known in the art, including, for example Asano *et al.*, *J Immunol.*, 180(5):2796-804 (2008); Hoare *et al.*, *Nat Cell Biol.*, 18(9):979-92 (2016); Falk *et al.*, *Methods.*, 58(1):69-78 (2012); Thermo Fisher Scientific Cat. # MA5-45604; Gerhardt *et al.*, *Genes Dev.*, 28(6):576-93 (2014); Adamia *et al.*, *Blood.*, 123(18):2816-25 (2014); Machuca-Parra *et al.*, *J Exp Med.*, 214(8):2271-2282 (2017); Xu *et al.*, *Structure.*, 23(7):1227-35 (2015); and Li *et al.*, *J Biol Chem.*, 283(12):8046-54 (2008). In some embodiments, the anti-Notch antibody moiety is selected from the group consisting of a full-length antibody, a Fab, a Fab', a F(ab')₂, an scFv, and an sdAb.

C. Linkers

[0444] The first binding moiety, the second binding moiety, and other components of bifunctional protein constructs described herein can be connected via one or more optional linkers. The domains within the first binding moiety can be connected via one or more optional linkers. The domains within the second binding moiety can be connected via one or more optional linkers.

[0445] In some embodiments, the linker is a peptide linker. The peptide linker may have a naturally occurring sequence, or a non-naturally occurring sequence. For example, a

sequence derived from the hinge region of heavy chain only antibodies may be used as the linker. See, for example, WO1996/034103.

[0446] The peptide linker can be of any suitable length. In some embodiments, the peptide linker is at least about any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35, 40, 50, 75, 100, or more, amino acids long. In some embodiments, the peptide linker is no more than about any of 100, 75, 50, 40, 35, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, or fewer, amino acids long. In some embodiments, the length of the peptide linker is any of about 1 amino acid to about 10 amino acids, about 1 amino acid to about 20 amino acids, about 1 amino acid to about 30 amino acids, about 5 amino acids to about 15 amino acids, about 10 amino acids to about 25 amino acids, about 5 amino acids to about 30 amino acids, about 10 amino acids to about 30 amino acids long, about 30 amino acids to about 50 amino acids, about 50 amino acids to about 100 amino acids, or about 1 amino acid to about 100 amino acids.

[0447] In some embodiments, the peptide linker does not comprise any polymerization activity. The characteristics of a peptide linker, which comprise the absence of the promotion of secondary structures, are known in the art and described, e.g., in Dall'Acqua et al. (Biochem. (1998) 37, 9266-9273), Cheadle et al. (Mol Immunol (1992) 29, 21-30) and Raag and Whitlow (FASEB (1995) 9(1), 73-80). In some embodiments, the peptide linker does not promote the formation of any secondary structures. The linkage of the domains to each other can be provided by, e.g., genetic engineering. Methods for preparing fused and operatively linked bispecific single chain constructs and expressing them in mammalian cells or bacteria are well-known in the art (e.g. WO1999/054440, Ausubel, Current Protocols in Molecular Biology, Green Publishing Associates and Wiley Interscience, N. Y. 1989 and 1994 or Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y., 2001).

[0448] The peptide linker can be a stable linker, which is not cleavable by proteases, especially by Matrix metalloproteinases (MMPs).

[0449] In some embodiments, the peptide linker is a flexible linker. Exemplary flexible linkers include glycine polymers (G)_n, where n is an integer of at least one, and glycine-serine polymers (including, for example, (GS)_n, where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art. In some embodiments, the linker is a GS linker.

[0450] In some embodiments, the peptide linker comprises the amino acid sequence of LE (SEQ ID NO: 222) or the amino acid sequence of any one of SEQ ID NOs: 207-221, 337

and 338. In some embodiments, the peptide linker comprises the amino acid sequence of any one of SEQ ID NOs: 211, 212, 337, and 338.

III. Methods of Making Binding Moieties and Bifunctional Protein Constructs

[0451] Also provided are methods of preparing any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) and bifunctional protein constructs described herein.

[0452] The bifunctional protein constructs and binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein can be made by introducing a nucleic acid into a host cell, allowing expression of the protein, and purifying the protein from the host cell extract or supernatant. Methods of making proteins constructs and constructing nucleic acids or vectors encoding thereof, as well as purifying protein constructs are known in the art. Also see US20220204602 and Examples 1 and 2 as described herein for exemplary methods.

[0453] Proteins comprising antibody moieties can be obtained using methods known in the art, such as by immunizing a non-human mammal and obtaining hybridomas therefrom, or by cloning a library of antibodies using molecular biology techniques known in the art and subsequence selection or by using phage display. Nucleic acid constructs encoding any one of the first binding moieties, second binding moieties, or bifunctional protein constructs described herein, vectors, and host cells for preparation are also provided.

[0454] The polypeptide portion of the bifunctional protein constructs or binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein may be prepared by any of the known protein expression and purification methods in the art. DNA sequence encoding the polypeptide portion of the bifunctional protein constructs or binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) can be fully synthesized. After obtaining such sequence, it is cloned into a suitable expression vector, then transfected into a suitable host cell. The transfected host cells are cultured, and the supernatant is harvested and purified to obtain the polypeptide portion of the bifunctional protein constructs or binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein. The antibody moieties described herein can also be obtained by conventional immunization methods, such as by immunizing a mammal (e.g., mouse, llama), and obtaining the antibody

moieties from the serum; or from a hybridoma, such as by fusing B cells from lymph nodes and/or spleen of immunized animal with myeloma cells. Purification can be followed.

[0455] The expression vectors may contain a variety of elements for controlling expression, including without limitation, promoter sequences, transcription initiation sequences, enhancer sequences, selectable markers, and signal sequences. These elements may be selected as appropriate by a person of ordinary skill in the art. For example, the promoter sequences may be selected to promote the transcription of the polynucleotide in the vector. Suitable promoter sequences include, without limitation, T7 promoter, T3 promoter, SP6 promoter, beta-actin promoter, EF1a promoter, CMV promoter, and SV40 promoter. Enhancer sequences may be selected to enhance the transcription of the nucleic acids. Selectable markers may be selected to allow selection of the host cells inserted with the vector from those not, for example, the selectable markers may be genes that confer antibiotic resistance. Signal sequences may be selected to allow the expressed polypeptide to be transported outside of the host cell.

[0456] In some embodiments, the two or more polypeptides of a bifunctional protein construct or a binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) are encoded by a single vector. In some embodiments, the two or more polypeptides of a bifunctional protein construct or a binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) are encoded by two or more vectors. In some embodiments the two or more polypeptides of a functional protein construct or a binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) are Host cells containing the vector may be useful in expression or cloning of the isolated nucleic acids. Suitable host cells can include, without limitation, prokaryotic cells, fungal cells, yeast cells, or higher eukaryotic cells such as mammalian cells. The expression of binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) in prokaryotic cells such as *E. coli* is well established in the art. For a review, see for example Pluckthun, A. *BioTechnology* 9: 545-551 (1991). Expression in eukaryotic cells in culture is also available to those skilled in the art as an option for production of antibodies or antigen-binding fragments thereof, see recent reviews, for example Ref, M. E. (1993) *Curr. Opinion Biotech.* 4: 573-576; Trill J. J. *et al.* (1995) *Curr. Opinion Biotech* 6: 553-560. Higher eukaryotic cells, in particular, those derived from multicellular organisms can be used for expression of glycosylated polypeptides. Suitable higher eukaryotic cells include, without

limitation, invertebrate cells and insect cells, and vertebrate cells. In some embodiments, the host cell is *E. coli*. In some embodiments, the host cell is a Chinese hamster ovary (CHO) cell or an HEK293 cell.

[0457] The vector can be introduced to the host cell using any suitable methods known in the art, including, but not limited to, DEAE-dextran mediated delivery, calcium phosphate precipitate method, cationic lipids mediated delivery, liposome mediated transfection, electroporation, microprojectile bombardment, receptor-mediated gene delivery, delivery mediated by polylysine, histone, chitosan, and peptides. Standard methods for transfection and transformation of cells for expression of a vector of interest are well known in the art. In some embodiments, the host cells comprise two or more vectors each encoding a polypeptide of any of the protein constructs or targeting moieties described herein. In some embodiments, the host cells comprise a single vector comprising isolated nucleic acids encoding two or more polypeptides of any of the bifunctional protein constructs or binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein. In some embodiments, the two or more vectors are introduced to the host cell at the same time. In some embodiments, the two or more vectors are introduced to the host cell sequentially.

[0458] In some embodiments, the present application provides methods of making the polypeptide portion of any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein, comprising i) culturing an isolated host cell comprising any of the isolated nucleic acids described herein or any of the vectors described herein, or any of the isolated host cells described herein, under a condition suitable for the expression of the polypeptide portion of any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein, and ii) obtaining the expressed polypeptide portion of any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein from said host cell (e.g., from the cell culture). In some embodiments, the method further comprises introducing one or more isolated nucleic acids or one or more vectors into the host cell. The isolated host cells are cultured under conditions that allow expression of the isolated nucleic acids inserted in the vectors. Suitable conditions for expression of polynucleotides may include, without limitation, suitable medium, suitable density of host cells in the culture medium, presence of necessary nutrients, presence of

supplemental factors, suitable temperatures and humidity, and absence of microorganism contaminants. A person with ordinary skill in the art can select the suitable conditions as appropriate for the purpose of the expression. In some embodiments, the methods of making further comprises purifying any of the obtained polypeptide portion of any of the binding (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) moieties or bifunctional protein constructs described herein.

[0459] In some embodiments, the polypeptides expressed by the host cell can assemble together (*e.g.*, form a polypeptide complex such as a dimer) and produce any of the polypeptide portion of any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein. In some embodiments, the polypeptide complex may be formed inside the host cell. For example, the polypeptide complex may be formed inside the host cell with the aid of relevant enzymes and/or cofactors. In some embodiments, the polypeptide complex may be secreted out of the cell. In some embodiments, individual polypeptides may be secreted out of the host cell then form a polypeptide complex outside of the host cell.

[0460] In some embodiments, the two or more polypeptides of any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein may be separately expressed and allowed to form (*e.g.*, dimerize) a protein complex under suitable conditions. For example, the first polypeptide and the second polypeptide may be combined in a suitable buffer and allow the first protein monomer and the second protein monomer to dimerize through appropriate interactions such as hydrophobic interactions. In some embodiments, the first polypeptide and the second polypeptide may be combined in a suitable buffer containing an enzyme and/or a cofactor which can promote the dimerization of the first polypeptide and the second polypeptide. In some embodiments, the first polypeptide and the second polypeptide may be combined in a suitable vehicle and allow them to react with each other in the presence of a suitable reagent and/or catalyst.

[0461] The expressed polypeptide(s) and/or the polypeptide complex can be collected using any suitable methods. The polypeptide(s) and/or the polypeptide complex can be expressed intracellularly, in the periplasmic space or be secreted outside of the cell into the medium. If the polypeptide and/or the polypeptide complex are expressed intracellularly, the host cells containing the polypeptide and/or the polypeptide complex may be lysed and polypeptide and/or the polypeptide complex may be isolated from the lysate by removing the

unwanted debris by centrifugation or ultrafiltration. If the polypeptide and/or the polypeptide complex is secreted into periplasmic space of *E. coli*, the cell paste may be thawed in the presence of agents such as sodium acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) for about 30 min, and cell debris can be removed by centrifugation (Carter *et al.*, BioTechnology 10:163-167 (1992)). If the polypeptide and/or the polypeptide complex is secreted into the medium, the supernatant of the cell culture may be collected and concentrated using a commercially available protein concentration filter, for example, an Amincon or Millipore Pellicon ultrafiltration unit. A protease inhibitor and/or an antibiotic may be included in the collection and concentration steps to inhibit protein degradation and/or growth of contaminated microorganisms.

[0462] The expressed polypeptide(s) and/or the polypeptide complex can be further purified by a suitable method, such as without limitation, affinity chromatography, hydroxylapatite chromatography, size exclusion chromatography, gel electrophoresis, dialysis, ion exchange fractionation on an ion-exchange column, ethanol precipitation, reverse phase HPLC, chromatography on silica, chromatography on heparin sepharose, chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation (*see*, for review, Bonner, P. L., Protein purification, published by Taylor & Francis. 2007; Janson, J. C., *et al.*, Protein purification: principles, high resolution methods and applications, published by Wiley-VCH, 1998).

[0463] In some embodiments, the polypeptides and/or polypeptide complexes can be purified by affinity chromatography. In some embodiments, protein A chromatography or protein A/G (fusion protein of protein A and protein G) chromatography can be useful for purification of polypeptides and/or polypeptide complexes comprising a component derived from antibody CH2 domain and/or CH3 domain (Lindmark *et al.*, J. Immunol. Meth. 62:1-13 (1983)); Zettlitz, K. A., Antibody Engineering, Part V, 531-535, 2010). In some embodiments, protein G chromatography can be useful for purification of polypeptides and/or polypeptide complexes comprising IgG γ 3 heavy chain (Guss *et al.*, EMBO J. 5:1567 1575 (1986)). In some embodiments, protein L chromatography can be useful for purification of polypeptides and/or polypeptide complexes comprising κ light chain (Sudhir, P., Antigen engineering protocols, Chapter 26, published by Humana Press, 1995; Nilson, B. H. K. *et al.*, J. Biol. Chem., 267, 2234-2239 (1992)). The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrenedivinyl) benzene allow for faster flow rates and shorter

processing times than can be achieved with agarose. Where any of the bifunctional protein constructs comprises an additional CH3 domain, the bakerbond ABX resin (J. T. Baker, Phillipsburg, N.J.) is useful for purification. In some embodiments, MabSelect SuRe is used for purification. In some embodiments, the method further comprises analyzing the purified protein product, such as by SDS-PAGE and/or SEC-HPLC.

Nucleic Acids and Vectors

[0464] In one aspect, provided herein is one or more nucleic acids (e.g., isolated) encoding one or more polypeptides of the bifunctional protein constructs, or various binding moieties described herein. The one or more nucleic acids can be RNA (e.g., mRNA) or DNA. In some embodiments, the one or more nucleic acids are mRNA(s) and the mRNA(s) is formulated in liposomes or lipid nanoparticles. Further provided are vectors comprising any of the nucleic acids (e.g., isolated nucleic acids) described herein, such as viral vectors (e.g., AAV vector or lentiviral vector).

[0465] Also contemplated here are isolated host cell comprising or expressing (e.g., one or more polypeptide components of) any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein. Also provided are isolated host cells comprising one or more nucleic acids encoding (e.g., one or more polypeptide components of) any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein. Also provided are isolated host cells comprising one or more vectors comprising one or more nucleic acids encoding (e.g., one or more polypeptide components of) any of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs described herein. In some embodiments, one vector comprises one or more isolated nucleic acids encoding the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct. In some embodiments, one vector comprises two or more isolated nucleic acids encoding two or more polypeptide components of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct. In some embodiments, two or more vectors comprise two or more isolated nucleic acids encoding two or more polypeptide components of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and

protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct. In some embodiments, the two or more isolated nucleic acids encoding two or more polypeptide components of the binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct are under the control of the same promoter on the same vector (e.g., linked via IRES, or nucleic acid encoding self-cleaving 2A peptide such as P2A, T2A, E2A, F2A, BmCPV 2A, BmIFV 2A in between), the same promoter on different vectors (e.g., both TetOn), different promoters on the same vector, or different promoters on different vectors (e.g., one is inducible, one is constitutive). In some embodiments, the host cell is a Chinese hamster ovary (CHO) cell or an HEK293 cell.

[0466] The present application also includes variants to these nucleic acid sequences. For example, the variants include nucleotide sequences that hybridize to the nucleic acid sequences encoding the bifunctional protein constructs or various binding moieties (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein under at least moderately stringent hybridization conditions. In some embodiments, the variants to nucleic acid sequences comprises degenerate nucleotide codes. Those skilled in the art can determine the different nucleotides comprising degenerate codons.

[0467] The present application also provides vectors in which a nucleic acid of the present application is inserted.

[0468] The nucleic acid(s) can be cloned into a number of types of vectors. For example, the nucleic acid(s) can be cloned into a vector including, but not limited to a plasmid, a phagemid, a phage derivative, an animal virus, and a cosmid. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors, and sequencing vectors.

[0469] Further, the expression vector may be provided to a cell in the form of a viral vector. Viral vector technology is well known in the art and is described, for example, in Sambrook *et al.* (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory, New York), and in other virology and molecular biology manuals. Viruses which are useful as vectors include, but are not limited to, retroviruses, adenoviruses, adeno-associated viruses, herpes viruses, and lentiviruses. In general, a suitable vector contains an origin of replication functional in at least one organism, a promoter sequence, convenient restriction endonuclease sites, and one or more selectable markers (*see, e.g.,* WO 01/96584;

WO 01/29058; and U.S. Pat. No. 6,326,193). In some embodiments, the viral vector is an adeno-associated virus (AAV) vector or a lentiviral vector.

[0470] In some embodiments, the nucleic acid encoding the binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct comprises sequences or features in addition to the coding sequence encoding the binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct. For example, the nucleic acid can be an mRNA (or a DNA sequence encoding the mRNA) comprising optional features that improve targeting of the binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct encoded by the mRNA and to increase stability of the mRNA.

[0471] In some embodiments, the nucleic acid(s) encoding polypeptide chain(s) of the bifunctional protein construct comprises a nucleic acid sequence encoding a signal peptide. Signal peptides are short peptides that may be present at the N-terminus or the C-terminus of a newly synthesized protein, that may function to properly translocate the protein. In some embodiments, the signal peptide assists with translocating the polypeptide chain(s) of the bifunctional protein construct encoded by the nucleic acid(s). In some embodiments, the signal peptide translocates the polypeptide chain(s) of the bifunctional protein construct to the cellular membrane. In some embodiments, the signal peptide comprises the amino acid sequence of SEQ ID NO: 253 or 336.

IV. Pharmaceutical Compositions, Kits, and Articles of Manufacture

[0472] The present invention also provides pharmaceutical compositions comprising i) any of the bifunctional protein constructs described herein, any of the engineered DLL4 ECD and protein constructs comprising the DLL4 ECD described herein, any of the isolated nucleic acids (DNA or RNA) encoding the bifunctional protein constructs, any of the isolated nucleic acids (DNA or RNA) encoding the engineered DLL4 ECD and protein constructs comprising the DLL4 ECD described herein, or any of the vectors (e.g., viral vector) comprising such isolated nucleic acids; and ii) an optional pharmaceutically acceptable carrier.

[0473] Suitable formulations (e.g., pharmaceutical composition) of the bifunctional protein construct described herein, a nucleic acid encoding the bifunctional protein construct described herein, a vector (e.g., viral vector) comprising a nucleic acid encoding the

bifunctional protein construct, the engineered DLL4 ECD and protein constructs comprising the DLL4 ECD described herein, a nucleic acid encoding the engineered DLL4 ECD and protein constructs comprising the DLL4 ECD described herein, a vector (e.g., viral vector) comprising a nucleic acid encoding the engineered DLL4 ECD and protein constructs comprising the DLL4 ECD described herein can be obtained by mixing the bifunctional protein construct (or the nucleic acid encoding the bifunctional protein construct, or the vector (e.g., viral vector) comprising a nucleic acid encoding the bifunctional protein construct), the engineered DLL4 ECD (or the nucleic acid encoding the engineered DLL4 ECD, or the vector (e.g., viral vector) comprising a nucleic acid encoding the engineered DLL4 ECD), or the protein constructs comprising the DLL4 ECD described herein (or the nucleic acid encoding the protein constructs comprising the DLL4 ECD described herein, or the vector (e.g., viral vector) comprising a nucleic acid encoding the protein constructs comprising the DLL4 ECD described herein) having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)).

[0474] In some embodiments, the pharmaceutical composition further comprises additional ingredients. Additional ingredients include, but are not limited to, one or more of the following: excipients; surface active agents; dispersing agents; inert diluents; granulating and disintegrating agents; binding agents; lubricating agents; sweetening agents; flavoring agents; coloring agents; preservatives; physiologically degradable compositions such as gelatin; aqueous vehicles and solvents; oily vehicles and solvents; suspending agents; dispersing or wetting agents; emulsifying agents, demulcents; buffers; salts; thickening agents; fillers; emulsifying agents; antioxidants; antibiotics; antifungal agents; stabilizing agents; and pharmaceutically acceptable polymeric or hydrophobic materials. Other “additional ingredients” which may be included in the pharmaceutical compositions of the invention are known in the art and described, for example in *Remington's Pharmaceutical Sciences* (1985, Genaro, ed., Mack Publishing Co., Easton, Pa.), which is incorporated herein by reference. Additional excipients include agents which can serve as one or more of the following: (1) bulking agents, (2) solubility enhancers, (3) stabilizers and (4) agents preventing denaturation or adherence to the container wall (e.g., surfactant, such as polysorbate (e.g., polysorbate 80) or poloxamer). The excipient is different depending on whether a pharmaceutical composition comprises a protein, nucleic acid, or vector (e.g., viral vector). Those skilled in the art can determine the appropriate excipient for a pharmaceutical composition.

[0475] For example, acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propylparaben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG). In some embodiments, lyophilized formulations are provided.

[0476] Pharmaceutical compositions to be used for in vivo administration must be sterile. This is readily accomplished by, e.g., filtration through sterile filtration membranes. The pharmaceutical compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0477] The pharmaceutical compositions may be prepared by any method known or hereafter developed in the art of pharmacology. Preparations include but are not limited to, bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single- or multi-dose unit. The pharmaceutical compositions may be prepared, packaged, or sold in the form of a sterile injectable aqueous or oily suspension or solution. This suspension or solution may be formulated according to the known art, and may comprise, in addition to the active ingredient, additional ingredients such as the dispersing agents, wetting agents, or suspending agents. Such sterile injectable formulations may be prepared using a non-toxic parenterally-acceptable diluent or solvent, such as water or 1,3-butane diol, for example. Other acceptable diluents and solvents include, but are not limited to, Ringer's solution, isotonic sodium chloride solution, and fixed oils such as synthetic mono- or di-glycerides. Other parentally-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form, in a liposomal

preparation, or as a component of a biodegradable polymer systems. Compositions for sustained release or implantation may comprise pharmaceutically acceptable polymeric or hydrophobic materials such as an emulsion, an ion exchange resin, a sparingly soluble polymer, or a sparingly soluble salt.

[0478] Pharmaceutical compositions that are useful in the methods of the invention may be prepared, packaged, or sold in formulations suitable for parenteral, intraperitoneal, intramuscular, intradermal, subcutaneous, or intravenous routes of administration. Other contemplated formulations include projected nanoparticles, liposomal preparations, resealed erythrocytes containing the active ingredient, and immunologically-based formulations.

[0479] A pharmaceutical composition of the invention may be prepared, packaged, or sold in bulk, as a single unit dose, or as a plurality of single unit doses. A unit dose is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to an individual or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[0480] Also provided are kits comprising any one of the binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein constructs (or the nucleic acid encoding the binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct described herein, or the vector comprising a nucleic acid encoding the binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) or bifunctional protein construct) described herein. The kits may be useful for any of the methods of treatment described herein.

[0481] The kits of the present application are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. Kits may optionally provide additional components such as buffers and interpretative information.

[0482] The present application thus also provides articles of manufacture. The article of manufacture can comprise a container and a label or package insert on or associated with the container. Suitable containers include vials (such as sealed vials), bottles, jars, flexible packaging, and the like. Generally, the container holds a composition, and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle).

V. Methods of Treatment

[0483] Also provided herein are methods of treating a muscle-related disease in an individual (e.g., human), comprising administering to the individual an effective amount of any of the bifunctional protein constructs described herein, or nucleic acid(s) or vector(s) (e.g., viral vector) encoding thereof (or pharmaceutical composition thereof). In some embodiments, the muscle-related disease is selected from the group consisting of Pompe disease, centronuclear myopathy, fibrodysplasia ossificans progressive (FOP), Friedreich's ataxia (FRDA), familial hypertrophic cardiomyopathy, Laing distal myopathy, myofibrillar myopathy, and muscular dystrophy. A list of muscular dystrophies with associated genetic defects that may be treated by the claimed bifunctional protein constructs are presented in **Table 9**.

Table 9: Muscular Dystrophies with Associated Genetic Defects

Muscular Dystrophy	Gene Involved	Inheritance patten
Duchenne	Dystrophin, X-linked	Recessive
Becker	Dystrophin, X-linked	Recessive
Emery-Dreifuss Muscular Dystrophy (EDMD)	Emerin, X-linked	Recessive
	lamin A	
	lamin C	
Congenital Muscular Dystrophies		
CMD with cardiomyopathy	Titin	Recessive
CMD with desmin inclusions	SEPN1	Recessive
CMD with integrin alpha 7 mutations	integrin-alpha 7 gene	Recessive
CMD with familial junctional epidermolysis bullosa	plectin	Recessive
CMD with muscle hypertrophy; also called MDC1C	fukutin-related protein (FKRP)	Recessive
MDC1D	LARGE gene	Recessive
CMD with myasthenic syndrome	DOK7	Recessive
CMD with (early) spinal rigidity	SEPN1	Recessive
CMD with spinal rigidity and lamin A/C abnormality	lamin A/C	Dominant
CMD with spinal rigidity and selenoprotein deficiency	SBP2	
Fukuyama CMD	fukutin	Recessive
Merosin-deficient CMD; also called MDC1A	Laminin-211	Recessive
Santavuori muscle-eye-brain disease	POMGnT1	Recessive
Ullrich CMD	COLGA1, COL6A2 or COL6A3	Recessive or dominant
Walker-Warburg syndrome		Recessive
MDDGA	B3GNT1	Recessive
MDDGA1	POMT1	Recessive
MDDGA2	POMT2	Recessive
MDDGA 3-6	Overlap with other CMD	Recessive
MDDGA7	ISPD	Recessive

MDDGA8 type	GTDC2	Recessive
MDDGA10	TMEM5	Recessive
MDDGA11	B3GALNT2	Recessive
MDDGA12	SGK196	Recessive
Facioscapulohumeral Muscular Dystrophy (FSH, FSHD)	DUX4 duplication 4q35	
Limb-Girdle Muscular Dystrophy (LGMD)		
LGMD1		
LGMD1A	Myotilin	Dominant
LGMD1B	LMNA	Dominant
LGMD1C	CAV3	Dominant
LGMD1D	DNAJB6	Dominant
LGMD1E	DES	Dominant
LGMD1F	TNP03	Dominant
LGMD1G	HNRNPDL	Dominant
LGMD1H	Unknown	
LGMD2A	CAPN3	Recessive
LGMD2B	DYSF	Recessive
LGMD2C	SGCG	Recessive
LGMD2D	SGCA	Recessive
LGMD2E	SGCB	Recessive
LGMD2F	SGCD	Recessive
LGMD2G	TCAP	Recessive
LGMD2H	TRIM32	Recessive
LGMD2I	FKRP	Recessive
LGMD2J	TTN	Recessive
LGMD2K	POMT1	Recessive
LGMD2L	ANO5	Recessive
LGMD2M	FKTN	Recessive
LGMD2N	POMT2	Recessive
LGMD2O	POMGnT1	Recessive
LGMD2P	DAG1	Recessive
LGMD2Q	PLEC1	Recessive
LGMD2R	DES	Recessive
LGMD2S	TRAPPC11	Recessive
LGMD2T	GMPPB	Recessive
LGMD2U	ISPD	Recessive
LGMD2V	GAA	Recessive
LGMD2W	LIMS2	Recessive
LGMD2X	BVES	Recessive
LGMD2Y	TOR1A1P1	Recessive
Myotonic Dystrophy		
DM1	DMPK CTG repeat expansion >50	
DM2	ZNF9 expansion	
Oculopharyngeal Muscular Dystrophy (OPMD)	PABPN1	Dominant
Congenital Myopathies		

Myotubular myopathy	Myotubularin	X-linked recessive
Nemaline myopathy	A variety of genetic defects	Recessive/dominant
Distal Myopathies		
Gowers-Laing distal myopathy	MYH7	
Miyoshi distal myopathy	dysferlin	
Nonaka distal myopathy	GNE	
Hereditary inclusion-body myositis (myopathy) type 1 (HIBM1)	A variety of genetic defects	
Charcot-Marie Tooth		
Type 1a	PMP22	Dominant
Type 1b	MPZ	Recessive
Type X	Connexin 32/GJB	Recessive

[0484] In some embodiments, the muscle disease is muscular dystrophy. In some embodiments, the muscular dystrophy comprises one or more of: Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), limb-girdle muscular dystrophy (LGMD), congenital muscular dystrophy (CMD), facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy (DM), oculopharyngeal muscular dystrophy (OPMD), distal muscular dystrophy (DD), congenital myopathy, Charcot-Marie-Tooth (CMT) disorder, and Emery-Dreifuss muscular dystrophy (EDMD). In some embodiments, the limb-girdle muscular dystrophy type is selected from the group consisting of LGMD2A, LGMD2B, LGMD2C, LGMD2D, LGMD2E, LGMD2F, LGMD2G, LGMD2H, LGMD2I, LGMD2J, LGMD2K, LGMD2L, LGMD2M, LGMD2N, LGMD2O, LGMD2P, LGMD2Q, LGMD2R, LGMD2S, LGMD2T, LGMD2U, LGMD2V, LGMD2W, LGMD2X, and LGMD2Y. In some embodiments, the myotonic dystrophy type is selected from the group consisting of DM1 and DM2. In some embodiments, the Charcot-Marie-Tooth disorder type is selected from the group consisting of Type 1a, Type 1b, and Type X. In some embodiments, the muscle disease is sarcopenia.

[0485] In some embodiments, there is provided a method of renewing satellite cells in a muscle tissue, comprising contacting the muscle tissue with an effective amount of any of the bifunctional protein constructs or binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein, or the vector (e.g., viral vector) comprising a nucleic acid encoding the bifunctional protein constructs or binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein. In some embodiments, the method allows myoblast differentiation in the muscle tissue. In some embodiments, there is provided a method of repairing and/or regenerating a muscle tissue, comprising contacting the muscle tissue with an effective amount of any of the bifunctional

protein constructs or binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein, or the vector (e.g., viral vector) comprising a nucleic acid encoding the bifunctional protein constructs or binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein) described herein. In some embodiments, the muscle tissue is a damaged muscle tissue. In some embodiments, the muscle tissue is from an individual (e.g., human) with a muscle-related disease, such as Pompe disease, centronuclear myopathy, fibrodysplasia ossificans progressive (FOP), Friedreich's ataxia (FRDA), familial hypertrophic cardiomyopathy, Laing distal myopathy, myofibrillar myopathy, and muscular dystrophy.

[0486] In some embodiments, the treatment methods for muscle-related diseases described herein can achieve one or more following effects: (i) increase or maintain muscle strength compared with a preexisting state or compared with a state which would occur in the absence of treatment, (ii) delay progression of muscular dystrophy, (iii) reduce loss of muscle, (iv) improve or maintain motor skills compared with a preexisting state or compared with a state which would occur in the absence of treatment, (v) repair or maintain muscle cell or tissue, (vi) increase regeneration of muscle cell or tissue compared with a preexisting state or compared with a state which would occur in the absence of treatment, (vii) enhance satellite cell renewal, and/or (viii) increase myoblast differentiation. In some embodiments, muscle strength is increased by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, compared with a preexisting state or compared with a state which would occur in the absence of treatment. In some embodiments, motor skills is improved by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, compared with a preexisting state or compared with a state which would occur in the absence of treatment. In some embodiments, regeneration of muscle cell or tissue is increased by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, compared with a preexisting state or compared with a state which would occur in the absence of treatment. In some embodiments, satellite cell renewal is enhanced by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%,

about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, compared with a preexisting state or compared with a state which would occur in the absence of treatment. In some embodiments, myoblast differentiation is increased by at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, compared with a preexisting state or compared with a state which would occur in the absence of treatment.

[0487] In some embodiments, the bifunctional protein construct or binding moiety (e.g., antibody moieties, engineered DLL4 ECD, and protein constructs comprising the DLL4 ECD described herein), or a nucleic acid or vector (e.g., viral vector) encoding thereof, or pharmaceutical composition thereof, is administered to the individual once. In some embodiments, the bifunctional protein construct, or a nucleic acid or vector (e.g., viral vector) encoding thereof, or pharmaceutical composition thereof, is administered to the individual two or more times, for example every week, every two weeks, every three weeks, every month, every two months, every three months, every six months, and the like.

[0488] In some embodiments, the bifunctional protein construct, or a nucleic acid or vector (e.g., viral vector) is delivered to the tissue of interest by, for example, an intramuscular injection, while other times the delivery is via intravenous, subcutaneous, transdermal, mucosal, intraperitoneal, or other delivery methods. Such delivery may be either via a single dose, or multiple doses. One skilled in the art understands that the actual dosage to be delivered herein may vary greatly depending upon a variety of factors, such as the vector choice, the target cell, organism, or tissue, the general condition of the subject to be treated, the degree of transformation/modification sought, the administration route, the administration mode, the type of transformation/modification sought, etc.

[0489] The relative amounts of the active ingredient, the pharmaceutically acceptable carrier, and any additional ingredients in a pharmaceutical composition of the invention will vary, depending upon the identity, size, and condition of the individual treated and further depending upon the route by which the composition is to be administered.

EXAMPLES

[0490] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are

they 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 (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. The examples below are intended to be purely exemplary of the application and should therefore not be considered to limit the application in any way.

[0491] The present disclosure is not to be limited in scope by the specific embodiments described which are intended as single illustrations of individual aspects of the disclosure, and any compositions or methods which are functionally equivalent are within the scope of this disclosure. It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present disclosure without departing from the spirit or scope of the disclosure. For example, due to codon redundancy, changes can be made in the underlying DNA sequence without affecting the protein sequence. Moreover, due to biological functional equivalency considerations, changes can be made in protein structure without affecting the biological action in kind or amount. Thus, it is intended that the present disclosure cover the modifications and variations of this disclosure provided they come within the scope of the appended claims and their equivalents.

[0492] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Example 1: Generation of an exemplary bifunctional fusion protein comprising mouse DLL4 variant containing C2-DSL and EGF1-5, mIgG1 Fc, and mouse Laminin-211 alpha2 LG4-5 domains (Construct muDLL4v-Fc-muLAMA2 LG4-5)

[0493] Mouse DLL4 (Accession: AAF76428.1) containing C2-DSL-EGF1-5 (aa 28-401) with rat DLL4EL12 variant mutations (Luca et al., 2015, Science 47(6224):847-53) was used to generate the DLL4v-Fc-LAMA2 LG4-5 construct (SEQ ID NO: 242). The mouse DLL4 variant containing C2-DSL and EGF1-5 was fused to the N-terminus of mouse IgG1 Fc engineered to remove effector function. The C-terminus of the Fc was fused to a (GGGGS)₃ linker (SEQ ID NO: 211) and mouse Laminin-2alpha (Accession: NP_032507.2) LG domains 4-5 (aa 2870-3118) (SEQ ID NO: 250). The whole DNA sequence was assembled with codon optimization for expression in CHO or HEK293 cells. The DNA was cloned into the pcDNA3.x vector (Thermo Fisher Scientific). pcDNA3.x with the cloned construct was transformed into *E. coli* bacteria (DH5α competent cells), a single colony was picked, the DNA sequence was validated, the colony was propagated by an overnight culture, and

plasmid DNA was obtained using a commercial plasmid purification kit. pcDNA3.x plasmid DNA was transfected into CHO or HEK293 cells for expression, either transiently or stably after establishing a stable cell pool. Recombinant protein was purified from the cell culture supernatants with a 25 ml MabSelect™ SuRe™ column (Cytiva). Proteins were eluted from the column with 0.1 M glycine pH 3.0, and immediately neutralized using 20% volume of 1M Tris pH 8.0. The eluted samples were then buffer exchanged to 1X PBS for monodispersity analysis using analytical size exclusion chromatography (SEC). A second step of purification with preparative SEC in 1X PBS was implemented when the monodispersity of the recombinant protein was below 93%. Purity and integrity of purified proteins were analyzed with analytical HPLC-SEC (FIG. 3B) and SDS-PAGE (FIG. 3A). HPLC-SEC (FIG. 3B) and SDS-PAGE analysis (FIG. 3A) showed that the DLL4v-Fc-LAMA2 LG4-5 construct had the predicted molecular weight. Purified proteins with higher than 93% monodispersity were used for functional studies.

[0494] A bifunctional protein with DLL4 wildtype sequence (Construct DLL4wt-Fc-LAMA2 LG4-5) was similarly expressed (FIGs. 4A and 4B). SDS-PAGE (FIG. 4A) and HPLC-SEC (FIG. 4B) analyses showed that the DLL4wt-Fc-LAMA2 LG4-5 construct (SEQ ID NO: 241) had the predicted molecular weight.

