(2006)). Blockade of DLL4 potently inhibited primary tumor growth in multiple models (Noguera-Troise et al., *Nature*, 444(7122): 1032-1037 (2006); Ridgway et al., *Nature*, 444(7122): 1083-1087 (2006); Scehnet et al., *Blood*, 109(11): 4753-4760 (2007)). The inhibition of DLL4 was even effective against tumors that are resistant to anti-VEGF therapy. The combinatorial inhibition of both DLL4 and VEGF provided an enhanced anti-tumor activity. Interestingly, unlike VEGF inhibition that reduces tumor vessel formation, DLL4 blockade leads to an increase in tumor vasculature density wherein the vessels are abnormal, cannot support efficient blood transport, and are effectively nonfunctional. Thus, DLL4 provides a potential target for cancer treatment.

There is a need in the art for therapeutic agents capable of targeting the DLL4-Notch pathway and thereby inhibiting, or even preventing, tumor angiogenesis and growth.

Summary of the Disclosure~~Invention~~

The disclosure~~invention~~ provides proteins that bind DLL4, including antibodies, CDR-grafted antibodies, and binding fragments thereof, that are capable of binding DLL4. Preferably, a binding protein described herein binds DLL4 with high affinity. More preferably, a binding protein according to the disclosure~~invention~~ is capable of neutralizing DLL4. The disclosure~~invention~~ also provides methods of making and using DLL4 binding proteins, including human DLL4 binding proteins. Advantageously, the disclosure~~invention~~ eliminates the need to prepare humanized DLL4 binding proteins; thereby, eliminating the complications associated with humanized DLL4 binding proteins.

One aspect of this disclosure~~invention~~ pertains to a binding protein comprising an antigen binding domain capable of binding human DLL4, said antigen binding domain comprising at least one or more CDRs selected from the group consisting of:

CDR-H1: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$ (SEQ ID NO:99), wherein;

$X_1$ is S or N;

$X_2$ is S, G, or N;

$X_3$ is S, N, T, G, or R;

$X_4$ is Y;

$X_5$ is Y or H;

$X_6$ is W; and

$X_7$ is G;

CDR-H2: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$-$X_{11}$-$X_{12}$-$X_{13}$-$X_{14}$-$X_{15}$-$X_{16}$ (SEQ ID NO:100), wherein;

$X_1$ is D;

$X_2$ is I;

$X_3$ is Y, N, or S;

$X_4$ is Y;

$X_5$ is T, N, A, I, S, or R;

$X_{11}$ is S;

CDR-L2: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$ (SEQ ID NO:103), wherein;

$X_1$ is E or Q;

$X_2$ is D;

$X_3$ is S, L, T, A, E, or F;

$X_4$ is K, T, E, N, Q, S, or M;

$X_5$ is R;

$X_6$ is P; and

$X_7$ is S;

and

CDR-L3: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$ (SEQ ID NO:104), wherein;

$X_1$ is Q;

$X_2$ is A;

$X_3$ is W;

$X_4$ is D;

$X_5$ is R, S, M, E, N, G, or K;

$X_6$ is D or E;

$X_7$ is T, V, A, S, or M;

$X_8$ is G, A, or C; and

$X_9$ is V.

Preferably, the antigen binding domain of a DLL4 binding protein of the disclosure~~invention~~ comprises at least one CDR comprising an amino acid sequence selected from the group consisting of:

residues 31-37 of SEQ ID NO:1 (CDR-H1); residues 52-67 of SEQ ID NO:1 (CDR-H2); residues 100-110 of SEQ ID NO:1 (CDR-H3);

residues 23-33 of SEQ ID NO:111 (CDR-L1); residues 49-55 of SEQ ID NO:111 (CDR-L2); residues 88-96 of SEQ ID NO:111 (CDR-L3);

SEQ ID NO:117 (CDR-H1); SEQ ID NO:118 (CDR-H2); SEQ ID NO:119 (CDR-H3);

SEQ ID NO:121 (CDR-H1); SEQ ID NO:122 (CDR-H2); SEQ ID NO:123 (CDR-H3);

SEQ ID NO:125 (CDR-H1); SEQ ID NO:126 (CDR-H2); SEQ ID NO:127 (CDR-H3);

SEQ ID NO:129 (CDR-H1); SEQ ID NO:130 (CDR-H2); SEQ ID NO:131 (CDR-H3);

SEQ ID NO:133 (CDR-H1); SEQ ID NO:134 (CDR-H2); SEQ ID NO:135 (CDR-H3);

SEQ ID NO:137 (CDR-H1); SEQ ID NO:138 (CDR-H2); SEQ ID NO:139 (CDR-H3);

SEQ ID NO:141 (CDR-H1); SEQ ID NO:142 (CDR-H2); SEQ ID NO:143 (CDR-H3);

SEQ ID NO:145 (CDR-H1); SEQ ID NO:146 (CDR-H2); SEQ ID NO:147 (CDR-H3);

SEQ ID NO:149 (CDR-H1); SEQ ID NO:150 (CDR-H2); SEQ ID NO:151 (CDR-H3);

SEQ ID NO:153 (CDR-H1); SEQ ID NO:154 (CDR-H2); SEQ ID NO:155 (CDR-H3);

residues 24-34 of SEQ ID NO:351 (CDR-L1); residues 50-56 of SEQ ID NO:351 (CDR-L2); residues 89-97 of SEQ ID NO:351 (CDR-L3);
residues 31-37 of SEQ ID NO:352 (CDR-H1); residues 52-67 of SEQ ID NO:352 (CDR-H2); residues 100-110 of SEQ ID NO:352 (CDR-H3);
residues 24-34 of SEQ ID NO:353 (CDR-L1); residues 50-56 of SEQ ID NO:353 (CDR-L2); residues 89-97 of SEQ ID NO:353 (CDR-L3);
residues 31-37 of SEQ ID NO:354 (CDR-H1); residues 52-67 of SEQ ID NO:354 (CDR-H2); residues 100-110 of SEQ ID NO:354 (CDR-H3);
residues 24-34 of SEQ ID NO:355 (CDR-L1); residues 50-56 of SEQ ID NO:355 (CDR-L2); residues 89-97 of SEQ ID NO:355 (CDR-L3);
residues 31-37 of SEQ ID NO:356 (CDR-H1); residues 52-67 of SEQ ID NO:356 (CDR-H2); residues 100-110 of SEQ ID NO:356 (CDR-H3);
residues 23-33 of SEQ ID NO:357 (CDR-L1); residues 49-55 of SEQ ID NO:357 (CDR-L2); residues 88-96 of SEQ ID NO:357 (CDR-L3);
residues 31-37 of SEQ ID NO:358 (CDR-H1); residues 52-67 of SEQ ID NO:358 (CDR-H2); residues 100-110 of SEQ ID NO:358 (CDR-H3);
residues 23-33 of SEQ ID NO:359 (CDR-L1); residues 49-55 of SEQ ID NO:359 (CDR-L2); residues 88-96 of SEQ ID NO:359 (CDR-L3);
residues 31-37 of SEQ ID NO:360 (CDR-H1); residues 52-67 of SEQ ID NO:360 (CDR-H2); residues 100-110 of SEQ ID NO:360 (CDR-H3);
residues 23-33 of SEQ ID NO:361 (CDR-L1); residues 49-55 of SEQ ID NO:361 (CDR-L2); residues 88-96 of SEQ ID NO:361 (CDR-L3).

In one embodiment, there is provided a binding protein comprising an antigen binding domain, said binding protein being

capable of binding human DLL4, said antigen binding domain comprising six CDRs: CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, wherein:

CDR-H1 is selected from the group consisting of:

residues 31-37 of SEQ ID NO:1;

SEQ ID NO:117;

SEQ ID NO:121;

SEQ ID NO:125;

SEQ ID NO:129;

SEQ ID NO:133;

SEQ ID NO:137;

SEQ ID NO:141;

SEQ ID NO:145;

SEQ ID NO:149;

SEQ ID NO:153;

SEQ ID NO:157;

SEQ ID NO:161;

SEQ ID NO:165;

SEQ ID NO:169;

SEQ ID NO:173;

SEQ ID NO:177;

SEQ ID NO:181;

SEQ ID NO:185;

SEQ ID NO:189;

SEQ ID NO:193;

SEQ ID NO:197;

SEQ ID NO:201;

SEQ ID NO:205;

SEQ ID NO:209;

SEQ ID NO:213;

residues 31-37 of SEQ ID NO:334;

residues 31-37 of SEQ ID NO:336;

residues 31-37 of SEQ ID NO:338;

residues 31-37 of SEQ ID NO:340;

residues 31-37 of SEQ ID NO:342;

residues 31-37 of SEQ ID NO:344;
residues 31-37 of SEQ ID NO:346;
residues 31-37 of SEQ ID NO:348;
residues 31-37 of SEQ ID NO:350;
residues 31-37 of SEQ ID NO:352;
residues 31-37 of SEQ ID NO:354;
residues 31-37 of SEQ ID NO:356;
residues 31-37 of SEQ ID NO:358; and
residues 31-37 of SEQ ID NO:360;

CDR-H2, selected from the group consisting of:

residues 52-67 of SEQ ID NO:1;
SEQ ID NO:118;
SEQ ID NO:122;
SEQ ID NO:126;
SEQ ID NO:130;
SEQ ID NO:134;
SEQ ID NO:138;
SEQ ID NO:142;
SEQ ID NO:146;
SEQ ID NO:150;
SEQ ID NO:154;
SEQ ID NO:158;
SEQ ID NO:162;
SEQ ID NO:166;
SEQ ID NO:170;
SEQ ID NO:174;
SEQ ID NO:178;
SEQ ID NO:182;
SEQ ID NO:186;
SEQ ID NO:190;
SEQ ID NO:194;
SEQ ID NO:198;
SEQ ID NO:202;
SEQ ID NO:206;
SEQ ID NO:210;
SEQ ID NO:214;
residues 52-67 of SEQ ID NO:334;

residues 52-67 of SEQ ID NO:336;
residues 52-67 of SEQ ID NO:338;
residues 52-67 of SEQ ID NO:340;
residues 52-67 of SEQ ID NO:342;
residues 52-67 of SEQ ID NO:344;
residues 52-67 of SEQ ID NO:346;
residues 52-67 of SEQ ID NO:348;
residues 52-67 of SEQ ID NO:350;
residues 52-67 of SEQ ID NO:352;
residues 52-67 of SEQ ID NO:354;
residues 52-67 of SEQ ID NO:356;
residues 52-67 of SEQ ID NO:358; and
residues 52-67 of SEQ ID NO:360;

CDR-H3 is selected from the group consisting of:
residues 100-110 of SEQ ID NO:1;
SEQ ID NO:119;
SEQ ID NO:123;
SEQ ID NO:127;
SEQ ID NO:131;
SEQ ID NO:135;
SEQ ID NO:139;
SEQ ID NO:143;
SEQ ID NO:147;
SEQ ID NO:151;
SEQ ID NO:155;
SEQ ID NO:159;
SEQ ID NO:163;
SEQ ID NO:167;
SEQ ID NO:171;
SEQ ID NO:175;
SEQ ID NO:179;
SEQ ID NO:183;
SEQ ID NO:187;
SEQ ID NO:191;
SEQ ID NO:195;
SEQ ID NO:199;
SEQ ID NO:203;

SEQ ID NO:207;

SEQ ID NO:211;

SEQ ID NO:215;

residues 100-110 of SEQ ID NO:334;

residues 100-110 of SEQ ID NO:336;

residues 100-110 of SEQ ID NO:338;

residues 100-110 of SEQ ID NO:340;

residues 100-110 of SEQ ID NO:342;

residues 100-110 of SEQ ID NO:344;

residues 100-110 of SEQ ID NO:346;

residues 100-110 of SEQ ID NO:348;

residues 100-110 of SEQ ID NO:350;

residues 100-110 of SEQ ID NO:352;

residues 100-110 of SEQ ID NO:354;

residues 100-110 of SEQ ID NO:356;

residues 100-110 of SEQ ID NO:358; and

residues 100-110 of SEQ ID NO:360;

CDR-L1 is selected from the group consisting of:

residues 23-33 of SEQ ID NO:111;

SEQ ID NO:217;

SEQ ID NO:221;

SEQ ID NO:225;

SEQ ID NO:229;

SEQ ID NO:233;

SEQ ID NO:237;

SEQ ID NO:241;

SEQ ID NO:245;

SEQ ID NO:249;

SEQ ID NO:253;

SEQ ID NO:257;

SEQ ID NO:261;

SEQ ID NO:265;

SEQ ID NO:269;

SEQ ID NO:273;

SEQ ID NO:277;

SEQ ID NO:281;

SEQ ID NO:285;

SEQ ID NO:289;
SEQ ID NO:293;
SEQ ID NO:297;
SEQ ID NO:301;
SEQ ID NO:305;
SEQ ID NO:309;
SEQ ID NO:313;
residues 23-33 of SEQ ID NO:335;
residues 23-33 of SEQ ID NO:337;
residues 23-33 of SEQ ID NO:339;
residues 23-33 of SEQ ID NO:341;
residues 23-33 of SEQ ID NO:343;
residues 24-34 of SEQ ID NO:345;
residues 23-33 of SEQ ID NO:347;
residues 24-34 of SEQ ID NO:349;
residues 24-34 of SEQ ID NO:351;
residues 24-34 of SEQ ID NO:353;
residues 24-34 of SEQ ID NO:355;
residues 23-33 of SEQ ID NO:357;
residues 23-33 of SEQ ID NO:359; and
residues 23-33 of SEQ ID NO:361;

CDR-L2 is selected from the group consisting of:

residues 49-55 of SEQ ID NO:111;
SEQ ID NO:230;
SEQ ID NO:234;
SEQ ID NO:238;
SEQ ID NO:242;
SEQ ID NO:246;
SEQ ID NO:250;
SEQ ID NO:254;
SEQ ID NO:258;
SEQ ID NO:262;
SEQ ID NO:266;
SEQ ID NO:270;
SEQ ID NO:218;
SEQ ID NO:222;
SEQ ID NO:226;

SEQ ID NO:274;
SEQ ID NO:278;
SEQ ID NO:302;
SEQ ID NO:294;
SEQ ID NO:282;
SEQ ID NO:290;
SEQ ID NO:298;
SEQ ID NO:286;
SEQ ID NO:306;
SEQ ID NO:310;
SEQ ID NO:314;
residues 49-55 of SEQ ID NO:335;
residues 49-55 of SEQ ID NO:337;
residues 49-55 of SEQ ID NO:339;
residues 49-55 of SEQ ID NO:341;
residues 49-55 of SEQ ID NO:343;
residues 50-56 of SEQ ID NO:345;
residues 49-55 of SEQ ID NO:347;
residues 50-56 of SEQ ID NO:349;
residues 50-56 of SEQ ID NO:351;
residues 50-56 of SEQ ID NO:353;
residues 50-56 of SEQ ID NO:355;
residues 49-55 of SEQ ID NO:357;
residues 49-55 of SEQ ID NO:359; and
residues 49-55 of SEQ ID NO:361;

and

CDR-L3 is selected from the group consisting of:

residues 88-96 of SEQ ID NO:111;
SEQ ID NO:231;
SEQ ID NO:235;
SEQ ID NO:239;
SEQ ID NO:243;
SEQ ID NO:247;
SEQ ID NO:251;
SEQ ID NO:255;
SEQ ID NO:259;
SEQ ID NO:263;

SEQ ID NO:267;
SEQ ID NO:271;
SEQ ID NO:219;
SEQ ID NO:223;
SEQ ID NO:227;
SEQ ID NO:275;
SEQ ID NO:279;
SEQ ID NO:303;
SEQ ID NO:295;
SEQ ID NO:283;
SEQ ID NO:291;
SEQ ID NO:299;
SEQ ID NO:287;
SEQ ID NO:307;
SEQ ID NO:311;
SEQ ID NO:315;
residues 88-96 of SEQ ID NO:335;
residues 88-96 of SEQ ID NO:337;
residues 88-96 of SEQ ID NO:339;
residues 88-96 of SEQ ID NO:341;
residues 88-96 of SEQ ID NO:343;
residues 89-97 of SEQ ID NO:345;
residues 88-96 of SEQ ID NO:347;
residues 89-97 of SEQ ID NO:349;
residues 89-97 of SEQ ID NO:351;
residues 89-97 of SEQ ID NO:353;
residues 89-97 of SEQ ID NO:355;
residues 88-96 of SEQ ID NO:357;
residues 88-96 of SEQ ID NO:359; and
residues 88-96 of SEQ ID NO:361.