Example 2: Generation of an exemplary bifunctional fusion protein comprising mouse DLL4 variant containing C2-DSL and (EGF1-5), mIgG1 Fc, and anti-laminin-2alpha (Construct muDLL4v-Fc-LAMA2scFv)

[0495] Mouse DLL4 (Accession: AAF76428.1) containing C2-DSL-EGF1-5 (aa 28-401) with rat DLL4EL12 variant mutations (Luca et al., 2015, Science. 47(6224):847-53) was used to generate the DLL4v-Fc-LAMA2scFv construct. The mouse DLL4 variant containing C2-DSL and EGF1-5 was fused to the N-terminus of mouse IgG1 Fc engineered to remove effector function. The C-terminus of the Fc was fused to a (GGGGS)₃ linker and anti-mouse Laminin-2alpha (SEQ ID NO: 251). The whole DNA sequence was assembled with codon optimization for expression in CHO or HEK293 cells, which was cloned into the pcDNA3.x vector (Thermo Fisher Scientific). pcDNA3.x with the cloned construct was transformed into *E. coli* bacteria (DH5α competent cells), a single colony was picked, the DNA sequence was validated, the colony propagated by overnight culture, and plasmid DNA was obtained using a commercial plasmid purification kit. pcDNA3.x plasmid DNA was transfected into CHO or HEK293 cells for expression, either transiently or stably after establishing a stable cell pool. Recombinant protein was purified from the cell culture supernatants with a 25 ml

MabSelect™ SuRe™ column (Cytiva). Proteins were eluted from the column with 0.1 M glycine pH 3.0, and immediately neutralized using 20% volume of 1M Tris pH 8.0. The eluted samples were then buffer exchanged to 1X PBS for monodispersity analysis using analytical size exclusion chromatography (SEC). A second step of purification with preparative SEC in 1X PBS was implemented when the monodispersity of the recombinant protein was below 93%. Purity and integrity of purified proteins were analyzed with analytical HPLC-SEC (FIG. 5B) and SDS-PAGE (FIG. 5A). SDS-PAGE (FIG. 5A) and HPLC-SEC (FIG. 5B) analyses showed that the DLL4v-Fc-LAMA2scFv construct had the predicted molecular weight. Purified proteins with higher than 93% monodispersity were used for functional studies.

[0496] Sequences for exemplary bifunction proteins comprising muscle-targeting and Notch activation moieties for preclinical testing are listed in Table 5.

Example 3: Expression of human LG4-5 domain

[0497] Human LG5 (aa 2870-3118 of Accession: NP_000417.3) was cloned into pcDNA3.x with an N-terminal signal peptide (SEQ ID NO: 252) and His6 tag. The recombinant protein was expressed in HEK293 cells as described above and was purified from cell culture supernatant on a Ni-NTA nickel-chelating resin column (ThermoFisher Scientific) using manufacturer's protocol. The eluent containing the recombinant protein was buffer exchanged into PBS in Slide-A-Lyzer dialysis cassettes (ThermoFisher Scientific) with molecular weight cutoffs (MWCOs) of 10 kDa.

Example 4: Confirmation of binding of murine bifunctional constructs to targets

[0498] Binding to Notch of the muDLL4v-Fc-LAMA2scFv, muDLL4wt-Fc-LAMA2 LG4-5, and muDLL4v-Fc-LAMA2 LG4-5 constructs was confirmed using a sandwich ELISA with a mouse recombinant Notch1 protein (Sino Biologicals). A 96-well ELISA plate was coated with 2 ug/ml of recombinant Notch 1 protein at 100 µL/well at 4°C. After 16 hours, wells were washed five times with 200 µL/well of 0.05% PBST, blocked with 200 µL/well of 1% BSA at 25°C for 1h, and washed with 200 µL/well of 0.05% PBST five times. 10 µL/ml bifunctional protein were serially diluted three times in the wells at 100 µL/well at 25°C for 1h, washed with 200 uL/well of 0.05% PBST five times, and incubated with 100 µL/well of goat Anti-Mouse IgG-HRP (1:10000) at 25°C for 1h. After washing with 200 µL/well of 0.05% PBST five times, 100 ul/well of TMB was added at 25°C for 10 min in the absence of light, 50 ul/well of 1M HCl was added, and OD at 450 nm was read on a plate

reader. As shown in FIG. 6, DLL4v-Fc-LAMA2 LG4-5 and DLL4v-Fc-LAMA2scFv have higher binding affinity to Notch 1, compared to the DLL4wt-Fc-LAMA2 LG4-5.

Example 5: Binding of recombinant bifunctional proteins containing murine laminin-2 LG4-5 to matriglycan

[0499] Matriglycan on alpha-dystroglycan was purified with WGA agarose beads from rabbit muscle homogenate following published methods (Michele et al., 2002, Nature. 418(6896):417-22). Binding between the DLL4v-Fc-LG4-5 construct and matriglycan was analyzed using Biacore T200 (Cytiva). The DLL4v-Fc-LG4-5 construct was captured on anti-Fc chips at a concentration of 10 ug/ml, and TBST buffer was used as a reference for signal subtraction on the same anti-Fc chip. Matriglycan samples were injected to confirm binding. Binding of the DLL4v-Fc-LG4-5 construct to matriglycan was clearly indicated on a sensorgram, however, binding kinetics were not calculated due to the undetermined matriglycan concentration (FIG. 7A). As shown in FIG. 7B, binding between the DLL4v-Fc-LG4-5 construct and matriglycan (on alpha-dystroglycan) was also confirmed by Western blot following a laminin overlay assay (Michele et al., 2002, Nature. 418(6896):417-22).

Example 6: Confirmation of binding of murine DLL4v-Fc-LAMA2scFv to recombinant human LG4-5 by Biacore

[0500] Binding of the muLL4v-Fc-LAMA2scFv construct was tested as described above. The DLL4v-Fc-LAMA2scFv construct was captured on anti-Fc chips at a concentration of 10 ug/ml, and TBST buffer was used as a reference for signal subtraction on the same anti-Fc chip. Using single cycle kinetics, recombinant LG5 at different concentrations of 0.16 nM, 0.8 nM, 4 nM, 20 nM, and 100 nM were injected to confirm binding. Binding kinetics were generated using 1:1 binding model. As shown in FIG. 8, the binding signal increased as the concentration of recombinant LG5 was increased. Kinetics analysis indicated a KD of 12 nM in binding affinity ($k_a = 1.65E+5$ 1/Ms, $k_d = 0.002$ 1/s, KD = 12 nM).

Example 7: Assessment of efficacy of recombinant constructs in D2.mdx model

[0501] *Animals.* This study used male mice of the DBA/2J mouse strain (The Jackson Laboratory, stock #000671) for the control group and mdx on the DBA/2J background (D2.mdx; The Jackson Laboratory, stock #013141) for the experimental group. Mice were housed 3–5 mice per cage, provided access to food (NIH-31 Open formulation diet; Envigo #7917) and water *ad libitum*, and enrichment. Mice were maintained on a 12 h light/dark cycle. All animal study protocols were reviewed and approved by the Tufts University's

Institutional Animal Care and Use Committee (IACUC) and were conducted accordingly. Male mice of the DBA/2J and D2.mdx backgrounds at 5-6 weeks of age were purchased from the Jackson Laboratory. After about one week of acclimation, mice were trained for forelimb grip strength testing. D2.mdx mice were randomly assigned into control and treatment groups based on forelimb grip strength.

[0502] *Dosing of test articles.* D2.mdx male mice at about 7-8 weeks of age were injected with 5 mg/kg of muDLL4v-Fc-LAMA2scFv i.p. (FIG. 9A). D2.mdx male mice of similar age in the control group were injected with 20 mg/kg of an isotype control antibody against trinitrophenol (TNP). The D2.mdx mice in the control and treatment groups were given injections every three weeks. From the second dose onwards, mice were pretreated with 5 mg/kg of diphenhydramine (i.p.) 10 minutes prior to dosing with the isotype control or DLL4v-Fc-LAMA2scFv to avoid potential anaphylactic reaction.

[0503] *Forelimb grip strength test.* Grip strength of the forelimbs was assessed using a grid attached to an isometric force transducer (Columbus Instruments, Columbus, OH, USA) according to a previously published protocols (Aartsma-Rus and van Putten, 2014, J Vis Exp. (85):51303) and TREAT-NMD Standard Operation Protocol DMD_M.2.2.001). Briefly, mice were picked up by their tails and their forelimbs were allowed to grab the wire attached to the force transducer on the grip strength meter. Mice were pulled backwards by the tail until they released the wire. The maximum force required to break the mice's grip from the mesh surface was recorded by the transducer. Five repeats were performed with 30 seconds in between for the same mouse, and the maximum grip strength was recorded. The test was conducted in the morning every month for all the groups.

[0504] As shown in FIG. 9B, DBA/2J wildtype mice showed decreased grip strength over time. Although grip strength between the D2.mdx control and treatment groups was comparable at 13 weeks, D2.mdx injected with the isotype control exhibited progressively weaker forelimb grip strength, compared to D2.mdx mice injected with muDLL4v-Fc-LAMA2scFv (FIG. 9B). By 35 weeks, although both control- and treatment-injected mice possessed less overall forelimb grip strength than the DBA/2J wildtype mice, the forelimb grip strength of mice administered DLL4v-Fc-LAMA2scFv was 65% greater than that of mice administered the isotype control (FIG. 9B). Additionally, the body weights of both control and treatment groups plateaued and were overall less than that of the DBA/2J wildtype mice (FIG. 9C), suggesting that despite low body weight, mice provided the DLL4v-Fc-LAMA2scFv construct were able to maintain muscle function. Taken together,

the data demonstrated that use of the DLL4v-Fc-LAMA2scFv construct has long-term benefits on muscle function maintenance or improvement.

Example 8: Generation of a bifunctional fusion protein comprising human DLL4 variant containing C2-DSL and EGF1-5, hIgG1 Fc, and anti-LAMA2 scFv

[0505] Human DLL4 containing C2-DSL-EGF1-5 with G2S, F81L, and H168Y mutations, relative to wild-type DLL4 comprising the N-terminus to EGF5 (SEQ ID NO: 126), was used to generate the parental human DLL4v (SEQ ID NO: 260). The parental human DLL4v was fused to the N-terminus of human IgG1 Fc engineered to remove effector function. The C-terminus of the Fc was fused to a (GGGGS)₃ linker and anti-human LAMA2 scFv (SEQ ID NO: 268). Since rat DLL4EL12 variant mutations (US2019/0248894; Luca et al., 2015, Science 47(6224):847-53; WO2020/223610; and WO2021/007573) led to low yields and high aggregation in the context of human DLL4, mutations were introduced to overcome the poor chemistry, manufacturing and controls (CMC) developability. From the huD4v_G2S_F81L_H168Y-FcAAG-LG21DS parental construct, N-glycosylation sites were reintroduced to positions T52 and T135 of human DLL4v (SEQ ID NO: 260) and new mutations identified from yeast display screening were incorporated to determine DLL4 mutations that would confer higher affinity to Notch receptors. The following seven variant human DLL4 were generated based off of the parental human DLL4v (SEQ ID NO: 260): DLL4v11 (SEQ ID NO: 261), DLL4v12 (SEQ ID NO: 262), DLL4v13 (SEQ ID NO: 263), DLL4v14 (SEQ ID NO: 264), DLL4v22 (SEQ ID NO: 265), DLL4v23 (SEQ ID NO: 266), and DLL4v24 (SEQ ID NO: 267). The seven variant human DLL4 were further fused to an anti-LAMA2 scFv (SEQ ID NO: 268) to make bifunctional constructs (e.g., SEQ ID NOs: 270-276). The N-glycosylation site and yeast display mutations are outlined in **Table 10**. Bold amino acids indicate an amino acid mutations and non-bold amino acids are the original amino acids, relative to wild-type DLL4 (SEQ ID NO: 126).

Table 10: Human DLL4 mutations

	Amino acid positions							
	14	52	66	80	135	220	231	260
huDLL4v11	E	N	R	P	N	Q	N	N
huDLL4v12	E	N	S	P	N	Q	N	N
huDLL4v13	H	N	T	L	N	Q	D	N
huDLL4v14	E	N	T	L	N	H	N	D
huDLL4v22	E	T	S	P	T	Q	N	N

huDLL4v23	H	T	T	L	T	Q	D	N
huDLL4v24	E	T	T	L	T	H	N	D

[0506] The whole DNA sequence was assembled with codon optimization for expression in CHO or HEK293 cells. The DNA was cloned into the pcDNA3.x vector (Thermo Fisher Scientific). pcDNA3.x with the cloned construct was transformed into *E. coli* bacteria (DH5 α competent cells), a single colony was picked, the DNA sequence was validated, the colony was propagated by an overnight culture, and plasmid DNA was obtained using a commercial plasmid purification kit. pcDNA3.x plasmid DNA was transfected into CHO or HEK293 cells for expression, either transiently or stably after establishing a stable cell pool. Recombinant protein was purified from the cell culture supernatants with a 25 ml MabSelect™ SuRe™ column (Cytiva). Proteins were eluted from the column with 0.1 M glycine pH 3.0, and immediately neutralized using 20% volume of 1M Tris pH 8.0. The eluted samples were then buffer exchanged to 1× PBS for monodispersity analysis using analytical size exclusion chromatography (SEC). A second step of purification with preparative SEC in 1× PBS was implemented when the monodispersity of the recombinant protein was below 93%. Purity and integrity of purified proteins were analyzed with analytical HPLC-SEC, which showed that the initial fractions of v11, v12, v13, and v14 contained 92%, 92%, 78%, and 84% monomeric protein, respectively (FIGs. 10A and 10B). Additionally, from 30 ml of starting material, high yields were obtained for v11 and v12 and moderate yields were obtained for v13 and v14 (FIG. 10B). Thus, the constructs with N-glycosylation sites (v11, v12, v13, and v14) demonstrated excellent expression, stability, and high recovery of protein, compared to the v22, v23 and v24 constructs. As shown in FIGs. 11A and 11B, when v11, v12, v13, and v14 were tested for binding affinity to murine Notch1 receptor in an ELISA assay, the constructs had comparable binding affinity to the huD4v_G2S_F81L_H168Y-Fc(AAG)-LG21scFvDS parental construct (SEQ ID NO: 269) and better binding affinity than the mouse surrogate molecule (muD4v; SEQ ID NO: 349) at higher concentrations of the fusion protein. The data show that v11, v12, v13, and v14 have superior CMC developability.

SEQUENCE LISTING

SEQ ID NO: 1 Anti-LAMA2 LG03 HC-CDR1
SYTMS

SEQ ID NO: 2 Anti-LAMA2 LG03 HC-CDR2
SISSGGGNTYYPDsvKG

SEQ ID NO: 3 Anti-LAMA2 LG03 HC-CDR3

FDYGSSLDS

SEQ ID NO: 4 Anti-LAMA2 LG03 LC-CDR1
RASQISNNLH

SEQ ID NO: 5 Anti-LAMA2 LG03 LC-CDR2
YASQIS

SEQ ID NO: 6 Anti-LAMA2 LG03 LC-CDR3
QQSKNWPRT

SEQ ID NO: 7 Anti-LAMA2 LG21 parent/huVH7/huVH10 HC-CDR1
SYTMS

SEQ ID NO: 8 Anti-LAMA2 LG21 parent/huVH7/huVH10 HC-CDR2
TISSSGDNTYYPDSVKG

SEQ ID NO: 9 Anti-LAMA2 LG21 parent/huVH7/huVH10 HC-CDR3
FDYGSSLDS

SEQ ID NO: 10 Anti-LAMA2 LG21 parent/huVL3/huVL7 LC-CDR1
RASQISNYLH

SEQ ID NO: 11 Anti-LAMA2 LG21 parent/huVL3/huVL7 LC-CDR2
YASQIS

SEQ ID NO: 12 Anti-LAMA2 LG21 parent/huVL3/huVL7 LC-CDR3
QQSKSWPRT

SEQ ID NO: 13 Anti-LAMA2 LG21 huVH1 HC-CDR1
RYTMS

SEQ ID NO: 14 Anti-LAMA2 LG21 huVH1 HC-CDR2
TISSSGDNTYYPDSVKG

SEQ ID NO: 15 Anti-LAMA2 LG21 huVH1 HC-CDR3
FDYGSSLDS

SEQ ID NO: 16 Anti-LAMA2 LG21 huVH2 HC-CDR1
SYTMS

SEQ ID NO: 17 Anti-LAMA2 LG21 huVH2 HC-CDR2
TIESSGDNTYYPDSVKG

SEQ ID NO: 18 Anti-LAMA2 LG21 huVH2 HC-CDR3
FDYGSSLDS

SEQ ID NO: 19 Anti-LAMA2 LG21 huVH3 HC-CDR1
RYTMS

SEQ ID NO: 20 Anti-LAMA2 LG21 huVH3 HC-CDR2
TIESSGQITYYPDSVKG

SEQ ID NO: 21 Anti-LAMA2 LG21 huVH3 HC-CDR3
FDYGSSLDS

SEQ ID NO: 22 Anti-LAMA2 LG21 huVH4 HC-CDR1
RYTMS

SEQ ID NO: 23 Anti-LAMA2 LG21 huVH4 HC-CDR2

TISSSGQETYYPDSVKG

SEQ ID NO: 24 Anti-LAMA2 LG21 huVH4 HC-CDR3
FDYGSSLDS

SEQ ID NO: 25 Anti-LAMA2 LG21 huVH5 HC-CDR1
SYTMS

SEQ ID NO: 26 Anti-LAMA2 LG21 huVH5 HC-CDR2
TISSSGSNTYYPDSVKG

SEQ ID NO: 27 Anti-LAMA2 LG21 huVH5 HC-CDR3
FDYGSSLDS

SEQ ID NO: 28 Anti-LAMA2 LG21 huVH6 HC-CDR1
SYTMS

SEQ ID NO: 29 Anti-LAMA2 LG21 huVH6 HC-CDR2
TISNSGDNTYYPDSVKG

SEQ ID NO: 30 Anti-LAMA2 LG21 huVH6 HC-CDR3
FDYGSSLDS

SEQ ID NO: 31 Anti-LAMA2 LG21 huVH8 HC-CDR1
FDYGSSLDS

SEQ ID NO: 32 Anti-LAMA2 LG21 huVH8 HC-CDR2
FDYGSSLDS

SEQ ID NO: 33 Anti-LAMA2 LG21 huVH8 HC-CDR3
FDYGSSLDS

SEQ ID NO: 34 Anti-LAMA2 LG21 huVH9 HC-CDR1
SYTMS

SEQ ID NO: 35 Anti-LAMA2 LG21 huVH9 HC-CDR2
TISSSGDITYYPDSVKG

SEQ ID NO: 36 Anti-LAMA2 LG21 huVH9 HC-CDR3
FDYGSSLDL

SEQ ID NO: 37 Anti-LAMA2 LG21 huVL1 LC-CDR1
RASQISNYLH

SEQ ID NO: 38 Anti-LAMA2 LG21 huVL1 LC-CDR2
YASQIS

SEQ ID NO: 39 Anti-LAMA2 LG21 huVL1 LC-CDR3
QQRSWPRT

SEQ ID NO: 40 Anti-LAMA2 LG21 huVL2 LC-CDR1
RASQISNYLH

SEQ ID NO: 41 Anti-LAMA2 LG21 huVL2 LC-CDR2
YASQIS

SEQ ID NO: 42 Anti-LAMA2 LG21 huVL2 LC-CDR3
QQSKYWPRT

SEQ ID NO: 43 Anti-LAMA2 LG21 huVL4/huVL5 LC-CDR1

RASQISISNYLH

SEQ ID NO: 44 Anti-LAMA2 LG21 huVL4/huVL5 LC-CDR2
YASQIS

SEQ ID NO: 45 Anti-LAMA2 LG21 huVL4/huVL5 LC-CDR3
QQKSFPRT

SEQ ID NO: 46 Anti-LAMA2 LG21 huVL6/huVL8 LC-CDR1
RASQISISNYLH

SEQ ID NO: 47 Anti-LAMA2 LG21 huVL6/huVL8 LC-CDR2
YASQIS

SEQ ID NO: 48 Anti-LAMA2 LG21 huVL6/huVL8 LC-CDR3
QQKSDPRT

SEQ ID NO: 49 Anti-LAMA2 LG03 VH (CDR sequences are underlined)
DVMLVESGGDLVKPGGSLKLSAASGFTFSSYTMSWVRQTPEKRLEWVVASISSGGGNTYYPDSVKGRF
TISRDNANKNNLYLQMSSLRSEDALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 50 Anti-LAMA2 LG03 VL (CDR sequences are underlined)
DIVLTQSPATLSVTPGDSVSLSCRASQISNNLHWYQQKSHESPRLLIKYASQISIGIPSRFSGSGSGTDFT
LSINSVETEDFGMYFCQQSKNWPRTFGGGTKLEIK

SEQ ID NO: 51 Anti-LAMA2 LG03 scFv (CDR sequences are underlined)
DIVLTQSPATLSVTPGDSVSLSCRASQISNNLHWYQQKSHESPRLLIKYASQISIGIPSRFSGSGSGTDFT
LSINSVETEDFGMYFCQQSKNWPRTFGGGTKLEIKGGGGSGGGSGGGSGGGGSDVMLVESGGDLV
KPGGSLKLSAASGFTFSSYTMSWVRQTPEKRLEWVVASISSGGGNTYYPDSVKGRFTISRDNANKNNLY
LQMSSLRSEDALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 52 Anti-LAMA2 LG03 VH-CH1 (CDR sequences are underlined)
DVMLVESGGDLVKPGGSLKLSAASGFTFSSYTMSWVRQTPEKRLEWVVASISSGGGNTYYPDSVKGRF
TISRDNANKNNLYLQMSSLRSEDALYYCARFDYGSSLDSWGQGTTLTVSSAKTTPPSVYPLAPGSAAQ
TNSMVTGLCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTPVPSSTWPSETVTCNVAHP
ASSTKVDKKIVPRDC

SEQ ID NO: 53 Anti-LAMA2 LG03 VL-CL (CDR sequences are underlined)
DIVLTQSPATLSVTPGDSVSLSCRASQISNNLHWYQQKSHESPRLLIKYASQISIGIPSRFSGSGSGTDFT
LSINSVETEDFGMYFCQQSKNWPRTFGGGTKLEIKRADAAPTIVSIFPPSSEQLTSGGASVVCFLNNFYPK
DINVWKIDGSRQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCEATHKTSTSPIVKSFNR
NEC

SEQ ID NO: 54 Anti-LAMA2 LG21 huVHpar (CDR sequences are underlined)
EVQLVESGGGLVQPGGSLRLSAAASGFTFSSYTMSWVRQAPGKGLEWVVATISSSGDNTYYPDSVKGRF
TISRDNANKNTLYLQMSSLRAEDTALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 55 Anti-LAMA2 LG21 huVH1 (CDR sequences are underlined)
EVQLVESGGGLVQPGGSLRLSAAASGFTFSRYTMSWVRQAPGKGLEWVVATISSSGDNTYYPDSVKGRF
TISRDNANKNTLYLQMSSLRAEDTALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 56 Anti-LAMA2 LG21 huVH2 (CDR sequences are underlined)
EVQLVESGGGLVQPGGSLRLSAAASGFTFSSYTMSWVRQAPGKGLEWVVATISSSGDNTYYPDSVKGRF
TISRDNANKNTLYLQMSSLRAEDTALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 57 Anti-LAMA2 LG21 huVH3 (CDR sequences are underlined)
EVQLVESGGGLVQPGGSLRLSAAASGFTFSRYTMSWVRQAPGKGLEWVVATISSSGOITYYPDSVKGRF
TISRDNANKNTLYLQMSSLRAEDTALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 58 Anti-LAMA2 LG21 huVH4 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYTMSWVRQAPGKGLEWVATISSSGOETYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 59 Anti-LAMA2 LG21 huVH5 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSTMSWVRQAPGKGLEWVATISSSGSNTYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 60 Anti-LAMA2 LG21 huVH6 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSTMSWVRQAPGKGLEWVATISNSGDNTYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 61 Anti-LAMA2 LG21 huVH7 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 62 Anti-LAMA2 LG21 huVH8 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLDL WGQGTTLTVSS

SEQ ID NO: 63 Anti-LAMA2 LG21 huVH9 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSTMSWVRQAPGKGLEWVATISSSGDITYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLDL WGQGTTLTVSS

SEQ ID NO: 64 Anti-LAMA2 LG21 huVH10 (CDR sequences are underlined)

EVQLVESGGGLVQPGGSLRLSCAASGFEFSSYTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRF
TISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 65 Anti-LAMA2 LG21 huVLpar (CDR sequences are underlined)

EIVLTQSPDFLSVTPKEKVTLSRASQISNYLHWYQQKSDQSPKLLIKYASQISGIPSRFSGSGSGTDFT
LSINSVEAEDAATYFCQQKSWPRTFGGGTKLEIK

SEQ ID NO: 66 Anti-LAMA2 LG21 huVL1 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVILTCRASQISNYLHWYQQKSDQSPKLLIKYASQISGVPSRFSGSGSGTDFT
TLTISSVEAEDVATYFCQQSRWPRTFGGGTKLEIK

SEQ ID NO: 67 Anti-LAMA2 LG21 huVL2 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVILTCRASQISNYLHWYQQKSDQSPKLLIKYASQISGVPSRFSGSGSGTDFT
TLTISSVEAEDVATYFCQQSKYWPRTFGGGTKEIK

SEQ ID NO: 68 Anti-LAMA2 LG21 huVL3 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVILTCRASQISNYLHWYQQKSDQSPKLLIKYASQISGIPSRFSGSGSGTDFT
LSINSVEAEDAATYFCQQKSWPRTFGGGTKLEIK

SEQ ID NO: 69 Anti-LAMA2 LG21 huVL4 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVILTCRASQISNYLHWYQQKSDQSPKLLIKYASQISGIPSRFSGSGSGTDFT
LSINSVEAEDAATYFCQQKSFPRTFGGGTKEIK

SEQ ID NO: 70 Anti-LAMA2 LG21 huVL5 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVILTCRASQISNYLHWYQQKSDQSPKLLIKYASQISGIPSRFSGSGSGTDFT
LTINSVEAEDAATYFCQQKSFPRTFGGGTKEIK

SEQ ID NO: 71 Anti-LAMA2 LG21 huVL6 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVILTCRASQISNYLHWYQQKSDQSPKLLIKYASQISGIPSRFSGSGSGTDFT
LTINSVEAEDAATYFCQQKSDPRTFGGGTKLEIK

SEQ ID NO: 72 Anti-LAMA2 LG21 huVL7 (CDR sequences are underlined)

EIVLTQSPDFLSVTPKEKVTLSRASQISNYLHWYQQKSDQPPKLLIKYASQISGIPSRFSGSGSGTDFT
LSINSVEAEDAATYFCQQKSWPRTFGGGTKLEIK

SEQ ID NO: 73 Anti-LAMA2 LG21 huVL8 (CDR sequences are underlined)

EIVLTQSPDFLSVTPGEKVTLSCRASQSISNYLHWYQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFT
LSINSVEAEDAATYFCQQSKSDPRTFGGGTKLEIK

SEQ ID NO: 74 Anti-ADG41/huVH1/huVH2 HC-CDR1
GYTMN

SEQ ID NO: 75 Anti-ADG41/huVH1/huVH2 HC-CDR2
LINPYNGGTSYNQKFKG

SEQ ID NO: 76 Anti-ADG41/huVH1/huVH2 HC-CDR3
GTMATGFAY

SEQ ID NO: 77 Anti-ADG41 LC-CDR1
SASSSVSSIYLY

SEQ ID NO: 78 Anti-ADG41 LC-CDR2
STSNLAS

SEQ ID NO: 79 Anti-ADG41 LC-CDR3
HQWSSYPLT

SEQ ID NO: 80 Anti-ADG41 huVH3/huVH4 HC-CDR1
GYTMN

SEQ ID NO: 81 Anti-ADG41 huVH3/huVH4 HC-CDR2
LINPYNGGTSYAQKFQG

SEQ ID NO: 82 Anti-ADG41 huVH3/huVH4 HC-CDR3
GTMATGFAY

SEQ ID NO: 83 Anti-ADG41 huVL1/huVL2 LC-CDR1
RASSSVSSIYLY

SEQ ID NO: 84 Anti-ADG41 huVL1/huVL2 LC-CDR2
STSNLAS

SEQ ID NO: 85 Anti-ADG41 huVL1/huVL2 LC-CDR3
HQWSSYPLT

SEQ ID NO: 86 Anti-ADG41 huVL3/huVL4 LC-CDR1
RASSSVSSIYLY

SEQ ID NO: 87 Anti-ADG41 huVL3/huVL4 LC-CDR2
STSNRAT

SEQ ID NO: 88 Anti-ADG41 huVL3/huVL4 LC-CDR3
HQWSSYPLT

SEQ ID NO: 89 Anti-ADG41 VH (CDR sequences are underlined)
EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTSYNQKFKGK
ATLTVDKSSTTAYMELLSLTSEDSAVYYCASGTMATGFAYWGQGLTVTVSA

SEQ ID NO: 90 Anti-ADG41 huVH1 (CDR sequences are underlined)
EVQLVQSGPEVVKPGASMKISCKASGYSFTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGR
ATLTVDKSSTTAYMELSSLTSEDTAVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 91 Anti-ADG41 huVH2 (CDR sequences are underlined)
EVQLVQSGAEVKKPGASMKVSKASGYSFTGYTMNWVRQAPGQGLEWMGLINPYNGGTSYNQKFK
GRATLTVDKSSTTAYMELSSLTSEDTAVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 92 Anti-ADG41 huVH3 (CDR sequences are underlined)

QVQLVQSGAEVKKPGASMKVSKASGYSFTGYTMNWVRQAPGQGLEWMGLINPYNGGTSYAQKFQ
GRVTLTVDKSTTTAYMELSSLTSEDNAVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 93 Anti-ADG41 huVH4 (CDR sequences are underlined)

QVQLVQSGAEVKKPGASVKVSKASGYSFTGYTMNWVRQAPGQGLEWMGLINPYNGGTSYAQKFQ
GRVTMTVDKSTTTAYMELSSLTSEDNAVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 94 Anti-ADG41 VL (CDR sequences are underlined)

QIVLTQSPAISASPGKEKVTLTCSASSSVSSIIYLYWYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTS
YSLTISSMEAEDAASYFCHQWSSYPLTFGAGTKLELK

SEQ ID NO: 95 Anti-ADG41 huVL1 (CDR sequences are underlined)

QIVLTQSPGTLSPGERATLSCRASSSVSSIIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGT
DYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIK

SEQ ID NO: 96 Anti-ADG41 huVL2 (CDR sequences are underlined)

QIVLTQSPGTLSPGERATLSCRASSSVSSIIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGT
DYTLTISSLEAEDAASYFCHQWSSYPLTFGQGTKLEIK

SEQ ID NO: 97 Anti-ADG41 huVL3 (CDR sequences are underlined)

EIVLTQSPGTLSPGERATLSCRASSSVSSIIYLYWYQQKPGQAPRLWIYSTSNRATGVPDRFSGSGSGT
DYTLTISSLEPEDAAVYYFCHQWSSYPLTFGQGTKLEIK

SEQ ID NO: 98 Anti-ADG41 huVL4 (CDR sequences are underlined)

EIVLTQSPGTLSPGERATLSCRASSSVSSIIYLYWYQQKPGQAPRLWIYSTSNRATGIPDRFSGSGSGTD
FTLTISRLEPEDAAVYYFCHQWSSYPLTFGQGTKLEIK

SEQ ID NO: 99 Anti-ADG41 scFv (CDR sequences are underlined)

QIVLTQSPAISASPGKEKVTLTCSASSSVSSIIYLYWYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTS
YSLTISSMEAEDAASYFCHQWSSYPLTFGAGTKLELKGGGGSGGGSGGGSGGGGSEVQLQQSGPEL
VKGASMKISKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTSYNQKFKGKATLTVDKSSTT
AYMELSLTSEDSAVYYCASGTMATGFAYWGQGLTVTVSA

SEQ ID NO: 100 Anti-ADG41 VH-CH1 (CDR sequences are underlined)

EVQLQQSGPELVKPGASMKISKASGYSFTGYTMNWVKQSHGKNLEWIGLINPYNGGTSYNQKFKGK
ATLTVDKSSTTAYMELSLTSEDSAVYYCASGTMATGFAYWGQGLTVTVSAAKTTPPSVYPLAPGSA
AQTNMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTPSSWTPSETVTCNV
AHPASSTKVDDKIVPRDC

SEQ ID NO: 101 Anti-ADG41 VL-CL (CDR sequences are underlined)

QIVLTQSPAISASPGKEKVTLTCSASSSVSSIIYLYWYQQKPGSSPKLWIYSTSNLASGVPARFSGSGSGTS
YSLTISSMEAEDAASYFCHQWSSYPLTFGAGTKLELKRAAAPTVSIFPPSSEQLTSGGASVVCFLNNFY
PKDINVWKIDGSEKQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCEATHKTSTSPIVKSF
NRNEC

SEQ ID NO: 102 Anti-CDH15 HC-CDR1

SYDMS

SEQ ID NO: 103 Anti-CDH15 HC-CDR2

SINRGGSYTFYPDSVKG

SEQ ID NO: 104 Anti-CDH15 HC-CDR3

GDDGYFFSWFAY

SEQ ID NO: 105 Anti-CDH15 LC-CDR1

RSSQSIVHSSGNTYLE

SEQ ID NO: 106 Anti-CDH15 LC-CDR2

KVSNRFS

SEQ ID NO: 107 Anti-CDH15 LC-CDR3
FQGSHPFT

SEQ ID NO: 108 Anti-CDH15 VH (CDR sequences are underlined)
EVKLVESGGGLVKPGGALRLSCAASGFGFSSYDMSWVRQTSEKRLEWVVASINRGGSYTFYPDSVKGRF
TISRDNARNTLYLQMNSLRSEDSALYYCARGDDGYFFSWFAYWGQGTLLVTVSA

SEQ ID NO: 109 Anti-CDH15 VL (CDR sequences are underlined)
DVLMTQTPLSLPVSLGDQASISCRSSQSIHSSGNTYLEWYLQKPGQSPKLLIYKVSNRFSQVDPDRFSGS
GSGTDFTLKISRLEAEDLGYYCFQGSHPFTFGSGTKLEIK

SEQ ID NO: 110 Anti-CDH15 scFv (CDR sequences are underlined)
DVLMTQTPLSLPVSLGDQASISCRSSQSIHSSGNTYLEWYLQKPGQSPKLLIYKVSNRFSQVDPDRFSGS
GSGTDFTLKISRLEAEDLGYYCFQGSHPFTFGSGTKLEIKGGGGSGGGGSGGGGSGGGGSEVKLVES
GGGLVKPGGALRLSCAASGFGFSSYDMSWVRQTSEKRLEWVVASINRGGSYTFYPDSVKGRFTISRDN
ARNTLYLQMNSLRSEDSALYYCARGDDGYFFSWFAYWGQGTLLVTVSA

SEQ ID NO: 111 Anti-CDH15 VH-CH1 (CDR sequences are underlined)
EVKLVESGGGLVKPGGALRLSCAASGFGFSSYDMSWVRQTSEKRLEWVVASINRGGSYTFYPDSVKGRF
TISRDNARNTLYLQMNSLRSEDSALYYCARGDDGYFFSWFAYWGQGTLLVTVSAAKTPPSVYPLAPGS
AAQTNSMVTGLCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTPSSWTPSETVTCN
VAHPASSTKVDKIVPRDC

SEQ ID NO: 112 Anti-CDH15 VL-CL (CDR sequences are underlined)
DVLMTQTPLSLPVSLGDQASISCRSSQSIHSSGNTYLEWYLQKPGQSPKLLIYKVSNRFSQVDPDRFSGS
GSGTDFTLKISRLEAEDLGYYCFQGSHPFTFGSGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFL
NNFYPKDINVKWKIDGSEKQNGVLNSWTDQDSKDSTYSMSSTLTTLTKDEYERHNSYTCEATHKSTSP
IVKSFNRNEC

SEQ ID NO: 113 Human LAMA2 LG domain
SVSSGGDCIRTYKPEIKKGSYNNIVNVKTAVADNLLFYLGSAKFIDFLAIEMRKGVKVSFLWDVGSVG
RVEYPLDTIDDSYWYRIVASRTGRNGTISVRALDGPASIVPSTHHSTSPPGYTILDVDANAMLFVGGT
GKLKKAADAVRVITFTGCMGETYFDNKPIGLWNFREKEGDCKGCTVSPQVEDSEGTFQDGEYALVSR
PIRWYPNISTVMFKFRTFSSALLMYLATRDLRDFMSVELTDGHIKVSYDLGSGMASVVSNNHNDGK
WKSFTLSRIQKQANISIVDIDTNQEENIATSSSGNFGDLKADDKIYFGGLPTLRNLSMKARPEVNLKK
YSGCLKDIEISRTYPNLSPPDYVGVTKGCSLENNYTVSFPKPGFVELSPVPIDVGTEINLSFSTKNESGIL
LGSGGTPAPRRKRRTGTQAYYAILNRRGRLEVHLSTGARTMRKIVIRPEPNLFHDGREHVS HVERTRG
IFTVQVDENRRYMQNLTVEQPIEVKKLFVGGAPPEFQPSPLRNIPPFGCIWNLVINSVPMDFARPVSKF
NADIGRCAHQKLEDEDAAPAEIVIQPEPVPTPAFPTPTVLTGPCAAESEPALLIGSKQFGLSRNSHI
AIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKIN
DGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTRRIGPVYTSIDGCVRN
LHMAEAPADLEQPTSSFHVGTCFANAQRGTIFYDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLGI
SSQKMDGMGIEMIDEKLMFHVDNAGRFTAVIDAGVPGHLCDGQWHKVTANKIKHRIELTV DGNQV
EAQSPNPASTSADTNDPVFVGGFDDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQP
VSPAN

SEQ ID NO: 114 Human LAMA1 LG domain
YNTLTNLNVKTQEPDNLLFYLGSSASDFLAVEMRRGRVAFWLGLGSGSTRLEFPDFPIDDNRWHSIHV
ARFGNIGSLSVKEMSSNQKSPKTSKSPGTANVLDVNNSTLMFVGGGLGGQIKKSPAVKVTHFKGCLGE
AFLNGKISGLWNYIEREGKCRGCFGSSQNEPDSFHDGSGYSVVEKSLPATVTQIIMLFNTFSPNGLLLY
LGSYGTKDFLSIELFRGRVKVMTDLGSGPITLLTDRRYNNGTWYKIAFQRNRKQGVLAVIDAYNTSNK
ETKQGETPGASSDLNRLDKDPIYVGGPLRSRVVRRGVTTKSFVGCINKLEISRSTFDLLRNSYGVKGC
LLEPIRSVSFLKGGYIELPPKSLSPSEWLVTFATTNSSGIIAALGGDVEKRGDREEAHVPFFSVMLIGG
NIEVHVNPBGDTGLRKALLHAPTGTCSGQAHSISLVRNRRITVQLDENNPVEMKGLTLVESRTINVS
NLYVGGIPEGEGTSLLTMRRSFHGCINKLIFNLELLDFNSAVGHEQVDLDTCWLSERPKLAPDAEDSKL
LPEPRAFPEQCVVDAALEYVPGAHQFGLTQNSHFILPFNQSAVRKKLSVELSIRTFASSGLIYYMAHQN
QADYAVLQLHGGRLHFMFDLGKGRTKVSHPALSDGKWHTVKT DYVKRKGFTVDGRESPMVTVVG
DGTMLDVEGLFYLGGLPSQYQARKIGNITHSIPACIGDVTVNSKQLDKDSPVSAFTVNRCYAVAQEGT
YFDGSGYAAALVKEGYKVQSDVNITLFTSSQNGVLLGISTAKVDAIGLELVDGKVGAS

SEQ ID NO: 115 Human LAMA3 LG domain

LQTVIKEDLPRKAKTLSSNSDKLLNEAKMTQKKLKQEVSPALNNLQQTLNIVTVQKEVIDTNLTTLRD
 GLHGIQRGDIDAMISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDTYGRNQNEDFKKALTDADNSV
 NKLTNKLPLDLWRKIESINQQLPLGNISDNMDRIELIQQARDAASKVAVPMRFNGKSGVEVRLPNDLE
 DLKGYTSLSLFLQRPNSRENGGTENMFVMYLGNKDAASRDYIGMAVVDGQLTCVYNLGDREAEQVD
 QILTKSETKEAVMDRVKQFQRIYQFARLNYTKGATSSKPEPGVYDMDGRNSNTLLNLDPENVVFFYVGG
 YPPDFKLPSRLSFPPYKGCIELDDLNNVLSLYNFKKTFNLNTTEVEPCRRRKEESDKNYFEGTGYARVP
 TQPHAPIPTFGQTIQTTVDRGLLFFAENGDRFISLNIEDGKLMVRYKLNSELPKERGVDGINNGRDHSI
 QIKIGKLQKRMWINVDVQNTIIDGEVFDFTSYLGGPIAIRERFNISTPAFRGCMKNLKKTSGVVRLND
 TVGVTKKCEDWKLVRSAFSGGQLSFTDLGLPPTDHLQASFGFQTFQPSGILLDHQWTRNLQVTLE
 DGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNGLRLLIDDQLLRNSKRLKHISSSRQSLRLGGSNF
 EGCISNVFVQRLSLSPVLDLTSNSLKRVDLSLGGCSLNKPPFLMLLKGSTFRNKTKTFRINQLLQDTPVA
 SPRSVKVVQDACSPPKTQANHGAHQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVFHTGTK
 NSFALYLSKGRLVFALGTDGKKLRISKEKCNDEGKWHVTVFGHDGEKGRVVDGLRAREGSLPGNS
 TISIRAPVYLGSPSPGPKSLPTNSFVGCLNFKQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGGHVVL
 AHSVLLGPEFKLVFSIRPSRLTGILIHIGSQPGKHLVCVYLEAGKVTASMDSGAGGTSTSVTPKQSLCDGQ
 WHSVAVTIKQHILHLELDTSSYTAGQIPFPASTQEPLHLGGAPANLTTLRIPVWKSFFGCLRNIHVNI
 PVPVTEALEVQGPVSLNGCPDQ

SEQ ID NO: 116 Human LAMA4 LG domain

FTSLSLYMKPPVKRPELTETADQFILYLGSKNAKKEYMGLAIKNDNLVYVYNLGTKDVEIPLDSKPVSS
 WPAYFSIVKIERVGKHGKVFLTVPSSLSTAEKFIKKGEFSGDDSLDLDPEDTVFYVGGVPSNFKLPTS
 LNLPGFVGCLELATLNNNDVISLYNFKHIYNMDPSTSVPCARDKLAFTQSRASYSFFDGSYAVVRDITR
 RGKFGQVTRFDIEVRTPADNGLILLMVNGSMFFRLEMNGYLHVFDYDFGSSGRVHLEDTLKKAQIND
 AKYHEISIIYHNDKKMILVDDRHHVKSMDNEKMKIPFTDIYIGGAPPEILQSRALRAHLPLDINFRGCMK
 GFQFQKKDFNLLEQTETLGVGYGCPEDSLISRRAYFNGQSFASIQKISFFDGFEGGFNFRTLQPNGLLFY
 YASGSDVFSISLDNGTVIMDVKGKIVQSVQYNDGLSHFVISSVSPTRYELIVDKSRVGSKNPTKGKIE
 QTQASEKKFYFGGSPISAQYANFTGCISNAYFTRVDRDVEVEDFQRYTEKVHTSLYECPIESSPLFLLHK
 KGKNLSKPKASQNKKGKSKDAPSWDPVALKLPERNTPRNSHCHLSNSPRAIEHAYQYGGTANSRQE
 FEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYN
 DGLWHDVIFIRERSGRLVIDGLRVLEESLPTEATWKIKGPIYLGAVAPGKAVKNVQINSIYSFSGCLSN
 LQLNGASITSASQTFSVTPCFEGPMETGTYFSTEGGYVVLDESFNIGLKFEIAFEVRPRSSSGTLVHGHSV
 NGEYLVNHMKNGQVIVKVNNGIRDFSTSVTPKQSLCDGRWHRTVIRDSNVQLDVEDSENVHVVGPL
 NPKPIDHREPVFVGGVPESLLTPRLAPSKPFTGCIRHFVIDGHPVVSFKAALVSGAVSINSCPA

SEQ ID NO: 117 Human LAMA5 LG domain

YTALKFYLGPEPEPGQGTEDRFVMYMGSRQATGDYMGVSLRDKKVHVVYQLGEAGPAVLSDIEDI
 GEQFAAVSLDRTLQFGHMSVTVRQMIQETKGDYVAPGAEGLLNLRPDDFVFYVGGYPSTFTPPPLLR
 FPGYRGCIEMDTLNEEVVSLYNFERTFQLDTAVDRPCARSKSTGDPWLTDGSLDGTGFAISFDSQIST
 TKRFEQELRLVSYSGVLFFLKQQSQFLCLAVQEGSLVLLYDFGAGLKKAVPLQPPPLTSASKAIQVFL
 GGSRRKRVLRVERATVYSVEQDNDLELADAYYLGAVPPDQLPPLSLRRLFPTGGSVRGCVKGKALGK
 YVDLKRNLNTTGVSAGCTADLLVGRAMTFHGHGFLRLALSNAVPLTGNVYSGFGFHSQAQDSALLYRA
 SPDGLCQVSLQQGRVSLQLLRTEVKTQAGFADGAPHYVAFYSNATGVWLVDQDLQQMCKPHRGPPP
 ELQPQPEGPPRLLGLLPESGTIYNFSGCISNVFVQRLGPRVFDLQQLGSLVNVSTGCAPALQAQTPG
 LGPRGLQATARKASRRSRQPARHPACMLPPLHRTTRDSYQFGGSLSSHLEFVGILARHRNWPSLSMHV
 LPRSSRGLLLFTARLRPGSPSLALFLSNGHFVAQMEGLGTRLRAQSRQSRPGRWHKVSVRWEKNRILL
 VTDGARAWSQEGPHRQHQAHPQPHTLFVGGPLPASSHSSKLPVTVGFGSCVKRLRLHGRPLGAPTR
 MAGVTPCILGPLEAGLFFPGSGGVITLDLPGATLPDVGLELEVRPLAVTGLIFHLGQARTPPYLQLQVTE
 KQVLLRADDGAGEFSTSVTRPSVLCDGQWHRLAVMKSNGVLRLEVDAQSNHTVGPLAAAAGAPAP
 LYLGLPEPMAVQWPAPYCGCMRRLAVNRSPVAMTRSVEVHGAVGASGCPAA

SEQ ID NO: 118 Mouse LAMA2 domains 4-5 "LG4-5"

VPTPAFFPAPTVMVHGPCVAESEPALLTGSKQFGLSRNSHIAIAFDFTKVKNRLTIELEVRTEAESGLLFY
 MARINHADFATVQLRNGFPYFSYDLGSGDTSTMIPTKINDGQWHKIKIVRVKQEGILYVDDASSQTISP
 KKADILDVVGILYVGGLPINYTTTRIGPVTYSLDGCVRLNHMEQAPVDLDQPTSSFHVGTCFANAESGT
 YFDGTGFAKAVGGFKVGLDLLVEFEFRTTRPTGVLLGVSSQKMDGMGIEMIDEKLMFHVNDGAGRFT
 AIYDAGIPGHMCNGQWHKVTAKKIKNRLELVVDGNQVDAQSPNSASTSADTNDPVFVGGFPGGLNQF
 GLTTNIRFRGCIRSLKLTGKTGKPLEVNFKALELRGVQPVSCPTT

SEQ ID NO: 119 Human LAMA2 domains 4-5 "LG4-5"

IQPEPVPTPAFTPTPVLTGHGPCAAESEPALIGSKQFGLSRNSHIAIAFD DTKVKNRLTIELEVRTEAESG
LLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASN
RTISPKKADILDVVGMLYVGGLPINYTTRIGPVITYSIDGCVRNLMHMAEAPADLEQPTSSFHVGTFCFAN
AQRGTIFYDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHV DNG
AGRFTAVYDAGVPGHLC DGQWHKVTANKIKHRIELTV DGNQVEAQSPNPASTSADTNDPVFVGGFPD
DLKQFGLTTSIPFRGCIRSLKLT KGTGKPLEVNF AKALELRGVQPVSCPAN

SEQ ID NO: 120 Human Perlecan LG domain

VKAFAHLQVPERVVYPYFTQTPYSFLPLPTIKDAYRKFEIKITFRPDSADGM LLYNGQKRVPGSPTNLAN
RQPDFISFGLVGG RPEFRFDAGSGMATIRHPTPLALGHFHTVTLLRSLTQGS LIVGDLAPVNGTSQ GKFO
GLDLNEELYLG GYPDYGAIPKAGLSSGFIGCVRELRIQGEI VFHDLNLTAHGISHCPTCRDRPCQNGGQ
CHDSESSSYVCVCPAGFTGSRCEHSQALHCHPEACGP DATCVNRPDGRGYTCRCHLGRSGLRCEE GVT
VTPSLSGAGSYLALPALTNTHHELRLDVEFKPLAPDGVLLFSGGKSGPVEDFVSLAMVGGHLEFRYEL
GSGLA VLRSAPALGRWHRVSAERLNKDGLRVNGGRPVLRSSPGKSQGLNLHTLLYLG GVEPSVPL
SPATNMSAHFRGCVGEVSVNGKRLDLTYSFLGSGGIGQCYDSSPCERQPCQH GATCMPAGEYEFQCLC
RDGFKGDLCEHEENPCQLREPC LHGGTCQGTRCLCLPGFSGPRCQQGSGHGIAESDWHLEGSGGNDAP
GQYGAYFHDDGFLAFPGHVFSRSLPEVPETIELEVRTSTASGLLLWQGV E VGEAGQGKDFISLGLQDGH
LVFRYQLGSGEARLVSEDPINDGEWHRVTALREGRRGSIQVDGEELVSGRSPGP NVAVNAKGSVYIGG
APDVATLTGGRFSSGITGCVKNLVLHSARPGAPPPQLDLQHRAQAGANTRPCPS

SEQ ID NO: 121 Human Agrin LG domain

TLRLALEFRALEPQGLLLYNGNARGKDFLALALLDGRVQLRFDTGSGPAVLTSAPVPEPGQWHRLELS
RHWRRGTLSDGETPVLGESPSGTDGLNLD TDLFVGGVPEDQAAVALERTFVGAGLRGCIRLLDVNN
QRLELGIGPGAATRGSGVGECGDHPCLPNPCHGGAPCQNLEAGRFHCQCPPGRVGP TCADEKSPCQPN
PCHGAAPCRVLPEGGAQCECPLGREGTFCQTASGQDGS GPFLADFN GFSHLELRGLHTFARDLGEKMA
LEV VFLARGPSGLLLYNGQKT DGKDFVSLALRDRRLEFRYDLGKGA AVIRSREPVT LGAWTRVSLER
NGRKGA LRVDGPRVLGESPKSRKVPHTVLNLKEPLYVGGAPDFSKLARA AA VSSGFDGAIQLVSLGG
RQLLTPEHVLRQVDVTSFAGHPCTRASGHPC L NGASCVPREAA YVCLCPGGFSGPHCEKGLVEKSAGD
VDTLAFDGRTFVEYLNAVTESELANEIPVPETLDSGALHSEKALQSNHFELSLRTEATQGLVLWSGKAT
ERADYVALAIVDGHQLSYNLGSQP VVLRSTVPVNTNRWLRVVAHREQREGSLQVGNEAPVTGSSPL
GATQLD TDGALWLGGLPELPVGPALPKAYGTGFVGC LRDVVVGRHPLHLL EDAVTKPELRPCPTP

SEQ ID NO: 122 Human Agrin laminin coiled-coil binding domain

CPERALERREEEANVVL TGTVEEILNVDPVQHTY SCKVRVWRYLKGKDLVARESLLDGGNKVVISGFG
DPLICDNQVSTGDTRIFFVNPAPPYLWPAHKNELMLNSSLMRITLRNLEEVEFCVEDKPGTHFTPV PPTP
PDACRGMLCGFGAVCEPNAEGPGRASCVCCKKSPCPSV VAPVCGSDASTYSNECELQRAQCSQQRIRL
LSRGPCGSRDPCSNVTC SFGSTCAR

SEQ ID NO: 123 Human Nidogen-1 laminin γ binding domain

CANNRHQCSVHAECRDYATGFCCSCVAGYTGNRQCV AEGSPQRVNGKVKGRI FVGSSQVPIVFENT
DLHSYVVMNHGRSYTAISTIPETVGYSLPLAPVGGIIGWMFAVEQDGFKN GFSITGGEFTRQAEVTFV
GHPGNLVIKQRFSGIDEHGLTIDTELEGRVPQIPFGSSVHIEPYTELYHYSTSVITSSSTREYTVTEPERD
GASPSRIYTYQWRQTITFQECVHDDSRPALPSTQQLSVDSVFVLYNQEEKILRYALSNSIGPVREGSPDA
LQNPCYIGTHGCDTNAACRPGPRTQFTCECSIGFRGDGRTCYDIDECSEQPSVCGSHTICNNHPGTFRCE
CVEGYQFSDEGTCVAVVDQRPINYCETGLHNC DIPQRAQCIYTGGSYTC SCLPGFSGDGQACQDVDE
CQPSRCHPD AFCYNTPGSFTCQCKPGYQGDGFRCPVGEVEKTRCQHEREHILGAAGATDPQRPIPPGLF
VPECDAHGHYAPTQCHGSTGYCWCVDRDGREVEGTRTRPGMT PPCLSTVAPPIHQGPAVPTAVIPLPP
GTHLLFAQTGKIERLPLEGNTMRKTEAKAFLHVP AKVIIGLAFDCVDKMVYWTDITEPSIGRASLHGGE
PTTIIRQDLGSPEGIAVDHLGRNIFWTD SNLDRIEVAKLDGTQRRVLFETDLVNPRGIVTDSVRGNLYWT
DWNDRNPKIETSYMDGTNRRLVQDDLGLPNGLTFDAFSSQLCWVDAGTNRAECLNPSQPSRRKALEG
LQYPFAVTSYGKNLYFTDWMNSVVALDLAISKETDAFQPHKQTRLYGITTALSQC PQGHNYCSVNN
GGCTHLCLATPGSRTCRCPDNTLGVDICIEQK

SEQ ID NO: 124 Human Nidogen-2 laminin γ binding domain

CEHNHRQCSRHAFCTDYATGFCCHCQSKFYGN GKHLCLPEGAPHRVNGKVS GHLHVGHTPVHFTDVD
LHAYIVGNDGRAYTAISHIPQPAQAALLPLTPIGGLFGWLF ALEKPGSENGFSLAGAAFTHDMEVTFYP
GEETVRITQTAEGLDPENYLSIKTNIQGQVPYVSANFTA HISPYKELYHYSDSTVTSTSSRDYSLTFGAIN
QTWSYRIHQNITYQVCRHAPRHPSFPTTQQLNVDRVFALYNDEERVLRFAVTNQIGPVKEDSDPTPGNP
CYDGSHMCDTTARCHPGTGVDYTCECASGYQGDGRNCVDENECATGFHRCGPNSVCINLP GSYRCEC

RSGYEFADDRHTCILITPPANPCEDGSHTCAPAGQARCVHHGGSTFSCACLPGYAGDGHQCTDVDECS
ENRCHPAATCYNTPGSFSCRCQPGYYGDGFQCPDSTSSLTPCEQQQRHAQAQYAYPGARFHIPQCDEQ
GNFLPLQCHGSTGFCWCVPDGDHEVPGTQTPPGSTPPHCGPSPEPTQRPTICERWRENLEHYGGTTPR
DDQYVPQCDDLGHFIPLQCHGKSDFCWCVDKDGREVQGTRSQPGTTPACIPTVAPPMVRPTPRPDVTP
PSVGTFLLYTQGGQIGYLPNGTRLQKDAAKTLLSLHGSIIVGIDYDCRERMVYWTDVAGRTISRAGLE
LGAEPETIVNSGLISPEGLAIDHIRRTMYWTDVLDKIESALLDGSERKVLFTDLVNPRAIADVPIRGNL
YWTDWNREAPKIETSSLDGENRRILINTDIGLPNGLTFDPFSKLLCWADAGTKKLECTLPDGTGRRVIQ
NNLKYPFSIVSYADHFYHTDWRDGVVSVNKHSGQFTDEYLPEQRSHLYGITAVYPYCPTGRK

SEQ ID NO: 125 DLL4wt 27-529 ECD

SGVFQLQLQEFINERGVLASGRPCEPGCARTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 126 DLL4wt Nterm to EGF5 ECD

SGVFQLQLQEFINERGVLASGRPCEPGCARTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 127 DLL4v1 Nterm to EGF5 ECD (G2S, F81L, I117F, H168Y, L180P)

SSVFQLQLQEFINERGVLASGRPCEPGCARTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLP[NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLT
RLRYSYRVICSDNYYGDNCSRLCKKRNDYFHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGY
CSKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGAT
CSNSGQRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCA
DSPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 128 DLL4max Nterm to EGF5 ECD (G2S, F81L, I117F, H168Y, L180P, N231P, T245L, F254Y, S275R, Q279P)

SSVFQLQLQEFINERGVLASGRPCEPGCARTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLP[NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLT
RLRYSYRVICSDNYYGDNCSRLCKKRNDYFHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGY
CSKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLYCDQDLNYCTHHSPCKNGA
TCTNSGPRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSC
ADSPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 129 DLL4v1_derisk ECD (G2S, F81L, H168Y, L180P)

SSVFQLQLQEFINERGVLASGRPCEPGCARTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLP[NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDYFHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 130 DLL1wt 18-545 ECD

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSVTP
VLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
EEWSQDLHSSGRDLDKYSYRFVCDHEHYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDICIRYPGLHGTCCQPWQCNCQEGWGGLFCNQDL
NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGF
YKICELSAMTCADGPCFNNGRCSDSPDGGYSCRCVPVYSGFNCEKKIDYCSSSPCSNGAKCVDLGA

YLCRCQAGFSGRHCDDNVDDCASSPCANGGTCRDGVNDFSCTCPGYTGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDLTEKLEGQGGFPW

SEQ ID NO: 131 DLL3wt 27-492 ECD

AGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWLLARVAGRRLAAGGPWARDIQRA
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAAGCSPEHGFCEQP
GECRCLEGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPD SAYICHCPPGFGQSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSLVCAACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYL

SEQ ID NO: 132 Jag1wt 31-1067 ECD

ASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFYQIRVTCDDYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNC DININDCLGQCQNDASCRDLVNGYRCICPPGYAGDHCERDIDECASNPCLNNGGHCQ
NEINRFQCLCPTGFSGNLCQLDIDYCEPNPCQNGAQCYNRASDYFCKCPEDYEGKNC SHLKDHCRTTP
CEVIDSCTVAMASNDTPEGVRYISSNVC GPHGKCKSQSGGKFTCDCNKGFTGT YCHENINDCESNPCR
NGGT CIDGVNSYKICSDGWEGAYCETNINDCSQNPCHNGGTCTRD LVNDFYCDCKNGWKGTCHSR
DSQCDEATCNGGTCTYDEGDAFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGT CVVNGESFTCVCKE
GWEGPICAQNTNDCSPHPCYNSGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCAFGATCVDEIN
GYRCVCPPGHSGAKCQEVSGRPCITMGSVIPDGAKWDDDCNTCQCLNGRIACSKVWCGPRPCLLHKG
HSECPSGQSCIPILDDQCFVHPCTGVGECRSSSLQPVKTKCTSDSY YQDNCANITFTFNKEMMSPLTTE
HICSELRLNLILKNVSAEYSIYIACEPSPSANNEIHVAISAEDIRDDGNPIKEITDKIIDLVSKRDGNSSLIA
AVAEVRVQRRPLKNRTD

SEQ ID NO: 133 Jag1wt Nterm to EGF6 ECD

ASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFYQIRVTCDDYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNC

SEQ ID NO: 134 Jag1v1 Nterm to EGF6 ECD

ALGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFYRIRVTCDDYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNC

SEQ ID NO: 135 Jag2wt 27-1080 ECD

MGYFELQLSALRVNNGELLSGACCDGDGR TTRAGGCGHDECNTYVRVCLKEYQAKVTPTGPCSYGH
GATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVVIPFQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCDQYG
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVPYPGCVHGSCVEPW
QCNCETNWGGLLCDKDLNYCGSHHPCTNGGT CINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCAN
GGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCTVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVND CRGQCQHG GTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDY YCA
CPDDFGGKNCSVPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVVSQPGGNFSCICDSGFT
GT YCHENIDDC LGQPCRNGGT CIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVND FY
CACDDGWKGK TCHSREFQCDAYTCSNGGT CYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG

GTCVSGSGASFSCICRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPCEAWGECGAEPPSTPCLPRSGHLD
NNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGAHAHIAAITQRGNSLLLAVENTEVKVETVVTGGSST

SEQ ID NO: 136 DLL4wt-LG4-5

SGVFQLQLQEFINERGVLASGRPCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGSGGGGSIQPEPVPTPAFPTPTPVLTHGP
CAAESEPALIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRN
GLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGG
LPINYTTTRRIGPVTYSIDGCVRLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFK
VGLDLLVEFEFRTTTTTTGVLGSSQKMDGMGIEMIDEKLMFHVNDGAGRFTAVYDAGVPGHLCDDGQ
WHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT
KGTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 137 DLL4v-LG4-5

SSVFQLQLQEFINERGVLASGRPCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGSGGGGSIQPEPVPTPAFPTPTPVLTHGP
CAAESEPALIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRN
GLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGG
LPINYTTTRRIGPVTYSIDGCVRLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFK
VGLDLLVEFEFRTTTTTTGVLGSSQKMDGMGIEMIDEKLMFHVNDGAGRFTAVYDAGVPGHLCDDGQ
WHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT
KGTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 138 DLL4max-LG4-5

SSVFQLQLQEFINERGVLASGRPCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGSGGGGSIQPEPVPTPAFPTPTPVLTHGP
CAAESEPALIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRN
GLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGG
LPINYTTTRRIGPVTYSIDGCVRLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFK
VGLDLLVEFEFRTTTTTTGVLGSSQKMDGMGIEMIDEKLMFHVNDGAGRFTAVYDAGVPGHLCDDGQ
WHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT
KGTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 139 DLL4deimmune (DLL4di)-LG4-5

SSVFQLQLQEFINERGVLASGRPCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGSGGGGSIQPEPVPTPAFPTPTPVLTHGP
CAAESEPALIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRN
GLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGG
LPINYTTTRRIGPVTYSIDGCVRLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFK
VGLDLLVEFEFRTTTTTTGVLGSSQKMDGMGIEMIDEKLMFHVNDGAGRFTAVYDAGVPGHLCDDGQ

WHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT
KGTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 140 DLL1wt-LG4-5

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSAVTP
VLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFSLIEALHTDSPDDLATENPERLISRLATQRHLTVG
EEWSQDLHSSGRITDLKYSYRFVCDHEYYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDICIRYPGCLHGTCQQPWQCNCQEGWGGGLFCNQDL
NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGF
YGKICELSAMTCADGPCFNGGRCSDSPDGGYSCRCVPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCDRGVNDFSCTCPGTYGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLPELPPGPAVVDLTEKLEGQGGPPFWGGGSGGGGSGGGGSG
IQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESG
LLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASN
RTISPKKADILDVVGMLYVGGLPINYTTTRRIGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTCFAN
AQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNG
AGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPD
DLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 141 DLL3wt-LG4-5

AGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDIQR
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
GECRCLEGWTGPLCTVPVSTSSCLSPRGSSATTGCLVPGPGCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSLVACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLGGGGSGGGGSGG
GGSIQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEA
ESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDG
ASNRTISPKKADILDVVGMLYVGGLPINYTTTRRIGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTC
FANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVD
NGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGF
PDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 142 Jag1wt-LG4-5

ASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECNTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFHEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNASKCKNLIASYYC
DCLPGWMGQNCDDGGGGSGGGGSGGGGSIQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSR
NSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPT
KINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTTRRIGPVTYSIDGC
VRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLL
GISSQKMDGMGIEMIDEKLMFHVDNGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDG
NQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRG
VQPVSCPAN

SEQ ID NO: 143 Jag1v-LG4-5

ALGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFHEYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNASKCKNLIASYYC
DCLPGWMGQNCDDGGGGSGGGGSGGGGSIQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSR
NSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPT
KINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTTRRIGPVTYSIDGC
VRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLL

LGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQWHKVTANKIKHRIELTVDG
NQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNF AKALELRG
VQPVSPAN

SEQ ID NO: 144 Jag2wt-LG4-5

MGYFELQLSALRNVNGELLSGACCDGDGR TTRAGGCGHDEC DTYVRVCLKEYQAKVTPTGPCSYGH
GATPVLGGNSFYLP PAGAAGDRARARARAGGDQDPGLVVIPFQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHV AHLELQIRVRCDENYY SATCNKFCRPRNDFFGHYTCDQYG
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGE CRCSYGWQGRFCDECVYPGCVHGSCVEPW
QCN CETNWGGLLCDKDLNYCGSHHPCTNGGT CINAEPDQYRCTCPDGYSGRNCEKA EHA CTSNPCAN
GGSCHEVPSGFEC HCPSGWSGPTCALDIDECASNPCAAGGT CVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGY CDCIPGWKG INCHINVND CRGQCQHGGTCKDLVNGYQCVCPRGFGGR
HCELERDECA SSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYYCA
CPDDFGGKNC SVPREPCPGGACRVIDGCGSDAGPGMPGT AASGVCGPHGRCV SQPGGNFSCICDSGFT
GT YCHENIDDC LGQPCRNGGT CIDEVDAFRFCFPCSGWEGELCDTNPNDCLPDPCHSRGRCYDLVND FY
CACDDGWKGKTSREFQCDAYTCSNGGT CYDSGD TFRACAPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVGS GSGAFSCIRDRGWEGRTCTHTNTDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCA YGATCVDEINGYRCSCPPGRAGPRCQEVI GFGRSCWSRGT PFPHGSSWVEDCNSCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRP PCEAWGECGAEEPPSTPCLPRSGHL D
NNCARLTLHFNRDHVPQGT TVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGA AHAIVAAITQRGNSSLLLA VTEVKVETVVTGSSSTGGGSGGGGSGGGGSIQPEPVPTPAF
PTPTPVLTHGPCAAESE PALLIGSKQFGLSRNSHIAIAFD DTKVKNRLTIELEVRTEAESGLLFYMARINH
ADFA TVQLRNLGPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISP KKADIL
DVVGMLYVGGLPINYTTTRRIGPV TYSIDGCVRN LHMAEAPADLEQPTSSFHVGTCFANAQRGT YFDGT
GFAKAVGGFKVGLDLLVEFEFR TTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA VYDA
GVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSI
PFRGCIRSLKLTGKTGKPLEVNF AKALELRGVQPVSPAN

SEQ ID NO: 145 LG21scFv

EIVLTQSPDFLSVTPKEKVTLSCRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFT
LSINSVEAEDAATYFCQQSKSWPRTFGGG TKLEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSL
RLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSL
RAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 146 DLL4wt-LG21scFv

SGVFQLQLQEFINERGVLASGRPCEPGC RTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNY YGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRLCNECIPHNGCRHGTCTPWQCTDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL S
CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKS
WPRTFGGG TKLEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVR
QAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD
SWGQGTTLTVSS

SEQ ID NO: 147 DLL4v-LG21scFv

SSVFQLQLQEFINERGVLASGRPCEPGC RTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNY YGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRLCNECIPHNGCRHGTCTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL S
CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKS
WPRTFGGG TKLEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVR
QAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD
SWGQGTTLTVSS

SEQ ID NO: 148 DLL4max-LG21scFv

SSVFQLQLQEFINERGVLASGRPCPEGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHPGCRHGTCTPWQCLCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGVDCLELSECDNSPCRNGGSGCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL
CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTL SINSVEAEDAATYFCQQSKS
WPRTFGGGTKLEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVR
QAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD
SWGQGTTLTVSS

SEQ ID NO: 149 DLL4di-LG21scFv

SSVFQLQLQEFINERGVLASGRPCPEGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTPWQCTCDEGWGGLFCQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNSPCRNGGSGCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL
CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTL SINSVEAEDAATYFCQQSKS
WPRTFGGGTKLEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVR
QAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD
SWGQGTTLTVSS

SEQ ID NO: 150 DLL1wt-LG21scFv

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFFRVCLKHFAQASVSPEPPCTYGS AVTP
VLGVDSFSLPDGGGADSAFSNPIRFPGFTWPGTFSLIIEALHTDSPDDLATENPERLISR LATQRH LTVG
EEWSQDLHSSGR TDLKYSYRFVCEHY YGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPGCDEQHGFCDKPGECKCRVGVWQGRY CDECIRYPGCLHGT CQPWQCNCQEGWGGLFCNQDL
NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYT GATCELGIDECDPSPCKNGGSC TDLENSYSCTCPPGF
YGKICELSAMTCADGPCFNGGRCS DSPDGGYSCRCPVGYSGFNCEKKIDYCSSSPCSNGAKCVDL GDA
YLCRCQAGFSGRHCDNDVDDCASSPCANGGT CRDGVNDFSTCPPGYTGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPA VVDL TEKLEGQGGPFPWGGGGSGGGSGGGGS
EIVLTQSPDFLSVTPKEKVTL SCRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDF
LSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPGGSL
RLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSL
RAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 151 DLL3wt-LG21scFv

AGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEA AESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDIQRA
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
GECRCLEGWTGPLCTVPVSTSSCLSPRGPSAT TGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPD SAYICHCPPGFGQSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGT CVEGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSGLVACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLGGGGSGGGSGGG
GGSEIVLTQSPDFLSVTPKEKVTL SCRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQM
SSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 152 Jag1wt-LG21scFv

ASGQFELEILSMQNVN GELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFN LKASRGNDRNRIVLPFSFAWPRSYTLLVEAWDSSNDTVQPD SIIEKASHSGMINPSRQW
QTLKQNTGVAHF EYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVH GICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCIEAHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVN AKSCKNLIASYYC
DCLPGWMGQNCDDGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL SCRASQSISNYLHWYQQKS
DQSPKLLIKYASQSISGIPSRFSGSGSGTDFTL SINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGG

SGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGDN
TYYPD SVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 153 Jag1v-LG21scFv

ALGQFELEILSMQNVN GELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSII EKASHSGMINPSRQW
QTLKQNTGVAHF EYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVH GICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTC SNTPGDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETS LGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVN AKSCKNLIASYYC
DCLPGWMGQNCDDGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLS CRASQSI SNY LHWYQQKS
DQSPKLLIKYASQSI SGIPSRFSGSGSGTDFTL SINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGG
SGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGDN
TYYPD SVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 154 Jag2wt-LG21scFv

MGYFELQLSALRNVN GELLSGACCDGDGRTRAGGCGHDECNTYVRVCLKEYQAKVTP TGPCSYGH
GATPVLGGNSFYLP PAGAAGDRARARARAGGDQDPGLVIPFQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCDQYG
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGE CRCSYGWQGRFCDECVYPGCVHGSCVEPW
QCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCAN
GGSCHEVPSGFEC HCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVND CRGQCQHGGTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDY YCA
CPDDFGGKNCSVPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSQPGGNFSCICDSGFT
GT YCHENIDDC LGQPCRNGGTCIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDFY
CACDDGWKGKTC H SREFQCDAYTCSNGGTCYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVGS GASFCICRDGWEGRTCTHNTDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCA YGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRP PCEAWGECGAEEPPSTPCLPRSGHLD
NNCARLTLHFNRDHVPQGT TVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGA AHAIVAAITQRGNSSLLLAVTEVKVETVVTGSSSTGGGSGGGGSGGGGSEIVLTQSPDFL
SVTPKEKVTLS CRASQSI SNY LHWYQQKSDQSPKLLIKYASQSI SGIPSRFSGSGSGTDFTL SINSVEAED
AATYFCQQSKSWPRTFGGGTKLEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFT
FSSYTMSWVRQAPGKGLEWVATISSSGDN TYYPD SVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYC
ARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 155 ADG41scFv

QIVLTQSPGTL SLSPGERATLS CRASSSVSSIIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGT
DYSLTISSMEAE DAASYFCHQWSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPG
ASMKISCKASGYSTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYME
LSSLTSED TAVYYCASGT MATGFAYWGQGT LTVTVSS

SEQ ID NO: 156 DLL4wt-ADG41scFv

SGVFQLQLQEFINERGV LASGRPCPGCRTFFRVCLKH FQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNY YGDNCSR LCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGR LCN ECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQ GANYACECPPNFTGSNCEGGGGSGGGGSGGGGSEIVLTQSPGTL SLSPGERATLS
CRASSSVSSIIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAE DAASYFCHQ
WSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYTMN
WVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSED TAVYYCASGTMA
TGFA YWGQGT LTVTVSS

SEQ ID NO: 157 DLL4v-ADG41scFv

SSVFQLQLQEFINERGV LASGRPCPGCRTFFRVCLKH FQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNY YGDNCSR LCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGR LCN ECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC

SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNNGGSCRERNQGAN YACECPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTLSLSPGERATLS
 CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQ
 WSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYTMN
 WVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSED TAVYYCASGTMA
 TGFAYWGQGLTVTVSS

SEQ ID NO: 158 DLL4max-ADG41scFv

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHPGCRHGTCTSTPWQCLCDEGWGGLYCDQDLNYCTHHSPCKNGATC
 RNSGPRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNNGGSCRERNQGAN YACECPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTLSLSPGERATLS
 CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQ
 WSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYTMN
 WVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSED TAVYYCASGTMA
 TGFAYWGQGLTVTVSS

SEQ ID NO: 159 DLL4di-ADG41scFv

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNNGGSCRERNQGAN YACECPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTLSLSPGERATLS
 CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQ
 WSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYTMN
 WVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSED TAVYYCASGTMA
 TGFAYWGQGLTVTVSS