In another embodiment, the binding protein comprises at least 3 CDRs disclosed above.

Preferably, a DLL4 binding protein according to the disclosure~~invention~~ comprises one or more CDRs disclosed above. More preferably, the binding protein comprises three or more CDRs disclosed above. Most preferably, a DLL4 binding protein according to the disclosure~~invention~~ comprises six CDRs described above, i.e., a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 described above.

In a preferred embodiment, the binding protein comprises at least 3 CDRs selected from the group consisting of the sequences disclosed above.

More preferably, the binding protein comprises 3 CDRs selected from a set of variable domain CDRs selected from the group below.

VH E9 CDR Set

| | |
|---|---|
| CDR-H1: | residues 31-37 of SEQ ID NO:1 |
| CDR-H2: | residues 52-67 of SEQ ID NO:1 |
| CDR-H3 | residues 100-110 of SEQ ID NO:1 |

VL E9-FR2 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:355

CDR-L2: residues 50-56 of SEQ ID NO:355

CDR-L3: residues 89-97 of SEQ ID NO:355

VH E9.71 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:356

CDR-H2: residues 52-67 of SEQ ID NO:356

CDR-H3: residues 100-110 of SEQ ID NO:356

VL E9.71 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:357

CDR-L2: residues 49-55 of SEQ ID NO:357

CDR-L3: residues 88-96 of SEQ ID NO:357

VH E9.71(M) CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:358

CDR-H2: residues 52-67 of SEQ ID NO:358

CDR-H3: residues 100-110 of SEQ ID NO:358

VL E9.71(M) CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:359

CDR-L2: residues 49-55 of SEQ ID NO:359

CDR-L3: residues 88-96 of SEQ ID NO:359

VH E9.71(L) CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:360

CDR-H2: residues 52-67 of SEQ ID NO:360

CDR-H3: residues 100-110 of SEQ ID NO:360

VL E9.71(L) CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:361

CDR-L2: residues 49-55 of SEQ ID NO:361

CDR-L3: residues 88-96 of SEQ ID NO:361

In another embodiment, a binding protein comprises a variable heavy chain (VH) set of 3 CDRs selected from any VH set of 3 CDRs in the group above and a variable light chain (VL) set of 3 CDRS selected from any VL set of 3 CDRs in the group above.

In still another embodiment a binding protein comprises a named VH set of 3 CDRs and a correspondingly named VL set of 3 CDRs from the group below. Preferably, a binding protein according to the disclosure~~invention~~ comprises at least two variable domain CDR sets selected from the group of variable domain CDR sets consisting of:

VH E9 CDR Set and VL E9 CDR Set,

VH E9.4 CDR Set and VL E9.4 CDR Set,

337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, and 361.

In another embodiment, a binding protein according to the disclosure~~invention~~ comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of: SEQ ID NOS:1 and 111, SEQ ID NOS:116 and 228, SEQ ID NOS:120 and 232, SEQ ID NOS:124 and 236, SEQ ID NOS:128 and 240, SEQ ID NOS:132 and 244, SEQ ID NOS:136 and 248, SEQ ID NOS:140 and 252, SEQ ID NOS:144 and 256, SEQ ID NOS:148 and 260, SEQ ID NOS:152 and 264, SEQ ID NOS:156 and 268, SEQ ID NOS: 160 and 216, SEQ ID NOS: 164 and 220, SEQ ID NOS:168 and 224, SEQ ID NOS:172 and 272, SEQ ID NOS:176 and 276, SEQ ID NOS:180 and 300, SEQ ID NOS:184 and 292, SEQ ID NOS:188 and 280, SEQ ID NOS:192 and 288, SEQ ID NOS:196 and 296, SEQ ID NOS:200 and 284, SEQ ID NOS:204 and 304, SEQ ID NOS:208 and 308, SEQ ID NOS:212 and 312, SEQ ID NOS:334 and 335, SEQ ID NOS:336 and 337, SEQ ID NOS:338 and 339, SEQ ID NOS:340 and 341, SEQ ID NOS:342 and 343, SEQ ID NOS:344 and 345, SEQ ID NOS:346 and 347, SEQ ID NOS:348 and 349, SEQ ID NOS:350 and 351, SEQ ID NOS:352 and 353, SEQ ID NOS:354 and 355, SEQ ID NOS:356 and 357, SEQ ID NOS:358 and 359, SEQ ID NOS:360 and 361.

In an embodiment, a binding protein according to the disclosure~~invention~~ comprises heavy chain variable domain ($V_H$), preferably wherein the $V_H$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360.

In yet another embodiment, a binding protein according to the disclosure~~invention~~ comprises a light chain variable domain (a $V_L$), preferably wherein the $V_L$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

In a preferred embodiment, a binding protein according to the disclosure~~invention~~ comprises a $V_H$ and a $V_L$, preferably wherein $V_H$ and a $V_L$ are any of those sequences disclosed above.

In another embodiment, the disclosure~~invention~~ provides a binding protein capable of binding human DLL-4, said binding protein comprising:

an Ig constant heavy region having an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3;

an Ig constant light region having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5;

an Ig variable heavy region having an amino acid sequence selected from the group consisting:

SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360; and

an Ig variable light region having an amino acid sequence selected from the group consisting:

SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

Another aspect of the disclosure~~invention~~ pertains to a binding protein comprising an antigen binding domain capable of binding human DLL4, said antigen binding domain comprising at least one or more CDRs selected from the group consisting of:

CDR-H1: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$ (SEQ ID NO:105), wherein;

$X_1$ is S, N, or D;

$X_2$ is H or Y;

$X_3$ is W;

$X_4$ is M;

$X_5$ is S or H;

CDR-H2: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$-$X_{11}$-$X_{12}$-$X_{13}$-$X_{14}$-$X_{15}$-$X_{16}$-$X_{17}$ (SEQ ID NO:106), wherein;

$X_1$ is I, D, M, or T;

$X_2$ is I;

$X_3$ is S;

$X_4$ is Y, N, S, Q, V, T, H, or D;

$X_5$ is D;

$X_6$ is G;

$X_7$ is S, R, I, T, G, K, H, or N;

$X_8$ is N, Y, S, I, or T;

$X_9$ is K, M, N, Q, E, T, R, S, A, or L;

$X_{10}$ is Y, D, or E;

$X_{11}$ is S or Y;

$X_{12}$ is A;

$X_{13}$ is D;

$X_{14}$ is S;

$X_{15}$ is V;

$X_{16}$ is K; and

$X_2$ is S or A;
$X_3$ is W;
$X_4$ is D;
$X_5$ is R, S, Q, P, A, V, W, or M;
$X_6$ is S, G, I, N, R, or T;
$X_7$ is D or G;
$X_8$ is V, A, P, or E; and
$X_9$ is V.

Preferably, the antigen binding domain of a DLL4 binding protein of the disclosure~~invention~~ comprises at least one CDR comprising an amino acid sequence selected from the group consisting of:

residues 31-35 of SEQ ID NO:112 (CDR-H1); residues 50-66 of SEQ ID NO:112 (CDR-H2); residues 99-108 of SEQ ID NO:112 (CDR-H3);
residues 23-33 of SEQ ID NO:113 (CDR-L1); residues 49-55 of SEQ ID NO:113 (CDR-L2); residues 88-96 of SEQ ID NO:113 (CDR-L3);
residues 31-35 of SEQ ID NO:316 (CDR-H1); residues 50-66 of SEQ ID NO:316 (CDR-H2); residues 99-108 of SEQ ID NO:316 (CDR-H3);
residues 31-35 of SEQ ID NO:317 (CDR-H1); residues 50-66 of SEQ ID NO:317 (CDR-H2); residues 99-108 of SEQ ID NO:317 (CDR-H3);
residues 31-35 of SEQ ID NO:318 (CDR-H1); residues 50-66 of SEQ ID NO:318 (CDR-H2); residues 99-108 of SEQ ID NO:318 (CDR-H3);
residues 31-35 of SEQ ID NO:319 (CDR-H1); residues 50-66 of SEQ ID NO:319 (CDR-H2); residues 99-108 of SEQ ID NO:319 (CDR-H3);
residues 31-35 of SEQ ID NO:320 (CDR-H1); residues 50-66 of SEQ ID NO:320 (CDR-H2); residues 99-108 of SEQ ID NO:320 (CDR-H3);
residues 31-35 of SEQ ID NO:321 (CDR-H1); residues 50-66 of SEQ ID NO:321 (CDR-H2); residues 99-108 of SEQ ID NO:321 (CDR-H3);
residues 31-35 of SEQ ID NO:322 (CDR-H1); residues 50-66 of SEQ ID NO:322 (CDR-H2); residues 99-108 of SEQ ID NO:322 (CDR-H3);
residues 31-35 of SEQ ID NO:323 (CDR-H1); residues 50-66 of SEQ ID NO:323 (CDR-H2); residues 99-108 of SEQ ID NO:323 (CDR-H3);
residues 31-35 of SEQ ID NO:324 (CDR-H1); residues 50-66 of SEQ ID NO:324 (CDR-H2); residues 99-108 of SEQ ID NO:324 (CDR-H3);
residues 31-35 of SEQ ID NO:325 (CDR-H1); residues 50-66 of SEQ ID NO:325 (CDR-H2); residues 99-108 of SEQ ID NO:325 (CDR-H3);
residues 31-35 of SEQ ID NO:326 (CDR-H1); residues 50-66 of SEQ ID NO:326 (CDR-H2); residues 99-108 of SEQ ID NO:326 (CDR-H3);

residues 23-33 of SEQ ID NO:327 (CDR-L1); residues 49-55 of SEQ ID NO:327 (CDR-L2); residues 88-96 of SEQ ID NO:327 (CDR-L3);
residues 23-33 of SEQ ID NO:328 (CDR-L1); residues 49-55 of SEQ ID NO:328 (CDR-L2); residues 88-96 of SEQ ID NO:328 (CDR-L3);
residues 23-33 of SEQ ID NO:329 (CDR-L1); residues 49-55 of SEQ ID NO:329 (CDR-L2); residues 88-96 of SEQ ID NO:329 (CDR-L3);
residues 23-33 of SEQ ID NO:330 (CDR-L1); residues 49-55 of SEQ ID NO:330 (CDR-L2); residues 88-96 of SEQ ID NO:330 (CDR-L3);
residues 23-33 of SEQ ID NO:331 (CDR-L1); residues 49-55 of SEQ ID NO:331 (CDR-L2); residues 88-96 of SEQ ID NO:331 (CDR-L3);
residues 23-33 of SEQ ID NO:332 (CDR-L1); residues 49-55 of SEQ ID NO:332 (CDR-L2); residues 88-96 of SEQ ID NO:332 (CDR-L3);
residues 23-33 of SEQ ID NO:333 (CDR-L1); residues 49-55 of SEQ ID NO:333 (CDR-L2); residues 88-96 of SEQ ID NO:333 (CDR-L3).

In another embodiment, the binding protein comprises at least 3 CDRs disclosed above.

Preferably, a DLL4 binding protein according to the disclosure~~invention~~ comprises one or more CDRs disclosed above. More preferably, the binding protein comprises three or more CDRs disclosed above. Most preferably, a DLL4 binding protein according to the disclosure~~invention~~ comprises six CDRs described above, i.e., a CDR-H1, a CDR-H2, a CDR-H3, a CDR-L1, a CDR-L2, and a CDR-L3 described above.

In a preferred embodiment, the binding protein comprises at least 3 CDRs selected from the group consisting of the sequences disclosed above.

In another preferred embodiment, a binding protein comprises 3 CDRs selected from a set of variable domain CDRs selected from the group below.

VH A10 CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:112
CDR-H2: residues 50-66 of SEQ ID NO:112
CDR-H3: residues 99-108 of SEQ ID NO:112

VL A10 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:113
CDR-L2: residues 49-55 of SEQ ID NO:113
CDR-L3: residues 88-96 of SEQ ID NO:113

VH A10.3 CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:316
CDR-H2: residues 50-66 of SEQ ID NO:316
CDR-H3: residues 99-108 of SEQ ID NO:316

In still another embodiment a binding protein comprises a named VH set of 3 CDRs and a correspondingly named VL set of 3 CDRs from the group below. Preferably, a binding protein according to the disclosure~~invention~~ comprises at least two variable domain CDR sets selected from the group of variable domain CDR sets consisting of:

VH A10 CDR Set and VL A10 CDR Set;
VH A10.3 CDR Set and VL A10.3 CDR Set:
VH A10.3A CDR Set and VL A10.3A Set;
VH A10.6B CDR Set and VL A10.6B Set;
VH A10.3D CDR Set and VL A10.3D CDR Set;
VH A10.4C CDR Set and VL A10.4C CDR Set;
VH A10.K30 CDR Set and VL A10.3 CDR Set;
VH A10.K42 CDR Set and VL A10.3 CDR Set;
VH A10.3 CDR Set and VL A10.L45 CDR Set;
VH A10.3 CDR Set and VL A10.L73 CDR Set;
VH A10.9A CDR Set and VL A10.3 CDR Set;
VH A10.8A CDR Set and VL A10.3 CDR Set;
VH A10.1A CDR Set and VL A10.3 CDR Set; and
VH A10.5D CDR Set and VL A10.3 CDR Set.

In yet another embodiment, a binding protein described above further comprises a human acceptor framework. Preferably, the human acceptor framework comprises an amino acid sequence selected from the group consisting of:

heavy chain acceptor framework sequences SEQ ID NOS:6-22,
heavy chain acceptor sequences SEQ ID NOS:35-62,
light chain acceptor sequences SEQ ID NOS:23-34, and
light chain acceptor sequences SEQ ID NOS:63-98.

In another embodiment a binding protein described above comprises a human acceptor framework, which comprises at least one framework region amino acid substitution, wherein the amino acid sequence of the framework is at least 65% identical to the sequence of said human acceptor framework and comprising at least 70 amino acid residues identical to said human acceptor framework.

In another embodiment a binding protein described herein comprises a human acceptor framework that comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;
a glycosylation site residue;
a rare residue;
a residue capable of interacting with human DLL4

a canonical residue;

a contact residue between heavy chain variable region and light chain variable region;

a residue within a Vernier zone; and

a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

Preferably, the key residue is selected from the group consisting of: 2H, 4H, 24H, 26H, 27H, 29H, 34H, 35H, 37H, 39H, 44H, 45H, 47H, 48H, 49H, 50H, 51H, 58H, 59H, 60H, 63H, 67H, 69H, 71H, 73H, 76H, 78H, 91H, 93H, 94H, 2L, 4L, 25L, 29L, 27bL, 33L, 34L, 36L, 38L, 43L, 44L, 46L, 47L, 48L, 49L, 55L, 58L, 62L, 64L, 71L, 87L, 89L, 90L, 91L, 94L, 95L.

In another embodiment, a binding protein described herein comprises a consensus human variable domain.

In a preferred embodiment, a binding protein described above comprises at least one variable domain having amino acid sequence selected from the group consisting of: SEQ ID NOS:112, 113, 316, 327, 317, 318, 319, 320, 321, 322, 323, 330, 324, 331, 325, 332, 326, 333, 328, and 329.

In another embodiment, a binding protein described above comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of: SEQ ID NOS:112 and 113, SEQ ID NOS:316 and 327, SEQ ID NOS:323 and 330, SEQ ID NOS:324 and 331, SEQ ID NOS:325 and 332, and SEQ ID NOS:326 and 333.

In an embodiment, a binding protein according to the disclosure~~invention~~ comprises heavy chain variable domain ($V_H$), preferably wherein the $V_H$ comprises an amino acid sequence selected from the group consisting of:

SEQ ID NOS:112, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, and 326.

In yet another embodiment, a binding protein according to the disclosure~~invention~~ comprises a light chain variable domain (a $V_L$), preferably wherein the $V_L$ comprises an amino acid sequence selected from the group consisting of:

SEQ ID NOS:113, 327, 328, 329, 330, 331, 332, and 333.

In another embodiment, the disclosure~~invention~~ provides a binding protein capable of binding human DLL-4, said binding protein comprising:

an Ig constant heavy region having an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3;

an Ig constant light region having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5;

an Ig variable heavy region having an amino acid sequence selected from the group consisting:

SEQ ID NOS: SEQ ID NOS:112, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, and 326; and

an Ig variable light region having an amino acid sequence selected from the group consisting:

SEQ ID NOS: 113, 327, 328, 329, 330, 331, 332, and 333.

In one embodiment, there is provided a binding protein capable of binding human DLL-4, said binding protein comprising:

an Ig constant heavy region having an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3;

an Ig constant light region having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5;

an Ig variable heavy region having an amino acid sequence selected from the group consisting:

SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360; and

an Ig variable light region having an amino acid sequence selected from the group consisting:

SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

According to the disclosure~~invention~~, variable heavy (VH) domains and variable light (VL) domains of DLL4 binding proteins described herein may also be shuffled using recombinant techniques available in the art to generate and select for additional DLL4 binding proteins that comprise various combinations of VH and VL domains described herein.

In a preferred embodiment, a DLL4 binding protein according to the disclosure~~invention~~ binds human DLL4 (hu DLL4) and at least one other species of DLL4. More preferably, a DLL4 binding protein described herein binds human DLL4 and a DLL4 selected from the group consisting of: a mouse DLL4 (mu DLL4), a cynomolgus monkey DLL4 (cynomolgus DLL4, cyno DLL4), a rat DLL4, and combinations thereof.

In another embodiment, a DLL4 binding protein is a fully human antibody or antigen binding portion thereof.

In another embodiment, a DLL4 binding protein is a CDR grafted antibody. More preferably, a DLL4 binding protein is a CDR-grafted antibody or antigen binding portion thereof comprising one or more CDRs described above.

Still more preferably, the CDR grafted antibody or antigen binding portion thereof comprise a variable domain described above. More preferably, a CDR grafted antibody or antigen binding portion thereof comprises two variable domains described above. Preferably, the CDR grafted antibody or antigen binding portion thereof comprises a human acceptor framework. More preferably, the human acceptor framework is any one of the human acceptor frameworks described above.

More preferably, a binding protein is capable of neutralizing an activity of a DLL4 selected from the group consisting of human DLL4, mouse DLL4, cynomolgus monkey DLL4, rat DLL4, and combinations thereof. Evaluating the neutralization of activity of DLL4 can be assessed via several *in vitro* and *in vivo* assays know in the art. Exemplary parameters for assessing neutralization of DLL4 activity include, but are not limited to, antibodies that inhibit DLL4 interaction with the Notch receptor, and/or Notch-signaling pathway with an $IC_{50}$ values of about at least $10^{-6}$ M; at least $10^{-7}$ M, or at least $10^{-8}$ M.

In one embodiment, the binding protein of the disclosure~~invention~~ has an on rate constant ($K_{ON}$) to DLL4 of at least about $10^2M^{-1}s^{-1}$; at least about $10^3M^{-1}s^{-1}$; at least about $10^4M^{-1}s^{-1}$; at least about $10^5M^{-1}s^{-1}$; or at least about $10^6M^{-1}s^{-1}$, as measured by surface plasmon resonance. Preferably, the binding protein of the disclosure~~invention~~ has an on rate constant ($K_{ON}$) to DLL4 between $10^2M^{-1}s^{-1}$ to $10^3M^{-1}s^{-1}$; between $10^3M^{-1}s^{-1}$ to $10^4M^{-1}s^{-1}$; between $10^4M^{-1}s^{-1}$ to $10^5M^{-1}s^{-1}$; or between $10^5M^{-1}s^{-1}$ to $10^6M^{-1}s^{-1}$, as measured by surface plasmon resonance.

In another embodiment, the binding protein of the ~~invention~~ disclosure has an off rate constant ($K_{OFF}$) for DLL4 of at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; or at most about $10^{-6}s^{-1}$, as measured by surface plasmon resonance. Preferably, the binding protein of the invention has an off rate constant ($K_{off}$) to DLL4 of $10^{-3}s^{-1}$ to $10^{-4}s^{-1}$; of $10^{-4}s^{-1}$ to $10^{-5}s^{-1}$; or of $10^{-5}s^{-1}$ to $10^{-6}s^{-1}$, as measured by surface plasmon resonance.

In another embodiment, the binding protein of the ~~invention~~ disclosure has a dissociation constant ($K_D$) to DLL4 of at most about $10^{-7}$ M; at most about $10^{-8}$ M; at most about $10^{-9}$ M; at most about $10^{-10}$ M; at most about $10^{-11}$ M; at most about $10^{-12}$ M; or at most $10^{-13}$ M. Preferably, the binding protein of the ~~invention~~ disclosure has a dissociation constant ($K_D$) to DLL4 of $10^{-7}$ M to $10^{-8}$ M; of $10^{-8}$ M to $10^{-9}$ M; of $10^{-9}$ M to $10^{-10}$ M; of $10^{-10}$ to $10^{-11}$ M; of $10^{-11}$ M to $10^{-12}$ M; or of $10^{-12}$ to M $10^{-13}$ M.

In one embodiment, there is provided a labeled binding protein comprising a binding protein as defined herein, wherein said binding protein is conjugated to a detectable label.

One embodiment of the ~~invention~~ disclosure provides an antibody construct comprising any one of the DLL4 binding proteins disclosed above and a linker polypeptide or an immunoglobulin constant domain.

In one embodiment, there is provided an antibody construct comprising a binding protein as defined herein and further comprising a linker polypeptide or an immunoglobulin constant domain.

In a preferred embodiment, an antibody construct according to the ~~invention~~ disclosure is selected from the group consisting of: an immunoglobulin molecule, a monoclonal antibody, a chimeric antibody, a CDR-grafted antibody, a humanized antibody, a Fab, a Fab', a $F(ab')_2$, a Fv, a disulfide linked Fv, a scFv, a single domain antibody, a diabody, a multispecific antibody, a dual specific antibody, and a bispecific antibody.

In a preferred embodiment, an antibody construct of the ~~invention~~ disclosure comprises a heavy chain immunoglobulin constant domain selected from the group consisting of a human IgM constant domain, a human IgG1 constant domain, a human IgG2 constant domain, a human IgG3 constant domain, a human IgG4 constant domain, a human IgE constant domain, and a human IgA constant domain, and mutants of the above Ig isotypes which may alter Fc gamma receptor binding, FcRn binding, C1q binding and may alter pharmacokinetic properties and/or Fc effector functions.

In another embodiment, an antibody construct is glycosylated. Preferably, the glycosylation is a human glycosylation pattern.

In another embodiment, a DLL4 binding protein described herein is conjugated to an agent. Binding protein conjugates of the ~~invention~~ disclosure include antibody conjugates in which an antibody construct described herein is conjugated to an agent. Preferably, the agent is selected from the group consisting of: an immunoadhesion molecule, an imaging agent, a therapeutic agent, and a cytotoxic agent.

In one embodiment, there is provided an antibody conjugate comprising an antibody construct as defined herein, wherein said antibody construct is conjugated to a therapeutic or cytotoxic agent.

In a preferred embodiment, the imaging agent is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin. More preferably the imaging agent is a radiolabel selected from the group consisting of: $^{3}H$, $^{14}C$, $^{35}S$, $^{90}Y$, $^{99}Tc$, $^{111}In$, $^{125}I$, $^{131}I$, $^{177}Lu$, $^{166}Ho$, and $^{153}Sm$. In a preferred embodiment, the therapeutic or cytotoxic agent is selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a

cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

In another embodiment, a DLL4 binding protein, an antibody construct, or a binding protein conjugate (including antibody conjugates) disclosed above exists as a crystal. Preferably, the crystal is a carrier-free pharmaceutical controlled release crystal. In a preferred embodiment, such a crystallized binding protein, crystallized antibody construct, or crystallized antibody conjugate has a greater half life *in vivo* than its soluble counterpart. In another preferred embodiment, the crystallized binding protein, crystallized antibody construct, or crystallized binding protein conjugate (including antibody conjugate) retains biological activity after crystallization.

One aspect of the disclosure~~invention~~ pertains to an isolated nucleic acid encoding a DLL4 binding protein, an antibody construct, a DLL4 binding antibody conjugate, or DLL4 binding portion thereof. Particularly preferred is an isolated nucleic acid that encodes a polypeptide selected from the group consisting of: a polypeptide comprising a heavy chain variable domain, wherein the heavy chain variable domain comprises a CDR-H1, a CDR-H2, or a CDR-H3 described above; a polypeptide comprising a light chain variable domain, wherein the light chain variable domain comprises a CDR-L1, a CDR-L2, or a CDR-L3 as described above; or a combination of both polypeptides.

In one embodiment there is provided an isolated nucleic acid encoding a polypeptide selected from the group consisting of: a polypeptide comprising a heavy chain variable domain, wherein the heavy chain variable domain comprises one or more of CDR-H1, a CDR-H2, or a CDR-H3 as defined herein; a polypeptide comprising a light chain variable domain, wherein the light chain variable domain comprises one or more of CDR-L1, a CDR-L2, or a CDR-L3 as defined herein; or a combination of both polypeptides.

A further embodiment provides a vector comprising an isolated nucleic acid disclosed above. In a preferred embodiment, the vector is selected from the group consisting of: pcDNA, pTT (Durocher et al., *Nucl. Acids Res.*, 30(2e9): 1-9 (2002)), pTT3 (pTT with additional multiple cloning sites), pEFBOS (Mizushima et al., *Nucl. Acids. Res.*, 18 (17): 5322 (1990)), pHybE, pBV, pJV, and pBJ, and any other expression vectors suitable for prokaryotic or eukaryotic cells.

In another aspect of the disclosure~~invention~~ there is provided a host cell is transformed with the vector disclosed above. The host cell may be prokaryotic or eukaryotic cell. A preferred prokaryotic host cell is *Escherichia coli*. Preferably, the eukaryotic cell is selected from the group consisting of: a protist cell, an animal cell, a plant cell, and a fungal cell. More preferably, the host cell is a mammalian cell including, but not limited to, CHO and COS cells. A preferred fungal cell is, but not limited to, *Saccharomyces cerevisiae*. A preferred insect cell is an Sf9 cell.

Another aspect of the disclosure~~invention~~ provides a method of producing a binding protein that binds human DLL4 comprising the step of culturing any one of the host cells disclosed above in a culture medium under conditions sufficient to produce a binding protein that binds human DLL4. Another embodiment provides a binding protein produced according to the method disclosed above.

One embodiment provides a composition for the release of a DLL4 binding protein according to the disclosure~~invention~~ wherein the composition comprises a formulation which in turn

comprises a crystallized DLL4 binding protein, crystallized antibody construct, or crystallized binding protein conjugate (including antibody conjugates) as disclosed above and an ingredient, and further at least one polymeric carrier. Preferably, the polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutryate), poly (caprolactone), poly (dioxanone); poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo)phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polyeaccharides, blends and copolymers thereof. Preferably the ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

Another embodiment provides a method for treating a mammal comprising the step of administering to the mammal an effective amount of a composition comprising a crystallized DLL4 binding protein, a crystallized antibody construct, or a crystallized protein conjugate (including antibody conjugates) disclosed above.

The disclosure~~invention~~ also provides a pharmaceutical composition comprising a DLL4 binding protein, an antibody construct, or a binding protein conjugate (including antibody conjugates) as disclosed above and a pharmaceutically acceptable carrier. In a further embodiment, the pharmaceutical composition comprises at least one additional agent. The additional agent may be a therapeutic agent for treating a disorder in which DLL4 is detrimental. Preferably, a pharmaceutical composition comprises an additional agent selected from the group consisting of: a therapeutic agent; an imaging agent; an antineoplastic agent; a chemtherapeutic agent (such as a DNA alkylating agent, cisplatin, carboplatin, an anti-tubulin agent, paclitaxel, docetaxel, doxorubicin, gemcitabine, gemzar, an anthracycline, adriamycin, a topoisiomersase I inhibitor, a topoisomerase II inhibitor, 5-fluorouracil (5-FU), leucovorin, irinotecan), and a receptor tyrosine kinase inhibitors (e.g., erlotinib, gefitinib), a COX-2 inhibitor (e.g., celecoxib), a kinase inhibitor, and an angiogenesis inhibitor (including but not limited to an anti-VEGF antibody or VEGF-trap); a co-stimulation molecule blocker (including but not limited to anti-B7.1 antibody, anti-B7.2 antibody, CTLA4-Ig, anti-CD20 antibody); an adhesion molecule blocker (including but not limited to an anti-LFA-1 antibody, an anti-E/L selectin antibody, and a small molecule inhibitor); anti-cytokine antibody or functional fragment thereof (including but not limited to an anti-IL-18, an anti-TNF, and an anti-IL-6/cytokine receptor antibody); methotrexate; cyclosporine; rapamycin; FK506; a detectable label or reporter molecule; a TNF antagonist; an antirheumatic; a muscle relaxant; a narcotic; a non-steroid anti-inflammatory drug (NSAID); an analgesic; an anesthetic; a sedative; a local anesthetic; a neuromuscular blocker; an antimicrobial agent; an

antipsoriatic agent; a corticosteroid; an anabolic steroid; an erythropoietin; an immunization; an immunoglobulin; an immunosuppressive agent; a growth hormone; a hormone replacement drug; a radiopharmaceutical drug; an antidepressant; an antipsychotic drug; a stimulant; an asthma medication; a beta agonist; an inhaled steroid; an epinephrine or analog thereof; a cytokine; and a cytokine antagonist.

In another aspect, the disclosure~~invention~~ provides a method for inhibiting human DLL4 activity comprising contacting human DLL4 with a binding protein disclosed above such that human DLL4 is inhibited or neutralized. In a related aspect, the invention provides a method for inhibiting DLL4 activity in a human subject suffering from a disorder in which DLL4 is detrimental, comprising administering to the human subject a binding protein disclosed above such that human DLL4 in the human subject is inhibited and treatment is achieved. Preferably, the disorder is selected from the group comprising primary and metastatic cancers, including carcinomas of breast, colon, rectum, lung, oropharynx, hypopharynx, esophagus, stomach, pancreas, liver, gallbladder and bile ducts, small intestine, urinary tract (including kidney, bladder, and urothelium), female genital tract (including cervix, uterus, and ovaries as well as choriocarcinoma and gestational trophoblastic disease), male genital tract (including prostate, seminal vesicles, testes, and germ cell tumors), endocrine glands (including the thyroid, adrenal, and pituitary glands), and skin, as well as hemangiomas, melanomas, sarcomas (including those arising from bone and soft tissues as well as Kaposi's sarcoma), tumors of the brain, nerves, eyes, and meninges (including astrocytomas, gliomas, glioblastomas, retinoblastomas, neuromas, neuroblastomas, Schwannomas, and meningiomas), solid tumors arising from hematopoietic malignancies such as leukemias and lymphomas (both Hodgkin's and non-Hodgkin's lymphomas), tumor metastases, ocular neovascularization (including diabetic blindness, retinopathies, age-induced macular degeneration and rubeosis), edema, rheumatoid arthritis, multiple sclerosis, atheroscleorotic plaques, Crohn's disease, inflammatory bowel disease, refractory ascites, psoriasis, sarcoidosis, arterial arteriosclerosis, sepsis, peptic ulcers, burns, and pancreatitis, polycystic ovarian disease (POD), endometriosis, uterine fibroids, benign prostate hypertrophy, and other angiogenesis independent and dependent diseases characterized by abberant DLL4 activity.