SEQ ID NO: 160 DLL1wt-ADG41scFv

QVWSSGVFELKLQEFVNKKGLGNRNCCRGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGS AVTP
 VLGVD SFLPDGGGADSAFSNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
 EEWSQDLHSSGRDLDKYSYRFVCDHEHYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
 PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDCEIRYPGLHGTCCQPWQCNCQEGWGGLFCNQDL
 NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGF
 YGKICELSAMTCADGPCFNNGRCSDSPDGGYSCRCPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
 YLCRCQAGSFHCDDNVDDCASSPCANGGTCRCDGVNDFSTCTPPGYTGRNCAPVSRCEHAPCHNG
 ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDLTEKLEGQGGPFPWGGGGSGGGGSGGGGS
 QIVLTQSPGTLSLSPGERATLS CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGT
 DYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPG
 ASMKISCKASGYSTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYME
 LSSLTSED TAVYYCASGTMATGFA YWGQGLTVTVSS

SEQ ID NO: 161 DLL3wt-ADG41scFv

AGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEA AESPCALGAALSARGPVYTEQPGA
 PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQR
 GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
 GECRCLGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
 YGLRCEVSGVTCADGPCFNGLCVGGADPD SAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
 HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDRCRERADPCAARPC
 AHGGRCYAHFSLVCA CAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLGGGGSGGGGSGG
 GGSQIVLTQSPGTLSLSPGERATLS CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
 GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVK
 PGASMKISCKASGYSTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAY
 MELSSLTSED TAVYYCASGTMATGFA YWGQGLTVTVSS

SEQ ID NO: 162 Jag1wt-ADG41scFv

ASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSG
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
 QTLKQNTGVAHFHEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
 CRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSNTGPDKEYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETS LGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
 DCLPGWMGQNCDDGGGSGGGGSGGGGSGQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKP
 GQSPRLWIYSTNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGG
 GSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSFTGYTMNWVRQAPGQGLEWIGLINPY
 NGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSEDNAVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 163 Jag1v-ADG41scFv

ALGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
 QTLKQNTGVAHFHEYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
 CRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSNTGPDKEYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETS LGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
 DCLPGWMGQNCDDGGGSGGGGSGGGGSGQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKP
 GQSPRLWIYSTNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGG
 GSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSFTGYTMNWVRQAPGQGLEWIGLINPY
 NGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSEDNAVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 164 Jag2wt-ADG41scFv

MGYFELQLSALRVNNGELLSGACCDGDGRTTTRAGGCGHDECNTYVRVCLKEYQAKVTPTGPCSYGH
 GATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVVIFFQFAWPRSFTLIVEAWDWDNDTTPNE
 ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCQYQY
 NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGEGRCSYGWQGRFCDECVPYPGCVHGSCVEPW
 QCNCETNWGGLLCDKDLNYCGSHHPCTNGGTICINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCAN
 GGSCHVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCDVDQVDGFECICPEQWVGATCQLDANE
 CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDRCRGQCQHGHTCKDLVNGYQCVCPRGFGR
 HCELEDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYCA
 CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSPGGNFSCICDSGFT
 GTYCHENIDDCLGQPCRNGGTICIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDY
 CACDDGWKGKTCHSREFQCDAYTCSNGGTICYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
 GTCVSGSASFSCICRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDRCRINIDEC
 QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNCRCLDGRR
 DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLKAPGQCLRPPEAWGECGAEEPPSTPCLPRSGHLD
 NNCARLTLHFNRDHPVQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
 PDSSLIQGAHAHAIVAAITQRGNSSLLLA VTEVKVETVVTGGSSTGGGSGGGGSGGGGSGQIVLTQSPGT
 LSLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTNLASGVPARFSGSGSGTDYSLTISSME
 AEDAASYFCHQWSSYPLTFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKAS
 GYSFTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSEDNA
 VYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 165 LG21-VH-CH1

EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRF
 TISRDNSKNTLYLQMSSLRAEDTALYYCARFDYGGSLDSWGQGTTLTVSSASTKGPSVFPLAPSSKSTS
 GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHK
 PSNTKVDKRVEPKSC

SEQ ID NO: 166 LG21-VL-CL

EIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGTDFT
 LSINSVEAEDAATYFCQQSKSWPRTFGGGTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
 EAKVQWKVDNALQSGNSQESVTEQDSKSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSF
 NRGE

SEQ ID NO: 167 DLL4wt-LG21-Fab

SGVFQLQLQEFINERGVLASGRPCCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL
 CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKS
 WPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
 SVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 168 DLL4v-LG21-Fab

SSVFQLQLQEFINERGVLASGRPCCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL
 CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKS
 WPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
 SVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 169 DLL4max-LG21-Fab

SSVFQLQLQEFINERGVLASGRPCCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCLCDEGWGGLYCDQDLNYCTHHSPCKNGATC
 RNSGPRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL
 CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKS
 WPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
 SVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 170 DLL4di-LG21-Fab

SSVFQLQLQEFINERGVLASGRPCCEPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANACECPPNFTGSNCEGGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTL
 CRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKS
 WPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
 SVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 171 DLL1wt-LG21-Fab

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHQYQASVSPEPPCTYGSVTP
 VLGVDLSLPLDGGGADSAFSNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
 EEWSQDLHSSGRDLDKYSYRFVCEHYHGECSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
 PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDICIRYPGCLHGTCCQPWQCNCQEGWGGLFCNQDL
 NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYTGTATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGF
 YGKICELSAMTCADGPCFNGGRCSDDSPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
 YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCTRDGVNDFSTCTPPGYTGRNCSAPVSRCEHAPCHNG
 ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDLTEKLEGQGGPFPWGGGGSGGGGSGGGGS
 EIVLTQSPDFLSVTPKEKVTLSCRASQSISNYLHWYQQKSDQSPKLLIKYASQSISGIPSRFSGSGSGTDFT
 LSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP
 EAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
 NRGEC

SEQ ID NO: 172 DLL3wt-LG21-Fab

AGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
 PAPDLPLPDGLLQVPRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRA
 GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
 GECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
 YGLRCEVSGVTCADGPCFNGGLCVGGADPD SAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
 HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDRCRERADPCAARPC
 AHGGRCYAHFSLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLGGGGSGGGSGG
 GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
 DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
 YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVT
 KSFNRGEC

SEQ ID NO: 173 Jag1wt-LG21-Fab

ASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECNTYFKVCLKEYQSRVTAGGPCSFSGS
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
 QTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
 CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHIGICNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCEIAEHAACLSDPCHNRGSKETSLGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNASKCKNLIASYYC
 DCLPGWMGQNCDDGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKS
 DQSPKLLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVA
 APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 174 Jag1v-LG21-Fab

ALGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFSGS
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
 QTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
 CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHIGICNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCEIAEHAACLSDPCHNRGSKETSLGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNASKCKNLIASYYC
 DCLPGWMGQNCDDGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKS
 DQSPKLLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVA
 APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
 LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 175 Jag2wt-LG21-Fab

MGYFELQSLARNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQAKVTPGTGPCSYPH
 GATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVIPFQFAWPRSFTLIVEAWDWDNDTTPNE
 ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCQYQ
 NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGEGRCSYGWQGRFCDECVPYPGCVHGSCVEPW
 QCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCTINAEPDQYRCTCPDGYSGRNCEKAETHACTSNPCAN
 GGSCHVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQLDANE
 CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDRCGQCQHGGTCKDLVNGYQCVCPRGFGGR
 HCELEDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYCA
 CPDDFGGKNCSVPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSPGGNFSCICDSGFT
 GTYCHENIDDLGQPCRNGGTCTIDEVDAFRFCFCPSGWEGLCDTNPNDCLPDPCHSRGRCYDLVNDY
 CACDDGWKGKTCHSREFQCDAYTCSNGGTCTYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
 GTCVSGSASFSCICRDGWEGRTCTHTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
 QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDGRR
 DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLKAPGQCLRPCEAWGECGAEPPSTPCLPRSGHLD
 NNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
 PDSSLIQGAHAHAIVAAITQRGNSSLLLAVTEVKVETVVTGSSSTGGGGSGGGSGGGGSEIVLTQSPDFL
 SVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAED
 AATYFCQQSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
 DNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 176 ADG41-VH-CH1

EVQLVQSGPEVVKPGASMKISCKASGYSFTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGR
ATLTVDKSTTTAYMELSSLTSED TAVYYCASGT MATGFAYWGQGLTVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVT VSWNSGAL TSGVHTFPAVLQSSGLYSLSSV VTPSSSLGTQTYICNVN
HKPSNTKVDKRV EPKSC

SEQ ID NO: 177 LG21-VL-CL

QIVLTQSPGTL SLS PGERATLS CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGV PARFSGSGSGT
DYSLTISSMEAE DAASYFCHQWSSYPLTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVT
KSFNRGEC

SEQ ID NO: 178 DLL4wt-ADG41-Fab

SGVFQQLQEFINERGV LASGRPCEPGC RTFFRVCLKH FQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGR LCN ECI PHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTL SLS PGERATLS
CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGV PARFSGSGSGTDYSLTISSMEAE DAASYFCHQ
WSSYPLTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSK DSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

SEQ ID NO: 179 DLL4v-ADG41-Fab

SSVFQQLQEFINERGV LASGRPCEPGC RTFFRVCLKH FQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGR LCN ECI PHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTL SLS PGERATLS
CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGV PARFSGSGSGTDYSLTISSMEAE DAASYFCHQ
WSSYPLTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSK DSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

SEQ ID NO: 180 DLL4max-ADG41-Fab

SSVFQQLQEFINERGV LASGRPCEPGC RTFFRVCLKH FQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGR LCN ECI PHNGCRHGTCSTPWQCTCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTL SLS PGERATLS
CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGV PARFSGSGSGTDYSLTISSMEAE DAASYFCHQ
WSSYPLTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSK DSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

SEQ ID NO: 181 DLL4di-ADG41-Fab

SSVFQQLQEFINERGV LASGRPCEPGC RTFFRVCLKH FQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFS LIIEAWHAPGDDL RPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGR LCN ECI PHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGV DCELELSECD SNPCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEGGGGSGGGGSGGGGSGQIVLTQSPGTL SLS PGERATLS
CRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGV PARFSGSGSGTDYSLTISSMEAE DAASYFCHQ
WSSYPLTFGQGTKLEIKRTVAAPS VFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNS
QESVTEQDSK DSTYSL SSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC

SEQ ID NO: 182 DLL1wt-ADG41-Fab

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKH YQASVSPEPPCTYGS AVTP
VLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFS LIIEALHTDSPDDLATENPERLISR LATQRHLTVG
EEWSQDLHSSGR TD LKYSYRFV CDEHY YGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE

PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDDECIRYPGCLHGTCCQPWQCNCQEGWGGLFCNQDL
 NYCTHHKPKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSDTLENSYSCTCPPGF
 YGKICELSAMTCADGPCFNNGRCSDDSPDGGYSCRCVPVYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
 YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCTRDGVNDFSTCTPPGYTGRNCSAPVSRCEHAPCHNG
 ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDLTKLEGQGGPFPWGGGGSGGGSGGGSG
 QIVLTQSPGTLSSLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGT
 DYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
 YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVT
 KSFNRGEC

SEQ ID NO: 183 DLL3wt-ADG41-Fab

AGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
 PAPDLPLPDGLLQVPRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDIQR
 GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
 GEGRCLGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
 YGLRCEVSGVTCADGPCFNGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
 HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCEVGGGAHRCSCALGFGGRDCRERADPCAARPC
 AHGGRCYAHFSGLVACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLGGGGSGGGSGGG
 GGSQIVLTQSPGTLSSLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
 GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN
 NFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSP
 VTKSFNRGEC

SEQ ID NO: 184 Jag1wt-ADG41-Fab

ASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECNTYFKVCLKEYQSRVTAGGPCSFGSG
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIIEKASHSGMINPSRQW
 QTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEMGWMGPECNRAI
 CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGCNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCEIAEHAACLSDPCHNRGSKETSLGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNASKCKNLIASYYC
 DCLPGWMGQNCDDGGGGSGGGSGGGSGQIVLTQSPGTLSSLSPGERATLSCRASSSVSSIYLYWYQQK
 GQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTV
 AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
 TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 185 Jag1v-ADG41-Fab

ALGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIIEKASHSGMINPSRQW
 QTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEMGWMGPECNRAI
 CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGCNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCEIAEHAACLSDPCHNRGSKETSLGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNASKCKNLIASYYC
 DCLPGWMGQNCDDGGGGSGGGSGGGSGQIVLTQSPGTLSSLSPGERATLSCRASSSVSSIYLYWYQQK
 GQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTV
 AAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLT
 TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 186 Jag2wt-ADG41-Fab

MGYFELQLSALRVNDELGSGACCDGDGRTRAGGCGHDECNTYVRVCLKEYQAKVTPTGPCSYGH
 GATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVVPFQFAWPRSFTLIVEAWDWDNDTTPNE
 ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCQY
 NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGEGRCSYGWQGRFCDECVPYPGCVHGSCEVPW
 QCNCETNWGGLLCKDLNYCGSHHPCTNGGTCTINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCAN
 GGSCEHVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCTVDQVDGFECICPEQWVGATCQLDANE
 CEGKPCLNAFSCKNLIGGYCDIPGWKGINCHINVNDCRGQCQHGHTCKDLVNGYQCVCPRGFGGR
 HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYCA
 CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSQPGGNFSCICDSGFT
 GTYCHENIDDLGQPCRNGGTCTIDEVDAFRFCFPCPSGWEGLCDTNPNDCLPDPCHSRGRCYDLVNDY
 CACDDGWKGKTCHSREFQCDAYTCSNGGTCTYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
 GTCVGSASGFSICRDLGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDICRINIDEC

QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPCEAWGECGAEPPSTPCLPRSGHLD
NNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSAPDL
PDSSLIQGAHAHAIVAAITQRGNSSLLAVTEVKVETVVTGGSSTGGGSGGGGSGGGGSGQIVLTQSPGT
LSLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSME
AEDAASYFCHQWSSYPLTFGQGKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 187 Human wildtype IgG1

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC
SVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 188 Human IgG1 Fc LALA + H435A

DKTHTCPPCPAPE[AA]GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFC
SVMHEALHN[AY]TQKSLSLSPGK

SEQ ID NO: 189 DLL4wt-Fc-LG21-Fab

SGVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFFQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNAYTQKSLSLSPGKGGGGSGGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSPVT
KSFNRGEC

SEQ ID NO: 190 DLL4v-Fc-LG21-Fab

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFFQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNAYTQKSLSLSPGKGGGGSGGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSPVT
KSFNRGEC

SEQ ID NO: 191 DLL4max-Fc-LG21-Fab

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFFQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCLCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNAYTQKSLSLSPGKGGGGSGGGGSGG

GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVT
KSFNRGEC

SEQ ID NO: 192 DLL4di-Fc-LG21-Fab

SSVFQLQLQEFINERGVLASGRPCPCGRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQSTLTTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCCQPPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNF
YPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVT
KSFNRGEC

SEQ ID NO: 193 DLL1wt-Fc-LG21-Fab

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHQYASVSPEPPCTYGSVTP
VLGVDSFSLPDGGGADSAFSPNIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
EEWSQDLHSSGRDLDKYSYRFVCDHEHYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDICIRYPGCLHGTCCQPWQCNCQEGWGGLFCNQDL
NYCTHHKPCCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGF
YGKICELSAMTCADGPCFNGGRCSDDSPDGGYSCRCVPGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCDGVDNFSTCPPGYTGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLPELPPGPAVVDLTKLEGQGGPFPWDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQK
SLSLSPGKGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPK
LLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADY
EKHKVYACEVTHQGLSSPVTKSFNRGEC

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AGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGLLQVPRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDIQRA
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
GECRCLEGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPDAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCEVGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLDKTHTCPPCPAPE
AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAY
TQKSLSLSPGKGGGGSGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQ
PKLLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVAAP
SVFIFPPSDEQLKSGTASVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSK
ADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 195 Jag1wt-Fc-LG21-Fab

ASGQFELEILSMQNVNGLQNGNCCGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFNLKASRGNDRNRIVLPFSFAWPRSYYTLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEMGWGMPECNRAI
CRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIHPGCVHIGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSNTGPDKYQCSCPEGYSNPNCEIAEHACLSDPCHNRGSCKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC

DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNAITQKSLSLSPGKGGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEK
VTLSCRASQSSISNYLHWYQQKSDQSPKLLIKYASQSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQ
QSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 196 Jag1v-Fc-LG21-Fab

ALGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFSGS
STPVIGGNTFNLKASRGNDRNRIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCNLGGTCSNTGPDKYQCSCEGYSGPNCEIAEHACLSDPCHNRGSCKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSKNLIASYYC
DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNAITQKSLSLSPGKGGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEK
VTLSCRASQSSISNYLHWYQQKSDQSPKLLIKYASQSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQ
QSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG
NSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 197 Jag2wt-Fc-LG21-Fab

MGYFELQLSALRVNDELGSGACCDGDGRTRAGGCGHDECNTYVRVCLKEYQAKVTPTGPCSYGH
GATPVLGGNSFYLPAGAAGDRARARARAGGDQDPLVVIQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCQDYG
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECRCYGWQGRFCDECVPYPGCVHGSCEPW
QCNCETNWGGLLCDKDLNYCGSHHPCTNGGTICINAEPDQYRCTCPDGYSGRNCEKAHACTSNPCAN
GGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCDVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGYCDIPGWKGINCHINVNDCRGQCQHGCTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYCA
CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSPGGNFSCICDSGFT
GTYPHENIDDCLGQPCRNGGTICIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDY
CACDDGWKGKTCHSREFQCDAYTCSNNGTICYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVGSASGFSICRDGWEGRTCTHTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPFHGSSWVEDCNCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLKAPGQCLRPPEAWGECGAEEPPSTPCLPRSGHLD
NNCARLTLHFNRDLHVPQGTTVGAICSGIRSLPATRAVARDRLVLLCDRASSGASAVEAVSFPARDL
PDSSLIQGAHAHAIVAAITQRGNSLLLAIVTEVKVETVVTGSSTDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAITQKSLSLSPGK
GGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLSRASCQSSISNYLHWYQQKSDQSPKLLIKYASQSI
SGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKSDSTYLSSTLTLSKADYEKHKVYA
CEVTHQGLSSPVTKSFNRGEC

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SGVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPPNFTGSNCEKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAITQKSLSLSPGKGGGGSGGGGSGG
GGSQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNN

NFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

SEQ ID NO: 199 DLL4v-Fc-ADG41-Fab

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEDKTHTCPPCAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

SEQ ID NO: 200 DLL4max-Fc-ADG41-Fab

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCLCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEDKTHTCPPCAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

SEQ ID NO: 201 DLL4di-Fc-ADG41-Fab

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGAN YACECPPNFTGSNCEDKTHTCPPCAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYFPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSP
VTKSFNRGEC

SEQ ID NO: 202 DLL1wt-Fc-ADG41-Fab

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFFRVCLKHFAQASVSPEPPCTYGS AVTP
VLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
EEWSQDLHSSGRITDLKYSYRFVCDHEHYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCDICIRYPGCLHGTCCQPWQCNCQEGWGGLFCNQDL
NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGF
YGKICELSAMTCADGPCFNGGRCSDSPDGGYSCRCVPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCTRDGVNDFSTCPCPGYTGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDLTKLEGQGGPFPPWDKTHTCPPCAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNAYTQK

SLSLSPGKGGGSGGGSGGGGSQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRL
WIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKRTVAAPSVF
IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLTKAD
YEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 203 DLL3wt-Fc-ADG41-Fab

AGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDIQR
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQP
GECRCLEGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPDASAYICHCPPGFGQSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLDKTHTCPPCPAPE
AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSGFFLYSKLTVDKSRWQQGNVFSCVMHEALHNAY
TQKSLSLSPGKGGGSGGGGSGGGGSQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQ
SPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKRTVA
PSVFIFFPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 204 Jag1wt-Fc-ADG41-Fab

ASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECNTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPSIIEKASHSGMINPSRQW
QTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSTNTGPDYKQCSCPEGYSGPNCEIAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGFFLYSKLT
VDKSRWQQGNVFSCVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGGGGSQIVLTQSPGTLSPGER
ATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASY
FCHQWSSYPLTFGQGTKLEIKRTVAAPSVFIFFPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 205 Jag1v-Fc-ADG41-Fab

ALGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLLVEAWDSSNDTVQPSIIEKASHSGMINPSRQW
QTLKQNTGVAHFYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSTNTGPDYKQCSCPEGYSGPNCEIAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGFFLYSKLT
VDKSRWQQGNVFSCVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGGGGSQIVLTQSPGTLSPGER
ATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASY
FCHQWSSYPLTFGQGTKLEIKRTVAAPSVFIFFPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQ
SGNSQESVTEQDSKDYSLSTLTLTKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 206 Jag2wt-Fc-ADG41-Fab

MGYFELQLSALRNVNDELGACCDGDGRTRAGGCGHDECNTYVRVCLKEYQAKVTPTGPCSYGH
GATPVLGGNSFYLPAGAAAGDRARARARAGGDQDPGLVVIFFQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCDQYG
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGEGRCSYGWQGRFCDECVYPGCVHGSCVEPW
QCNCEITNWGGLCDKDLNYCGSHHPCTNGGTICINAEPDQYRCTCPDGYSGRNCEKAHACTSNPCAN
GGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCDVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDRCGQCQHGCTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYYCA

CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSQPGGNFSCICDSGFT
GTYPHENIDDCLGQPCRNGGTCIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDY
CACDDGWKGKTCHSREFQCDAYTCSNGGTCYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVSGSGASFSCICRDGWEGRTCTHTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTFFPHGSSWVEDCNSCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPPCEAWGECGAEPPSTPCLPRSGHLD
NNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGAHAHAIVAAITQRGNSSLLAVTEVKVETVVTGGSSTDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGK
GGGSGGGSGGGSGGSIQVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNL
ASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQ
LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSYSTLSSTLTLSKADYEEKHKV
YACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 207 Linker

(GS)_n (n is an integer of at least 1)

SEQ ID NO: 208 Linker

(GGGS)_n (n is an integer of at least 1)

SEQ ID NO: 209 Linker

(GGGGS)_n (n is an integer of at least 1)

SEQ ID NO: 210 Linker

(GSGGS)_n (n is an integer of at least 1)

SEQ ID NO: 211 Linker

GGGSGGGSGGGSGGGS

SEQ ID NO: 212 Linker

GGGSGGGSGGGSGGGSGGGS

SEQ ID NO: 213 Linker

GGGS

SEQ ID NO: 214 Linker

GGGGGGG

SEQ ID NO: 215 Linker

GGGGG

SEQ ID NO: 216 Linker

EAAAKEAAAKEAAK

SEQ ID NO: 217 Linker

(EAAAK)_n (n is an integer of at least 1)

SEQ ID NO: 218 Linker

AEAAAKEAAAKEAAAKEAAKALEAAAKEAAAKEAAAKEAAKA

SEQ ID NO: 219 Linker

AEAAAKEAAKA

SEQ ID NO: 220 Linker

PAPAP

SEQ ID NO: 221 Linker

(AP)_n (n is an integer of at least 5)

SEQ ID NO: 222 Linker
LE

SEQ ID NO: 223 DLL4wt-Fc-LG21scFv

SGVFQLQLQEFINERGVLASGRPCPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQM
SSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 224 DLL4v-Fc-LG21scFv

SSVFQLQLQEFINERGVLASGRPCPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQM
SSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 225 DLL4max-Fc-LG21scFv

SSVFQLQLQEFINERGVLASGRPCPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRS YTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQM
SSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 226 DLL4di-Fc-LG21scFv

SSVFQLQLQEFINERGVLASGRPCPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT

DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSGDNTYYPDSVKGRFTISRDN SKNTLYLQM
SSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 227 DLL1wt-Fc-LG21scFv

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGS AVTP
VLGVDSFSLPDGGGADSAFSNPIRFPGFTWPGTFSLIIEALHTDSPDDLATENPERLISR LATQRHLTVG
EEWSQDLHSSGRITDLKYSYRFVCD EHYYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPGCDEQHGFCDKPGECKCRVGVWQGRYCD ECIYPGCLHGTCQQPWQCNCQEGWGGGLFCNQDL
NYCTHHKPKCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGF
YGKICELSAMTCADGPCFNGGRCS DSPDGGYSCRCPVGYSGFNCEKKIDYCSSSPCSNGAKCVDL GDA
YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCDRGVNDFSCTCPPGYTGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLPELPPGPAVVDLTEKLEGQGGPPFPWDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNAYTQK
SLSLSPGKGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLS CRASQSSISNYLHWYQQKSDQSPKL
LIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGSGGGGS
GGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSGDNTYYPDS
VKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 228 DLL3wt-Fc-LG21scFv

AGVFELQIHSFGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEA AESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDI QRA
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFC EQP
GECRCLEGWTGPLCTVPVSTSSCLSPRGPSA TTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPD SAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSLVCA CAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLDKTHTCPPCPAPE
AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNV FSCSV MHEALHNAY
TQKSLSLSPGKGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLS CRASQSSISNYLHWYQQKSDQS
PKLLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGSGG
GGGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSGDNTY
YPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 229 Jag1wt-Fc-LG21scFv

ASGQFELEILSMQNVN GELQNGNCCGGARNPGDRKCTRDEC DTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFN LKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPD SIIEKASHSGMINPSRQW
QTLKQNTGVAHF EYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVH GICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTC SNTGPDKYQCSCPEGYS GPNCIEAIEHA CLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVN AKSCKNLIASYYC
DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTV
DKSRWQQGNV FSCSV MHEALHNAYTQKSLSLSPGKGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEK
VTLS CRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQ
QSKSWPRTFGGGTKLEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTMS
WVRQAPGKGLEWVATISSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGS
SLDSWGQGTTLTVSS

SEQ ID NO: 230 Jag1v-Fc-LG21scFv

ALGQFELEILSMQNVN GELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
STPVIGGNTFN LKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPD SIIEKASHSGMINPSRQW
QTLKQNTGVAHF EYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVH GICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTC SNTGPDKYQCSCPEGYS GPNCIEAIEHA CLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVN AKSCKNLIASYYC

DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEK
VTLSCRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSISGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQ
QSKSWPRTFGGGTKLEIKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYTM
WVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTISRDN SKNTLYLQMSSLRAEDTALYYCARFDYGS
SLDSWGQGTTLTVSS

SEQ ID NO: 231 Jag2wt-Fc-LG21scFv

MGYFELQLSALRNVNGELLSGACCDGDGRTRAGGCGHDECPTYVRVCLKEYQAKVTPTGPCSYGH
GATPVLGGNSFYLPAGAAAGDRARARARAGGDQDPGLVVIPFQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDFGHYTCQYQ
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVYPGCVHGSCVEPW
QCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCTINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCAN
GGSCHPEVSGFECHCPSGWSGPTCALDIDEASNPAAAGGTCTVDQVDFECICPEQWVGATCQLDANE
CEGKPCPLNAFCKNLIGGYCDICPGWKGINCHINVDNCRGQCQHGGTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYYCA
CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSQPGGNFSCICDSGFT
GTYCHENIDDLGQPCRNGGTCIDEVDAFRFCFPCSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDY
CACDDGWKGKTCHSREFQCDAYTCSNGGTCYDSGDTFRACAPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVSGSGASFSCICRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCCEAPGFAGPDCRINDEC
QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDGR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPCEAWGECGAEPPSTPCLPRSGHLD
NNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGAHAIAITQRGNSSLLAVTEVKVETVVTGGSSTDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGK
GGGSGGGGSGGGGSEIVLTQSPDFLSVTPKEKVTLSKRASQSSISNYLHWYQQKSDQSPKLLIKYASQSI
SGIPSRFSGSGSGTDFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGSGGGGSGGGGSEV
QLVESGGGLVQPGGSLRLSCAASGFTFSSYTMWVRQAPGKGLEWVATISSSGDNTYYPDSVKGRFTIS
RDN SKNTLYLQMSSLRAEDTALYYCARFDYGS SLDSWGQGTTLTVSS

SEQ ID NO: 232 DLL4wt-Fc-ADG41scFv

SGVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTPWQCTDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLSPGERATLSCRASSVSSIYLYWYQQKPGQSPRLWIYSTNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTLEIKGGGSGGGGSGGGGSEVQLVQSGPEVVK
PGASKISKASGYSFTGYTMNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAY
MELSSLTSEDATVYYCASGTMATGFAYWGQGTTLTVSS

SEQ ID NO: 233 DLL4v-Fc-ADG41scFv

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTPWQCTDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLSPGERATLSCRASSVSSIYLYWYQQKPGQSPRLWIYSTNLASGVPARFSGSGS

GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGSGGGSGGGGSEVQLVQSGPEVVK
PGASKISKASGYSTGYTMNWVRQAPQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAY
MELSSLTSED AVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 234 DLL4max-Fc-ADG41scFv

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQSTLTRL
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCCQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHPGCRHGTCSTPWQCLDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGSGGGSGGGGSEVQLVQSGPEVVK
PGASKISKASGYSTGYTMNWVRQAPQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAY
MELSSLTSED AVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 235 DLL4di-Fc-ADG41scFv

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQSTLTRL
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCCQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSQIVLTQSPGTLTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGS
GTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGSGGGSGGGGSEVQLVQSGPEVVK
PGASKISKASGYSTGYTMNWVRQAPQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAY
MELSSLTSED AVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 236 DLL1wt-Fc-ADG41scFv

QVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPCACRTFFRVCLKHYQASVSPEPPCTYGS AVTP
VLGVDSFSLPDGGGADSAFSPNIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
EESWDLHSSGRDLDKYSYRFVCDHEY YGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
PICLPQCDEHQHGFCCKPECKCRVGVWQGRYGCIRYPGCLHGTCCQPWQCNCQEGWGGLFCNQDL
NYCTHHKPKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGF
YGKICELSAMTCADGPCFNGGRCS DSPDGGYSCRCVPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCRDGVNDFSCCTCPPGYTGRNCSAPVSRCEHAPCHNG
ATCHERGHRYVCECARGYGGPNCQFLLPELPPGPAVVDL TEKLEGQGGPFPWDKTHTCPPCPAPEAAG
GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQK
SLSLSPGKGGGSGGGGSGGGGSGQIVLTQSPGTLTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRL
WIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGSGGG
GSGGGGSEVQLVQSGPEVVKPGASKISKASGYSTGYTMNWVRQAPQGLEWIGLINPYNGGTSY
NQKFKGRATLTVDKSTTTAYMELSSLTSED AVYYCASGTMATGFAYWGQGLTVTVSS

SEQ ID NO: 237 DLL3wt-Fc-ADG41scFv

AGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEA AESPCALGAALSARGPVYTEQPGA
PAPDLPLPDGGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRLAAGGPWARDIQRA
GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCQEP
GECRCLEGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
YGLRCEVSGVTCADGPCFNGGLCVGGADPD SA YICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLG
HALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPC
AHGGRCYAHFSLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLDKTHTCPPCPAPE
AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR

VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAY
TQKSLSLSPGKGGGSGGGGSGGGGSGQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQ
SPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKEIKGGGGS
GGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYTMNWVRQAPGQGLEWIGLINPYNGG
TSYNQKFKGRATLTVDKSTTTAYMELSSLTSEDNAVYYCASGTMATGFAYWGQGTTLTVSS

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ASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECNTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFHEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSTNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGGGGSGQIVLTQSPGTLSPGER
ATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYF
CHQWSSYPLTFGQGTKEIKGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYT
MNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSEDNAVYYCASGT
MATGFAYWGQGTTLTVSS

SEQ ID NO: 239 Jag1v-Fc-ADG41scFv

ALGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFHEYRIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCLNGGTCSTNTGPDKYQCSCPEGYS GPNCIEAEHACLSDPCHNRGSKETSLGFECECSPGWTG
PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT
VDKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGGGGSGQIVLTQSPGTLSPGER
ATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNLASGVPARFSGSGSGTDYSLTISSMEAEDAASYF
CHQWSSYPLTFGQGTKEIKGGGSGGGGSGGGGSEVQLVQSGPEVVKPGASMKISCKASGYSTGYT
MNWVRQAPGQGLEWIGLINPYNGGTSYNQKFKGRATLTVDKSTTTAYMELSSLTSEDNAVYYCASGT
MATGFAYWGQGTTLTVSS

SEQ ID NO: 240 Jag2wt-Fc-ADG41scFv

MGYFELQLSALRNVNDELQNGNCCGGARNPGDRKCTRDECNTYFKVCLKEYQAKVTPGTPCSYGH
GATPVLGGNSFYLPAGAAAGDRARARARAGGDQDPGLVIPFQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCDQYG
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGEGRCSYGWQGRFCDECVPYPGCVHGSCVEPW
QCNCEITNWGGLLCKDLNYCGSHHPCTNGGTCTNAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCAN
GGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDRCGQCQHGGTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYYCA
CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPMPTGTAASGVCGPHGRCVVSQPGGNFSCICDSGFT
GTYPHENIDDCGQPCRNGGTCIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDY
CACDDGWKGKTCHSREFQCDAYTCSNGGTCYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVGSASGFSICRDLGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTFFPHGSSWVEDCNCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPCEAWGECGAEPPSTPCLPRSGHL
NNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGAHAIAAITQRGNSSLLAVTEVKVETVVTGGSSDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGK
GGGSGGGGSGGGGSGQIVLTQSPGTLSPGERATLSCRASSSVSSIYLYWYQQKPGQSPRLWIYSTSNL

ASGVPARFSGSGSGTDYSLTISSMEAEDAASYFCHQWSSYPLTFGQGTKLEIKGGGSGGGGSGGGGSE
VQLVQSGPEVVKPGASMKISCKASGYSFTGYTMNWVRQAPQGGLWIGLINPYNGGTSYNQKFKGRA
TLTVDKSTTTAYMELSSLTSEDNAVYYCASGTMATGFAYWGQGTLVTVSS

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SGVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGFLCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTP
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSIQPEPVPTPAFPTPTPVLTGHGCAAESEFALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEA
ESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDG
ASNRTISPKKADILDVVGMLYVGGPLINYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGT
FANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVD
NGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGF
PDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

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SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGFLCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTP
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSIQPEPVPTPAFPTPTPVLTGHGCAAESEFALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEA
ESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDG
ASNRTISPKKADILDVVGMLYVGGPLINYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGT
FANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVD
NGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGF
PDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 243 DLL4max-Fc-LG4-5

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKFAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCLCDEGWGGLYCDQDLNYCTHHSPCKNGATC
RNSGPRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSCKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCAPEAAAGGPSVFLFPPKPKDTLMISRTP
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNAYTQKSLSLSPGKGGGSGGGGSGG
GGSIQPEPVPTPAFPTPTPVLTGHGCAAESEFALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEA
ESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMIPTKINDGQWHKIKIMRSKQEGILYVDG
ASNRTISPKKADILDVVGMLYVGGPLINYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGT
FANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVD
NGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGF
PDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

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SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGFLCDQDLNYCTHHSPCKNGATC

SNSGQRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSCKDQEDGYHCLCPPGYGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANACECPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
 VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
 SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
 TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
 GGSIQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEA
 ESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDG
 ASNRTISPKKADILDVVGMLYVGGPLINYTTTRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGT
 FANAQRGTDFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLGSSQKMDGMGIEMIDEKLMFHVD
 NGAGRFTAVIDAGVPGHLCDDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGF
 PDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFKALELRGVQPVSPAN

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QVWSSGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSVPT
 VLGVDLSFLPDGGGADSAFSPNIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVG
 EEWSQDLHSSGRDLDKYSYRFVCDHEHYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTE
 PICLPQCDEQHGFCDKPGECKCRVGVWQGRYCDCEIRYPGCLHGTCQQPWQCNCQEGWGGFLCNQDL
 NYCTHHKPKNGATCTNTGQGSYTCSCRPGYTGTATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGF
 YGKICELSAMTCADGPCFNGGRCSDDSPDGGYSCRCVPVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGD
 YLCRCQAGFSGRHCDNDVDDCASSPCANGGTCRDGVNDFSCCTCPPGYTGRNCSAPVSRCEHAPCHNG
 ATCHERGHRYVCECARGYGGPNCQFLPELPPGPAVVDLTKLEGQGGPFPWDKTHTCPPCPAPEAAG
 GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVV
 VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGF
 YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAYTQK
 SLSLSPGKGGGGSGGGSGGGSGSIQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSRNSHIAI
 AFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDG
 QWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGPLINYTTTRIGPVTYSIDGCVRNLM
 HMAEAPADLEQPTSSFHVGTGFANAQRGTDFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLGSS
 QKMDGMGIEMIDEKLMFHVDNGAGRFTAVIDAGVPGHLCDDGQWHKVTANKIKHRIELTVDGNQVE
 AQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFKALELRGVQPV
 SPAN