In another aspect the disclosure~~invention~~ provides a method of treating a patient suffering from a disorder in which human DLL4 is detrimental comprising the step of administering any one of the binding proteins disclosed above before, concurrent, or after the administration of a second agent, as discussed above. In a preferred embodiment, the second agent is selected from the group consisting of: radiotherapeutic agent; an antineoplastic agent; a chemotherapeutic agent (such as a DNA alkylating agent, cisplatin, carboplatin, an anti-tubulin agent, paclitaxel, docetaxel, taxol, doxorubicin, gemcitabine, gemzar, an anthracycline, adriamycin, a topoisomerase I inhibitor, a topoisomerase II inhibitor, 5-fluorouracil (5-FU), leucovorin, irinotecan), a receptor tyrosine

kinase inhibitor (e.g., erlotinib, gefitinib), a COX-2 inhibitor (e.g., celecoxib), a kinase inhibitor, and an angiogenesis inhibitor (including but not limited to an anti-VEGF antibody or VEGF-trap); a co-stimulation molecule blocker (including but not limited to anti-B7.1, anti-B7.2, CTLA4-Ig, anti-CD20); an adhesion molecule blocker (including but not limited to an anti-LFA-1 antibody, an anti-E/L selectin antibody, a small molecule inhibitor); anti-cytokine antibody or functional fragment thereof (including but not limited to anti-IL-18, anti-TNF, anti-IL-6/cytokine receptor antibodies); methotrexate; cyclosporine; rapamycin; FK506; detectable label or reporter; a TNF antagonist; an antirheumatic; a muscle relaxant; a narcotic; a non-steroid anti-inflammatory drug (NSAID); an analgesic; an anesthetic; a sedative; a local anesthetic; a neuromuscular blocker; an antimicrobial agent; an antipsoriatic drug; a corticosteroid; an anabolic steroid; an erythropoietin; an immunization; an immunoglobulin; an immunosuppressive agent; a growth hormone; a hormone replacement drug; a radiopharmaceutical drug; an antidepressant; an antipsychotic drug; a stimulant; an asthma medication; a beta agonist; an inhaled steroid; an epinephrine or analog thereof; a cytokine; and a cytokine antagonist.

In one embodiment, there is provided the use of the binding protein as defined herein, in the manufacture of a pharmaceutical composition for reducing human DLL4 activity.

In one embodiment, there is provided the use of the binding protein as defined herein, in the manufacture of a pharmaceutical composition for reducing human DLL4 activity in a human subject suffering from a disorder in which DLL4 activity is detrimental.

In one embodiment, there is provided the use of the binding protein as defined herein, in the manufacture of a pharmaceutical composition for treating a patient suffering from a disorder in which DLL4 is detrimental, wherein said composition is for administration before, concurrent with, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an antibody or fragment thereof capable of binding human VEGFR2; methotrexate; an antibody, or fragment thereof, capable of binding human TNF; corticosteroids, cyclosporine, rapamycin, FK506, and non-steroidal anti-inflammatory agents.

In a preferred embodiment, the pharmaceutical compositions disclosed above are administered to the subject by at least one mode selected from the group consisting of: parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, and transdermal.

Another aspect of the disclosure~~invention~~ provides at least one DLL4 anti-idiotype antibody to at least one DLL4 binding protein of the present disclosure~~invention~~. The anti-idiotype antibody includes any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule such as, but not limited to, at least one complementarily determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, and any portion thereof, that can be incorporated into a binding protein of the present disclosure~~invention~~.

Any of a variety of immunodetection assay formats may be adapted to employ a DLL4 binding protein of the disclosure~~invention~~ to detect DLL4 in a mixture, solution, or biological sample. Such immunodetection assay formats include but are not limited to radioimmunoassay (RIA), immunoprecipitation, enzyme-linked immunosorbent assay (ELISA), immunoblot (e.g, Western), immunostrips (e.g., immunodipsticks) comprising a DLL4 binding protein of the disclosure~~invention~~ adsorbed or immobilized to substrate, FACS, and the like. Detection of DLL4 using a DLL4 binding protein of the disclosure~~invention~~ may be conducted *in vitro* on a mixture, solution, or in biological sample. A biological sample that may be contacted with binding protein of the invention to detect

What is claimed is:

1. A binding protein comprising an antigen binding domain capable of binding human DLL4, said antigen binding domain comprising at least one or more CDRs selected from the group consisting of:

CDR-H1: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$ (SEQ ID NO:99), wherein;
$X_1$ is S or N;
$X_2$ is S, G, or N;
$X_3$ is S, N, T, G, or R;
$X_4$ is Y;
$X_5$ is Y or H;
$X_6$ is W; and
$X_7$ is G;

CDR-H2: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$-$X_{11}$-$X_{12}$-$X_{13}$-$X_{14}$-$X_{15}$-$X_{16}$ (SEQ ID NO:100), wherein;
$X_1$ is D;
$X_2$ is I;
$X_3$ is Y, N, or S;
$X_4$ is Y;
$X_5$ is T, N, A, I, S, or R;
$X_6$ is G;
$X_7$ is S, N, T, or G;
$X_8$ is T;
$X_9$ is Y;
$X_{10}$ is Y;
$X_{11}$ is N;
$X_{12}$ is P;
$X_{13}$ is S;
$X_{14}$ is L;
$X_{15}$ is K; and
$X_{16}$ is S, N, D, or G;

CDR-H3: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$-$X_{11}$ (SEQ ID NO:101), wherein;
$X_1$ is E, Y, F, Q, W, L, or A;
$X_2$ is D, A, S, G, V, E, or N;
$X_3$ is V, M, L, P, or A;
$X_4$ is I, A, P, R, S, K, Q, V, G, M, or E;
$X_5$ is L, Y, F, or M;

$X_6$ is R, G, S, Q, or A;
$X_7$ is G;
$X_8$ is G, A, or S;
$X_9$ is S, A, L, V, R, or G;
$X_{10}$ is D; and
$X_{11}$ is Y, D, S, N, H, E, R, L, P, C, I, M, T, Q, or K;

CDR-L1: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$-$X_{11}$ (SEQ ID NO:102), wherein;
$X_1$ is S;
$X_2$ is G;
$X_3$ is Q, E, or D;
$X_4$ is R, S, G, M, K, L, or T;
$X_5$ is L;
$X_6$ is G;
$X_7$ is D or E;
$X_8$ is K;
$X_9$ is Y;
$X_{10}$ is A or V; and
$X_{11}$ is S;

CDR-L2: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$ (SEQ ID NO:103), wherein;
$X_1$ is E or Q;
$X_2$ is D;
$X_3$ is S, L, T, A, E, or F;
$X_4$ is K, T, E, N, Q, S, or M;
$X_5$ is R;
$X_6$ is P; and
$X_7$ is S;

and

CDR-L3: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$ (SEQ ID NO:104), wherein;
$X_1$ is Q;
$X_2$ is A;
$X_3$ is W;
$X_4$ is D;
$X_5$ is R, S, M, E, N, G, or K;
$X_6$ is D or E;
$X_7$ is T, V, A, S, or M;

$X_8$ is G, A, or C; and
$X_9$ is V.

2. The binding protein according to claim 1, wherein said at least one CDR comprises an amino acid sequence selected from the group consisting of:
residues 31-37 of SEQ ID NO:1 (CDR-H1); residues 52-67 of SEQ ID NO:1 (CDR-H2); residues 100-110 of SEQ ID NO:1 (CDR-H3);
residues 23-33 of SEQ ID NO:111 (CDR-L1); residues 49-55 of SEQ ID NO:111 (CDR-L2); residues 88-96 of SEQ ID NO:111 (CDR-L3);
SEQ ID NO:117 (CDR-H1); SEQ ID NO:118 (CDR-H2); SEQ ID NO:119 (CDR-H3);
SEQ ID NO:121 (CDR-H1); SEQ ID NO:122 (CDR-H2); SEQ ID NO:123 (CDR-H3);
SEQ ID NO:125 (CDR-H1); SEQ ID NO:126 (CDR-H2); SEQ ID NO:127 (CDR-H3);
SEQ ID NO:129 (CDR-H1); SEQ ID NO:130 (CDR-H2); SEQ ID NO:131 (CDR-H3);
SEQ ID NO:133 (CDR-H1); SEQ ID NO:134 (CDR-H2); SEQ ID NO:135 (CDR-H3);
SEQ ID NO:137 (CDR-H1); SEQ ID NO:138 (CDR-H2); SEQ ID NO:139 (CDR-H3);
SEQ ID NO:141 (CDR-H1); SEQ ID NO:142 (CDR-H2); SEQ ID NO:143 (CDR-H3);
SEQ ID NO:145 (CDR-H1); SEQ ID NO:146 (CDR-H2); SEQ ID NO:147 (CDR-H3);
SEQ ID NO:149 (CDR-H1); SEQ ID NO:150 (CDR-H2); SEQ ID NO:151 (CDR-H3);
SEQ ID NO:153 (CDR-H1); SEQ ID NO:154 (CDR-H2); SEQ ID NO:155 (CDR-H3);
SEQ ID NO:157 (CDR-H1); SEQ ID NO:158 (CDR-H2); SEQ ID NO:159 (CDR-H3);
SEQ ID NO:161 (CDR-H1); SEQ ID NO:162 (CDR-H2); SEQ ID NO:163 (CDR-H3);
SEQ ID NO:165 (CDR-H1); SEQ ID NO:166 (CDR-H2); SEQ ID NO:167 (CDR-H3);
SEQ ID NO:169 (CDR-H1); SEQ ID NO:170 (CDR-H2); SEQ ID NO:171 (CDR-H3);
SEQ ID NO:173 (CDR-H1); SEQ ID NO:174 (CDR-H2); SEQ ID NO:175 (CDR-H3);
SEQ ID NO:177 (CDR-H1); SEQ ID NO:178 (CDR-H2); SEQ ID NO:179 (CDR-H3);
SEQ ID NO:181 (CDR-H1); SEQ ID NO:182 (CDR-H2); SEQ ID NO:183 (CDR-H3);
SEQ ID NO:185 (CDR-H1); SEQ ID NO:186 (CDR-H2); SEQ ID NO:187 (CDR-H3);
SEQ ID NO:189 (CDR-H1); SEQ ID NO:190 (CDR-H2); SEQ ID NO:191 (CDR-H3);
SEQ ID NO:193 (CDR-H1); SEQ ID NO:194 (CDR-H2); SEQ ID NO:195 (CDR-H3);
SEQ ID NO:197 (CDR-H1); SEQ ID NO:198 (CDR-H2); SEQ ID NO:199 (CDR-H3);
SEQ ID NO:201 (CDR-H1); SEQ ID NO:202 (CDR-H2); SEQ ID NO:203 (CDR-H3);
SEQ ID NO:205 (CDR-H1); SEQ ID NO:206 (CDR-H2); SEQ ID NO:207 (CDR-H3);
SEQ ID NO:209 (CDR-H1); SEQ ID NO:210 (CDR-H2); SEQ ID NO:211 (CDR-H3);
SEQ ID NO:213 (CDR-H1); SEQ ID NO:214 (CDR-H2); SEQ ID NO:215 (CDR-H3);
SEQ ID NO:217 (CDR-L1); SEQ ID NO:218 (CDR-L2); SEQ ID NO:219 (CDR-L3);
SEQ ID NO:221 (CDR-L1); SEQ ID NO:222 (CDR-L2); SEQ ID NO:223 (CDR-L3);
SEQ ID NO:225 (CDR-L1); SEQ ID NO:226 (CDR-L2); SEQ ID NO:227 (CDR-L3);

SEQ ID NO:229 (CDR-L1); SEQ ID NO:230 (CDR-L2); SEQ ID NO:231 (CDR-L3); SEQ ID NO:233 (CDR-L1); SEQ ID NO:234 (CDR-L2); SEQ ID NO:235 (CDR-L3); SEQ ID NO:237 (CDR-L1); SEQ ID NO:238 (CDR-L2); SEQ ID NO:239 (CDR-L3); SEQ ID NO:241 (CDR-L1); SEQ ID NO:242 (CDR-L2); SEQ ID NO:243 (CDR-L3); SEQ ID NO:245 (CDR-L1); SEQ ID NO:246 (CDR-L2); SEQ ID NO:247 (CDR-L3); SEQ ID NO:249 (CDR-L1); SEQ ID NO:250 (CDR-L2); SEQ ID NO:251 (CDR-L3); SEQ ID NO:253 (CDR-L1); SEQ ID NO:254 (CDR-L2); SEQ ID NO:255 (CDR-L3); SEQ ID NO:257 (CDR-L1); SEQ ID NO:258 (CDR-L2); SEQ ID NO:259 (CDR-L3); SEQ ID NO:261 (CDR-L1); SEQ ID NO:262 (CDR-L2); SEQ ID NO:263 (CDR-L3); SEQ ID NO:265 (CDR-L1); SEQ ID NO:266 (CDR-L2); SEQ ID NO:267 (CDR-L3); SEQ ID NO:269 (CDR-L1); SEQ ID NO:270 (CDR-L2); SEQ ID NO:271 (CDR-L3); SEQ ID NO:273 (CDR-L1); SEQ ID NO:274 (CDR-L2); SEQ ID NO:275 (CDR-L3); SEQ ID NO:277 (CDR-L1); SEQ ID NO:278 (CDR-L2); SEQ ID NO:279 (CDR-L3); SEQ ID NO:281 (CDR-L1); SEQ ID NO:282 (CDR-L2); SEQ ID NO:283 (CDR-L3); SEQ ID NO:285 (CDR-L1); SEQ ID NO:286 (CDR-L2); SEQ ID NO:287 (CDR-L3); SEQ ID NO:289 (CDR-L1); SEQ ID NO:290 (CDR-L2); SEQ ID NO:291 (CDR-L3); SEQ ID NO:293 (CDR-L1); SEQ ID NO:294 (CDR-L2); SEQ ID NO:295 (CDR-L3); SEQ ID NO:297 (CDR-L1); SEQ ID NO:298 (CDR-L2); SEQ ID NO:299 (CDR-L3); SEQ ID NO:301 (CDR-L1); SEQ ID NO:302 (CDR-L2); SEQ ID NO:303 (CDR-L3); SEQ ID NO:305 (CDR-L1); SEQ ID NO:306 (CDR-L2); SEQ ID NO:307 (CDR-L3); SEQ ID NO:309 (CDR-L1); SEQ ID NO:310 (CDR-L2); SEQ ID NO:311 (CDR-L3); SEQ ID NO:313 (CDR-L1); SEQ ID NO:314 (CDR-L2); SEQ ID NO:315 (CDR-L3);

residues 31-37 of SEQ ID NO:334 (CDR-H1); residues 52-67 of SEQ ID NO:334 (CDR-H2); residues 100-110 of SEQ ID NO:334 (CDR-H3);

residues 23-33 of SEQ ID NO:335 (CDR-L1); residues 49-55 of SEQ ID NO:335 (CDR-L2); residues 88-96 of SEQ ID NO:335 (CDR-L3);

residues 31-37 of SEQ ID NO:336 (CDR-H1); residues 52-67 of SEQ ID NO:336 (CDR-H2); residues 100-110 of SEQ ID NO:336 (CDR-H3);

residues 23-33 of SEQ ID NO:337 (CDR-L1); residues 49-55 of SEQ ID NO:337 (CDR-L2); residues 88-96 of SEQ ID NO:337 (CDR-L3);

residues 31-37 of SEQ ID NO:338 (CDR-H1); residues 52-67 of SEQ ID NO:338 (CDR-H2); residues 100-110 of SEQ ID NO:338 (CDR-H3);

residues 23-33 of SEQ ID NO:339 (CDR-L1); residues 49-55 of SEQ ID NO:339 (CDR-L2); residues 88-96 of SEQ ID NO:339 (CDR-L3);

residues 31-37 of SEQ ID NO:340 (CDR-H1); residues 52-67 of SEQ ID NO:340 (CDR-H2); residues 100-110 of SEQ ID NO:340 (CDR-H3);