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AGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAESPCALGAALSARGPVYTEQPGA
 PAPDLPLPDGLLQVPFRDAWPGTFSFIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQR
 A GAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQ
 GECCRCLEGWTGPLCTVPVSTSSCLSPRGPSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGF
 YGLRCEVSGVTACDGPCFNGGLCVGGADPDASAYICHCPPGFGQGSNCEKRVDRCSLQPCRNGGLCLDLG
 HALRCRCRAGFACDGRCEHDLDDCAGRACANGGTCVEGGGAHRCSALGFGGRDCRERADPCAARPC
 AHGGRCYAHFSGLVACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLDKTHTCPPCPAPE
 AAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
 VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLV
 KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAY
 TQKSLSLSPGKGGGGSGGGSGGGSGSIQPEPVPTPAFPTPTPVLTGHGCAAESEPAALLIGSKQFGLSRNS
 HIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKI
 NDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGPLINYTTTRIGPVTYSIDGCVR
 NLHMAEAPADLEQPTSSFHVGTGFANAQRGTDFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLG
 ISSQKMDGMGIEMIDEKLMFHVDNGAGRFTAVIDAGVPGHLCDDGQWHKVTANKIKHRIELTVDGNQ
 VEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFKALELRGVQ
 PVSPAN

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ASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCSTRDECPTYFKVCLKEYQSRVTAGGPCSFGSG
 STPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
 QTLKQNTGVAHFQYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEMGWGMPECNRAI
 CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHIGICNEPWQCLCETNWGGQLCDKDLNY
 CGTHQPCLNGGTCSTNTGPDKYQCSCPEGYS GPNCIEAHACLSDPCHNRGSKETSLGFECECSPGWTG
 PTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYC
 DCLPGWMGQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
 WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ

REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGKGGGGSGGGGSGGGGSIQPEPVPTPAFPTPTPV
THGPCAAESEPALIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATV
QLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGML
YVGGLPINYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAV
GGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTAVIDAGVPGHL
CDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIR
SLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

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ALGQFELEILSMQNVNGLQNGNCCGARNPGDRKCTGDECNTYFKVCLKEYQSRVRAGGPCSFGSG
STPVIGGNTFNLKASRGNDRNRIVLPFSFAWPRS YTLLEAWDSSNDTVQPDSEIEKASHSGMINPSRQW
QTLKQNTGVAHFYRIRVTCDDYYYGFCNKFCRPRDDFFGHYACDQNGNKTCEGWMGPECNRAI
CRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKDLNY
CGTHQPCNLGGTCSNTGPDKYQCSCPEGYSNPCEIAEHAACLSDPCHNRGSKETSGLFECECSPGWGT
PTCSTNIDDCSPNCSHGTCQDLVNGFKCVCPQWTKGTCQLDANECEAKPCVNAKSCKNLIASYYC
DCLPGWMQNCDDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGKGGGGSGGGGSGGGGSIQPEPVPTPAFPTPTPV
THGPCAAESEPALIGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATV
QLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGML
YVGGLPINYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAV
GGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTAVIDAGVPGHL
CDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIR
SLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 249 Jag2wt-Fc-LG4-5

MGYFELQLSALRNVNGLLSGACCDGDGRTRAGGCGHDECNTYVRVCLKEYQAKVPTGPCSYGH
GATPVLGGNSFYLPAGAAAGDRARARARAGGDQDPGLVVIQFAWPRSFTLIVEAWDWDNDTTPNE
ELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYTCQYQ
NKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGEGRCSYGWQGRFCDECVPYPGCVHGSCVEPW
QCNCETNWGGLLCKDLNYCGSHHPCTNGGTICINAEPDQYRCTCPDGYSGRNCEKAHACTSNPCAN
GGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCTVDQVDGFECICPEQWVGATCQLDANE
CEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDRCGQCQHGCTCKDLVNGYQCVCPRGFGGR
HCELERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYCA
CPDDFGGKNCSPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSPGGNFSCICDSGFT
GTICHENIDDLGQPCRNGGTCTIDEVDAFRFCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDYF
CACDDGWKGKTCRSHREFQCDAYTCSNNGTCYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNG
GTCVGSASFCICRSDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDEC
QSSPCA YGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDGRR
DCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPCEAWGECGAEPPSTPCLPRSGHL
NNCARLTLHFNRDHPVPGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDL
PDSSLIQGAHAHAIVAAITQRGNSSLLAVTEVKVETVVTGSSTDKTHTCPPCPAPEAAGGPSVFLFPPK
PKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD
WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVE
WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNAYTQKSLSLSPGK
GGGGSGGGGSGGGGSIQPEPVPTPAFPTPTPVLTGHPCAAESSEPALIGSKQFGLSRNSHIAIAFDDTKV
NRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIM
RSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTRRIGPVTYSIDGCVRNLMHMAEAPADL
EQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGI
EMIDEKLMFHVDNGAGRFTAVIDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTS
ADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 250 Mouse DLL4wt-Fc-LG4-5

SGIFQLRLQEFVNQRGMLANGQSCEPGCRTFFRICLKHFQATFSEGPCTFGNVSTPVLGTNSFVVRDKN
SGSGRNPLQLPFNFTWPGTFSNLIAQWHTPGDDL RPETSPGNSLISQIIQGLAVGKIWRTEQNDTLTR
LSYSYRVICSDNYYGESCSRLCKKRDDHFGHYECQPDGSLSCLPGWTGKYCDQPICLSGCHEQNGYCS
KPDECICRPGWQGRCLNECIPHNGCRHGTCSIPWQCACDEGWGGLFCDQDLNYCTHHSCKNGSTCSN
SGPKGYTCTCLPGYTGEHCELGLSKCASNPCRNGGSKDQENSYHCLCPPGYGQHCEHSTLTCADSP

CFNGGSCRERNQGSSYACECPPNFTGSNCEVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLITLTPKVTC
 VVVDISKDDPEVQFSWFVDDVEVHTAQTPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFP
 APIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIM
 DTDGSYFVYSKLVNQKSNWEAGNTFTCSVLHEGLHNHHTTEKSLSHSPGKGGGGSGGGSGGGGSVPT
 PAFPPAPTVMHGPCVAESEPALLTGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMA
 RINHADFATVQLRNGFPYFSYDLGSGDTSTMIPTKINDGQWHKIKIVRVKQEGILYVDDASSQTISPCKA
 DILDVVGILYVGGLPINYTTRRIGPVTYSLDGCVRNLHMEQAPVDLDQPTSSFHVGTCTFANAESGTYFD
 GTGFAKAVGGFKVGLDLLVEFEFRTRPTGVLLGVSSQKMDGMGIEMIDEKLMFHVDNGAGRFTAIY
 DAGIPGHMCNGQWHKVTAKKIKNRLELVVDGNQVDAQSPNSASTSADTNDPVFVGGFPGGLNQFGLT
 TNIRFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPTT

SEQ ID NO: 251 Mouse DLL4v1-Fc-LG4-5

SSIFQLRLQEFVNQRGMLANGQSCEPGCRTFFRICLKHQATFSEGPCTFGNVSTPVLGTNSFVVRDKNS
 GSGRNPLQLPLNFTWPGTFSLIQAWHTPGDDLRLPETSPGNLSISQFIIQGSLAVGKIWRDEQNDLTRL
 SYSYRVICSDNYYGESCSRCLCKKRDDYFGHYECQPDGSPSCLPGWTGEYCDQPICLSGCHEQNGYCSK
 PDECICRPGWQGRCLCNECIPHNGCRHGTCSIPWQCACDEGWGGLFCDQDLNYCTHHSPCKNGSTCSNS
 GPKGYTCTCLPGYTGEHCELGLSKCASNPCRNGGSKDQENSYHCLCPPGYYGQHCEHSTLTCADSPC
 FNGGSCRERNQGSSYACECPPNFTGSNCEVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLITLTPKVTCV
 VVVDISKDDPEVQFSWFVDDVEVHTAQTPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFP
 PIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMD
 TDGSYFVYSKLVNQKSNWEAGNTFTCSVLHEGLHNHHTTEKSLSHSPGKGGGGSGGGSGGGGSVPTP
 AFPFPAPTVMHGPCVAESEPALLTGSKQFGLSRNSHIAIAFDDTKVKNRLTIELEVRTEAESGLLFYMAR
 INHADFATVQLRNGFPYFSYDLGSGDTSTMIPTKINDGQWHKIKIVRVKQEGILYVDDASSQTISPCKAD
 ILDVVGILYVGGLPINYTTRRIGPVTYSLDGCVRNLHMEQAPVDLDQPTSSFHVGTCTFANAESGTYFDG
 TGFAKAVGGFKVGLDLLVEFEFRTRPTGVLLGVSSQKMDGMGIEMIDEKLMFHVDNGAGRFTAIYD
 AGIPGHMCNGQWHKVTAKKIKNRLELVVDGNQVDAQSPNSASTSADTNDPVFVGGFPGGLNQFGLT
 TNIRFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPTT

SEQ ID NO: 252 Mouse DLL4v1-Fc-LG03scFv

SSIFQLRLQEFVNQRGMLANGQSCEPGCRTFFRICLKHQATFSEGPCTFGNVSTPVLGTNSFVVRDKNS
 GSGRNPLQLPLNFTWPGTFSLIQAWHTPGDDLRLPETSPGNLSISQFIIQGSLAVGKIWRDEQNDLTRL
 SYSYRVICSDNYYGESCSRCLCKKRDDYFGHYECQPDGSPSCLPGWTGEYCDQPICLSGCHEQNGYCSK
 PDECICRPGWQGRCLCNECIPHNGCRHGTCSIPWQCACDEGWGGLFCDQDLNYCTHHSPCKNGSTCSNS
 GPKGYTCTCLPGYTGEHCELGLSKCASNPCRNGGSKDQENSYHCLCPPGYYGQHCEHSTLTCADSPC
 FNGGSCRERNQGSSYACECPPNFTGSNCEVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLITLTPKVTCV
 VVVDISKDDPEVQFSWFVDDVEVHTAQTPREEQFNSTFRSVSELPIMHQDWLNGKEFKCRVNSAAFP
 PIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWNGQPAENYKNTQPIMD
 TDGSYFVYSKLVNQKSNWEAGNTFTCSVLHEGLHNHHTTEKSLSHSPGKGGGGSGGGSGGGGSDIVL
 TQSPATLSVTPGDSVLSCRASQISNNLHWYQQKSHESPRLLIKYASQSISGIPSRFSGSGSGTDFTLIN
 SVETEDFGMYFCQQSKNWPRTFGGGTKLEIKGGGGSGGGSGGGSGGGSGGGSDVMLVESGGDLVKPG
 GSLKLSAASGFTFSYTMWVRQTPEKRLEWVASISSGGGNTYYPDSVKGRFTISRDNKNNLYLQM
 SSLRSEDTALYYCARFDYGSSLDSWGQGTTLTVSS

SEQ ID NO: 253 Signal peptide

MHSSALLCCLVLLTGVR

SEQ ID NO: 254 Mouse Fc

ICTVPEVSSVFIFPPKPKDVLITLTPKVTCVVVDISKDDPEVQFSWFVDDVEVHTAQTPREEQFNSTFR
 SVSELPIMHQDWLNGKEFKCRVNSAAFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMIT
 DFFPEDITVEWQWNGQPAENYKNTQPIMDDTDGSYFVYSKLVNQKSNWEAGNTFTCSVLHEGLHNHHT
 EKSLSHSPGK

SEQ ID NO: 255 Human IgG1 Fc second subunit, wherein X₂ is Asp or Glu

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVSVLTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
 MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSX₂LTVDKSRWQQGNVFS
 CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 256 Fc Human IgG1 Fc + LALA, wherein X₃ is Arg, His, or Lys

DKTHTCPPCPAPE[AA]GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVX₃SDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 257 Human IgG1 Fc + LALA, wherein X₄ is Asp or Glu

DKTHTCPPCPAPE[AA]GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSX₄LTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 258 Human IgG1 Fc + LALA + H435A, wherein X₅ is Arg, His, or Lys

DKTHTCPPCPAPE[AA]GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVX₅SDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHN[AY]TQKSLSLSPGK

SEQ ID NO: 259 Human IgG1 Fc + LALA + H435A, wherein X₆ is Asp or Glu

DKTHTCPPCPAPE[AA]GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSX₆LTVDKSRWQQGNVFS
CSVMHEALHN[AY]TQKSLSLSPGK

SEQ ID NO: 260 Human DLL4v_G2S_F81L_H168Y

S[SV]VFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLP[Q]NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRND[Y]FGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDSNPCRNGGSKDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 261 Human DLL4v11_G2S_T52N_F81L_T135N_H168Y

S[SV]VFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFG[N]VSTPVLGTNSFAVRDDSS
SGGGRNPLQLP[Q]NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQ[N]STLT
RLRYSYRVICSDNYYGDNCSRLCKKRND[Y]FGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGY
CSKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGAT
CSNSGQRSYTCTCRPGYTGVDCLELSECDSNPCRNGGSKDKQEDGYHCLCPPGYGLHCEHSTLSCA
DSPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 262 Human DLL4v12_G2S_R66S_F81L_H168Y

S[SV]VFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAV[S]DDSS
GGGRNPLQLP[Q]NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYYGDNCSRLCKKRND[Y]FGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDSNPCRNGGSKDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 263 Human DLL4v13_G2S_E14H_T52N_R66T_P76L_F81L_T135N_H168Y_N231D

S[SV]VFQLQLQEFIN[HR]GVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFG[N]VSTPVLGTNSFAV[T]DDSS
SGGGRN[Q]LQLP[Q]NFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQ[N]STLT
TRLRYSYRVICSDNYYGDNCSRLCKKRND[Y]FGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNG
YCSKPAECLCRPGWQGRCLNECIPH[D]GCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNG
ATCSNSGQRSYTCTCRPGYTGVDCLELSECDSNPCRNGGSKDKQEDGYHCLCPPGYGLHCEHSTLS
CADSPCFNGGSCRERNQGANYACECPPNFTGSNCE

SEQ ID NO: 264 Human DLL4v14_G2S_T52N_R66T_P76L_F81L_T135N_H168Y_Q220H_N260D

S[VFQLQLQEFINERGVLASGRPCEPGC[RTFFRVCLKHFQAVVSPGPCTFG[NVSTPVLGTNSFAV[TDSS
SGGGRN[LQLP[NFTWPGTFSLIIEAWHAPGDDL[RPEALPPDALISKIAIQGSLAVGQNWLLDEQ[NSTL
TRLRYSYRVICSDNYGDNCSRLCKKRND[YFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNG
YCSKPAECLCRPGW[HGRLCNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDL[DYCTHHSPCKNG
ATCSNSGQ[RSYTCTCRPGYTGVDCLELSECD[SNPCRNGGSKDQEDGYHCLCPPGY[YLHCEHSTLS
CADSPCFNGGSCRERNQGAN[ACECPPNFTGSNCE

SEQ ID NO: 265 Human DLL4v22_G2S_R66S_F81L_H168Y

S[VFQLQLQEFINERGVLASGRPCEPGC[RTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAV[TDSS
GGGRNPLQLP[NFTWPGTFSLIIEAWHAPGDDL[RPEALPPDALISKIAIQGSLAVGQNWLLDEQ[STLTR
LRY[SYRVICSDNYGDNCSRLCKKRND[YFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRLCNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQ[RSYTCTCRPGYTGVDCLELSECD[SNPCRNGGSKDQEDGYHCLCPPGY[YLHCEHSTLSCAD
SPCFNGGSCRERNQGAN[ACECPPNFTGSNCE

SEQ ID NO: 266 Human DLL4v23_G2S_E14H_R66T_P76L_F81L_H168Y_N231D

S[VFQLQLQEFIN[RGVLASGRPCEPGC[RTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAV[TDSS
SGGGRN[LQLP[NFTWPGTFSLIIEAWHAPGDDL[RPEALPPDALISKIAIQGSLAVGQNWLLDEQ[STLTR
LRY[SYRVICSDNYGDNCSRLCKKRND[YFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGY
CSKPAECLCRPGWQGRLCNECIPH[GCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGAT
CSNSGQ[RSYTCTCRPGYTGVDCLELSECD[SNPCRNGGSKDQEDGYHCLCPPGY[YLHCEHSTLSCA
DSPCFNGGSCRERNQGAN[ACECPPNFTGSNCE

SEQ ID NO: 267 Human DLL4v24_G2S_R66T_P76L_F81L_H168Y_Q220H_N260D

S[VFQLQLQEFINERGVLASGRPCEPGC[RTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAV[TDSS
GGGRN[LQLP[NFTWPGTFSLIIEAWHAPGDDL[RPEALPPDALISKIAIQGSLAVGQNWLLDEQ[STLTR
LRY[SYRVICSDNYGDNCSRLCKKRND[YFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGW[HGRLCNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDL[DYCTHHSPCKNGAT
CSNSGQ[RSYTCTCRPGYTGVDCLELSECD[SNPCRNGGSKDQEDGYHCLCPPGY[YLHCEHSTLSCA
DSPCFNGGSCRERNQGAN[ACECPPNFTGSNCE

SEQ ID NO: 268 Anti-LAMA2_D178S scFv

EIVLTQSPDFLSVTPKEKVTLSRASQ[SI[SNYLHWYQKSDQSPKLLIKYASQ[SI[SGIPSRFSGSGSGTDF
LSINSVEAEDAATYFCQ[QSKSWPRTFGG[GT[KLEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGSL
RLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGSNTYYPDSVKGRFTISRDN[SKNTLYLQMS
SLRAEDTALYYCARFDYGSSLD[SWGQGTTLTVSS

SEQ ID NO: 269 huD4v_G2S_F81L_H168Y-Fc(AAG)-LG21scFvDS

SSVFQLQLQEFINERGVLASGRPCEPGC[RTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDL[RPEALPPDALISKIAIQGSLAVGQNWLLDEQ[STLTR
LRY[SYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRLCNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQ[RSYTCTCRPGYTGVDCLELSECD[SNPCRNGGSKDQEDGYHCLCPPGY[YLHCEHSTLSCAD
SPCFNGGSCRERNQGAN[ACECPPNFTGSNCKTHTCPPCAPEAAGGPSVFLFPPKPKDTLMISRTP
VTCVVVDVSHEDPEVKFNWYVDGVEVHNACTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNV[FSCSVMH[EAHNHYTQKSLSLSPGKGGGGSGGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQ[SI[SNYLHWYQKSDQSPKLLIKYASQ[SI[SGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQ[QSKSWPRTFGG[GT[KLEIKGGGGSGGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSSYTMSWVRQAPGKGLEWVATISSSGSNTYYPDSVKGRFTISRDN[SKNTLYLQMS
SLRAEDTALYYCARFDYGSSLD[SWGQGTTLTVSS

SEQ ID NO: 270 huD4v11_G2S_T52N_F81L_T135N_H168Y-Fc(AAG)-LG21scFvDS

SSVFQLQLQEFINERGVLASGRPCEPGC[RTFFRVCLKHFQAVVSPGPCTFGNVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDL[RPEALPPDALISKIAIQGSLAVGQNWLLDEQ[NSTLTR
LRY[SYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRLCNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQ[RSYTCTCRPGYTGVDCLELSECD[SNPCRNGGSKDQEDGYHCLCPPGY[YLHCEHSTLSCAD
SPCFNGGSCRERNQGAN[ACECPPNFTGSNCKTHTCPPCAPEAAGGPSVFLFPPKPKDTLMISRTP

VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSISGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSGSNTYYPDSVKGRFTISRDNKNTLYLQMS
SLRAEDTALYYCARFDYGSSLDWSWGQTTLTVSS

SEQ ID NO: 271 huD4v12_G2S_R66S_F81L_H168Y-Fc(AAG)-LG21scFvDS

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGNVSTPVLGTNSFAVSDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQNSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNSPCRNGGSCKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSISGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSGSNTYYPDSVKGRFTISRDNKNTLYLQMS
SLRAEDTALYYCARFDYGSSLDWSWGQTTLTVSS

**SEQ ID NO: 272 huD4v13_G2S_E14H_T52N_R66T_P76L_F81L_T135N_H168Y_N231D-Fc(AAG)-
LG21scFvDS**

SSVFQLQLQEFINHRGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGNVSTPVLGTNSFAVTDSS
GGGRNLLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQNSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHDGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNSPCRNGGSCKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSISGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSGSNTYYPDSVKGRFTISRDNKNTLYLQMS
SLRAEDTALYYCARFDYGSSLDWSWGQTTLTVSS

**SEQ ID NO: 273 huD4v14_G2S_T52N_R66T_P76L_F81L_T135N_H168Y_Q220H_N260D-Fc(AAG)-
LG21scFvDS**

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGNVSTPVLGTNSFAVTDSS
GGGRNLLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQNSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWHGRLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNSPCRNGGSCKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNYHTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSISGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSGSNTYYPDSVKGRFTISRDNKNTLYLQMS
SLRAEDTALYYCARFDYGSSLDWSWGQTTLTVSS

SEQ ID NO: 274 huD4v22_G2S_R66S_F81L_H168Y-Fc(AAG)-LG21scFvDS

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVSDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC

SNSGQRSYTCTCRPGYTGVDCELELSECDNSNPCRNGGSKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
 VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
 SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
 TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGG
 GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
 DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
 GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSSGSNTYYPDSVKGRFTISRDN SKNTLYLQMS
 SLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 275 huD4v23_G2S_E14H_R66T_P76L_F81L_H168Y_N231D-FcAAG-LG21DS

SSVFQLQLQEFINHRGVLASGRPCEPGCRTFFRVCLKHQAVVSPGPCTFGTVSTPVLGTNSFAVTDDSS
 GGGRNLLQLPLNFTWPGTFSLIIEAWHAPGDDLPEALPPDALISKIAIQGSLAVGQNWLLDEQSTLTLR
 LRYSYRVICSDNY YGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHGDGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDNSNPCRNGGSKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
 VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
 SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
 TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGG
 GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
 DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
 GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSSGSNTYYPDSVKGRFTISRDN SKNTLYLQMS
 SLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 276 huD4v24_G2S_R66T_P76L_F81L_H168Y_Q220H_N260D-FcAAG-LG21DS

SSVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHQAVVSPGPCTFGTVSTPVLGTNSFAVTDDSS
 GGGRNLLQLPLNFTWPGTFSLIIEAWHAPGDDLPEALPPDALISKIAIQGSLAVGQNWLLDEQSTLTLR
 LRYSYRVICSDNY YGDNCSRLCKKRNDYFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWHGRLCNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLDYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDNSNPCRNGGSKDQEDGYHCLCPPGY YGLHCEHSTLSCAD
 SPCFNGGSCRERNQGANYACECPPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
 VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
 SNKALGAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
 TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGGSGGGSGG
 GGSEIVLTQSPDFLSVTPKEKVTLSRASQSSISNYLHWYQQKSDQSPKLLIKYASQSSIGIPSRFSGSGSGT
 DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKLEIKGGGGSGGGSGGGSGGGSEVQLVESGGGLVQPG
 GSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISSSGSNTYYPDSVKGRFTISRDN SKNTLYLQMS
 SLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

SEQ ID NO: 277 Human IgG1 Fc LALA + P329G

DKHTCPCPAPAEAAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
 TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALGAPIEKTISKAKGQPREPQVYTLPPSRE
 EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
 CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 278 Jagged1 MNL (C2)

KVCGASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
 FGSGSTPVIGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINP
 SRQ

SEQ ID NO: 279 Jagged1 DSL

WQTLKQNTGVAHFYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGREG

SEQ ID NO: 280 Jagged1 EGF-like repeats 1-3

NRAICRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDKD
 LNYCGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCE

SEQ ID NO: 281 Jagged1 EGF-like repeats 4-6

IAEHACLSDPCHNRGSKETSLGFECECSPGWTGPTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQ
WTGKTCQLDANECEAKPCVNAKSCKNLIASYYCDCLPGWMGQNC

SEQ ID NO: 282 Jagged1 EGF-like repeats 7-16

ININDCLGQCQNDASCRDLVNGYRCICPPGYAGDHCERDIDECASNPCLDGGHCQNEINRFQCLCPTGF
SGNLCQLDIDYCEPNPCQNGAQCYNRASDYFKCPCEDYEGKNCNCSHLKDHCRTPCEVIDSCTVAMASN
DTPEGVRYISSNVCBPHGKCKSQSGGKFTCDCKNGFTGTCHENINDCESNPCRNNGGTCIDGVNSYKCI
CSDGWEGAYCETNINDCSQNPCHNGGTCRDLVNDFYCDCKNGWKGTCHSRDSQCDEATCNNGGTC
YDEGDAFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGTCVVNGESFTCVCKEGWEGPICAQNTNDCS
PHPCYNSGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCAFGATCVDEINGYRCVCPPGHSGAKC
Q

SEQ ID NO: 283 Jagged2 MNL (C2)

VQAARPMGYFELQLSALRVNNGELLSGACCDGDGRTRAGGCGHDECPTYVRVCLKEYQAKVTPTG
PCSYGHGATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVIPQFAWPRSFTLIVEAWDWDN
DTTPNEELLIERVSHAGMINPEDR

SEQ ID NO: 284 Jagged2 DSL

WKSLSHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFGHYTCDQYGNKACMDGWMGKECKE
AVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVYPGCVH

SEQ ID NO: 285 Jagged2 EGF-like repeats 1-3

GSCVEPWQCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAEHA
CTS NPCANGGSCHEVPSGFECPCSGWSGPTCA

SEQ ID NO: 286 Jagged2 EGF-like repeats 4-6

LDIDECASNPAAAGGTCVDQVDGFECICPEQWVGATCQLDANECEGKPCLNAFSCKNLIGGYCDCIP
GWKGINCHINVNDCRGQCQHGGTCKDLVNGYQCVCPRGFGGRHCEL

SEQ ID NO: 287 Jagged2 EGF-like repeats 7-15

LERDECASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYYCACPD
DFGGKNCSVPREPCPGGACRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSQPGGNFSCICDSGFTGT
CHENIDDCLGQPCRNGGTCIDEVDAFRFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDFYCAC
DDGWKGKTCHSREFQCDAYTCSNGGTCYDSGDTFRACPPGWKGSTCAVAKNSSCLPNPCVNGGTC
VGSGASFSCICRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCCECAPGFAGPDCRINIDECQSSP
CAYGATCVDEINGYRCSCPPGRAGPRCQ

SEQ ID NO: 288 DLL1 MNL (C2)

SGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHQYQASVSPEPPCTYGSATPVLGV
DSFSLPDGGGADSAFSPNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEE

SEQ ID NO: 289 DLL1 DSL

WSQDLHSSGRDLDKYSYRFVCDHYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEP

SEQ ID NO: 290 DLL1 EGF-like repeats 1-3

ICLPGCDEQHGFCDKPGECKRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLN
YCTHHKPCKNATCTNTGQGSYTCSCRPGYTATCE

SEQ ID NO: 291 DLL1 EGF-like repeats 4-6

LGIDECDPSPCKNGGSCDLENSYCTCPPGFYKICELSAMTCADGPCFNNGRCSDSPDGGYSCRCPV
GYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCRCQAGFSGRHCD

SEQ ID NO: 292 DLL1 EGF-like repeats 7-8

DNVDDCASSPCANGGTCRDGVNDFSCTCPPGYTGRNCSAPVSRCEHAPCHNGATCHERGHRYVCECA
RGYGGPNCQ

SEQ ID NO: 293 DLL4 MNL (C2)

SGVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHQYQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQN

SEQ ID NO: 294 DLL4 DSL

WLLDEQTSTLTRLRYSYRVICSDNYYGDNCSRLLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYC

SEQ ID NO: 295 DLL4 EGF-like repeats 1-3

QQPICLSGCHEQNGYCSKPAECLCRPGWQGRLCNECIPHNGCRHGTCTSTPWQCTCDEGWGGLFCDQD
LNYCTHHSPCKNGATCSNSGQRSYTCTCRPGYTGVDC

SEQ ID NO: 296 DLL4 EGF-like repeats 4-6

LELSECDSNPCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCADSPCFNGGSCRERNQGANYACEC
PPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSRMCRCRPGFTGTCE

SEQ ID NO: 297 DLL4 EGF-like repeats 7-8

LHVSDCARNPCAHHGTCHDLENGLMCTCPAGFSGRRCEVRTSIDACASSPCFNATCYTDLSTDTFVC
NCPYGFVGSRC

SEQ ID NO: 298 DLL3 MNL (C2) and DSL

SPCSARLPCRLFFRVCLKPGLSEEAESPALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAW
PGTFSFIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVG
TACTRLCRPRSAPSRCPGLRPCAPLED

SEQ ID NO: 299 DLL3 EGF-like repeats 1-3

ECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNP
CANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFNGGLCVGGADPDASAYICHCPPGFQGSNCE

SEQ ID NO: 300 DLL3 EGF-like repeats 4-6

KRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSC
ALGFGGRDCRERADPCAARPCAHHGRCYAHFSGLVACAPGYMGARCE

SEQ ID NO: 301 Human Laminin-alpha-2 LG domains 1-5

SVSSGGDCIRTYKPEIKKGSYNNIVNVKTAVADNLLFYLGSAKFIDFLAIEMRKGVKVSFLWDVGSVG
RVEYPLDTIDDSYWYRIVASRTGRNGTISVRALDGPKASIVPSTHHSTSPPGYTILDVDANAMLFVGGT
GKLKKADAVRVITFTGCMGETYFDNKPIGLWNFREKEGDCKGCTVSPQVEDSEGTIQFDGEGYALVSR
PIRWYPNISTVMFKFRTFSSALLMYLATRDLRDFMSVELTDGHIKVSYDLGSGMASVVSNNHNDGK
WKSFTLSRIQKQANISIVDIDTNQEENIATSSSGNNFGLDLKADDKIYFGGLPTLRNLSMKARPEVNLLK
YSGCLKDIEISRTYPNLSPPDYVGVTKGCSLENNYTVSFPKPGFVELSPVPIDVGTEINLSFSTKNESGIL
LGSGGTPAPRRKRRTGTQAYYAILNRRGRLEVHLSTGARTMRKIVIRPEPNLFHDGREHVSHVTRTG
IFTVQVDENRRYMQLNLTVEQPIEVKLVGGAPPEFQPSPLRNIPPFEQCIWNLVINSVPMDFAFPVSFK
NADIGRCAHVQKLREDEGAAPAEIVIQPEVPPTAFPTPTPVLTHGPCAAESEPALIGSKQFGLSRNSHI
AIAFDDTKVKNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNLPLPYFSYDLGSGDTHMTPTKIN
DGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTTRIGPVTYSIDGCVRN
LHMAEAPADLEQPTSSFHVGTCFANAQRGTGYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLGI
SSQKMDGMGIEMIDEKLMFHVDNAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQV
EAQSPNPASTADTNDPVFVGGFDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQP
VSPAN

SEQ ID NO: 302 Human Laminin-alpha-1 LG domains 1-5

YNTLTNLNVKTQEPDNLLFYLGSSSTASDFLAVEMRRGRVAFWLWDLGSGSTRLEFPDFPIDDNRWHSIHV
ARFGNIGSLSVKEMSSNQKSPKTSKSPGTANVLDVNNSTLMFVGGGLGGQIKKSPAVKVTHFKGCLGE
AFLNGKSIGLWNYIEREGKCRGCFGSSQNEPDSFHDGSGYSVVEKSLPATVTQIIMLFNTFSPNGLLLY
LGSYGTKDFLSIELFRGRVKVMTDLGSGPITLLTDRRYNNGTWYKIAFQRNRKQGVLAVIDAYNTSNK
ETKQGETPGASSDLNRLDKDPIYVGGPLRSRVRRGVTTKSFVGCINKLEISRSTFDLLRNSYGVKGC
LLEPIRSVSFLKGGYIELPPKSLSPSEWLVTATTNSSGILAAALGGDVEKRGDREEAHVPFFSVMLIGG
NIEVHVNPBGDTGLRKALLHAPTGTCSDGQAHSISLVRNRRITVQLDENNPVEMKGLTLVESRTINVS
NLYVGGIPEGEGTSLTMRRSFHGCIKNLIFNLELLDFNSAVGHEQVLDLTCWLSEPKLAPDAEDSKL
LPEPRAFPEQCVVDAALEYVPGAHQFGLTQNSHFILPFNQSAVRKKLSVELSIRTFASSGLIYYMAHQN
QADYAVLQLHGGRLHFMFDLGKGRTKVSHPALSDGKWHTVKTQDYVVKRKGFTVDGRESPMVTVVG
DGTMLDVEGLFYLGGLPSQYQARKIGNITHSIPACIGDVTVNSKQLDKDSPVSAFTVNRCYAVAQEGT
YFDGSGYAAALVKEGYKVQSDVNITLFTSSQNGVLLGISTAKVDAIGLELVDGKVGAS

SEQ ID NO: 303 Human Laminin-alpha-3 LG domains 1-5

LQTVIKEDLPRKAKTSSNSDKLLNEAKMTQKKLKQEVSPALNNLQQTLNIVTVQKEVIDTNLTTLRD
 GLHGIQRGDIDAMISSAKSMVRKANDITDEVLDGLNPIQTDVERIKDTYGRQTQNEDEFKALTDADNSV
 NKLTNKLPLDLWRKIESINQQLPLGNISDNMDRIELIQQARDAASKVAVPMRFNGKSGVEVRLPNDLE
 DLKGYTSLSLFLQRPNSRENGGTENMFVMYLGNKDAASRDYIGMAVVDGQLTCVYNLGDREAEQVD
 QILTKSETKEAVMDRVKQFRIYQFARLNYTKGATSSKPEPTPGVYDMDGRNSNTLLNLDPENVVFFYVGG
 YPPDFKLPSRLSFPPYKGCIELDDLNNVLSLYNFKKTFNLNTTEVEPCRRRKEESDKNYFEGTGYARVP
 TQPHAPIPTFGQTIQTTVDRGLLFFAENGDRFISLNIEDGKLMVRYKLNSELPKERGVDGINNGRDHSI
 QIKIGKLQKRMWINVDVQNTIIDGEVDFDSTYYLGGPIAIRERFNISTPAFRGCMKNLKKTSGVVRLND
 TVGVTKKCSWDKLVRSASFSGGQLSFTDLGLPPTDHLQASFGFQTFQPSGILLDHQWTRNLQVTLE
 DGYIELSTSDSGGPIFKSPQTYMDGLLHYVSVISDNGLRLLIDDQLLRNSKRLKHISSSRQSLRLGGSNF
 EGCISNVFVQRLSLSPVLDLTSNSLKRVDLSLGGCSLNKPPFLMLLKGSTFRNKTCTFRINQLLDTPVA
 SPRSVKVVQDACSPLPKTQANHGAHQFGDIPTSHLLFKLPQELLKPRSQFAVDMQTTSSRGLVFHTGTK
 NSFALYLSKGRVLFALGTDGKKLRISKEKCNKGKWHVTVFGHDGEKGRVVDGLRAREGSLPGNS
 TISRAPVYLGSPSGKPKSLPTNSFVGCLKNFQLDSKPLYTPSSSFGVSSCLGGPLEKGIYFSEEGGHVVL
 AHSVLLGPEFKLVFSIRPSLTGILIHIGSQPGKHLVYLEAGKVTASMDSGAGGTSTSVTPKQSLCDGQ
 WHSVAVTIKQHILHLELDTSSYTAGQIPFPASTQEPLHLGGAPANLTTLRIPVWKSFFGCLRNIHVNI
 PVPVTEALEVQGPVSLNGCPDQ

SEQ ID NO: 304 Human Laminin-alpha-4 LG domains 1-5

FTSLSLYMKPPVKRPELTETADQFILYLGSKNAKKEYMGLAIKNDNLVYVYNLGTKDVEIPLDSKPVSS
 WPAYFSIVKIERVGKHGKVFLTVPSLSSTAEEKFIKKGEFSGDDSLDLDPEDTVFYVGGVPSNFKLPTS
 LNLPGFVGCLELTLNNDVISLYNFKHIYNMDPSTSVPCARDKLAFTQSRAASYFFDGSYAVVRDITR
 RGKFGQVTRFDIEVRTPADNGLILLMVNGSMFFRLEMRNGYLHVFDYDFGSSGRVHLEDTLKKAQIND
 AKYHEISIIYHNDKKMILVDDRHVKSMDNEKMKIPFTDIYIGGAPPEILQSRALRAHLPLDINFRGCMK
 GFQFQKKDFNLLEQTETLGVGYGCPEDSLISRRAYFNGQSFASIQKISFFDGFEGGFNFRTLQPNGLLFY
 YASGSDVFSISLDNGTVIMDVKGIVQSVDKQYNDGLSHFVISSVSPTRYELIVDKSRVGSKNPTKGKIE
 QTQASEKKFYFGGSPISAQYANFTGCISNAYFTRVDRDVEVEDFQRYTEKVHTSLYECPIESSPLFLLHK
 KGKNLSKPKASQNKKGKSKDAPSWDPVALKLPERNTPRNSHCHLSNSPRAIEHAYQYGGTANSRQE
 FEHLKGDFGAKSQFSIRLRTRSSHGMIFYVSDQEEENDFMTLFLAHGRLVYMFNVGHKKLKIRSQEKYN
 DGLWHDVIFIRERSSGRLVIDGLRVLEESLPPTTEATWKIKGPIYLGGAAPGKAVKNVQINSIYSFSGCLSN
 LQLNGASITSASQTFSVTPCFEGPMETGTTFSTEGGYVVLDESFNIGLKFEIAFEVRPRSSSGTLVHGHSV
 NGEYLVNVMKNGQVIVKVNNGIRDFSTSVTPKQSLCDGRWHRTVIRDSNVVQLDVEDSENVHVVGPL
 NPKPIDHREPVFVGGVPESLLTPRLAPSKPFTGCIRHFVIDGHPVSFSKAALVSGAVSINSCPA

SEQ ID NO: 305 Human Laminin-alpha-5 LG domains 1-5

YTALKFYLGPEPEPGQGTEDRFVMYMGSRQATGDYMGVSLRDKKVHWVYQLGEAGPAVLSDIEDI
 GEQFAAVSLDRTLQFGHMSVTVRQMIQETKGDTPAPGAEGLLNLRPDDFVFYVGGYPSTFTPPPLLR
 FPGYRGCIEMDTLNEEVVSLYNFERTFQLDTAVDRPCARSKSTGDPWLTGDSYLDGTGFARISFDSQIST
 TKRFEQELRLVSYSGVLFLLKQSQFLCLAVQEGSLVLLYDFGAGLKKAVPLQPPPLTSASKAIQVFL
 GGSRKRVLVRVERATVYSVEQDNDLELADAYYLGGVPPDQLPPLRLRFLPTGGSVRGCVKGIKALGK
 YVDLKRNLNTTGVSAGCTADLLVGRAMTFHGHGFLRLALSNAPLTGNVYSGFGFHSQAQDSALLYRA
 SPDGLCQVSLQQGRVSLQLLRTEVKTQAGFADGAPHYVAFYSNATGVWLYVDDQLQQMCKPHRGPPP
 ELQPQPEGPPRLLGLPESGTIYNFSGCISNVFVQRLGLPQRFVLDLQQLGVSNNVSTGCAPALQAQTPG
 LGPRGLQATARKASRRSRQPARHPACMLPPLRLTRDSYQFGGSLSSHLEFVGILARHRNWPSLSMHV
 LPRSSRGLLLFTARLRPGSPSLALFLSNHGFVAQMEGLGTRLRAQSRQSRPGRWHKVSVRWEKNRILL
 VTDGARAWSQEGPHRQHQAHEHPQPHTLFVGGLPASSHSSKLPVTVGFGSCVKRLRLHGRPLGAPTR
 MAGVTPCILGPLEAGLFFPGSGGVITLDLPGATLPDVGLELEVRPLAVTGLIFHLGQARTPPYLQLQVTE
 KQVLLRADDGAGEFSTSVTRPSVLCDGQWHRLAVMKSNGVLRLEVDAQSNHTVGPLLAAGAPAP
 LYLGLPEPMAVQWPAPAYCGCMRRLAVNRSPVAMTRSEVHGAVGASGCPAA

SEQ ID NO: 306 Human Perlecan LG domains 1-5

VKAFAHLQVPERVVYPYFTQTPYSFLPLPTIKDAYRKFEIKITFRPDSADGMMLLYNGQKRVPGSPTNLN
 RQPDFISFGLVGGRPFRFDAGSGMATIRHPTPLALGHFHTVTLRLSLTQGSILVGDAPVNGTSQGGKFQ
 GLDLNEELYLGGYPDYGAIPKAGLSSGFIGCVRELRIQGEIIVFHDNLTAHGISHCPTCRDRPCQNGGQ
 CHDSESSSYVCVCPAGFTGSRCEHSQALHCHPEACGPDATCVNRPDGRGYTCRCHLGRSGLRCEEGVT
 VTTPSLSGAGSYLALPALTNTHHELRLDVEFKPLAPDGVLLFSGGKSGPVEDFVSLAMVGGHLEFRYEL
 GSGLAFLRSAEPLALGRWHRVSAERLNKDGSLRVNGGRPVLRSSPGKSQGLNLHTLLYLGGVEPSVPL
 SPATNMSAHFRGCVGEVSVNGKRLDLTYSFLGSQIGQCYDSSPCERQPCQHGATCMPAGEYEFQCLC
 RDGFKGDLCEHEENPCQLREPCLHGGTCQGTCLCLPGFSGPRCQQSGHGIAESDWHLEGGGNDAP

GQYGAYFHDDGFLAFPGHVFSRSLPEVPETIELEVRTSTASGLLLWQGVVEVGEAGQGKDFISLGLQDGH
LVFRYQLGSGEARLVSEDPINDGEWHRVTALREGRRGSIQVDGEELVSGRSPGNVAVNAKGSVYIGG
APDVATLTGGRFSSGITGCVKNLVLHSARPGAPPPQPLDLQHRAQAGANTRPCPS

SEQ ID NO: 307 Human Agrin LG domains 1-5

TLRLALEFRALEPQGLLLYNGNARGKDFLALALLDGRVQLRFDTGSGPAVLTSAPVPEPGQWHRLELS
RHWRRGTLSDVGETPVLGESPSGTDGLNLDLDFVGGVPEDQAAVALERTFVGAGLRGRCIRLLDVNN
QRLELGIGPGAATRGSGVGECGDHPCLPNPCHGGAPCQNL EAGRFHCQCPPGRVGP TCADEKSPCQPN
PCHGAAPCRVLPEGGAQCECPLGREGTFCQTASGQDGS GPFLADFN GFSHLELRGLHTFARDLGEKMA
LEV VFLARGPSGLLLYNGQKTDGK GDFVSLALDRRLEFRYDLGKGA AVIRSREPVT LGAWTRVSLER
NGRK GALRVGDGPRVLGESPKSRKVPHTVLNLKEPLYVGGAPDFSKLARAAAVSSGFDGAIQLVSLGG
RQLLTPEHVL RQVDVTSFAGHPCTRASGHPCLNGASCVPREAA YVCLCPGGFSGPHCEKGLVEKSAGD
VDTLAFDGRTFVEYLN AVTESELANEIPVPETLDSGALHSEKALQSNHFELSLRTEATQGLVLWSGKAT
ERADYVALAIVDGHQLSYNLG SQPVLRSTVPVNTNRWL RVVAHREQREGSLQV GNEAPVTGSSPL
GATQLD TDGALWLGGLPELPVGPALPKAYGTGFVGC LRDVVVGRHPLHLL EDAVTKEPRLPCPTP

5

SEQ ID NO: 308 Human Agrin Laminin-coil binding domain

CPERALERREEE ANVVL TGTVEEILNVDPVQHTY SCKVRVWRYLKGKDLVARESLLDGGNKVVISGFG
DPLICDNQVSTGDTRIFFVNPAPPYLWPAHKNELMLNSSLMRITLRNLEEVEFCVEDKPGTHFTVPPTP
PDACRGM LCGFGAVCEPNAEGPGRASCVCCKKSPCPSV VAPVCGSDASTYSNECELQRAQCSQRRIRL
LSRGPCGSRDPCSNVTC SFGSTCAR

SEQ ID NO: 309 Human Nidogen-1 Laminin-gamma ear binding domain

CANNRHQCSVHAECRDYATGFCCSCVAGYTGNRQCVAEGSPQRVNGKV KGRIFVGSSQVPIVFENT
DLHSYVVMNHGRSYTAISTIPETVGYSLPLAPVGGIIGWMFAVEQDGFKNFSITGGEFTRQAEVTFV
GHPGNLVIKQRFSGIDEHGLTIDTELEGRVPQIPFGSSVHIEPYTELYHYSTSVITSSSTREYTVTEPERD
GASPSRIYTYQWRQTITTFQECVHDDSRPALPSTQQLSVDSVFVLYNQEEKILRYALSNSIGPVREGSPDA
LQNPCYIGTHGCDTNAACRPGPRTQFTCECSIGFRGDGRTCYDIDECSEQPSVCGSHTICNNHPGTFRCE
CVEGYQFSDEGTCVAVVDQRPINYCETGLHNC DIPQRAQCIYTGSSYTC SCLPGFSGDGQACQDVDE
CQPSRCHPD AFCYNTPGSF TCQCKPGYQGDGFRCPGEVEKTRCQHEREHILGAAGATDPQRPIPPGLF
VPECDAHGHYAPTQCHGSTGYCWCVD RDGREVEGTRTRPGMTPPCLSTVAPPIHQGPAVPTAVIPLPP
GTHLLFAQTGKIERLPLEGNTMRKTEAKAFLHVP AKVIIGLAFDCVDKMVY WTDITEPSIGRASLHGGE
PTTIIRQDLGSPEGIAVDHLGRNIFWTD SNLDRIEVAKLDGTQRRVLFETDLVNPRGIVTDSVRGNLYWT
DWNRDNPKIETSYMDGTNRRLVQDDLGLPNGLTFDAFSSQLCWVDAGTNRAECLNPSQPSRRKALEG
LQYPFAVTSYGKNLYFTDWMNSVVALDLAISKETDAFQPHKQTRL YGITTALSQC PQGHNYCSVNN
GGCTHLCLATPGSRTCRCPDNTLGVD CIEQK

SEQ ID NO: 310 Human Nidogen-2 Laminin-gamma ear binding domain

CEHNHRQCSRHAFCTDYATGFCCHCQSKFYGNKGHCLPEGAPHRVNGKVSGHLHVGHTPVHFTD VD
LHAYIVGNDGRAYTAISHIPQAAQALLPLTPIGGLFGWLFAL EKPGSENGFSLAGAAFTHDMEVTFYP
GEETVRITQTAEGLDPENYLSIKTNIQGQVPYVSANFTAHS PYKELYHYSDSTVTSTSSRDYSLTFGAIN
QTWSYRIHQNITYQVCRHAPRHPSFPTTQQLNVDRVFALYNDEERVLRFAVTNQIGPVKEDSDPTPGNP
CYDGSHMCDTTARCHPGTGVDYTCECASGYQGDGRNCVDENECATGFHRCGPNSVCINLPGSYRCEC
RSGYEFADDRHTCILITPPANPCEDGSHTCAPAGQARCVHHGGSTFSCACLPGYAGDGHQCTDVDECS
ENRCHPAATCYNTPGSFSCRCQPGYYGDGFCIPDSTSSLTPCEQQQRHAQAQYAYPGARFHIPQCDEQ
GNFLPLQCHGSTGFCWCVDPDGHEVPGTQTPPGSTPPHCGPSPEPTQRPPTICERWRENLEHYGGTPR
DDQYVPQCDDLGHFIPLQCHGKSDFCWCVDKDGREVGQTRS QPGTTPACIPTVAPPMVRPTPRPDVTP
PSVGTFLLYTQGGQIGYLP LNLGTRLQKDA AKTLLSLHGSII VGIDYDCRERMVY WTDVAGRTISRAGLE
LGAEPETIVNSGLISPEGLAIDHIRRTMYWTD SVLDKIESALLDGSERKVL FYTDLVNPRAIADVPIRGNL
YWTDWNREAPKIETSSLDGENRRILINTDIGLPNGLTFDPFSKLLCWADAGTKKLECTLPDGTGRRVIQ
NNLKYPFSIVSYADHFYHTDWR RDGVVSVNKHSGQFTDEYLPEQRSHLYGITAVYPYCPTGRK

SEQ ID NO: 311 Signal peptide

MGWSCILFLVATATGVHS

SEQ ID NO: 312 hIgG1 heavy chain CH1-Fc-Knob

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKD TLYITREP
EVT CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCK

VSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNY
KTTTPVLDSGDSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 313 hIgG1 heavy chain Hinge-Fc-hole

EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLP
PSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSRWQQG
NVFSCSVMHEALHNRTQKSLSLSPGK

SEQ ID NO: 314 LC kappa

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSSTYSLS
STLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 315 DLL4(EGF1-6)-hIgG1-Fc Hole

SGVFQQLQEFINERGVLASGRPCPGCCTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTPWCQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANACECPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSRMCRCPGFTGT
CEEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDG
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCT
LPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLVSKLTVDKSRWQ
QGNVFSCSVMHEALHNRTQKSLSLSPGK

SEQ ID NO: 316 DLL1(EGF1-6)-hIgG1-Fc Hole

SGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHFAQAVVSPPEPCTYGSVTPVLGV
DSFSLPDGGGADSAFNPFRPFPGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWS
QDLHSSGRITDLKYSYRFVCDHYHGGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGYPCTEPICLP
GCDEQHGFCDKPGECKCRVWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGLFCNQDLNYCT
HHKPCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGFYGI
CELSAMTCADGPCFNGGRCSDSPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCR
CQAGFSGRHCDPEKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG
QPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSGDSFFLVSKL
TVDKSRWQQGNVFSCSVMHEALHNRTQKSLSLSPGK

SEQ ID NO: 317 Jagged1(EGF1-6)-hIgG1-Fc Hole

KVCGASGQFELEILSMQNVNGLQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
FGSGSTPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYYTLVEAWDSSNDTVQPDSEIEKASHSGMINP
SRQWQTLKQNTGVAHFEYQIRVTCDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCTMEGWMGRE
CNRAICRQGCSPKHGSCCKLPGDCRCQYGWQGLYCDKCIHPGCVHGICNEPWQCLCETNWGGQLCDK
DLNYCGTHQPCNLGGTCSNTGPDKYQCSCPEGYSGNCEIAEHACLSDPCHNRGSKETSLSGFECECSP
GWTGPTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSKNLI
ASYCYDCLPGWMGQNCDEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDV
HEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSG
SFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNRTQKSLSLSPGK

SEQ ID NO: 318 Jagged2(EGF1-6)-hIgG1-Fc Hole

VQAARPMGYFELQLSALRNVNGLLSGACCDGDGRTTRAGGCGHDECDTYVRVCLKEYQAKVTPTG
PCSYGHGATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVVIPIQFAWPRSFTLIVEAWDWDN
DTTPNEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHY
CDQYGNKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECCRSYGWQGRFCDECVPYPGCVHGS
CVEPWQCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAHACTS
NPCANGGSCHEVPSGFECPCSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQ
LDANECEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDRCRQCQHGCTCKDLVNGYQCVCPR
GFGGRHCELEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ

REPQVCTLPSPRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLVSKLTV
DKSRWQQGNVFSVMSHEALHNRTQKSLSPGK

SEQ ID NO: 319 DLL4(EGF1-6)-GSlinker-laminin-a2 LG4-5

SGVFQQLQEFINERGVLASGRPCPGCCTFFRVCLKHQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSRMCRCRPGFTGT
CEGGGSGGGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNLGPYFSYDLGSGDTHMTIP
TKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGPLINYTTTRIGPVTYSIDGC
VRNLHMAEAPADLEQPTSSFHVGTGFANAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDG
NQVEAQSPNPASTADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRG
VQPVSCPAN

SEQ ID NO: 320 DLL4(EGF1-6)-HSA-laminin-a2 LG4-5

SGVFQQLQEFINERGVLASGRPCPGCCTFFRVCLKHQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSRMCRCRPGFTGT
CEGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIQFAQYLQCPFEDHVKLNVNEVTEFAKTCVAD
ESAENDCKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLRLVRPEVDVM
CTAFHDNEETFLKKLYEIAARRHPYFYAPELLFFAKRYKAAFTCECCQAADKAACLLPKLDELREDEGKA
SSAKQRLKQSLQKQFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTQVHTECCHGDLLECADDRA
DLAKYICENQDSISSKLKECEKPLLEKSHCIAEVENDEMPADPLSLAADFVESKDVCKNYAEAKDVFL
GMFLYEYARRHPDYSVVLLRLAKTYETTLKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCLEF
EQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCV
LHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVEL
VKHKPKATKEQLKAVMDDFAAFVEKCKKADDKETCFAEKGKLVAAASQAALGLGGSGGGSGGGSNR
LTIELEVRTEAESGLLFYMARINHADFATVQLRNLGPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRS
KQEGILYVDGASNRTISPKKADILDVVGMLYVGGPLINYTTTRIGPVTYSIDGCVRLHMAEAPADLEQ
PTSSFHVGTGFANAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTAD
TNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 321 DLL4(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5

SGVFQQLQEFINERGVLASGRPCPGCCTFFRVCLKHQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
LRYSYRVICSDNYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTSPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSCDKQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNNGGSCRERNQGANACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSRMCRCRPGFTGT
CEEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY
TLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPVLDSGDSFFLYSKLTVDKSRWQ
QGNVFSVMSHEALHNHYTQKSLSPGKGGGSGGGSGGGSNRLTIELEVRTEAESGLLFYMARINHA
DFATVQLRNLGPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILD
VVGMLYVGGPLINYTTTRIGPVTYSIDGCVRLHMAEAPADLEQPTSSFHVGTGFANAGRFTAVYDAG
VPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTADTNDPVFVGGFPDDLKQFGLTTSIP
RGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSCPAN

SEQ ID NO: 322 DLL1(EGF1-6)-laminin-a2 LG4-5

SGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHQAVVSPPEPPCTYGSVTPVLGV
DSFSLPDGGGADSAFSPNIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWS
QDLHSSGRTDLKYSYRFVCDHEYHGGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLP

GCDEQHGFCDKPGECKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCT
HHKPCKNAGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGFYGKI
CELSAMTCADGPCFNGGRCS DSPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCR
CQAGFSGRHCDGGGSGGGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDL
GSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTTRR
IGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEF
EFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQWHKVTANKI
KHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEV
NFAKALELRGVQPVSPAN

SEQ ID NO: 323 DLL1(EGF1-6)-HSA-laminin-a2 LG4-5

SGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSAVTPVLGV
DSFSLPDGGGADSAFNSPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWS
QDLHSSGRDLDKYSYRFVCDHEYH YGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLP
GCDEQHGFCDKPGECKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCT
HHKPCKNAGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGFYGKI
CELSAMTCADGPCFNGGRCS DSPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCR
CQAGFSGRHCDGGGSGGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQCCPFEDHVKLVNEVT
EFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFQHKDDNPNLPR
LVRPEVDVMCTAFHDNEETFLKKYLYEIAARRHPYFYAPELLFFAKRYKAAAFTECCQAADKAACLLPKL
DELREDEGKASSAKQRLKCSLQKFGERAFAKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHGD
LLECADRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKN
YAEAKDVFLGMFLY EYARRHPDYSVLLLLRLAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQ
NLIKQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYL
SVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQI
KKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKADDKETCFAEEGKKLVAASQAALGLGGSG
GGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQ
WHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTTRRIGPVTYSIDGCVRNLHM
AEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQK
MDGMGIEMIDEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSP
NPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 324 DLL1(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5

SGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSAVTPVLGV
DSFSLPDGGGADSAFNSPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWS
QDLHSSGRDLDKYSYRFVCDHEYH YGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLP
GCDEQHGFCDKPGECKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCT
HHKPCKNAGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENSYSCTCPPGFYGKI
CELSAMTCADGPCFNGGRCS DSPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCR
CQAGFSGRHCDDEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYASTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAK
GQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK
LTVDKSRWQQGNV FSCSVMH EALHNHYTQKSLSLSPGKGGGSGGGSGGGSNRLTIELEVRTEAESGLL
FYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTI
SPKKADILDVVGMLYVGGLPINYTTTRRIGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTCFANAQR
GTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA
VYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQ
FGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 325 Jagged1(EGF1-6)-laminin-a2 LG4-5

KVCGASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
FGSGSTPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSIEKASHSGMINP
SRQWQTLKQNTGVAHFEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWGMGRE
CNRAICRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIHPHGCVHGICNEPWQCLCETNWWGQLCDK
DLNYCGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCEIAEHA CLSDPCHNRGSCKETS LGFECECSP
GWTGPTCSTNIDCSPNNCSHGGTCDLVNGFKVCVPPQWTGKTCQLDANECEAKPCVNAKSCKNLI
ASYCYDCLPGWMGQNCDDGGGSGGGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGL
PYFSYDLGSGDTHMTIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLP
INYTTTRRIGPVTYSIDGCVRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKV

LDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQWH
KVTANKIKHRIELTV DGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT KG
TGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 326 Jagged1(EGF1-6)-HSA-laminin-a2 LG4-5

KVCGASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
FGSGSTPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPDSIEKASHSGMINP
SRQWQTLKQNTGVAHFEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGRE
CNRAICRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIHPGCVHGCNEPWQCLCETNWWGGQLCDK
DLNYCGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCEIAEHA CLSDPCHNRGSKETS LGFECECSP
GWTGPTCSTNIDDCSPNNCSHG GTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLI
ASYCDCLPGWMGQNC DGGGSGGSDAHKSEVAHRFKDLGEENFKALVLI AFAQYLQQCPFEDHV
KLVNEVTEFAKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLQHKD
DNP NLPRLVRPEVDVMCTAFHDNEETFLKKYLYE IARRHPYFYAPELLFFAKRYKAAFT ECCQAADKA
ACLLPKLDEL RDEGKASSAKQRLK CASLQKFGERA FKA WAVARLSQRFPKAEFAEVSKLVTD LTKVH
TECCHGDLLECADDRADLAKYICENQDSISSKLEKCEKPLEKSHCIAEVENDEMPADLPSLAADFVE
SKDVCKNYAEAKDVFLGMFLY EYARRHPDYSVLLLR LAKTYETTLEKCCAAADPHECYAKVFDEFK
PLVEEPQNLIKQNC ELFELGEYKFQNAL LVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKHPEAKRM
PCAEDYLSVVLNQLC LVLHEKTPVSDRVTKCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICT
LSEKERQIKKQTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKADDKETCF AEEGKKLVAA SQA
ALGLGGSGGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTH TMI
PTKINDGQWHKIKIMRSKQEGILYVDGASNRTISP KKADILDVVGMLYVGGLPINYTTRRIGPVTYSIDG
CVRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTG
VLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQWHKVTANKIKHRIELTV D
GNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT KG TGKPLEVNFAKALELR
GVQPVSPAN

SEQ ID NO: 327 Jagged1(EGF1-6)-hIgG1-Fc-laminin-a2 LG4-5

KVCGASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
FGSGSTPVIGGNTFNLKASRGNDNRNIVLPFSFAWPRS YTLLEAWDSSNDTVQPDSIEKASHSGMINP
SRQWQTLKQNTGVAHFEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCEGWMGRE
CNRAICRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIHPGCVHGCNEPWQCLCETNWWGGQLCDK
DLNYCGTHQPCLNGGTCSNTGPDKYQCSCPEGYS GPNCEIAEHA CLSDPCHNRGSKETS LGFECECSP
GWTGPTCSTNIDDCSPNNCSHG GTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLI
ASYCDCLPGWMGQNCDEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDG
SFFLYSKLTVDKSRWQQGNV FSCSVMEALHNHYTQKSLSLSPGKGGSGGSGGGSNRLTIELEVR
TEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTH TMIPTKINDGQWHKIKIMRSKQEGILYVD
GASNRTISPKKADILDVVGMLYVGGLPINYTTRRIGPVTYSIDG CVRNLHMAEAPADLEQPTSSFHVG
TCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHV
DNGAGRFTA VYDAGVPGHLCDGQWHKVTANKIKHRIELTV DGNQVEAQSPNPASTSADTNDPVFV G
GFPDDLKQFGLTTSIPFRGCIRSLKLT KG TGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 328 Jagged2(EGF1-6)-laminin-a2 LG4-5

VQAARPMGYFELQLSALRNVNGELLSGACCDGDGR TTRAGGCGHDECDTYVRVCLKEYQAKVTPTG
PCSYGHGATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVVIPQFAWPRSFTLIVEAWDWDN
D TTPNEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDFFGHYT
CDQYGNKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGE CRCSYGWQGRFCDECVYPGCVHGS
CVEPWQCNCETNWWGLLCDKDLNYCGSHHPCTNGGTCINAE PDQYRCTCPDGYSGRNCEKA EHA CT
NPCANGGSCHEVPSGFEC HCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQ
LDANECEGKPCLNAFSCKNLIGGYCDCIPGWKG INCHINVND CRGQCQHGGTCKDLVNGYQCVCPR
GFGGRHCELGGSGGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGS
GDTH TMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISP KKADILDVVGMLYVGGLPINYTTRRIG
PVTYSIDG CVRNLHMAEAPADLEQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEF
RTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTA VYDAGVPGHLCDGQWHKVTANKIK
HRIELTV DGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLT KG TGKPLEVN
FAKALELRGVQPVSPAN

VQAAAPRMGYFELQLSALNRNVNGELLSGACCDGDGRTRTAGGCGHDECDTYVRVCLKEYQAKVPTPTG
PCSYGHGATPVLGGNSFYLLPAGAAGDRARARARAGGDQDPGLVVIPFQFAWPRSFTLIVEAWDWDN
DTPNEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFGHYT
CDQYGNKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVYPYPCGVHGS
CVEPWQCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAETHACTS
NPCANGGSCHEVPSGFECHCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQ
LDANECEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDCRGGCQHGGTCKDLVNGYQCVCPR
GFGGRHCELGGGGSGGSDAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLVNEVTEF
AKTCVADESAENCDKSLHTLFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPPLRLV
RPEVDVMCTAFHDNEETFLKKYLVEIARRHPYFYAPELFFAKRYKAAAFTECCQAADKAAACLLPKLDE
LRDEGKASSAKQRLKASLQKFGERAFAKAWAVARLSQRFPAEFAEVSCLVTDLTKVHTECCHGDL
ECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYA
EAKDVFLGMFLYEYARRHPDYSVVLRLAKTYETTLKCCAAADPHECYAKVFDEFKPLVEEPQNLI
KQNCLEFEQLGEYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKKHPEAKRMPCAEDYLSV
VLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKK
QTALVELVKHKPKATKEQLKAVMDDFAAFVEKCKKADDKETCFAEEGKKLVAASQAALGLGGSGGG
SGGGSNRLTIELEVRTEAESGLLFYMARINHADFATVQLRNLGYPSYDLGSGDTHMTIPTKINDGQWH
KIKIMRSKQEGILYVDGASNRITSPKKADILDVVGMLYVGGLPINYYTTRRIGPVTYSIDGCVRNLMHAE
APADLEQPTSSFHYVGTFCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFFRTTTTTGVLGLISSQKM
DGMGIEMIDEKLMFHVVDNAGRGFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSP
NPASTSADTNDPVPVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFALALELRGVQPVSCPA
N

VQAARPMGYFELQLSALRNVNGELLSGACCDGDGRTRTAGGCGHDECDDTYVRVCLKEYQAKVTPTG
PCSYGHGATPVLGGNSFYLPAGAAGDRARARARAGGDQDPGLVVIPFQFAWPRSFTLIVEAWDWDN
D'TTPNEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHYT
CDQYGNKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVYPYGCVHGS
CVEPWQCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAETHACTS
NPCANGGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQ
LDANECEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDCRGQCQHGGTCKDLVNGYQCVCPR
GFGGRHCELEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK'TTPPVLDSGDSFFLYSKLTV
DKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGKGGGSGGGSGGGSNRLTIELEVRTEAESGLLFY
MARINHADFATVQLRNLPLYFSYDLGSGD'THTMIPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISP
KKADILDVVGMLYVGGLPINYT'TRRIGPV'TYSIDGCVRNLMHMAEAPADLEQPTSSFHVGTCTFANAQRG
TYFDGTGFAKAVGGFKVGLDLLVEFEFRT'TTTTG'VLLGISSQKMDGMGIEMIDEKLMFHVNDGAGRFT
AVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQF
GLTTSIPFRGCIRSLKLT'KG'TGKPLEVNF'AKALELRGVOPVSPAN

SGVFQLQLQEFINERGVLASGRPCPCGRTFFRVCLKHFAQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPFNFTWPGTFSLLIEAWHAPGDDLRLPEALPPDALISKIAIQGSLAVGQNWLLDEQSTLTR
LRYSYRVICSDNYYGDNCSRCLKKRNDFHGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRLCNECIPHNGCRHGTCSTPWQCTCDEGWGGFLCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCELELSECDNPNCRNGGSKCDQEDGYHCLCPPGY YGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPRMCRCPGFTGT
CEESKYGPPCPPCPAPEFLGGPSVFLFPPPKPDKTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVH
NAKTKPREEQFNSTYRVVSVLTVLHQDWLXGKEYKCKVSSXKGLPSSIEKTISXAXGQPREPVYTLPPS
QEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSXWQEGNV
FSCSVMHREALHNHYTQKSLSLSLGKGGGSGGGSGGGSNRLTIELEVRTEAESGLLFYMARINHADFAT
VQLRNLPLPYFSYDLGSGDTHMTPIKINDGQWHKIKIMRSKQEGILYVDGASNRTISPCKADILDVVG
LYVGGLPINYTTRRIGSPVTSIDGCVRNLMHMAEAPADLEQPTSSFHVGTCFANAQRGT YFDGTGFAKA
VGGFKVQLDLLVEFEFRPTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVVDNGAGRFTA VYDAGVP
GHLCDGQVHWKVTANKIKHRIELTVDGNQVEAQSNPASTSADTNDPVFVGGFPDDLKQFGLTTSIPFRGCI
RSLKLTGKTGKPLEVNFAKALELRGVOPVSPAN

SEQ ID NO: 332 DLL1(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5

SGVFELKLQEFVNKKGLLGNRNCCRGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSVTPVLGV
DSFSLPDGGGADSAFNSPIRPFPGFTWPGTFSLLIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWS
QDLHSSGRTDLKYSYRFVCDHEYHGGCSVFCRPRDDAFGHFTCGERGEKVCNPGWGKPYCTEPICLP
GCDEQHGFCDKPGECKCRVGVQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGGLFCNQDLNYCT
HHKPCCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDTLENSYSCTCPPGFYGI
CELSAMTCADGPCFNGGRCSDSPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCR
CQAGFSGRHCDSESKYGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFN
WYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLXGKEYKCKVSXKGLPSSIEKTISXAXGQP
REPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTV
DKSXWQEGNVFSCSVMEALHNHYTQKSLSLSLGKGGGSGGGSGGGSNRLTIELEVRTEAESGLLFY
MARINHADFATVQLRNGLPYFSYDLGSGDTHMTPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISP
KKADILDVVGMLYVGGLPINYYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGTGFANAQRG
TYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFT
AVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQF
GLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 333 Jagged1(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5

KVCGASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
FGSGSTPVIGGNTFNKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSEIEKASHSGMINP
SRQWQTLKQNTGVAHFEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCTMEGWMGRE
CNRAICRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIPHPGCVHGICNEPWQCLCETNWWGGQLCDK
DLNYCGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGNCEIAEHAELSDPCHNRGSKETSLSGFECECSP
GWTGPTCSTNIDDCSPNNCSHGGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSKNLI
ASYCCLPGWMGQNCDESKYGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQED
PEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLXGKEYKCKVSXKGLPSSIEKTIS
XAXGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL
YSRLTVDKSXWQEGNVFSCSVMEALHNHYTQKSLSLSLGKGGGSGGGSGGGSNRLTIELEVRTEA
ESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTPTKINDGQWHKIKIMRSKQEGILYVDG
ASNRTISPKKADILDVVGMLYVGGLPINYYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGT
FANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVD
NGAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGF
PDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 334 Jagged2(EGF1-6)-hIgG4-Fc-laminin-a2 LG4-5

VQAARPMGYFELQLSALRNVNDELGSGACCDGDGRTRAGGCGHDECDTYVRVCLKEYQAKVTPTG
PCSYGHGATPVLGGSFYLPAGAAGDRARARAGGDQDPGLVIPFQFAWPRSFTLIVEAWDWDN
DTTPNEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDFFGHYT
CDQYGNKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECCRSYGWQGRFCDECVPYPGCVHGS
CVEPQNCNCETNWWGGLLDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAETHACTS
NPCANGGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQ
LDANECEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDCRGQCQHGCTCKDLVNGYQCVCPR
GFGGRHCELESKYGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWY
VDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLXGKEYKCKVSXKGLPSSIEKTISXAXGQPREP
QVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKS
XWQEGNVFSCSVMEALHNHYTQKSLSLSLGKGGGSGGGSGGGSNRLTIELEVRTEAESGLLFYMARI
NHADFATVQLRNGLPYFSYDLGSGDTHMTPTKINDGQWHKIKIMRSKQEGILYVDGASNRTISPKKAD
ILDVVGMLYVGGLPINYYTTRRIGPVTYSIDGCVRNLMHMAEAPADLEQPTSSFHVGTGFANAQRGTYFD
GTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGIEMIDEKLMFHVDNGAGRFTAVY
DAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTSADTNDPVFVGGFPDDLKQFGLT
TSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 335 Hinge-hIgG4-Fc S228P

ESKYGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLXGKEYKCKVSXKGLPSSIEKTISXAXGQPREPQVYTLPPSQE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSXWQEGNVF
SCSVMEALHNHYTQKSLSLSLGK

SEQ ID NO: 336 Signal peptide

MAAASRSASGVALLLLVALWQQRAAG

SEQ ID NO: 337 Linker

GGGSGGGSGGGS

SEQ ID NO: 338 Linker

GGGSGGGS

SEQ ID NO: 339 DLL4 EGF1-6

SGVFQLQLQEFINERGVLASGRPCPGCCTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
 GGGRNPLQLPFNFTWPGTFSLIIEAWHAPGDDLREALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTR
 LRYSYRVICSDNYYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYCQQPICLSGCHEQNGYC
 SKPAECLCRPGWQGRCLNECIPHNGCRHGTCTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
 SNSGQRSYTCTCRPGYTGVDCELELSECDSPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
 SPCFNNGSCRERNQGANACECPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSRMCRCRPGFTGT
 YCE

SEQ ID NO: 340 DLL1 EGF1-6

SGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSVTPVLGV
 DSFSLPDGGGADSAFNSNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWS
 QDLHSSGRTDLKYSYRFVCDHYHGGCVFCRPRDDAFGHFTCGERGEKVCNPGWKGYPCTEPICLP
 GCDEQHGFCDKPGECKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCT
 HHKPCKNGATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCDLENYSCTCPPGFYGI
 CELSAMTCADGPCFNGGRCSDDPDGGYSCRCVGYSGFNCEKKIDYCSSSPCSNGAKCVDLGDAYLCR
 CQAGFSGRHCD

SEQ ID NO: 341 Jag1 EGF1-6

KVCGASGQFELEILSMQNVNDELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCS
 FGSGSTPVIGNTFNLKASRGNDNRNIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDIIKASHSGMINP
 SRQWQTLKQNTGVAHFEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCTMEGWGRE
 CNRAICRQGCSPKHGSKLPGDCRCQYGWQGLYCDKCIHPHGCVHGICNEPWQCLCETNWWGQLCDK
 DLNYCGTHQPCLNNGGTCSTNTPDKYQCSCPEGYSGPNCIEAEHACLSDPCHNRGSCKETS LGFECECSP
 GWTGPTCSTNIDDCSPNNCSHGTCQDLVNGFKVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLI
 ASYYCDCLPGWMGQNC

SEQ ID NO: 342 Jag2 EGF1-6

VQAARPMGYFELQSLARNVNGELLSGACCDGDGRTTRAGGCGHDECDTYVRVCLKEYQAKVTPTG
 PCSYGHGATPVLGNSFYLPAGAAGDRARARAGGDQDPGLVIPFQFAWPRSFTLIVEAWDWDN
 DTTNPEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDDFFGHY
 CDQYGNKACMDGWMGKECKEAVCKGQCNLLHGGCTVPGEGRCSYGWQGRFCECVYPGCVHGS
 CVEPWQCNCETNWWGGLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAEHACTS
 NPCANGGSCHEVPSGFECPCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATCQ
 LDANECEGKPCLNAFSCKNLIGGYCDCIPGWKGINCHINVNDCRGQCQHGCTCKDLVNGYQVCVPR
 GFGGRHCEL

SEQ ID NO: 343 laminin-a2 LG4-5

NRLTIELEVRTEAESGLLFYMARINHADFATVQLRNGLPYFSYDLGSGDTHMTIPTKINDGQWHKIKIM
 RSKQEGILYVDGASNRTISPKKADILDVVGMLYVGGLPINYTTRIGPVTYSIDGCVRNLMHMAEAPADL
 EQPTSSFHVGTCFANAQRGTYFDGTGFAKAVGGFKVGLDLLVEFEFRTTTTTGVLLGISSQKMDGMGI
 EMIDEKLMFHVDNAGRFTAVYDAGVPGHLCDGQWHKVTANKIKHRIELTVDGNQVEAQSPNPASTS
 ADTNDPVFVGGFPDDLKQFGLTTSIPFRGCIRSLKLTGKTGKPLEVNFAKALELRGVQPVSPAN

SEQ ID NO: 344 HSA

DAHKSEVAHRFKDLGEENFKALVLIAFAQYLQQCPFEDHVKLNVNEVTEFAKTCVADESAENCCKSLHT
 LFGDKLCTVATLRETYGEMADCCAKQEPERNECFLOHKDDNPPLRLVRPEVDVMCTAFHDNEETFL
 KKYLYEIIARRHPYFYAPELFFAKRYKAAFTGCCQAADKAACLLPKLDELDEGKASSAKQRLKASL
 QKFGERAFAKAWAVARLSQRFPAEFAEVSKLVTDLT KVHTECCHGDLLECADRADLAKYICENQDSI
 SSKLKECCEKPLLEKSHCIAEVENDEMPADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHP
 DYSVVLLRLAKTYETTLKCCAAADPHECYAKVFDEFKPLVEEPQNLKQNCLEFEQLGEYKFQNAL
 LVRYTKKVPQVSTPTLVEVSRNLGKVGSKCKHPEAKRMPCAEDYLSVVLNQLCVLHEKTPVSDRVT

KCCTESLVNRRPCFSALEVDETYVPKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQ
LKAVMDDFAAFVEKCKKADDKETCFAEEGKKLVAASQAALGL

SEQ ID NO: 345 hIgG1 Fc

EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPSR
DELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMEALHNHYTQKSLSLSPGK

SEQ ID NO: 346 hIgG4 Fc

ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNA
KTKPREEQFNSTYRVVSVLTVLHQDWLXGKEYKCKVSNKALPAPIEKTISXAXGQPREPQVYTLPPSQE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKXSXWQEGNVFS
CSVMHEALHNHYTQKSLSLGLGKG

SEQ ID NO: 347 Fc

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRD
ELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 348 Human IgG1 Fc first subunit, wherein X₁ is a Arg, His, or Lys

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK
TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVX₁SDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 349 muD4v

SSVFQLQLQEFINERGVLASGRPCPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSS
GGGRNPLQLPLNFTWPGTFSLIIEAWHAPGDDLRLPEALPPDALISKFAIQGSLAVGQNWLLDEQSTLTRL
LRYSYRVICSDNYYGDNCSRLCKKRNDYFGHYVCQPDGNPSCLPGWTGEYCQQPICLSGCHEQNGYC
SKPAECLCRPGWQGRCLNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATC
SNSGQRSYTCTCRPGYTGVDCLELSECDNPNCRNGGSKDQEDGYHCLCPPGYGLHCEHSTLSCAD
SPCFNGGSCRERNQGANYACECPNFTGSNCEDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPE
VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV
SNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK
TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS
CSVMHEALHNAYTQKSLSLSPGKGGGGSGGGSGG
GGSEIVLTQSPDFLSVTPKEKVTLSRASQISNYLHWYQQKSDQSPKLLIKYASQSIGIPSRFSGSGSGT
DFTLSINSVEAEDAATYFCQQSKSWPRTFGGGTKEIKGGGGSGGGSGGGGSEVQLVESGGGLVQPG
GSLRLSCAASGFTFSYTMSTWVRQAPGKGLEWVATISSGDNITYPDSPVKGRFTISRDN SKNTLYLQM
SSLRAEDTALYYCARFDYGSSLD SWGQGTTLTVSS

CLAIMS

1. A bifunctional protein construct comprising a first binding moiety and a second binding moiety, wherein the first binding moiety specifically binds to a muscle-specific molecule, and wherein the second binding moiety specifically binds to a Notch receptor and activates the Notch receptor.
2. The bifunctional protein construct of claim 1, wherein the muscle-specific molecule is a target antigen on the sarcolemma, between the sarcolemma and the basal lamina, or in the basal lamina.
3. The bifunctional protein construct of claim 2, wherein the target antigen is selected from the group consisting of laminin, agrin, nidogen, perlecan, and M-cadherin (CDH15).
4. The bifunctional protein construct of claim 2 or 3, wherein the target antigen is a component of the dystrophin-associated glycoprotein complex (DGC).
5. The bifunctional protein construct of claim 4, wherein the target antigen is selected from the group consisting of α -dystroglycan (α -DG), β -DG, laminin-211, perlecan, collagen, α -sarcoglycan, β -sarcoglycan, γ -sarcoglycan, δ -sarcoglycan, ϵ -sarcoglycan, ζ -sarcoglycan, biglycan, sarcospan, and matriglycan on α -DG.
6. The bifunctional protein construct of any one of claims 3-5, wherein the target antigen is laminin subunit alpha-2 (LAMA2) of laminin-211, CDH15, α -DG, or matriglycan on α -DG.
7. The bifunctional protein construct of any one of claims 1-6, wherein the first binding moiety comprises an antibody moiety specifically binding to the muscle-specific molecule.
8. The bifunctional protein construct of claim 7, wherein the antibody moiety is selected from the group consisting of a full-length antibody, a Fab, a Fab', a F(ab')₂, an scFv, and an sdAb.