residues 23-33 of SEQ ID NO:341 (CDR-L1); residues 49-55 of SEQ ID NO:341 (CDR-L2); residues 88-96 of SEQ ID NO:341 (CDR-L3);
residues 31-37 of SEQ ID NO:342 (CDR-H1); residues 52-67 of SEQ ID NO:342 (CDR-H2); residues 100-110 of SEQ ID NO:342 (CDR-H3);
residues 23-33 of SEQ ID NO:343 (CDR-L1); residues 49-55 of SEQ ID NO:343 (CDR-L2); residues 88-96 of SEQ ID NO:343 (CDR-L3);
residues 31-37 of SEQ ID NO:344 (CDR-H1); residues 52-67 of SEQ ID NO:344 (CDR-H2); residues 100-110 of SEQ ID NO:344 (CDR-H3);
residues 24-34 of SEQ ID NO:345 (CDR-L1); residues 50-56 of SEQ ID NO:345 (CDR-L2); residues 89-97 of SEQ ID NO:345 (CDR-L3);
residues 31-37 of SEQ ID NO:346 (CDR-H1); residues 52-67 of SEQ ID NO:346 (CDR-H2); residues 100-110 of SEQ ID NO:346 (CDR-H3);
residues 23-33 of SEQ ID NO:347 (CDR-L1); residues 49-55 of SEQ ID NO:347 (CDR-L2); residues 88-96 of SEQ ID NO:347 (CDR-L3);
residues 31-37 of SEQ ID NO:348 (CDR-H1); residues 52-67 of SEQ ID NO:348 (CDR-H2); residues 100-110 of SEQ ID NO:348 (CDR-H3);
residues 24-34 of SEQ ID NO:349 (CDR-L1); residues 50-56 of SEQ ID NO:349 (CDR-L2); residues 89-97 of SEQ ID NO:349 (CDR-L3);
residues 31-37 of SEQ ID NO:350 (CDR-H1); residues 52-67 of SEQ ID NO:350 (CDR-H2); residues 100-110 of SEQ ID NO:350 (CDR-H3);
residues 24-34 of SEQ ID NO:351 (CDR-L1); residues 50-56 of SEQ ID NO:351 (CDR-L2); residues 89-97 of SEQ ID NO:351 (CDR-L3);
residues 31-37 of SEQ ID NO:352 (CDR-H1); residues 52-67 of SEQ ID NO:352 (CDR-H2); residues 100-110 of SEQ ID NO:352 (CDR-H3);
residues 24-34 of SEQ ID NO:353 (CDR-L1); residues 50-56 of SEQ ID NO:353 (CDR-L2); residues 89-97 of SEQ ID NO:353 (CDR-L3);
residues 31-37 of SEQ ID NO:354 (CDR-H1); residues 52-67 of SEQ ID NO:354 (CDR-H2); residues 100-110 of SEQ ID NO:354 (CDR-H3);
residues 24-34 of SEQ ID NO:355 (CDR-L1); residues 50-56 of SEQ ID NO:355 (CDR-L2); residues 89-97 of SEQ ID NO:355 (CDR-L3);
residues 31-37 of SEQ ID NO:356 (CDR-H1); residues 52-67 of SEQ ID NO:356 (CDR-H2); residues 100-110 of SEQ ID NO:356 (CDR-H3);
residues 23-33 of SEQ ID NO:357 (CDR-L1); residues 49-55 of SEQ ID NO:357 (CDR-L2); residues 88-96 of SEQ ID NO:357 (CDR-L3);
residues 31-37 of SEQ ID NO:358 (CDR-H1); residues 52-67 of SEQ ID NO:358 (CDR-H2); residues 100-110 of SEQ ID NO:358 (CDR-H3);

residues 23-33 of SEQ ID NO:359 (CDR-L1); residues 49-55 of SEQ ID NO:359 (CDR-L2); residues 88-96 of SEQ ID NO:359 (CDR-L3);
residues 31-37 of SEQ ID NO:360 (CDR-H1); residues 52-67 of SEQ ID NO:360 (CDR-H2); residues 100-110 of SEQ ID NO:360 (CDR-H3);
residues 23-33 of SEQ ID NO:361 (CDR-L1); residues 49-55 of SEQ ID NO:361 (CDR-L2); residues 88-96 of SEQ ID NO:361 (CDR-L3).

3. The binding protein according to claim 2, wherein said binding protein comprises at least 3 CDRs.

4. The binding protein according to claim 3, wherein said at least 3 CDRs comprises a variable domain CDR set selected from the group consisting of:

VH E9 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:1
CDR-H2: residues 52-67 of SEQ ID NO:1
CDR-H3 residues 100-110 of SEQ ID NO:1

VL E9 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:111
CDR-L2: residues 49-55 of SEQ ID NO:111
CDR-L3: residues 88-96 of SEQ ID NO:111

VH E9.4 CDR Set

CDR-H1: SEQ ID NO:117
CDR-H2: SEQ ID NO:118
CDR-H3: SEQ ID NO:119

VL E9.4 CDR Set

CDR-L1: SEQ ID NO:229
CDR-L2: SEQ ID NO:230
CDR-L3: SEQ ID NO:231

VH E9.11 CDR Set

CDR-H1: SEQ ID NO:121
CDR-H2: SEQ ID NO:122
CDR-H3: SEQ ID NO:123

VL E9.11 CDR Set

CDR-L1: SEQ ID NO:233
CDR-L2: SEQ ID NO:234
CDR-L3: SEQ ID NO:235

VH E9.14 CDR Set

CDR-H1: SEQ ID NO:125

CDR-H2: SEQ ID NO:126

CDR-H3: SEQ ID NO:127

VL E9.14 CDR Set

CDR-L1: SEQ ID NO:237

CDR-L2: SEQ ID NO:238

CDR-L3: SEQ ID NO:239

VH E9.17 CDR Set

CDR-H1: SEQ ID NO:129

CDR-H2: SEQ ID NO:130

CDR-H3: SEQ ID NO:131

VL E9.17 CDR Set

CDR-L1: SEQ ID NO:241

CDR-L2: SEQ ID NO:242

CDR-L3: SEQ ID NO:243

VH E9.18 CDR Set

CDR-H1: SEQ ID NO:133

CDR-H2: SEQ ID NO:134

CDR-H3: SEQ ID NO:135

VL E9.18 CDR Set

CDR-L1: SEQ ID NO:245

CDR-L2: SEQ ID NO:246

CDR-L3: SEQ ID NO:247

VH E9.19 CDR Set

CDR-H1: SEQ ID NO:137

CDR-H2: SEQ ID NO:138

CDR-H3: SEQ ID NO:139

VL E9.19 CDR Set

CDR-L1: SEQ ID NO:249

CDR-L2: SEQ ID NO:250

CDR-L3: SEQ ID NO:251

VH E9.22 CDR Set

CDR-H1: SEQ ID NO:141

CDR-H2: SEQ ID NO:142

CDR-H3: SEQ ID NO:143

VL E9.22 CDR Set

CDR-L1: SEQ ID NO:253

CDR-L2: SEQ ID NO:254

CDR-L3: SEQ ID NO:255

VH E9.48 CDR Set

CDR-H1: SEQ ID NO:145

CDR-H2: SEQ ID NO:146

CDR-H3: SEQ ID NO:147

VL E9.48 CDR Set

CDR-L1: SEQ ID NO:257

CDR-L2: SEQ ID NO:258

CDR-L3: SEQ ID NO:259

VH E9.65 CDR Set

CDR-H1: SEQ ID NO:149

CDR-H2: SEQ ID NO:150

CDR-H3: SEQ ID NO:151

VL E9.65 CDR Set

CDR-L1: SEQ ID NO:261

CDR-L2: SEQ ID NO:262

CDR-L3: SEQ ID NO:263

VH E9.66 CDR Set

CDR-H1: SEQ ID NO:153

CDR-H2: SEQ ID NO:154

CDR-H3: SEQ ID NO:155

VL E9.66 CDR Set

CDR-L1: SEQ ID NO:265

CDR-L2: SEQ ID NO:266

CDR-L3: SEQ ID NO:267

VH E9.71 CDR Set

CDR-H1: SEQ ID NO:157

CDR-H2: SEQ ID NO:158

CDR-H3: SEQ ID NO:159

VL E9.71 CDR Set

CDR-L1: SEQ ID NO:269

CDR-L2: SEQ ID NO:270

CDR-L3: SEQ ID NO:271

VH E9.13 CDR Set

CDR-H1: SEQ ID NO:161

CDR-H2: SEQ ID NO:162

CDR-H3: SEQ ID NO:163

VL E9.13 CDR Set

CDR-L1: SEQ ID NO:217

CDR-L2: SEQ ID NO:218

CDR-L3: SEQ ID NO:219

VH E9.16 CDR Set

CDR-H1: SEQ ID NO:165

CDR-H2: SEQ ID NO:166

CDR-H3: SEQ ID NO:167

VL E9.16 CDR Set

CDR-L1: SEQ ID NO:221

CDR-L2: SEQ ID NO:222

CDR-L3: SEQ ID NO:223

VH E9.38 CDR Set

CDR-H1: SEQ ID NO:169

CDR-H2: SEQ ID NO:170

CDR-H3: SEQ ID NO:171

VL E9.38 CDR Set

CDR-L1: SEQ ID NO:225

CDR-L2: SEQ ID NO:226

CDR-L3: SEQ ID NO:227

VH E9.2B CDR Set

CDR-H1: SEQ ID NO:173

CDR-H2: SEQ ID NO:174

CDR-H3: SEQ ID NO:175

VL E9.2B CDR Set

CDR-L1: SEQ ID NO:273

CDR-L2: SEQ ID NO:274

CDR-L3: SEQ ID NO:275

VH E9.1F CDR Set

CDR-H1: SEQ ID NO:177

CDR-H2: SEQ ID NO:178

CDR-H3: SEQ ID NO:179

VL E9.1F CDR Set

CDR-L1: SEQ ID NO:277

CDR-L2: SEQ ID NO:278

CDR-L3: SEQ ID NO:279

VH E9.10H CDR Set

CDR-H1: SEQ ID NO:181

CDR-H2: SEQ ID NO:182

CDR-H3: SEQ ID NO:183

VL E9.10H CDR Set

CDR-L1: SEQ ID NO:301

CDR-L2: SEQ ID NO:302

CDR-L3: SEQ ID NO:303

VH E9.5E CDR Set

CDR-H1: SEQ ID NO:185

CDR-H2: SEQ ID NO:186

CDR-H3: SEQ ID NO:187

VL E9.5E CDR Set

CDR-L1: SEQ ID NO:293

CDR-L2: SEQ ID NO:294

CDR-L3: SEQ ID NO:295

VH E9.10C CDR Set

CDR-H1: SEQ ID NO:189

CDR-H2: SEQ ID NO:190

CDR-H3: SEQ ID NO:191

VL E9.10C CDR Set

CDR-L1: SEQ ID NO:281

CDR-L2: SEQ ID NO:282

CDR-L3: SEQ ID NO:283

VH E9.7E CDR Set

CDR-H1: SEQ ID NO:193

CDR-H2: SEQ ID NO:194

CDR-H3: SEQ ID NO:195

VL E9.7E CDR Set

CDR-L1: SEQ ID NO:289

CDR-L2: SEQ ID NO:290

CDR-L3: SEQ ID NO:291

VH E9.12B CDR Set

CDR-H1: SEQ ID NO:197

CDR-H2: SEQ ID NO:198

CDR-H3: SEQ ID NO:199

VL E9.12B CDR Set

CDR-L1: SEQ ID NO:297

CDR-L2: SEQ ID NO:298

CDR-L3: SEQ ID NO:299

VH E9.10E CDR Set

CDR-H1: SEQ ID NO:201

CDR-H2: SEQ ID NO:202

CDR-H3: SEQ ID NO:203

VL E9.10E CDR Set

CDR-L1: SEQ ID NO:285

CDR-L2: SEQ ID NO:286

CDR-L3: SEQ ID NO:287

VH E9.6A CDR Set

CDR-H1: SEQ ID NO:205

CDR-H2: SEQ ID NO:206

CDR-H3: SEQ ID NO:207

VL E9.6A CDR Set

CDR-L1: SEQ ID NO:305

CDR-L2: SEQ ID NO:306

CDR-L3: SEQ ID NO:307

VH E9.7A CDR Set

CDR-H1: SEQ ID NO:209

CDR-H2: SEQ ID NO:210

CDR-H3: SEQ ID NO:211

VL E9.7A CDR Set

CDR-L1: SEQ ID NO:309

CDR-L2: SEQ ID NO:310

CDR-L3: SEQ ID NO:311

VH E9.8H CDR Set

CDR-H1: SEQ ID NO:213

CDR-H2: SEQ ID NO:214

CDR-H3: SEQ ID NO:215

VL E9.8H CDR Set

CDR-L1: SEQ ID NO:313

CDR-L2: SEQ ID NO:314

CDR-L3: SEQ ID NO:315

VH E9.1 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:334

CDR-H2: residues 52-67 of SEQ ID NO:334

CDR-H3: residues 100-110 of SEQ ID NO:334

VL E9.1 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:335

CDR-L2: residues 49-55 of SEQ ID NO:335

CDR-L3: residues 88-96 of SEQ ID NO:335

VH E9-SE1 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:336

CDR-H2: residues 52-67 of SEQ ID NO:336

CDR-H3: residues 100-110 of SEQ ID NO:336

VL E9-SE1 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:337

CDR-L2: residues 49-55 of SEQ ID NO:337

CDR-L3: residues 88-96 of SEQ ID NO:337

VH E9-SE2 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:338

CDR-H2: residues 52-67 of SEQ ID NO:338

CDR-H3: residues 100-110 of SEQ ID NO:338

VL E9-SE2 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:339

CDR-L2: residues 49-55 of SEQ ID NO:339

CDR-L3: residues 88-96 of SEQ ID NO:339

VH E9-SE3 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:340

CDR-H2: residues 52-67 of SEQ ID NO:340

CDR-H3: residues 100-110 of SEQ ID NO:340

VL E9-SE3 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:341

CDR-L2: residues 49-55 of SEQ ID NO:341

CDR-L3: residues 88-96 of SEQ ID NO:341

VH E9-SE4 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:342

CDR-H2: residues 52-67 of SEQ ID NO:342

CDR-H3: residues 100-110 of SEQ ID NO:342

VL E9-SE4 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:343

CDR-L2: residues 49-55 of SEQ ID NO:343

CDR-L3: residues 88-96 of SEQ ID NO:343

VH E9-SE5 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:344

CDR-H2: residues 52-67 of SEQ ID NO:344

CDR-H3: residues 100-110 of SEQ ID NO:344

VL E9-SE5 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:345

CDR-L2: residues 50-56 of SEQ ID NO:345

CDR-L3: residues 89-97 of SEQ ID NO:345

VH E9-SE6 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:346

CDR-H2: residues 52-67 of SEQ ID NO:346

CDR-H3: residues 100-110 of SEQ ID NO:346

VL E9-SE6 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:347

CDR-L2: residues 49-55 of SEQ ID NO:347

CDR-L3: residues 88-96 of SEQ ID NO:347

VH E9-SE7 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:348

CDR-H2: residues 52-67 of SEQ ID NO:348

CDR-H3: residues 100-110 of SEQ ID NO:348

VL E9-SE7 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:349

CDR-L2: residues 50-56 of SEQ ID NO:349

CDR-L3: residues 89-97 of SEQ ID NO:349

VH E9-SE8 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:350

CDR-H2: residues 52-67 of SEQ ID NO:350

CDR-H3: residues 100-110 of SEQ ID NO:350

VL E9-SE8 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:351

CDR-L2: residues 50-56 of SEQ ID NO:351

CDR-L3: residues 89-97 of SEQ ID NO:351

VH E9-FR1 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:352

CDR-H2: residues 52-67 of SEQ ID NO:352

CDR-H3: residues 100-110 of SEQ ID NO:352

VL E9-FR1 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:353

CDR-L2: residues 50-56 of SEQ ID NO:353

CDR-L3: residues 89-97 of SEQ ID NO:353

VH E9-FR2 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:354

CDR-H2: residues 52-67 of SEQ ID NO:354

CDR-H3: residues 100-110 of SEQ ID NO:354

VL E9-FR2 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:355

CDR-L2: residues 50-56 of SEQ ID NO:355

CDR-L3: residues 89-97 of SEQ ID NO:355

VH E9.71 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:356

CDR-H2: residues 52-67 of SEQ ID NO:356

CDR-H3: residues 100-110 of SEQ ID NO:356

VL E9.71 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:357

CDR-L2: residues 49-55 of SEQ ID NO:357

CDR-L3: residues 88-96 of SEQ ID NO:357

VH E9.71(M) CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:358

CDR-H2: residues 52-67 of SEQ ID NO:358

CDR-H3: residues 100-110 of SEQ ID NO:358

VL E9.71(M) CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:359

CDR-L2: residues 49-55 of SEQ ID NO:359

CDR-L3: residues 88-96 of SEQ ID NO:359

VH E9.71(L) CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:360

CDR-H2: residues 52-67 of SEQ ID NO:360

CDR-H3: residues 100-110 of SEQ ID NO:360

VL E9.71(L) CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:361

CDR-L2: residues 49-55 of SEQ ID NO:361

CDR-L3: residues 88-96 of SEQ ID NO:361

5. The binding protein according to claim 4, comprising at least two variable domain CDR sets.

6. The binding protein according to claim 5, wherein said at least two variable domain CDR sets are selected from a group consisting of:

VH E9 CDR Set and VL E9 CDR Set,
VH E9.4 CDR Set and VL E9.4 CDR Set,
VH E9.11 CDR Set and VL E9.11 CDR Set,
VH E9.14 CDR Set and VL E9.14 CDR Set,
VH E9.17 CDR Set and VL E9.17 CDR Set,
VH E9.18 CDR Set and VL E9.18 CDR Set,
VH E9.19 CDR Set and VL E9.19 CDR Set,
VH E9.22 CDR Set and VL E9.22 CDR Set,
VH E9.48 CDR Set and VL E9.48 CDR Set,
VH E9.65 CDR Set and VL E9.65 CDR Set,
VH E9.66 CDR Set and VL E9.66 CDR Set,
VH E9.71 CDR Set and VL E9.71 CDR Set,
VH E9.13 CDR Set and VL E9.13 CDR Set,
VH E9.16 CDR Set and VL E9.16 CDR Set,
VH E9.38 CDR Set and VL E9.38 CDR Set,
VH E9.2B CDR Set and VL E9.2B CDR Set,
VH E9.1F CDR Set and VL E9.1F CDR Set,
VH E9.10H CDR Set and VL E9.10H CDR Set,
VH E9.5E CDR Set and VL E9.5E CDR Set,
VH E9.10C CDR Set and VL E9.10C CDR Set,
VH E9.7E CDR Set and VL E9.7E CDR Set,
VH E9.12B CDR Set and VL E9.12B CDR Set,
VH E9.10E CDR Set and VL E9.10E CDR Set,

VH E9.6A CDR Set and VL E9.6A CDR Set,
VH E9.7A CDR Set and VL E9.7A CDR Set,
VH E9.8H CDR Set and VL E9.8H CDR Set,
VH E9-SE1 CDR Set and VL E9-SE1 CDR Set,
VH E9-SE2 CDR Set and VL E9-SE2 CDR Set,
VH E9-SE3 CDR Set and VL E9-SE3 CDR Set,
VH E9-SE4 CDR Set and VL E9-SE4 CDR Set,
VH E9-SE5 CDR Set and VL E9-SE5 CDR Set,
VH E9-SE6 CDR Set and VL E9-SE6 CDR Set,
VH E9-SE7 CDR Set and VL E9-SE7 CDR Set,
VH E9-SE8 CDR Set and VL E9-SE8 CDR Set,
VH E9-FR1 CDR Set and VL E9-FR1 CDR Set,
VH E9-FR2 CDR Set and VL E9-FR2 CDR Set,
VH E9.71 CDR Set and VL E9.71 CDR Set,
VH E9.71(M) CDR Set and VL E9.71(M) CDR Set, and
VH E9.71(L) CDR Set and VL E9.71(L) CDR Set.

7. The binding protein according to any one of Claims 1-6, further comprising a human acceptor framework.

8. The binding protein according to claim 7, wherein said human acceptor framework comprises an amino acid sequence selected from the group consisting of:
heavy chain acceptor framework sequences SEQ ID NOS:6-22,
heavy chain acceptor sequences SEQ ID NOS:35-62,
light chain acceptor sequences SEQ ID NOS:23-34, and
light chain acceptor sequences SEQ ID NOS:63-98.

9. The binding protein according to claim 7 or claim 8, wherein said human acceptor framework comprises at least one framework region amino acid substitution, wherein the amino acid sequence of the framework is at least 65% identical to the sequence of said human acceptor framework and comprising at least 70 amino acid residues identical to said human acceptor framework.

10. The binding protein according to claim 8, wherein said human acceptor framework comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;

a glycosylation site residue;
a rare residue;
a residue capable of interacting with human DLL4
a canonical residue;
a contact residue between heavy chain variable region and light chain variable region;
a residue within a Vernier zone; and
a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

11. The binding protein according to claim 10, wherein key residue selected from the group consisting of: 2H, 4H, 24H, 26H, 27H, 29H, 34H, 35H, 37H, 39H, 44H, 45H, 47H, 48H, 49H, 50H, 51H, 58H, 59H, 60H, 63H, 67H, 69H, 71H, 73H, 76H, 78H, 91H, 93H, 94H, 2L, 4L, 25L, 29L, 27bL, 33L, 34L, 36L, 38L, 43L, 44L, 46L, 47L, 48L, 49L, 55L, 58L, 62L, 64L, 71L, 87L, 89L, 90L, 91L, 94L, 95L.

12. The binding protein according to claim 11, where the binding protein is a consensus human variable domain.

13. The binding protein according to claim 1, where said binding protein comprises at least one variable domain having amino acid sequence selected from the group consisting of: SEQ ID NOS:1, 111, 116, 228, 120, 232, 124, 236, 128, 240, 132, 244, 136, 248, 140, 252, 144, 256, 148, 260, 152, 264, 156, 268, 160, 216, 164, 220, 168, 224, 172, 272, 176, 276, 180, 300, 184, 292, 188, 280, 192, 288, 196, 296, 200, 284, 204, 304, 208, 308, 212, 312, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, and 361.

14. The binding protein according to claim 13, wherein said binding protein comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of: SEQ ID NOS:1 and 111, SEQ ID NOS:116 and 228, SEQ ID NOS:120 and 232, SEQ ID NOS:124 and 236, SEQ ID NOS:128 and 240, SEQ ID NOS:132 and 244, SEQ ID NOS:136 and 248, SEQ ID NOS:140 and 252, SEQ ID NOS:144 and 256, SEQ ID NOS:148 and 260, SEQ ID NOS:152 and 264, SEQ ID NOS:156 and 268, SEQ ID NOS: 160 and 216, SEQ ID NOS: 164 and 220, SEQ ID NOS:168 and 224, SEQ ID NOS:172 and 272, SEQ ID NOS:176 and 276, SEQ ID NOS:180 and 300, SEQ ID NOS:184 and 292, SEQ ID NOS:188 and 280, SEQ ID NOS:192 and 288, SEQ ID NOS:196 and 296, SEQ ID NOS:200 and 284, SEQ ID

NOS:204 and 304, SEQ ID NOS:208 and 308, SEQ ID NOS:212 and 312, SEQ ID NOS:334 and 335, SEQ ID NOS:336 and 337, SEQ ID NOS:338 and 339, SEQ ID NOS:340 and 341, SEQ ID NOS:342 and 343, SEQ ID NOS:344 and 345, SEQ ID NOS:346 and 347, SEQ ID NOS:348 and 349, SEQ ID NOS:350 and 351, SEQ ID NOS:352 and 353, SEQ ID NOS:354 and 355, SEQ ID NOS:356 and 357, SEQ ID NOS:358 and 359, SEQ ID NOS:360 and 361.

15. The binding protein according to claim 11, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of: SEQ ID NOS:1, 111, 116, 228, 120, 232, 124, 236, 128, 240, 132, 244, 136, 248, 140, 252, 144, 256, 148, 260, 152, 264, 156, 268, 160, 216, 164, 220, 168, 224, 172, 272, 176, 276, 180, 300, 184, 292, 188, 280, 192, 288, 196, 296, 200, 284, 204, 304, 208, 308, 212, 312, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, and 361.

16. The binding protein according to claim 2 wherein said antigen binding domain comprises a $V_H$.

17. The binding protein according to claim 16 wherein said $V_H$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360.

18. The binding protein according to claim 2 wherein said antigen binding domain comprises a $V_L$.

19. The binding protein according to claim 18 wherein said $V_L$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

20. The binding protein according to claim 2 wherein said antigen binding domain comprises a $V_H$ and a $V_L$.

21. The binding protein according to claim 19 further comprising a $V_H$ wherein said $V_H$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360.

22. The binding protein according to claim 20 wherein said $V_L$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

23. The binding protein according to claim 2, further comprising a heavy chain immunoglobulin constant domain selected from the group consisting of: a human IgM constant domain; a human IgG1 constant domain; a human IgG2 constant domain; a human IgG3 constant domain; a human IgG4 constant domain; a human IgE constant domain and a human IgA constant domain.

24. The binding protein according to claim 23 wherein said heavy chain immunoglobulin constant region domain is a human IgG1 constant domain.

25. The binding protein according to claim 24 wherein said human IgG1 constant domain comprises amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3.

26. The binding protein according to claim 2, further comprising a light chain immunoglobulin constant domain selected from the group consisting of: a human Ig kappa constant domain and a human Ig lambda constant domain.

27. The binding protein according to claim 26 wherein said light chain immunoglobulin constant region domain is a human Ig kappa constant domain comprising amino acid sequence SEQ ID NO:4.

28. The binding protein according to claim 26 wherein said light chain immunoglobulin constant region domain is a human Ig lambda constant domain comprising amino acid sequence SEQ ID NO:5.

29. The binding protein according to Claim 1 wherein said binding protein is selected from the group consisting of: an immunoglobulin molecule, an scFv, a monoclonal antibody, a human antibody, a chimeric antibody, a humanized antibody, a single domain antibody, a Fab fragment, a Fab' fragment, an $F(ab')_2$, an Fv, a disulfide linked Fv, a single domain antibody, a diabody, a multispecific antibody, a bispecific antibody, and a dual specific antibody.

30. The binding protein according to claim 29 wherein said binding protein is a human antibody.

31. A binding protein capable of binding human DLL-4, said binding protein comprising:
an Ig constant heavy region having an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3;
an Ig constant light region having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5;
an Ig variable heavy region having an amino acid sequence selected from the group consisting:
SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360; and
an Ig variable light region having an amino acid sequence selected from the group consisting:
SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

32. The binding protein according to Claim 31, wherein the Ig constant light region is SEQ ID NO:5.

33. The binding protein according to any one of Claims 1-32, wherein the binding protein is capable of blocking DLL4 interaction with a Notch protein selected from the group consisting of Notch-1, Notch-2, Notch-3, Notch-4, and combinations thereof.

34. The binding protein according to Claim 33, wherein the binding protein is capable of blocking DLL4 interaction with Notch-1 and Notch-4.

35. The binding protein according to Claim 33, wherein the binding protein is capable of blocking DLL4 interaction with Notch-1.

36. The binding protein according to claim 33, wherein the binding protein is capable of blocking DLL4 interaction with Notch-4.

37. The binding protein according to any one of Claims 1-32, wherein the binding protein is capable of modulating a biological function of DLL4.

38. The binding protein according to any one of Claims 1-32, wherein said binding protein is capable of neutralizing a DLL4.

39. The neutralizing binding protein according to claim 38 wherein said DLL4 is selected from the group consisting of: human DLL4, mouse DLL4, cynomolgus DLL4, and rat DLL4.

40. The neutralizing binding protein according to Claim 38 wherein said neutralizing binding protein diminishes the ability of DLL4 to bind to its receptor.

41. The neutralizing binding protein according to claim 38 wherein said neutralizing binding protein is capable of reducing normal angiogenesis.

42. The neutralizing binding protein according to claim 38, wherein said neutralizing binding protein has a dissociation constant ($K_D$) selected from the group consisting of: at most about $10^{-7}$ M; at most about $10^{-8}$ M; at most about $10^{-9}$ M; at most about $10^{-10}$ M; at most about $10^{-11}$ M; at most about $10^{-12}$ M; and at most $10^{-13}$ M.

43. The neutralizing binding protein according to claim 38, wherein said neutralizing binding protein has an on rate selected from the group consisting of: at least about $10^{2}M^{-1}s^{-1}$; at least about $10^{3}M^{-1}s^{-1}$; at least about $10^{4}M^{-1}s^{-1}$; at least about $10^{5}M^{-1}s^{-1}$; and at least about $10^{6}M^{-1}s^{-1}$.

44. The neutralizing binding protein according to claim 38, wherein said neutralizing binding protein has an off rate selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$.

45. A labeled binding protein comprising a binding protein of any one of Claims 1-32, wherein said binding protein is conjugated to a detectable label.

46. The labeled binding protein of Claim 45, wherein the detectable label is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

47 The labeled binding protein of claim 46, wherein said label is a radiolabel selected from the group consisting of: $^{3}H$, $^{14}C$, $^{35}S$, $^{90}Y$, $^{99}Tc$, $^{111}In$, $^{125}I$, $^{131}I$, $^{177}Lu$, $^{166}Ho$, and $^{153}Sm$.

48. An antibody construct comprising a binding protein described in any of Claims 1-32 and further comprising a linker polypeptide or an immunoglobulin constant domain.

49. The antibody construct according to claim 48, selected from the group consisting of:

an immunoglobulin molecules,
a monoclonal antibody,
a chimeric antibody,
a CDR-grafted antibody,
a humanized antibody,
a Fab,
a Fab',
a $F(ab')_2$,
a Fv,
a disulfide linked Fv,
a scFv,
a single domain antibody,
a diabody,
a multispecific antibody,
a dual specific antibody, and
a bispecific antibody.

50. The antibody construct according to claim 48, wherein said antibody construct comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

a human IgM constant domain,
a human IgG1 constant domain,
a human IgG2 constant domain,
a human IgG3 constant domain,

a human IgG4 constant domain,
a human IgE constant domain,
a human IgA constant domain,
and a IgG constant domain variant with one or more mutations altering binding strength to Fc neonatal receptor, Fc gamma receptors, or C1q.

51. The antibody construct according to claim 48, comprising an immunoglobulin constant domain having an amino acid sequence selected from consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and combinations thereof.

52. An antibody conjugate comprising an antibody construct as described in Claim 48, wherein said antibody construct is conjugated to a therapeutic or cytotoxic agent.

53. The antibody conjugate of Claim 52, wherein said therapeutic or cytotoxic agent is selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

54. An isolated nucleic acid encoding a polypeptide selected from the group consisting of: a polypeptide comprising a heavy chain variable domain, wherein the heavy chain variable domain comprises one or more of CDR-H1, a CDR-H2, or a CDR-H3 as described in Claim 1; a polypeptide comprising a light chain variable domain, wherein the light chain variable domain comprises one or more of CDR-L1, a CDR-L2, or a CDR-L3 as described in Claim 1; or a combination of both polypeptides.

55. A vector comprising an isolated nucleic acid according to Claim 54.

56. The vector of Claim 55 wherein said vector is selected from the group consisting of: pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pHybE and pBJ.

57. A host cell comprising a vector according to any one of Claims 55 and 56.

58. The host cell according to claim 57, wherein said host cell is a prokaryotic cell.

59. The host cell according to claim 58, wherein said host cell is *Escherichia coli*.

60. The host cell according to claim 59, wherein said host cell is a eukaryotic cell.

61. The host cell according to claim 60, wherein said eukaryotic cell is selected from the group consisting of: a protist cell, an animal cell, a plant cell, and a fungal cell.

62. The host cell according to claim 61, wherein said eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

63. The host cell according to claim 62, wherein said mammalian cell is a CHO cell.

64. The host cell according to claim 62, wherein said mammalian cell is a COS cell.

65. The host cell according to claim 61, wherein said fungal cell is *Saccharomyces cerevisiae*.

66. The host cell according to claim 62, wherein said insect cell is an Sf9 cell.

67. A method of producing a binding protein that binds human DLL4, comprising culturing the host cell of any one of claims 57-66 in a culture medium under conditions sufficient to produce a binding protein that binds human DLL4.

68. A binding protein produced according to the method of claim 67.

69. A crystallized binding protein comprising a binding protein according to any one of Claims 1-32, wherein said binding protein exists as a crystal.

70. The crystallized binding protein according to claim 69, wherein said crystal is a carrier-free pharmaceutical controlled release crystal.