9. The bifunctional protein construct of claim 7 or 8, wherein the antibody moiety specifically binds to LAMA2 (anti-LAMA2 antibody moiety).
10. The bifunctional protein construct of claim 9, wherein the anti-LAMA2 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 1, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 2, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 3, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 4, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 5, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 6.
11. The bifunctional protein construct of claim 10, wherein the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 49, and a VL comprising the amino acid sequence of SEQ ID NO: 50.
12. The bifunctional protein construct of claim 9, wherein the anti-LAMA2 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 7, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 8, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 9, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 10, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 11, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 12.
13. The bifunctional protein construct of claim 12, wherein the anti-LAMA2 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 54, and a VL comprising the amino acid sequence of SEQ ID NO: 65.
14. The bifunctional protein construct of claim 7 or 8, wherein the antibody moiety specifically binds to matriglycan on α -DG (anti-matriglycan antibody moiety).
15. The bifunctional protein construct of claim 14, wherein the anti-matriglycan antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 74, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 75, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 76, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 83, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 84, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 85.

16. The bifunctional protein construct of claim 15, wherein the anti-matriglycan antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 90, and a VL comprising the amino acid sequence of SEQ ID NO: 95.
17. The bifunctional protein construct of claim 7 or 8, wherein the antibody moiety specifically binds to CDH15 (anti-CDH15 antibody moiety).
18. The bifunctional protein construct of claim 17, wherein the anti-CDH15 antibody moiety comprises an HC-CDR1 comprising the amino acid sequence of SEQ ID NO: 102, an HC-CDR2 comprising the amino acid sequence of SEQ ID NO: 103, an HC-CDR3 comprising the amino acid sequence of SEQ ID NO: 104, an LC-CDR1 comprising the amino acid sequence of SEQ ID NO: 105, an LC-CDR2 comprising the amino acid sequence of SEQ ID NO: 106, and an LC-CDR3 comprising the amino acid sequence of SEQ ID NO: 107.
19. The bifunctional protein construct of claim 18, wherein the anti-CDH15 antibody moiety comprises a VH comprising the amino acid sequence of SEQ ID NO: 108, and a VL comprising the amino acid sequence of SEQ ID NO: 109.
20. The bifunctional protein construct of any one of claims 1-6, wherein the first binding moiety comprises a non-antibody moiety specifically binding to the muscle-specific molecule.
21. The bifunctional protein construct of claim 20, wherein the non-antibody moiety comprises a protein domain selected from the group consisting of a laminin G-like domain (LG domain) of laminin, an LG domain of agrin, an LG domain of nidogen, an LG domain of perlecan, the laminin coiled-coil binding domain of agrin, and the laminin γ binding domain of nidogen.
22. The bifunctional protein construct of claim 21, wherein the non-antibody moiety comprises an LG domain of laminin.

23. The bifunctional protein construct of claim 22, wherein the non-antibody moiety comprises LG4-5 domains of LAMA2 (LAMA2 LG4-5).
24. The bifunctional protein construct of claim 23, wherein LAMA2 LG4-5 comprises the amino acid sequence of SEQ ID NO: 118 or 119.
25. The bifunctional protein construct of any one of claims 1-24, wherein the second binding moiety comprises an extracellular domain (ECD) or a variant thereof of a Notch ligand selected from the group consisting of Delta-like 1 (DLL1), DLL3, DLL4, Jagged1 (Jag1), and Jag2.
26. The bifunctional protein construct of claim 25, wherein the second binding moiety comprises:
- a) a DLL4 ECD or a variant thereof, wherein the DLL4 ECD comprises the amino acid sequence of SEQ ID NO: 125, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267;
 - b) a DLL1 ECD or a variant thereof, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130;
 - c) a DLL3 ECD or a variant thereof, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131;
 - d) a Jag1 ECD or a variant thereof, wherein the Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 132, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134; or
 - e) a Jag2 ECD or a variant thereof, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135.
27. The bifunctional protein construct of any one of claims 1-26, wherein the first binding moiety is fused to the second binding moiety via an optional linker.
28. The bifunctional protein construct of claim 27, wherein:
- a) the second binding moiety comprises a variant DLL4 ECD comprising the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267;
 - b) the second binding moiety comprises a DLL1 ECD comprising the amino acid sequence of SEQ ID NO: 130;

c) the second binding moiety comprises a DLL3 comprising the amino acid sequence of SEQ ID NO: 131;

d) the second binding moiety comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133 or 134; or

e) wherein the second binding moiety comprises a Jag2 ECD comprising the amino acid sequence of SEQ ID NO: 135.

29. The bifunctional protein construct of claim 28, wherein the bifunctional protein construct comprises the amino acid sequence of any of SEQ ID NOs: 136-144.

30. The bifunctional protein construct of claim 28, wherein the first binding moiety comprises a Fab specifically binding to a muscle-specific molecule.

31. The bifunctional protein construct of claim 30, wherein the second binding moiety is fused to the N-terminus of the VL of the Fab via an optional linker.

32. The bifunctional protein construct of any one of claims 1-26, wherein the bifunctional protein construct further comprises an Fc domain comprising a first subunit and a second subunit.

33. The bifunctional protein construct of claim 32, wherein:

a) wherein the Fc domain is derived from human IgG1 comprising the amino acid sequence of SEQ ID NO: 187;

b) each subunit of the Fc domain comprises an L234A/L235A mutation (EU numbering);

c) each subunit of the Fc domain comprises an H435A mutation (EU numbering);

d) each subunit of the Fc domain comprises an P329G mutation (EU numbering);

e) each subunit of the Fc domain comprises the amino acid sequence of SEQ ID NO: 188 or 277;

f) either the first subunit of the Fc domain or the second subunit of the Fc domain comprises an H435R/Y436F mutation (EU numbering); and/or

g) the Fc domain comprises knob-into-hole mutations, and wherein:

i) the first subunit of the Fc domain comprises a knob mutation, and the second subunit of the Fc domain comprises a hole mutation; or

ii) the second subunit of the Fc domain comprises a knob mutation, and the first subunit of the Fc domain comprises a hole mutation.

34. The bifunctional protein construct of claim 33, wherein the knob mutation is T366W (EU numbering), and the hole mutation is T366S/L368A/Y407V (EU numbering).

35. The bifunctional protein construct of any one of claims 32-34, wherein:

a) the bifunctional protein construct comprises: i) a first unit of a second binding moiety specifically binding to a first Notch receptor, and ii) a second unit of a second binding moiety specifically binding to a second Notch receptor, and wherein the first unit of the second binding moiety and the second unit of the second binding moiety each independently comprises an ECD or a variant thereof of a Notch ligand selected from the group consisting of DLL1, DLL3, DLL4, Jag1, and Jag2; and/or

b) the bifunctional protein construct comprises: i) a first unit of a first binding moiety specifically binding to a first muscle-specific molecule, and ii) a second unit of a first binding moiety specifically binding to a second muscle-specific molecule.

36. The bifunctional protein construct of any one of claims 32-35, wherein the first unit of the first binding moiety comprises a first antibody moiety specifically binding to the first muscle-specific molecule, the second unit of the first binding moiety comprises a second antibody moiety specifically binding to the second muscle-specific molecule, and wherein the first antibody moiety and the second antibody moiety are each independently selected from the group consisting of a Fab, an scFv, and an sdAb.

37. The bifunctional protein construct of claim 36, wherein the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2);

wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – VH1-(H1-CH1);

ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – VH2-(H2-CH1);

iii) a third polypeptide comprising from N' to C': VL1-(L1-CL); and

iv) a fourth polypeptide comprising from N' to C': VL2-(L2-CL); and
wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

38. The bifunctional protein construct of claim 36, wherein the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2);

wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – VL1-(L1-CL);

ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – VL2-(L2-CL);

iii) a third polypeptide comprising from N' to C': VH1-(H1-CH1); and

iv) a fourth polypeptide comprising from N' to C': VH2-(H2-CH1); and

wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

39. The bifunctional protein construct of claim 37 or 38, wherein Fab1 and Fab2 both specifically bind to LAMA2, and wherein anti-LAMA2 Fab1 and/or anti-LAMA2 Fab2 comprises a first polypeptide comprising the amino acid sequence of SEQ ID NO: 165, and a second polypeptide comprising the amino acid sequence of SEQ ID NO: 166.

40. The bifunctional protein construct of any one of claims 35-39, wherein:

a) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267;

b) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130;

c) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131;

d) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134; or

e) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135.

41. The bifunctional protein construct of claim 36, wherein the first antibody moiety is a first sdAb (sdAb1), and the second antibody moiety is a second sdAb (sdAb2);

wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – sdAb1; and

ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – sdAb2.

42. The bifunctional protein construct of claim 36, wherein the first antibody moiety is a first scFv (scFv1), and the second antibody moiety is a second scFv (scFv2);

wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – scFv1; and

ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – scFv2.

43. The bifunctional protein construct of claim 42, wherein scFv1 and scFv2 both specifically bind to LAMA2, and wherein anti-LAMA2 scFv1 and/or anti-LAMA2 scFv2 comprises the amino acid sequence of SEQ ID NO: 145 or 268.

44. The bifunctional protein construct of any one of claims 41-43, wherein:

a) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD comprising the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267;

b) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD comprising the amino acid sequence of SEQ ID NO: 130;

c) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD comprising the amino acid sequence of SEQ ID NO: 131;

d) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD comprising the amino acid sequence of SEQ ID NO: 133 or 134; or

e) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD comprising the amino acid sequence of SEQ ID NO: 135.

45. The bifunctional protein construct of claim 44, wherein the bifunctional protein construct comprises a first polypeptide and a second polypeptide each comprising the amino acid sequence of any of SEQ ID NOs: 223-231 and 269-276.

46. The bifunctional protein construct of claim 35 or 36, wherein the first antibody moiety is a first Fab (Fab1), and the second antibody moiety is a second Fab (Fab2);

wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – VH1-(H1-CH1) – optional linker – the first subunit of the Fc domain;

ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – VH2-(H2-CH1) – optional linker – the second subunit of the Fc domain;

iii) a third polypeptide comprising from N' to C': a third unit of a second binding moiety specifically binding to a third Notch receptor – optional linker – VL1-(L1-CL); and

iv) a fourth polypeptide comprising from N' to C': a fourth unit of a second binding moiety specifically binding to a fourth Notch receptor – optional linker – VL2-(L2-CL); and

wherein VL1-(L1-CL) and VH1-(H1-CH1) form Fab1, and VH2-(H2-CH1) and VL2-(L2-CL) form Fab2.

47. The bifunctional protein construct of any one of claims 32-35, wherein the first unit of the first binding moiety comprises a first non-antibody moiety specifically binding to the first muscle-specific molecule, the second unit of the first binding moiety comprises a second non-antibody moiety specifically binding to the second muscle-specific molecule, and wherein the first non-antibody moiety and the second non-antibody moiety are each independently selected from the group consisting of an LG domain of laminin, an LG domain of agrin, an LG domain of nidogen, and an LG domain of perlecan.

48. The bifunctional protein construct of claim 47, wherein the first non-antibody moiety and/or the second non-antibody moiety comprises LAMA2 LG4-5 comprising the amino acid sequence of SEQ ID NO: 118 or 119.

49. The bifunctional protein construct of claim 47 or 48, wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': the first unit of the first binding moiety – optional linker – the first subunit of the Fc domain – optional linker – a first unit of a second binding moiety specifically binding to a first Notch receptor; and

ii) a second polypeptide comprising from N' to C': the second unit of the first binding moiety – optional linker – the second subunit of the Fc domain – optional linker – a second unit of a second binding moiety specifically binding to a second Notch receptor.

50. The bifunctional protein construct of claim 47 or 48, wherein the bifunctional protein construct comprises:

i) a first polypeptide comprising from N' to C': a first unit of a second binding moiety specifically binding to a first Notch receptor – optional linker – the first subunit of the Fc domain – optional linker – the first unit of the first binding moiety; and

ii) a second polypeptide comprising from N' to C': a second unit of a second binding moiety specifically binding to a second Notch receptor – optional linker – the second subunit of the Fc domain – optional linker – the second unit of the first binding moiety.

51. The bifunctional protein construct of any one of claims 47-50, wherein:

a) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant DLL4 ECD, and wherein the variant DLL4 ECD comprises the amino acid sequence of any of SEQ ID NOs: 126-129 and 260-267;

b) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL1 ECD, and wherein the DLL1 ECD comprises the amino acid sequence of SEQ ID NO: 130;

c) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a DLL3 ECD, and wherein the DLL3 ECD comprises the amino acid sequence of SEQ ID NO: 131;

d) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a variant Jag1 ECD, and wherein the variant Jag1 ECD comprises the amino acid sequence of SEQ ID NO: 133 or 134; or

e) the first unit of the second binding moiety and/or the second unit of the second binding moiety comprises a Jag2 ECD, and wherein the Jag2 ECD comprises the amino acid sequence of SEQ ID NO: 135.

52. The bifunctional protein construct of claim 32, wherein:

i) the first binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional first linker, and the second binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional second linker; or

ii) the first binding moiety is fused to the N-terminus of the second subunit of the Fc domain via an optional first linker, and the second binding moiety is fused to the N-terminus of the first subunit of the Fc domain via an optional second linker.

53. One or more isolated nucleic acids encoding the bifunctional protein construct of any one of claims 1-52.

54. One or more vectors comprising the one or more isolated nucleic acids of claim 53.

55. The one or more vectors of claim 54, which is a viral vector.

56. A host cell expressing the bifunctional protein construct of any one of claims 1-52, comprising the one or more isolated nucleic acids of claim 53, or comprising the one or more vectors of claim 54 or 55.

57. A pharmaceutical composition comprising: i) the bifunctional protein construct of any one of claims 1-52, the one or more isolated nucleic acids of claim 53, or the one or more vectors of claim 54 or 55; and ii) a pharmaceutically acceptable excipient.

58. A method of producing a bifunctional protein construct, comprising:

- i) culturing a host cell comprising the one or more isolated nucleic acids of claim 53 or the one or more vectors of claim 54 or 55, or the host cell of claim 56, under a condition suitable for the expression of the bifunctional protein construct; and
- ii) recovering the expressed bifunctional protein construct from the cultured host cell.

59. A method of treating a muscle-related disease in an individual, comprising administering to the individual an effective amount of the bifunctional protein construct of any one of claims 1-52 or the pharmaceutical composition of claim 57.

60. The method of claim 59, wherein the muscle-related disease is selected from the group consisting of Pompe disease, centronuclear myopathy, fibrodysplasia ossificans progressiva (FOP), Friedreich's ataxia (FRDA), familial hypertrophic cardiomyopathy, Laing distal myopathy, myofibrillar myopathy, and muscular dystrophy.

61. The method of claim 60, wherein the muscle disease is muscular dystrophy.

62. The method of claim 61, wherein the muscular dystrophy comprises one or more of: Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), limb-girdle muscular dystrophy (LGMD), congenital muscular dystrophy (CMD), facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy (DM), oculopharyngeal muscular dystrophy (OPMD), distal muscular dystrophy (DD), congenital myopathy, Charcot-Marie-Tooth (CMT) disorder, and Emery-Dreifuss muscular dystrophy (EDMD).

63. The method of any one of claims 59-62, wherein the bifunctional protein construct or the pharmaceutical composition is administered intravenously, subcutaneously, or intramuscularly.

64. An engineered DLL4 extracellular domain (ECD), wherein the engineered DLL4 ECD comprises a mutation selected from the group consisting of T52N and T135N, and wherein the amino acid position is in reference to a reference DLL4 ECD comprising the amino acid sequence of SEQ ID NO: 126.
65. The engineered DLL4 ECD of claim 64, wherein the engineered DLL4 ECD further comprises a mutation at one or more amino acid positions selected from the group consisting of G2, E14, R66, P80, F81, H168, Q220, N231, and N260.
66. The engineered DLL4 ECD of claim 65, wherein the further mutation is selected from the group consisting of G2S, E14H, R66S, R66T, P80L, F81L, H168Y, Q220H, N231D, and N260D.
67. The engineered DLL4 ECD of any one of claims 64-66, wherein the engineered DLL4 ECD comprises a mutation selected from the group consisting of:
- (i) T52N and T135N;
 - (ii) T52N, R66S, and T135N;
 - (iii) E14H, T52N, R66T, P80L, T135N, and N231D;
 - (iv) T52N, R66T, P80L, T135N, Q220H, and N260D;
 - (v) G2S, T52N, F81L, T135N, and H168Y;
 - (vi) G2S, T52N, F81L, R66S, T135N, and H168Y;
 - (vii) G2S, E14H, T52N, F81L, R66T, P80L, T135N, H168Y, and N231D; and
 - (viii) G2S, T52N, R66T, P80L, F81L, T135N, H168Y, Q220H, and N260D.
68. The engineered DLL4 ECD of claim 67, wherein the engineered DLL4 ECD comprises an amino acid sequence selected from the group consisting of any one of SEQ ID NOs: 261-264.
69. A protein construct comprising the engineered DLL4 ECD of any one of claims 64-68.
70. The protein construct of claim 69, wherein the protein construct further comprises a binding moiety that specifically binds to a muscle-specific molecule.

FIG. 1A

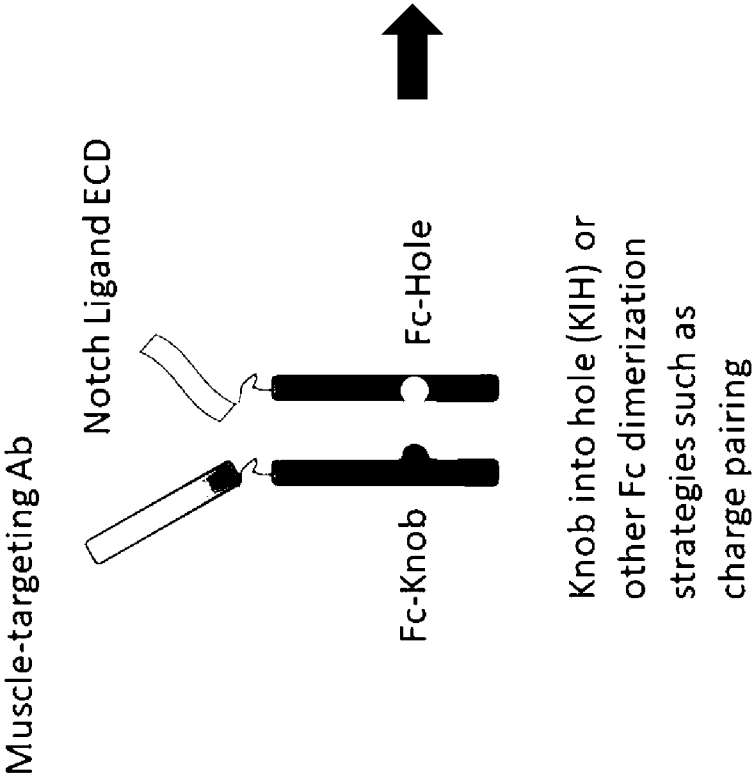


FIG. 1B

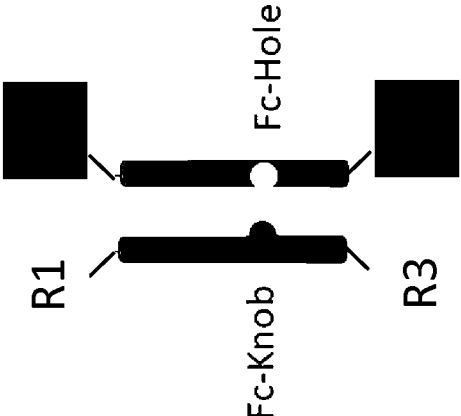


FIG. 1C

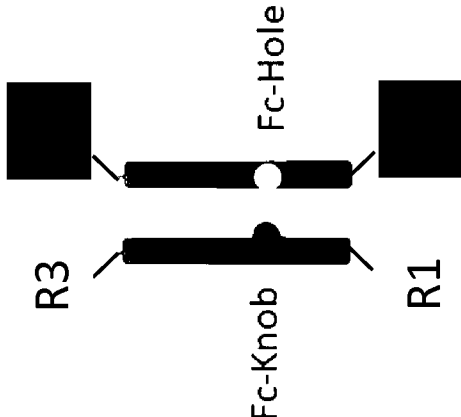
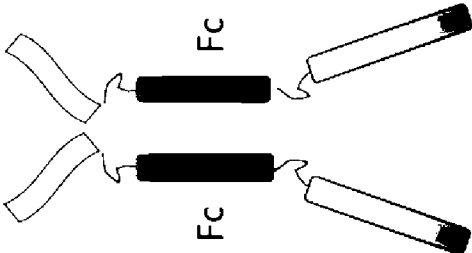


FIG. 1D

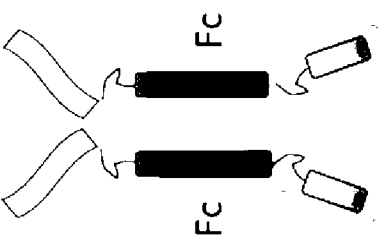
Notch Ligand ECD



Muscle-targeting Fab

FIG. 1E

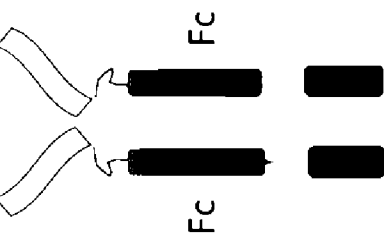
Notch Ligand ECD



Muscle-targeting scFv

FIG. 1F

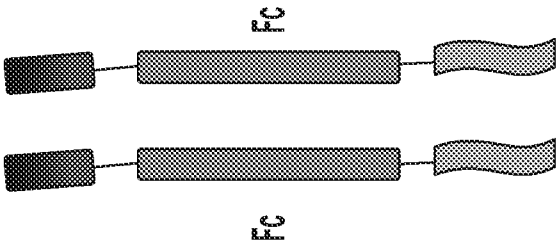
Notch Ligand ECD



Muscle-targeting
VHH or Nanobody

FIG. 1I

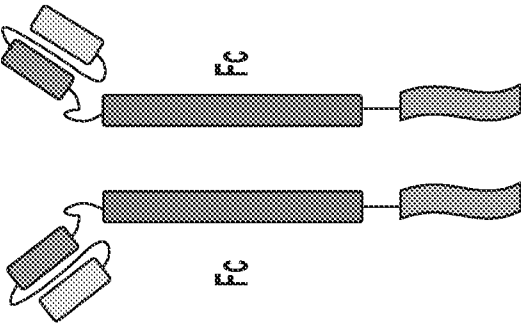
Muscle-targeting
VHH/Nanobody



Notch Ligand ECD

FIG. 1H

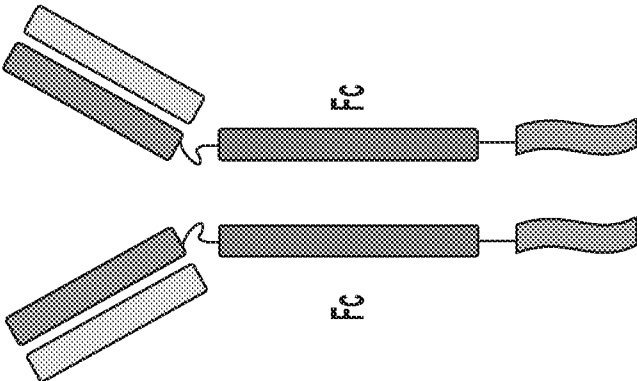
Muscle-targeting scFv



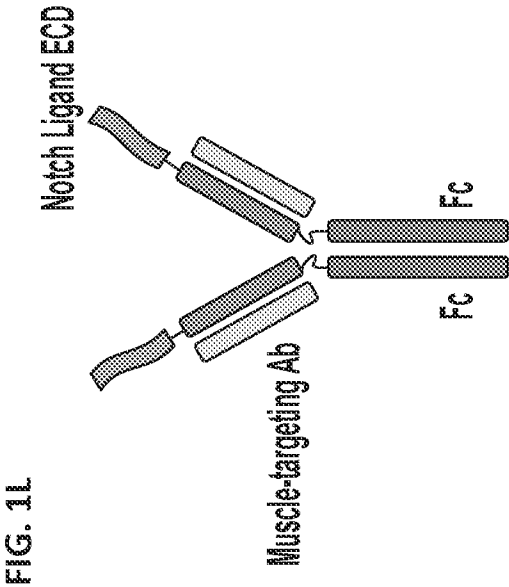
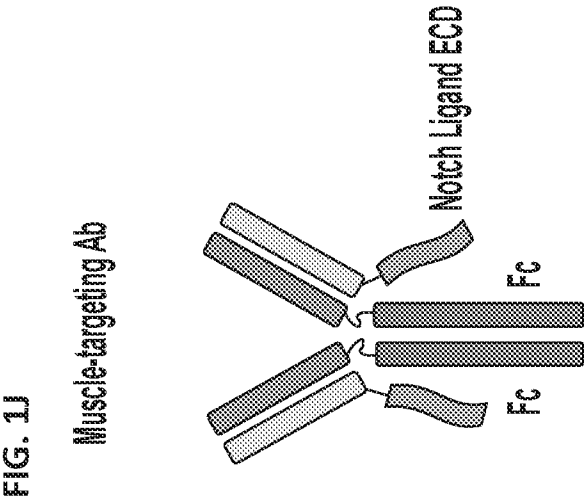
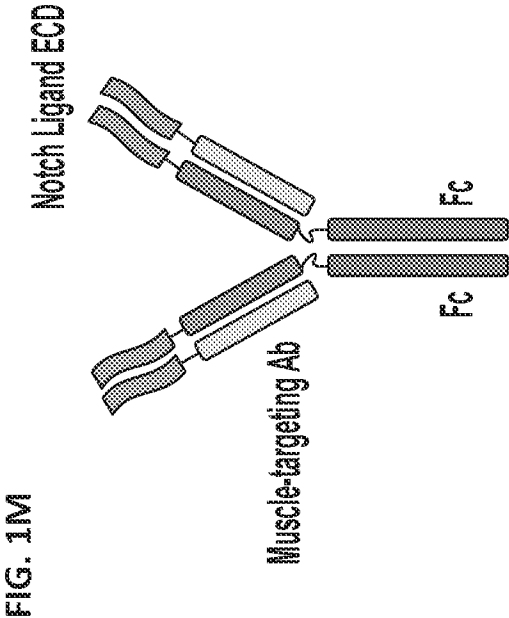
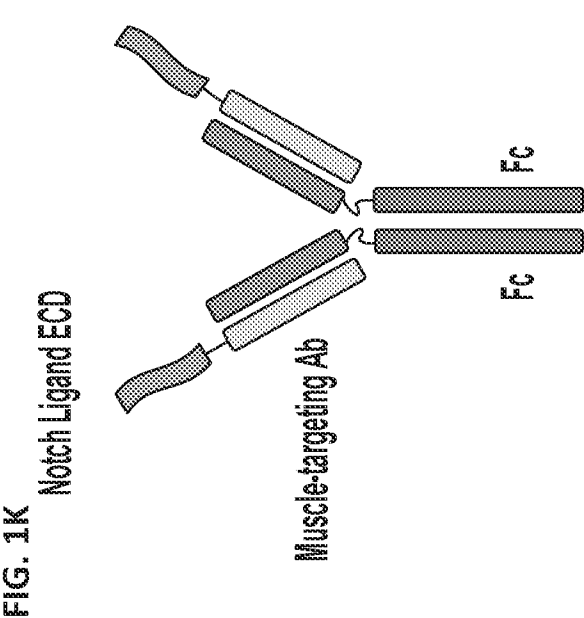
Notch Ligand ECD

FIG. 1G

Muscle-targeting Ab



Notch Ligand ECD



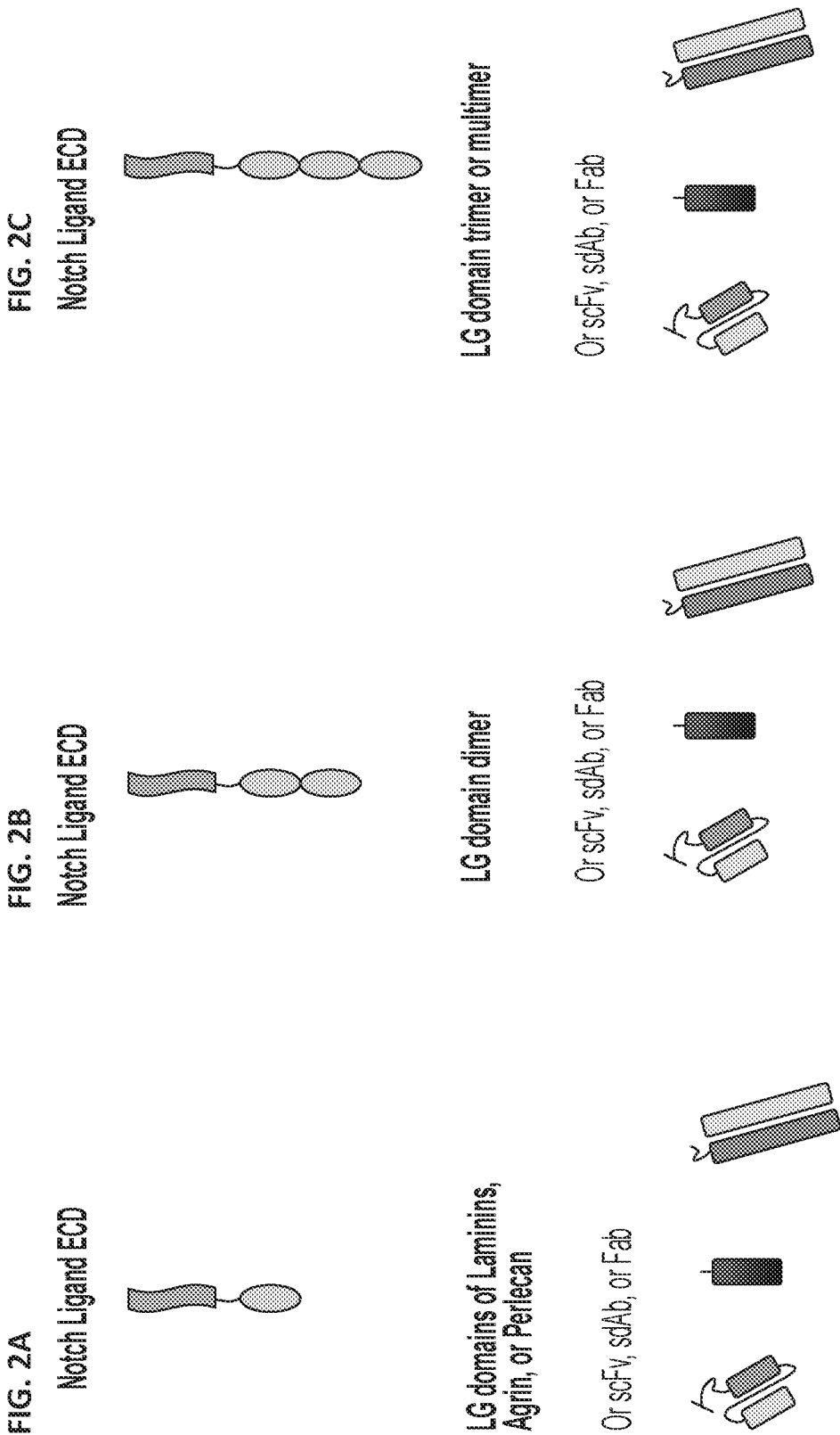
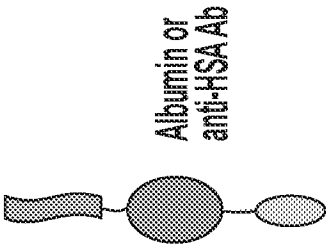


FIG. 2D

Notch Ligand ECD



LG domains of Laminins,
Agrin, or Perlecan

Or a monomeric Fc

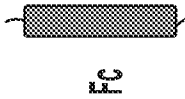
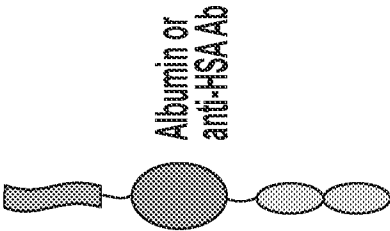


FIG. 2E

Notch Ligand ECD



LG domain dimer

Or a monomeric Fc

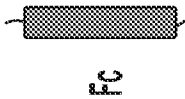
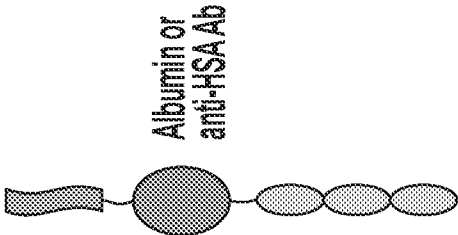


FIG. 2F

Notch Ligand ECD



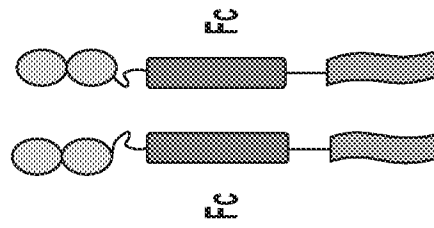
LG domain trimer or multimer

Or a monomeric Fc



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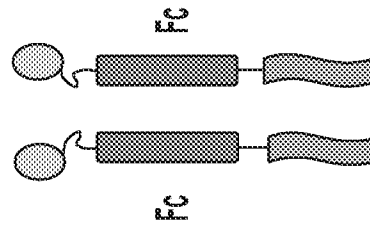
LG domains



GOALS FOR

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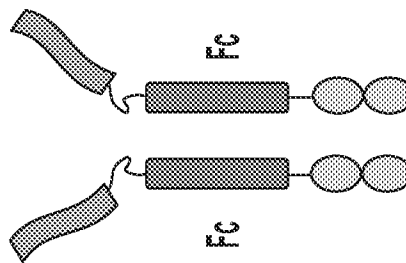
Ldomain



COLE

326

Not Landed



550

FIG. 2G

Department of

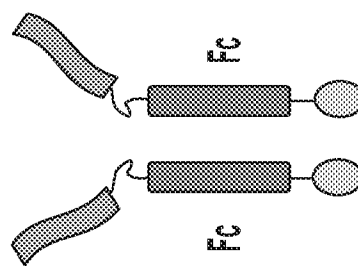


FIG. 3A

Reduced
Non-Reduced
MW (kDa)



FIG. 3B

Protein standards (upper SEC profile)
Recombinant bifunctional protein DLL4v-Fc-LG4-5 (lower SEC profile)

670 kDa
150 kDa

Standards
DLL4v-Fc-LG4-5



FIG. 4A

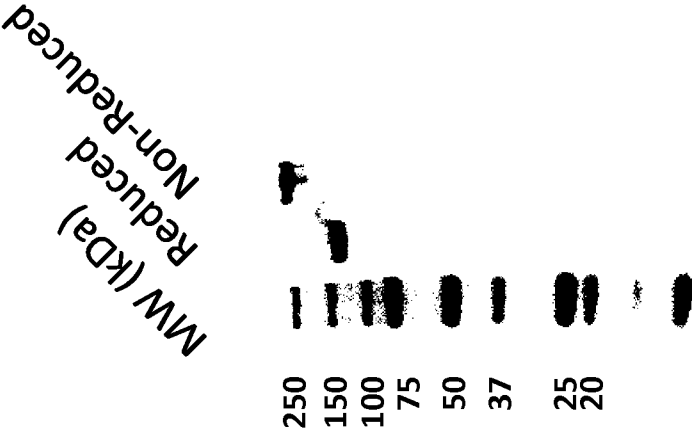


FIG. 4B

Protein standards (upper SEC profile)
Recombinant bifunctional protein DLL4wt-Fc-LG4-5 (lower SEC profile)

SEC-HPLC

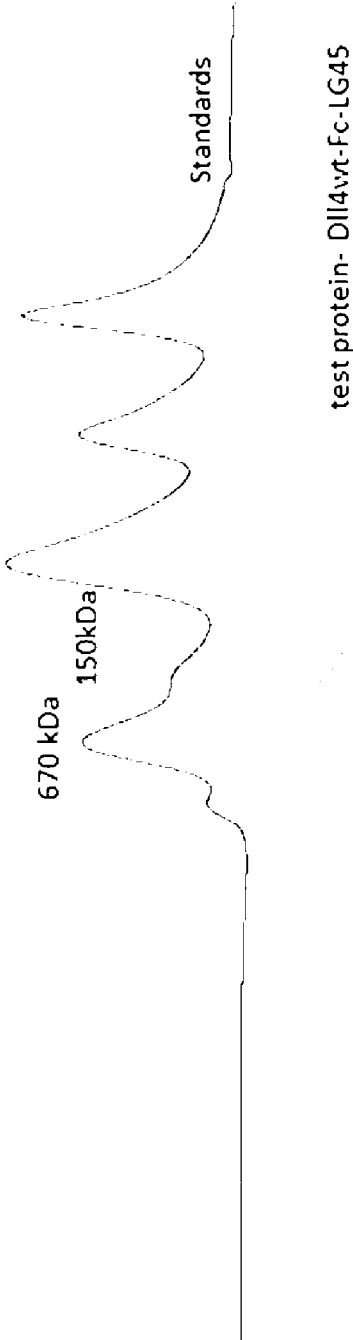


FIG. 5A

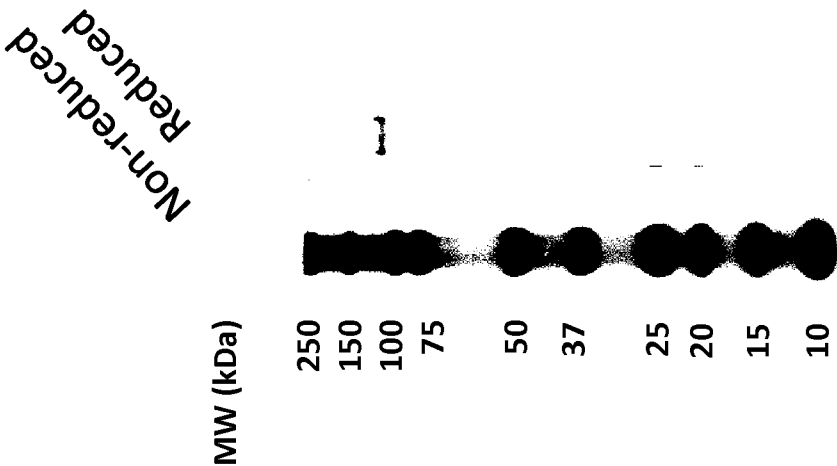


FIG. 5B

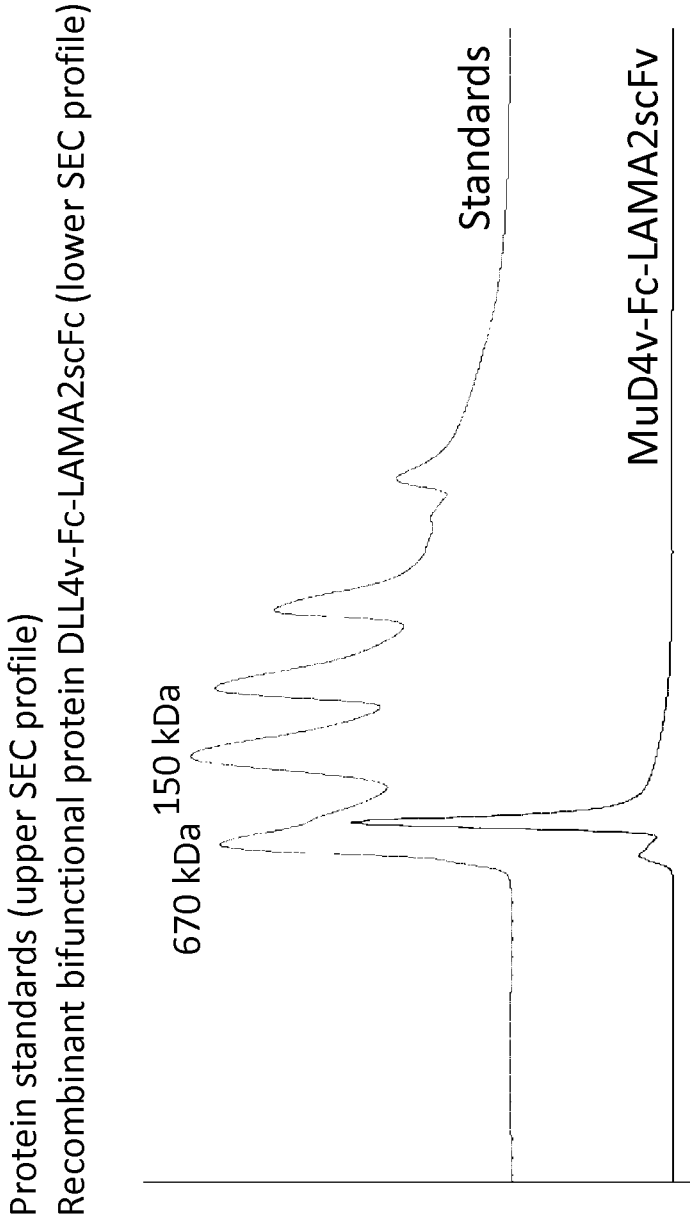


FIG. 6

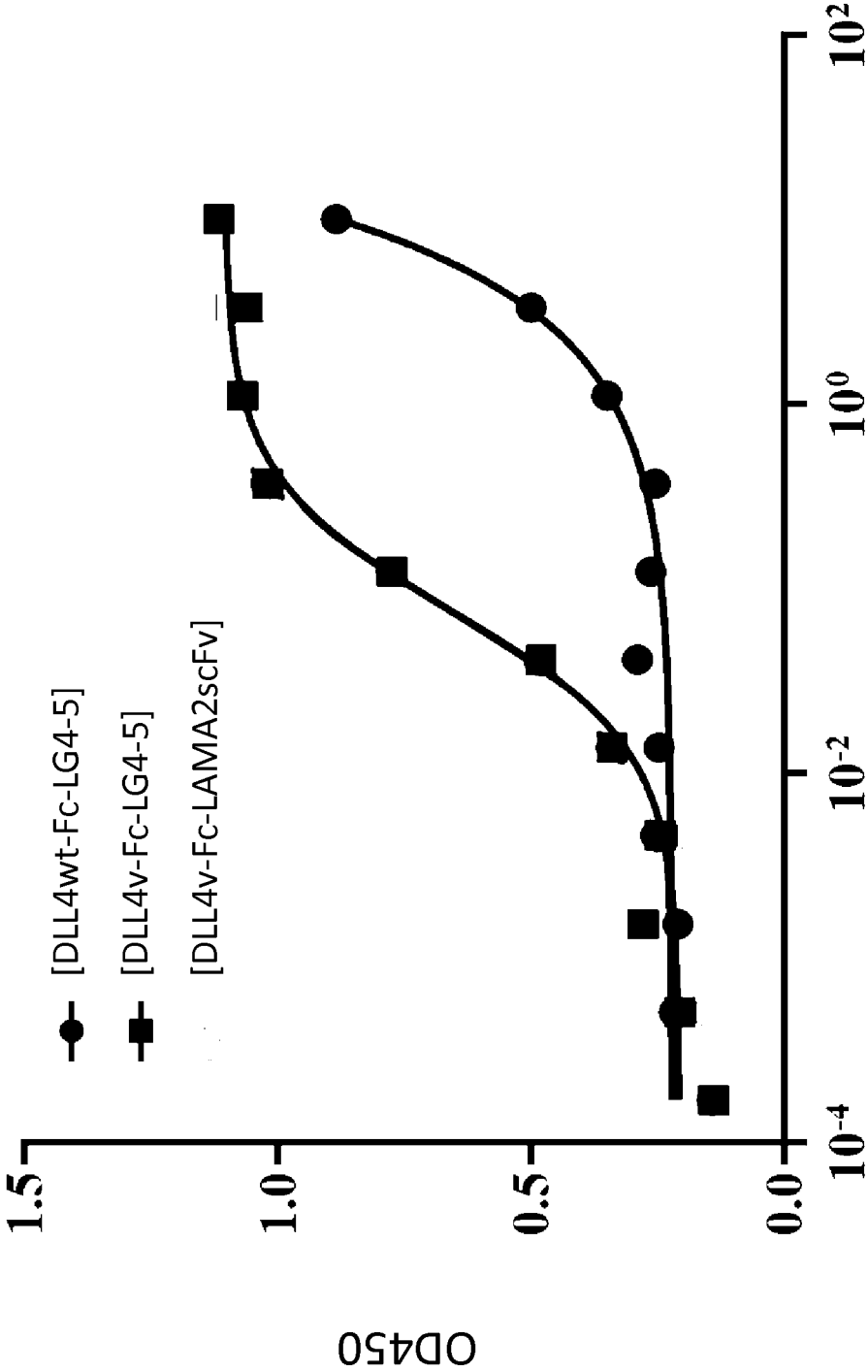


FIG. 7A

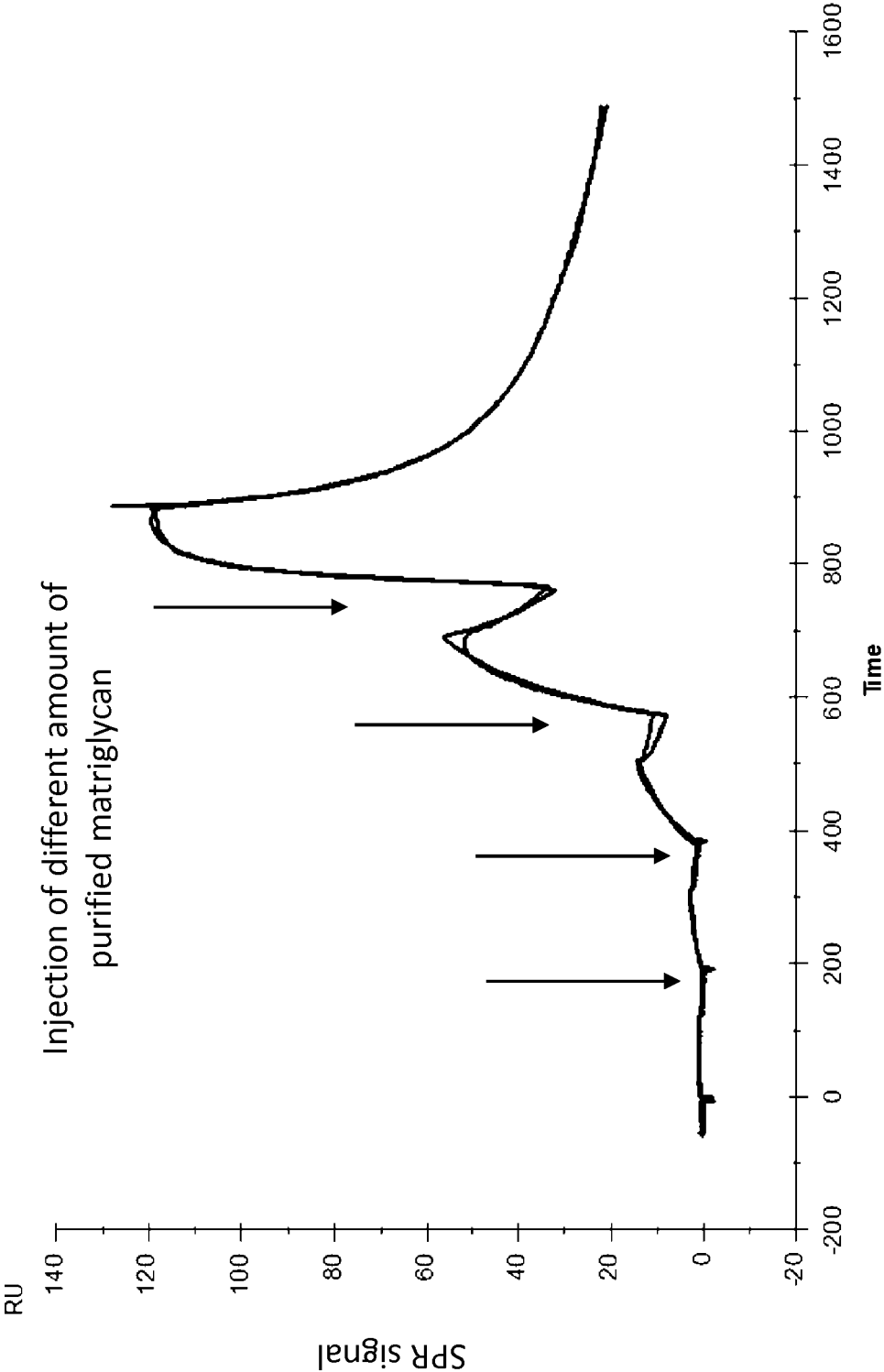


FIG. 7B

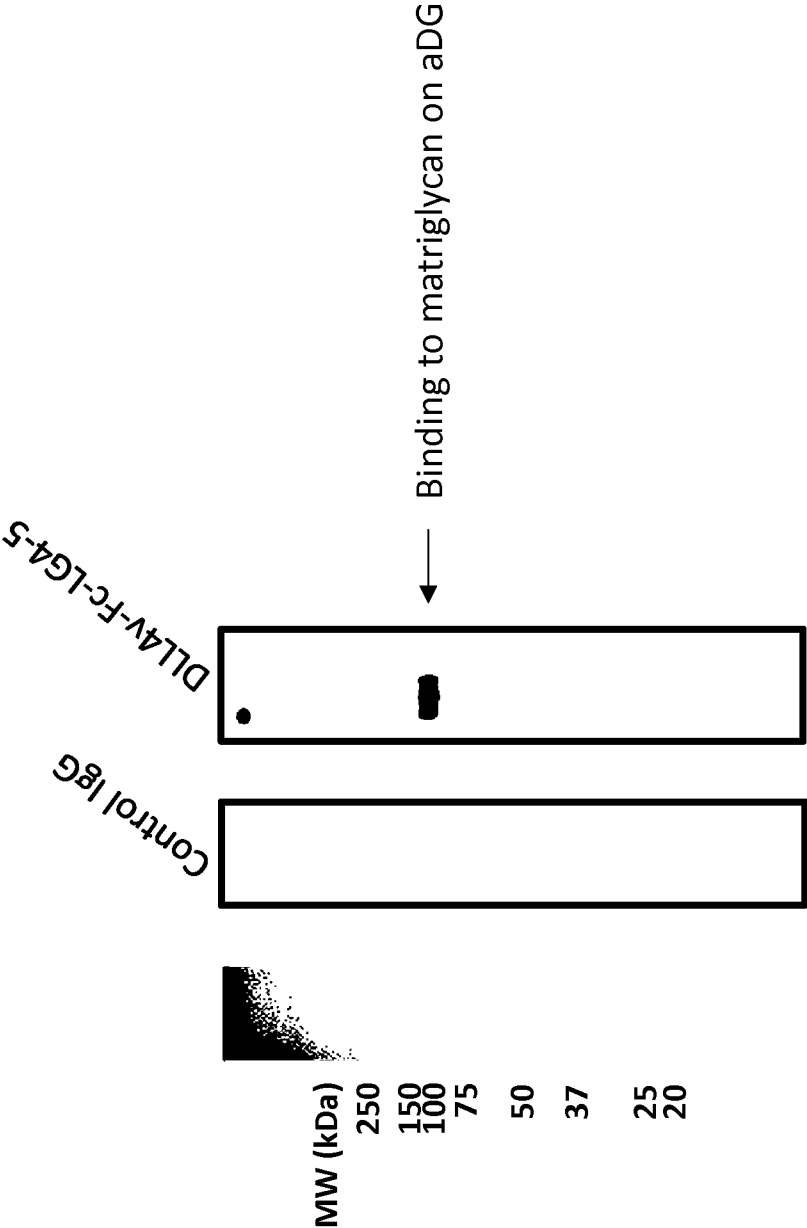


FIG. 8

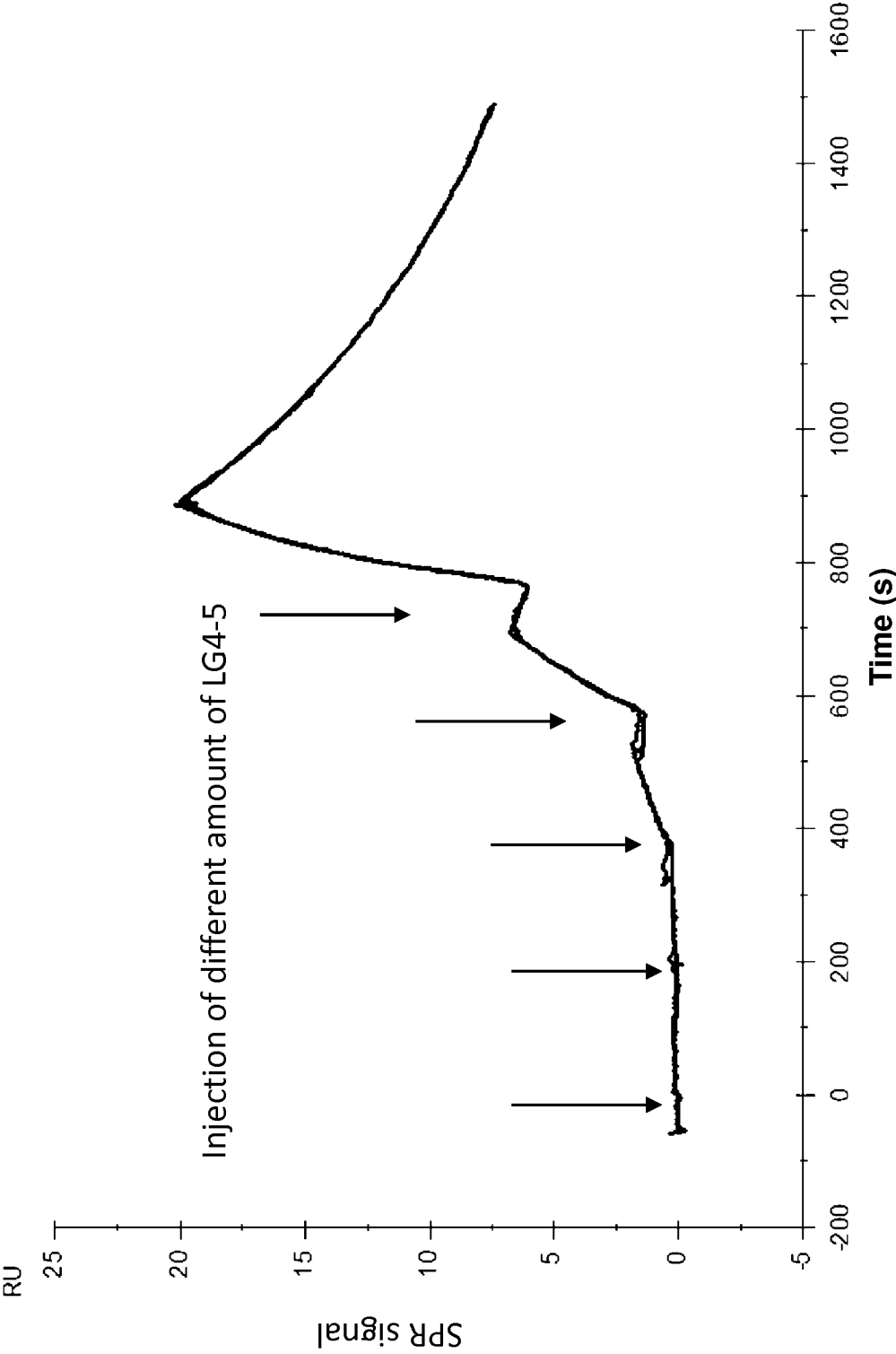


FIG. 9A

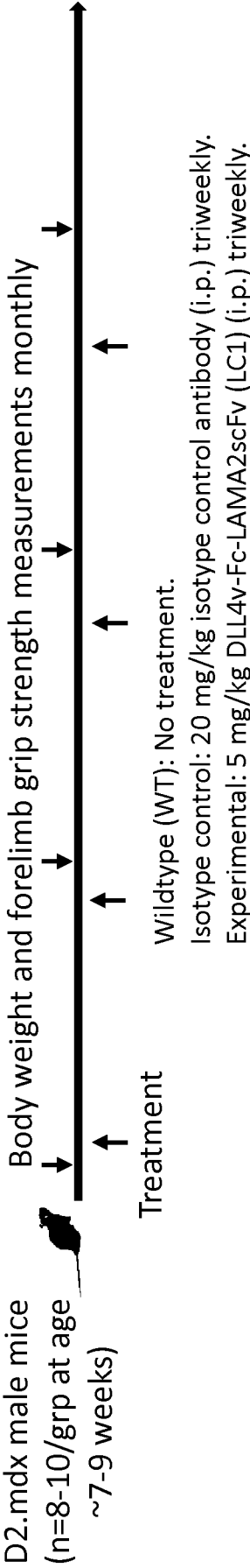
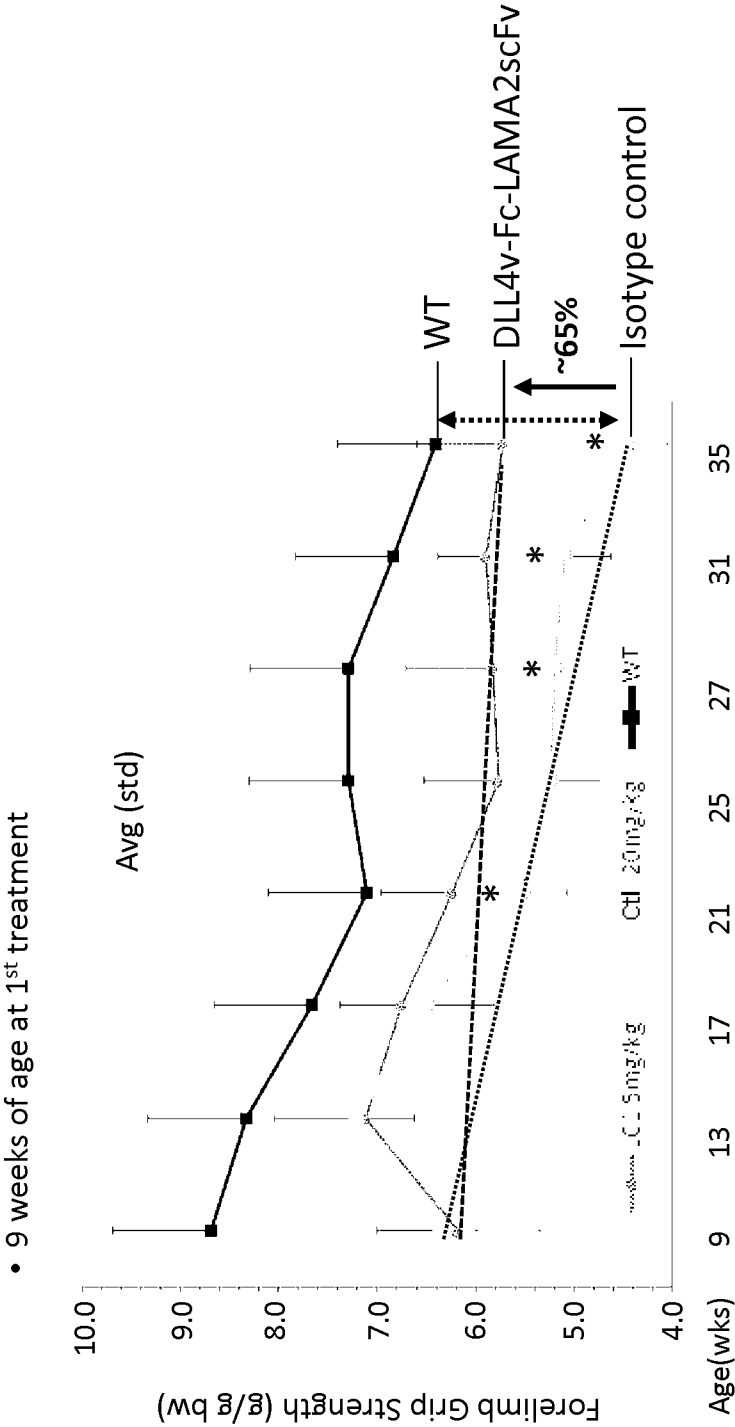


FIG. 9B



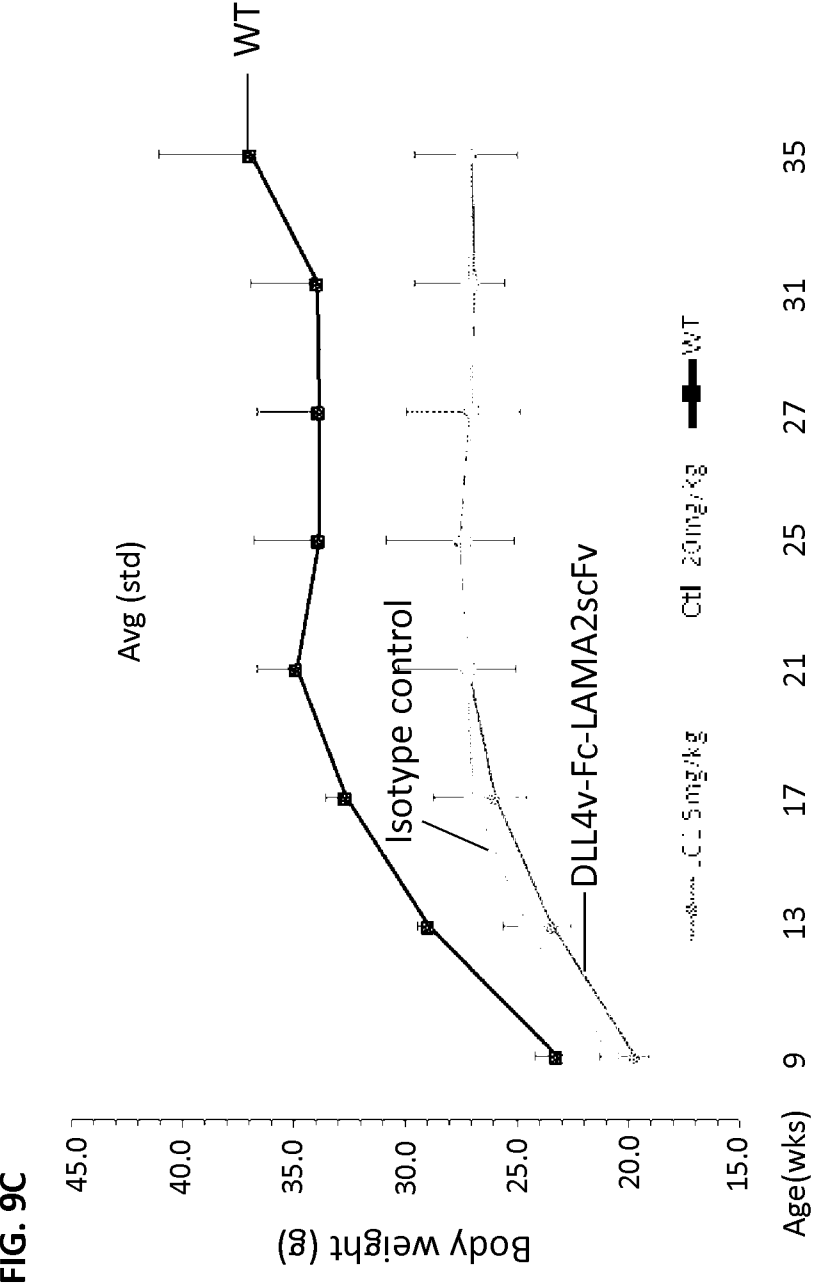


FIG. 10A

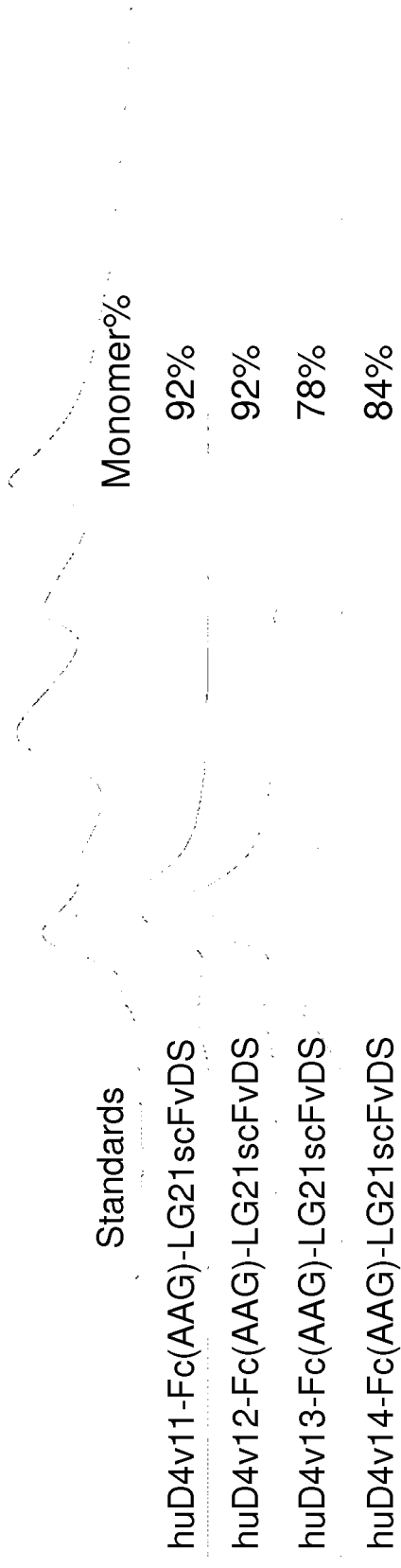


FIG. 10B

Construct	Yield from 30mL (µg)	aSEC % main peak
huD4v11-Fc(AAG)-LG21scFvDS	600	92
huD4v12-Fc(AAG)-LG21scFvDS	850	92
huD4v13-Fc(AAG)-LG21scFvDS	390	78
huD4v14-Fc(AAG)-LG21scFvDS	160	84
huD4v22-Fc(AAG)-LG21scFvDS	~0	N/A
huD4v23-Fc(AAG)-LG21scFvDS	~0	N/A
huD4v24-Fc(AAG)-LG21scFvDS	~0	N/A

FIG. 11A

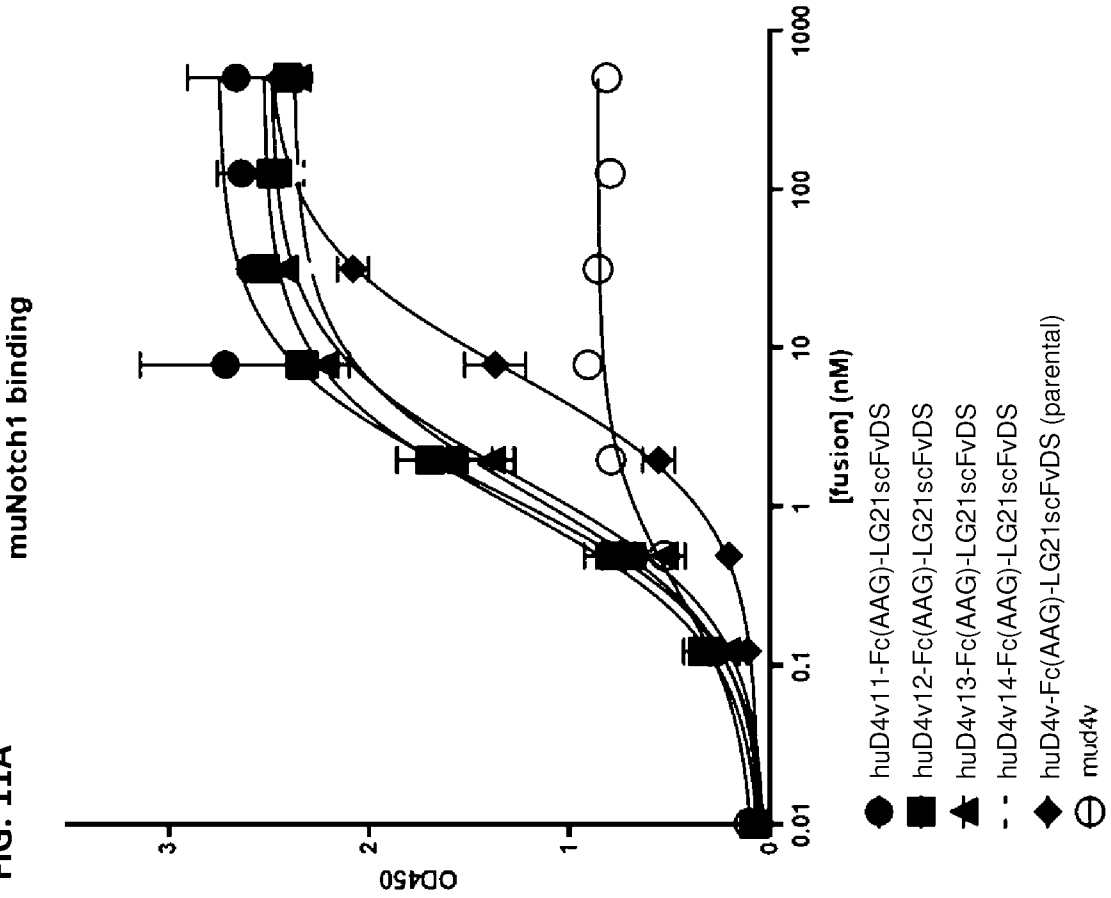


FIG. 11B

Fusion	K _D (nM)
huD4v11-Fc(AAG)-LG21scFvDS	1.3
huD4v12-Fc(AAG)-LG21scFvDS	1.0
huD4v13-Fc(AAG)-LG21scFvDS	1.5
huD4v14-Fc(AAG)-LG21scFvDS	1.2
huD4v-Fc(AAG)-LG21scFvDS (parental)	7.0
muD4v	0.3