71. The crystallized binding protein according to claim 69, wherein said binding protein has a greater half life *in vivo* than the soluble counterpart of said binding protein.

72. The crystallized binding protein according to claim 69, wherein said binding protein retains biological activity.

73. A composition for the release of a binding protein said composition comprising:

(a) a formulation, wherein said formulation comprises a crystallized binding protein, according to any one of claims 69-72, and an ingredient; and

(b) at least one polymeric carrier.

74. The composition according to claim 73, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutryate), poly (caprolactone), poly (dioxanone), poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo)phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polyeaccharides, blends and copolymers thereof.

75. The composition according to claim 73, wherein said ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

76. A method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition according to claim 73.

77. A pharmaceutical composition comprising the binding protein of any one of Claims 1-32, and a pharmaceutically acceptable carrier.

78. The pharmaceutical composition of claim 77 which further comprises at least one additional therapeutic agent for treating a disorder in which DLL4 activity is detrimental.

79. The pharmaceutical composition of claim 78, wherein said additional agent is selected from the group consisting of: angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; corticosteroids; cyclosporine; rapamycin; FK506; and non-steroidal anti-inflammatory agents.

80. A method for reducing human DLL4 activity comprising contacting human DLL4 with the binding protein of any one of Claims 1-32 such that human DLL4 activity is reduced.

81. A method for reducing human DLL4 activity in a human subject suffering from a disorder in which DLL4 activity is detrimental, comprising administering to the human subject the

binding protein of any one of Claims 1-32 such that human IL-17 activity in the human subject is reduced.

82. A method for treating a subject for a disease or a disorder in which DLL4 activity is detrimental by administering to the subject the binding protein of any one of Claims 1-32 such that treatment is achieved.

83. The method of claim 82, wherein said disorder is selected from the group consisting of: breast cancer, colon cancer, rectal cancer, lung cancer, oropharynx cancer, hypopharynx cancer, esophageal cancer, stomach cancer, pancreas cancer, liver cancer, gallbladder cancer, bile duct cancer, small intestine cancer, urinary tract cancer, female genital tract cancer, male genital tract cancer, endocrine gland cancer, skin cancer, hemangiomas, melanomas, sarcomas, brain tumor, nerve cancer, eye tumor, meninges cancer, solid tumors from hematopoietic malignancies, tumor metastases, ocular neovascularization, edema, rheumatoid arthritis, multiple sclerosis, atheroscleorotic plaques, Crohn's disease, inflammatory bowel disease, refractory ascites, psoriasis, sarcoidosis, arterial arteriosclerosis, sepsis, peptic ulcers, burns, and pancreatitis, polycystic ovarian disease (POD), endometriosis, uterine fibroids, benign prostate hypertrophy, and other angiogenesis independent and dependent diseases characterized by abberant DLL4 activity.

84. The method according to Claim 83, wherein the disorder is a primary and metastatic cancer.

85. The method according to Claim 83, wherein the urinary tract cancer is selected from the group consisting of renal cancer, bladder cancer, and urothelium cancer.

86. The method according to Claim 83, wherein the female genital tract cancer is selected from the group consisting of cervical cancer, uterine cancer, ovarian cancer, choriocarcinoma, and gestational trophoblastic disease.

87. The method according to Claim 83, wherein the male genital tract cancer is selected from the group consisting of prostate cancer, seminal vesicles cancer, testicular cancer, and germ cell tumor.

88. The method according to Claim 83, wherein the endocrine gland cancer is selected from the group consisting of thyroid cancer, adrenal cancer, and pituitary gland cancer.

89. The method according to Claim 83, wherein the sarcoma is selected from the group consisting of a bone sarcoma, a soft tissue sarcoma, and Kaposi's sarcoma.

90. The method according to Claim 83, wherein the meninges cancer is selected from the group consisting of an astrocytoma, a glioma, a glioblastoma, a retinoblastoma, a neuroma, a neuroblastoma, a Schwannoma, and a meningiomas.

91. The method according to Claim 83, wherein the solid tumor from a hematopoietic malignancy is a leukemia, a Hodgkin's leukemia, a non-Hodgkin's leukemia, a lymphoma, a Hodgkin's lymphoma, and a non-Hodgkin's lymphomas.

92. The method according to Claim 83, wherein the ocular neovascularization is selected from the group consisting of diabetic blindness, a retinopathy, an age-induced macular degeneration, and a rubeosis.

93. A method of treating a patient suffering from a disorder in which DLL4 is detrimental comprising the step of administering the binding protein of any one of claims 1-32 before, concurrent with, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an antibody or fragment thereof capable of binding human VEGFR2; methotrexate; an antibody, or fragment thereof, capable of binding human TNF; corticosteroids, cyclosporine, rapamycin, FK506, and non-steroidal anti-inflammatory agents.

94. A binding protein comprising an antigen binding domain capable of binding human DLL4, said antigen binding domain comprising at least one or more CDRs selected from the group consisting of:

CDR-H1: $X_1-X_2-X_3-X_4-X_5$ (SEQ ID NO:105), wherein;
$X_1$ is S, N, or D;
$X_2$ is H or Y;
$X_3$ is W;
$X_4$ is M;
$X_5$ is S or H;

CDR-H2: $X_1-X_2-X_3-X_4-X_5-X_6-X_7-X_8-X_9-X_{10}-X_{11}-X_{12}-X_{13}-X_{14}-X_{15}-X_{16}-X_{17}$ (SEQ ID NO:106), wherein;
$X_1$ is I, D, M, or T;
$X_2$ is I;

$X_3$ is S;
$X_4$ is Y, N, S, Q, V, T, H, or D;
$X_5$ is D;
$X_6$ is G;
$X_7$ is S, R, I, T, G, K, H, or N;
$X_8$ is N, Y, S, I, or T;
$X_9$ is K, M, N, Q, E, T, R, S, A, or L;
$X_{10}$ is Y, D, or E;
$X_{11}$ is S or Y;
$X_{12}$ is A;
$X_{13}$ is D;
$X_{14}$ is S;
$X_{15}$ is V;
$X_{16}$ is K; and
$X_{17}$ is G;

CDR-H3: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$ (SEQ ID NO:107), wherein;
$X_1$ is A;
$X_2$ is G, A, or R;
$X_3$ is G;
$X_4$ is G, S, or A;
$X_5$ is N;
$X_6$ is V or M;
$X_7$ is G;
$X_8$ is F, L, Y, or M;
$X_9$ is D; and
$X_{10}$ is I, S, or L;

CDR-L1: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$-$X_{10}$-$X_{11}$ (SEQ ID NO:108), wherein;
$X_1$ is S;
$X_2$ is A or G;
$X_3$ is D;
$X_4$ is K, N, L, Q, M, E, S, T, G, or D;
$X_5$ is L;
$X_6$ is G;
$X_7$ is T, S, N, A, G, or E;
$X_8$ is K, Q, N, or R;

$X_9$ is Y;

$X_{10}$ is V or I; and

$X_{11}$ is S;

CDR-L2: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$ (SEQ ID NO:109), wherein;

$X_1$ is Q;

$X_2$ is D;

$X_3$ is A, G, W, S, or D;

$X_4$ is K, M, Q, N, L, T, I, or E;

$X_5$ is R;

$X_6$ is P; and

$X_7$ is S;

and

CDR-L3: $X_1$-$X_2$-$X_3$-$X_4$-$X_5$-$X_6$-$X_7$-$X_8$-$X_9$ (SEQ ID NO:110), wherein;

$X_1$ is Q;

$X_2$ is S or A;

$X_3$ is W;

$X_4$ is D;

$X_5$ is R, S, Q, P, A, V, W, or M;

$X_6$ is S, G, I, N, R, or T;

$X_7$ is D or G;

$X_8$ is V, A, P, or E; and

$X_9$ is V.

95. The binding protein according to Claim 94, wherein said at least one CDR comprises an amino acid sequence selected from the group consisting of:

residues 31-35 of SEQ ID NO:112 (CDR-H1); residues 50-66 of SEQ ID NO:112 (CDR-H2); residues 99-108 of SEQ ID NO:112 (CDR-H3);

residues 23-33 of SEQ ID NO:113 (CDR-L1); residues 49-55 of SEQ ID NO:113 (CDR-L2); residues 88-96 of SEQ ID NO:113 (CDR-L3);

residues 31-35 of SEQ ID NO:316 (CDR-H1); residues 50-66 of SEQ ID NO:316 (CDR-H2); residues 99-108 of SEQ ID NO:316 (CDR-H3);

residues 31-35 of SEQ ID NO:317 (CDR-H1); residues 50-66 of SEQ ID NO:317 (CDR-H2); residues 99-108 of SEQ ID NO:317 (CDR-H3);

residues 31-35 of SEQ ID NO:318 (CDR-H1); residues 50-66 of SEQ ID NO:318 (CDR-H2); residues 99-108 of SEQ ID NO:318 (CDR-H3);

residues 31-35 of SEQ ID NO:319 (CDR-H1); residues 50-66 of SEQ ID NO:319 (CDR-H2); residues 99-108 of SEQ ID NO:319 (CDR-H3);

residues 31-35 of SEQ ID NO:320 (CDR-H1); residues 50-66 of SEQ ID NO:320 (CDR-H2); residues 99-108 of SEQ ID NO:320 (CDR-H3);
residues 31-35 of SEQ ID NO:321 (CDR-H1); residues 50-66 of SEQ ID NO:321 (CDR-H2); residues 99-108 of SEQ ID NO:321 (CDR-H3);
residues 31-35 of SEQ ID NO:322 (CDR-H1); residues 50-66 of SEQ ID NO:322 (CDR-H2); residues 99-108 of SEQ ID NO:322 (CDR-H3);
residues 31-35 of SEQ ID NO:323 (CDR-H1); residues 50-66 of SEQ ID NO:323 (CDR-H2); residues 99-108 of SEQ ID NO:323 (CDR-H3);
residues 31-35 of SEQ ID NO:324 (CDR-H1); residues 50-66 of SEQ ID NO:324 (CDR-H2); residues 99-108 of SEQ ID NO:324 (CDR-H3);
residues 31-35 of SEQ ID NO:325 (CDR-H1); residues 50-66 of SEQ ID NO:325 (CDR-H2); residues 99-108 of SEQ ID NO:325 (CDR-H3);
residues 31-35 of SEQ ID NO:326 (CDR-H1); residues 50-66 of SEQ ID NO:326 (CDR-H2); residues 99-108 of SEQ ID NO:326 (CDR-H3);
residues 23-33 of SEQ ID NO:327 (CDR-L1); residues 49-55 of SEQ ID NO:327 (CDR-L2); residues 88-96 of SEQ ID NO:327 (CDR-L3);
residues 23-33 of SEQ ID NO:328 (CDR-L1); residues 49-55 of SEQ ID NO:328 (CDR-L2); residues 88-96 of SEQ ID NO:328 (CDR-L3);
residues 23-33 of SEQ ID NO:329 (CDR-L1); residues 49-55 of SEQ ID NO:329 (CDR-L2); residues 88-96 of SEQ ID NO:329 (CDR-L3);
residues 23-33 of SEQ ID NO:330 (CDR-L1); residues 49-55 of SEQ ID NO:330 (CDR-L2); residues 88-96 of SEQ ID NO:330 (CDR-L3);
residues 23-33 of SEQ ID NO:331 (CDR-L1); residues 49-55 of SEQ ID NO:331 (CDR-L2); residues 88-96 of SEQ ID NO:331 (CDR-L3);
residues 23-33 of SEQ ID NO:332 (CDR-L1); residues 49-55 of SEQ ID NO:332 (CDR-L2); residues 88-96 of SEQ ID NO:332 (CDR-L3);
residues 23-33 of SEQ ID NO:333 (CDR-L1); residues 49-55 of SEQ ID NO:333 (CDR-L2); residues 88-96 of SEQ ID NO:333 (CDR-L3).

96. The binding protein according to claim 95, wherein said binding protein comprises at least 3 CDRs.

97. The binding protein according to claim 96, wherein said at least 3 CDRs comprises a variable domain CDR set selected from the group consisting of:

VH A10 CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:112

CDR-H2: residues 50-66 of SEQ ID NO:112

CDR-H3: residues 99-108 of SEQ ID NO:112

VL A10 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:113

CDR-L2: residues 49-55 of SEQ ID NO:113

CDR-L3: residues 88-96 of SEQ ID NO:113

VH A10.3 CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:316

CDR-H2: residues 50-66 of SEQ ID NO:316

CDR-H3: residues 99-108 of SEQ ID NO:316

VL A10.3 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:327

CDR-L2: residues 49-55 of SEQ ID NO:327

CDR-L3: residues 88-96 of SEQ ID NO:327

VH A10.K30 CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:317

CDR-H2: residues 50-66 of SEQ ID NO:317

CDR-H3: residues 99-108 of SEQ ID NO:317

VH A10.K42 CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:318

CDR-H2: residues 50-66 of SEQ ID NO:318

CDR-H3: residues 99-108 of SEQ ID NO:318

VH A10.9A CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:319

CDR-H2: residues 50-66 of SEQ ID NO:319

CDR-H3: residues 99-108 of SEQ ID NO:319

VH A10.8A CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:320

CDR-H2: residues 50-66 of SEQ ID NO:320

CDR-H3: residues 99-108 of SEQ ID NO:320

VH A10.1A CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:321

CDR-H2: residues 50-66 of SEQ ID NO:321

CDR-H3: residues 99-108 of SEQ ID NO:321

VH A10.5D CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:322

CDR-H2: residues 50-66 of SEQ ID NO:322

CDR-H3: residues 99-108 of SEQ ID NO:322

VH A10.3A CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:323

CDR-H2: residues 50-66 of SEQ ID NO:323

CDR-H3: residues 99-108 of SEQ ID NO:323

VL A10.3A CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:330

CDR-L2: residues 49-55 of SEQ ID NO:330

CDR-L3: residues 88-96 of SEQ ID NO:330

VH A10.6B CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:324

CDR-H2: residues 50-66 of SEQ ID NO:324

CDR-H3: residues 99-108 of SEQ ID NO:324

VL A10.6B CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:331

CDR-L2: residues 49-55 of SEQ ID NO:331

CDR-L3: residues 88-96 of SEQ ID NO:331

VH A10.3D CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:325

CDR-H2: residues 50-66 of SEQ ID NO:325

CDR-H3: residues 99-108 of SEQ ID NO:325

VL A10.3D CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:332

CDR-L2: residues 49-55 of SEQ ID NO:332

CDR-L3: residues 88-96 of SEQ ID NO:332

VH A10.4C CDR Set

CDR-H1: residues 31-35 of SEQ ID NO:326

CDR-H2: residues 50-66 of SEQ ID NO:326

CDR-H3: residues 99-108 of SEQ ID NO:326

VL A10.4C CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:333

CDR-L2: residues 49-55 of SEQ ID NO:333

CDR-L3: residues 88-96 of SEQ ID NO:333

VL A10.L45 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:328

CDR-L2: residues 49-55 of SEQ ID NO:328

CDR-L3: residues 88-96 of SEQ ID NO:328

VL A10.L73 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:329

CDR-L2: residues 49-55 of SEQ ID NO:329

CDR-L3: residues 88-96 of SEQ ID NO:329

98. The binding protein according to claim 97, comprising at least two variable domain CDR sets.

99. The binding protein according to claim 98, wherein said at least two variable domain CDR sets are selected from a group consisting of:

VH A10 CDR Set and VL A10 CDR Set;
VH A10.3 CDR Set and VL A10.3 CDR Set:
VH A10.3A CDR Set and VL A10.3A Set;
VH A10.6B CDR Set and VL A10.6B Set;
VH A10.3D CDR Set and VL A10.3D CDR Set;
VH A10.4C CDR Set and VL A10.4C CDR Set;
VH A10.K30 CDR Set and VL A10.3 CDR Set;
VH A10.K42 CDR Set and VL A10.3 CDR Set;
VH A10.3 CDR Set and VL A10.L45 CDR Set;
VH A10.3 CDR Set and VL A10.L73 CDR Set;
VH A10.9A CDR Set and VL A10.3 CDR Set;
VH A10.8A CDR Set and VL A10.3 CDR Set;
VH A10.1A CDR Set and VL A10.3 CDR Set; and
VH A10.5D CDR Set and VL A10.3 CDR Set.

100. The binding protein according to any one of Claims 94-99, further comprising a human acceptor framework.

101. The binding protein according to claim 100, wherein said human acceptor framework comprises an amino acid sequence selected from the group consisting of:
heavy chain acceptor framework sequences SEQ ID NOS:6-22,
heavy chain acceptor sequences SEQ ID NOS:35-62,
light chain acceptor sequences SEQ ID NOS:23-34, and
light chain acceptor sequences SEQ ID NOS:63-98.

102. The binding protein according to claim 100 or claim 101, wherein said human acceptor framework comprises at least one framework region amino acid substitution, wherein the

amino acid sequence of the framework is at least 65% identical to the sequence of said human acceptor framework and comprising at least 70 amino acid residues identical to said human acceptor framework.

103. The binding protein according to claim 101, wherein said human acceptor framework comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;

a glycosylation site residue;

a rare residue;

a residue capable of interacting with human DLL4

a canonical residue;

a contact residue between heavy chain variable region and light chain variable region;

a residue within a Vernier zone; and

a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

104. The binding protein according to claim 103, wherein key residue selected from the group consisting of: 2H, 4H, 24H, 26H, 27H, 29H, 34H, 35H, 37H, 39H, 44H, 45H, 47H, 48H, 49H, 50H, 51H, 58H, 59H, 60H, 63H, 67H, 69H, 71H, 73H, 76H, 78H, 91H, 93H, 94H, 2L, 4L, 25L, 29L, 27bL, 33L, 34L, 36L, 38L, 43L, 44L, 46L, 47L, 48L, 49L, 55L, 58L, 62L, 64L, 71L, 87L, 89L, 90L, 91L, 94L, 95L.

105. The binding protein according to claim 104, where the binding protein is a consensus human variable domain.

106. The binding protein according to claim 94, where said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of:

SEQ ID NOS:112, 113, 316, 327, 317, 318, 319, 320, 321, 322, 323, 330, 324, 331, 325, 332, 326, 333, 328, and 329.

107. The binding protein according to claim 106, wherein said binding protein comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of: SEQ ID NOS:112 and 113, SEQ ID NOS:316 and 327,

SEQ ID NOS:323 and 330, SEQ ID NOS:324 and 331, SEQ ID NOS:325 and 332, and SEQ ID NOS:326 and 333.

108. The binding protein according to claim 104, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of: SEQ ID NOS: 112, 113, 316, 327, 317, 318, 319, 320, 321, 322, 323, 330, 324, 331, 325, 332, 326, 333, 328, and 329.

109. The binding protein according to claim 95 wherein said antigen binding domain comprises a $V_H$.

110. The binding protein according to claim 109 wherein said $V_H$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:112, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, and 326.

111. The binding protein according to claim 95 wherein said antigen binding domain comprises a $V_L$.

112. The binding protein according to claim 111 wherein said $V_L$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS:113, 327, 328, 329, 330, 331, 332, and 333.

113. The binding protein according to claim 95 wherein said antigen binding domain comprises a $V_H$ and a $V_L$.

114. The binding protein according to claim 112 further comprising a $V_H$ wherein said $V_H$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS: SEQ ID NOS:112, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, and 326.

115. The binding protein according to claim 20 wherein said $V_L$ comprises an amino acid sequence selected from the group consisting of:
SEQ ID NOS: 113, 327, 328, 329, 330, 331, 332, and 333.

116. The binding protein according to claim 95, further comprising a heavy chain immunoglobulin constant domain selected from the group consisting of: a human IgM constant domain; a human IgG1 constant domain; a human IgG2 constant domain; a

human IgG3 constant domain; a human IgG4 constant domain; a human IgE constant domain and a human IgA constant domain.

117. The binding protein according to claim 117 wherein said heavy chain immunoglobulin constant region domain is a human IgG1 constant domain.

118. The binding protein according to claim 117 wherein said human IgG1 constant domain comprises amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3.

119. The binding protein according to claim 95, further comprising a light chain immunoglobulin constant domain selected from the group consisting of: a human Ig kappa constant domain and a human Ig lambda constant domain.

120. The binding protein according to claim 119 wherein said light chain immunoglobulin constant region domain is a human Ig kappa constant domain comprising amino acid sequence SEQ ID NO:4.

121. The binding protein according to claim 119 wherein said light chain immunoglobulin constant region domain is a human Ig lambda constant domain comprising amino acid sequence SEQ ID NO:5.

122. The binding protein according to Claim 94 wherein said binding protein is selected from the group consisting of: an immunoglobulin molecule, an scFv, a monoclonal antibody, a human antibody, a chimeric antibody, a humanized antibody, a single domain antibody, a Fab fragment, a Fab' fragment, an $F(ab')_2$, an Fv, a disulfide linked Fv, a single domain antibody, a diabody, a multispecific antibody, a bispecific antibody, and a dual specific antibody.

123. The binding protein according to claim 122 wherein said binding protein is a human antibody.

124. A binding protein capable of binding human DLL-4, said binding protein comprising:
an Ig constant heavy region having an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3;
an Ig constant light region having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5;

an Ig variable heavy region having an amino acid sequence selected from the group consisting:
SEQ ID NOS: SEQ ID NOS:112, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, and 326; and
an Ig variable light region having an amino acid sequence selected from the group consisting:
SEQ ID NOS: 113, 327, 328, 329, 330, 331, 332, and 333.

125. The binding protein according to Claim 124, wherein the Ig constant light region is SEQ ID NO:5.

126. The binding protein according to any one of Claims 94-125, wherein the binding protein is capable of blocking DLL4 interaction with a Notch protein selected from the group consisting of Notch-1, Notch-2, Notch-3, Notch-4, and combinations thereof.

127. The binding protein according to Claim 126, wherein the binding protein is capable of blocking DLL4 interaction with Notch-1 and Notch-4.

128. The binding protein according to Claim 126, wherein the binding protein is capable of blocking DLL4 interaction with Notch-1.

129. The binding protein according to claim 126, wherein the binding protein is capable of blocking DLL4 interaction with Notch-4.

130. The binding protein according to any one of Claims 94-125, wherein the binding protein is capable of modulating a biological function of DLL4.

131. The binding protein according to any one of Claims 94-125, wherein said binding protein is capable of neutralizing a DLL4.

132. The neutralizing binding protein according to claim 131 wherein said DLL4 is selected from the group consisting of: human DLL4, mouse DLL4, cynomolgus DLL4, and rat DLL4.

133. The neutralizing binding protein according to Claim 131 wherein said neutralizing binding protein diminishes the ability of DLL4 to bind to its receptor.

134. The neutralizing binding protein according to claim 131 wherein said neutralizing binding protein is capable of reducing normal angiogenesis.

135. The neutralizing binding protein according to claim 131, wherein said neutralizing binding protein has a dissociation constant ($K_D$) selected from the group consisting of: at most about $10^{-7}$ M; at most about $10^{-8}$ M; at most about $10^{-9}$ M; at most about $10^{-10}$ M; at most about $10^{-11}$ M; at most about $10^{-12}$ M; and at most $10^{-13}$ M.

136. The neutralizing binding protein according to claim 131, wherein said neutralizing binding protein has an on rate selected from the group consisting of: at least about $10^{2}M^{-1}s^{-1}$; at least about $10^{3}M^{-1}s^{-1}$; at least about $10^{4}M^{-1}s^{-1}$; at least about $10^{5}M^{-1}s^{-1}$; and at least about $10^{6}M^{-1}s^{-1}$.

137. The neutralizing binding protein according to claim 131, wherein said neutralizing binding protein has an off rate selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$.

138. A labeled binding protein comprising a binding protein of any one of Claims 94-137, wherein said binding protein is conjugated to a detectable label.

139. The labeled binding protein of Claim 138, wherein the detectable label is selected from the group consisting of a radiolabel, an enzyme, a fluorescent label, a luminescent label, a bioluminescent label, a magnetic label, and biotin.

140 The labeled binding protein of claim 139, wherein said label is a radiolabel selected from the group consisting of: $^{3}H$, $^{14}C$, $^{35}S$, $^{90}Y$, $^{99}Tc$, $^{111}In$, $^{125}I$, $^{131}I$, $^{177}Lu$, $^{166}Ho$, and $^{153}Sm$.

141. An antibody construct comprising a binding protein described in any of Claims 94-137 and further comprising a linker polypeptide or an immunoglobulin constant domain.

142. The antibody construct according to claim 141, selected from the group consisting of:

an immunoglobulin molecules,
a monoclonal antibody,
a chimeric antibody,
a CDR-grafted antibody,
a humanized antibody,
a Fab,

a Fab',
a $F(ab')_2$,
a Fv,
a disulfide linked Fv,
a scFv,
a single domain antibody,
a diabody,
a multispecific antibody,
a dual specific antibody, and
a bispecific antibody.

143. The antibody construct according to claim 141, wherein said antibody construct comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

a human IgM constant domain,
a human IgG1 constant domain,
a human IgG2 constant domain,
a human IgG3 constant domain,
a human IgG4 constant domain,
a human IgE constant domain,
a human IgA constant domain,
and a IgG constant domain variant with one or more mutations altering binding strength to Fc neonatal receptor, Fc gamma receptors, or C1q.

144. The antibody construct according to claim 141, comprising an immunoglobulin constant domain having an amino acid sequence selected from consisting of: SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, and combinations thereof.

145. An antibody conjugate comprising an antibody construct as described in Claim 141, wherein said antibody construct is conjugated to a therapeutic or cytotoxic agent.

146. The antibody conjugate of Claim 145, wherein said therapeutic or cytotoxic agent is selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

147. An isolated nucleic acid encoding a polypeptide selected from the group consisting of: a polypeptide comprising a heavy chain variable domain, wherein the heavy chain variable domain comprises one or more of CDR-H1, a CDR-H2, or a CDR-H3 as described in Claim 94; a polypeptide comprising a light chain variable domain, wherein the light chain variable domain comprises one or more of CDR-L1, a CDR-L2, or a CDR-L3 as described in Claim 94; or a combination of both polypeptides.

148. A vector comprising an isolated nucleic acid according to Claim 147.

149. The vector of Claim 148 wherein said vector is selected from the group consisting of: pcDNA, pTT, pTT3, pEFBOS, pBV, pJV, pHybE and pBJ.

150. A host cell comprising a vector according to any one of Claims 148 and 149.

151. The host cell according to claim 150, wherein said host cell is a prokaryotic cell.

152. The host cell according to claim 151, wherein said host cell is *Escherichia coli*.

153. The host cell according to claim 152, wherein said host cell is a eukaryotic cell.

154. The host cell according to claim 153, wherein said eukaryotic cell is selected from the group consisting of: a protist cell, an animal cell, a plant cell, and a fungal cell.

155. The host cell according to claim 154, wherein said eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

156. The host cell according to claim 155, wherein said mammalian cell is a CHO cell.

157. The host cell according to claim 155, wherein said mammalian cell is a COS cell.

158. The host cell according to claim 154, wherein said fungal cell is *Saccharomyces cerevisiae*.

159. The host cell according to claim 155, wherein said insect cell is an Sf9 cell.

160. A method of producing a binding protein that binds human DLL4, comprising culturing the host cell of any one of claims 150-159 in a culture medium under conditions sufficient to produce a binding protein that binds human DLL4.

161. A binding protein produced according to the method of claim 160.

162. A crystallized binding protein comprising a binding protein according to any one of Claims 94-137, wherein said binding protein exists as a crystal.

163. The crystallized binding protein according to claim 162, wherein said crystal is a carrier-free pharmaceutical controlled release crystal.

164. The crystallized binding protein according to claim 162, wherein said binding protein has a greater half life *in vivo* than the soluble counterpart of said binding protein.

165. The crystallized binding protein according to claim 162, wherein said binding protein retains biological activity.

166. A composition for the release of a binding protein said composition comprising:
(a) a formulation, wherein said formulation comprises a crystallized binding protein, according to any one of claims 162-165, and an ingredient; and
(b) at least one polymeric carrier.

167. The composition according to claim 166, wherein said polymeric carrier is a polymer selected from one or more of the group consisting of: poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), poly (esters), poly (lactic acid), poly (lactic-co-glycolic acid) or PLGA, poly (b-hydroxybutryate), poly (caprolactone), poly (dioxanone), poly (ethylene glycol), poly ((hydroxypropyl) methacrylamide, poly [(organo)phosphazene], poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride- alkyl vinyl ether copolymers, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polyeaccharides, blends and copolymers thereof.

168. The composition according to claim 166, wherein said ingredient is selected from the group consisting of albumin, sucrose, trehalose, lactitol, gelatin, hydroxypropyl-β-cyclodextrin, methoxypolyethylene glycol and polyethylene glycol.

169. A method for treating a mammal comprising the step of administering to the mammal an effective amount of the composition according to claim 166.

170. A pharmaceutical composition comprising the binding protein of any one of Claims 94-137, and a pharmaceutically acceptable carrier.

172. The pharmaceutical composition of claim 170 which further comprises at least one additional therapeutic agent for treating a disorder in which DLL4 activity is detrimental.

173. The pharmaceutical composition of claim 172, wherein said additional agent is selected from the group consisting of: angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; corticosteroids; cyclosporine; rapamycin; FK506; and non-steroidal anti-inflammatory agents.

174. A method for reducing human DLL4 activity comprising contacting human DLL4 with the binding protein of any one of Claims 94-137 such that human DLL4 activity is reduced.

175. A method for reducing human DLL4 activity in a human subject suffering from a disorder in which DLL4 activity is detrimental, comprising administering to the human subject the binding protein of any one of Claims 94-137 such that human IL-17 activity in the human subject is reduced.

176. A method for treating a subject for a disease or a disorder in which DLL4 activity is detrimental by administering to the subject the binding protein of any one of Claims 94-137 such that treatment is achieved.

177. The method of claim 176, wherein said disorder is selected from the group consisting of: breast cancer, colon cancer, rectal cancer, lung cancer, oropharynx cancer, hypopharynx cancer, esophageal cancer, stomach cancer, pancreas cancer, liver cancer, gallbladder cancer, bile duct cancer, small intestine cancer, urinary tract cancer, female genital tract cancer, male genital tract cancer, endocrine gland cancer, skin cancer, hemangiomas, melanomas, sarcomas, brain tumor, nerve cancer, eye tumor, meninges cancer, solid tumors from hematopoietic malignancies, tumor metastases, ocular neovascularization, edema, rheumatoid arthritis, multiple sclerosis, atherosclerotic plaques, Crohn's disease,

inflammatory bowel disease, refractory ascites, psoriasis, sarcoidosis, arterial arteriosclerosis, sepsis, peptic ulcers, burns, and pancreatitis, polycystic ovarian disease (POD), endometriosis, uterine fibroids, benign prostate hypertrophy, and other angiogenesis independent and dependent diseases characterized by abberant DLL4 activity.

178. The method according to Claim 177, wherein the disorder is a primary and metastatic cancer.

179. The method according to Claim 177, wherein the urinary tract cancer is selected from the group consisting of renal cancer, bladder cancer, and urothelium cancer.

180. The method according to Claim 177, wherein the female genital tract cancer is selected from the group consisting of cervical cancer, uterine cancer, ovarian cancer, choriocarcinoma, and gestational trophoblastic disease.

181. The method according to Claim 177, wherein the male genital tract cancer is selected from the group consisting of prostate cancer, seminal vesicles cancer, testicular cancer, and germ cell tumor.

182. The method according to Claim 177, wherein the endocrine gland cancer is selected from the group consisting of thyroid cancer, adrenal cancer, and pituitary gland cancer.

183. The method according to Claim 177, wherein the sarcoma is selected from the group consisting of a bone sarcoma, a soft tissue sarcoma, and Kaposi's sarcoma.

184. The method according to Claim 177, wherein the meninges cancer is selected from the group consisting of an astrocytoma, a glioma, a glioblastoma, a retinoblastoma, a neuroma, a neuroblastoma, a Schwannoma, and a meningiomas.

185. The method according to Claim 177, wherein the solid tumor from a hematopoietic malignancy is a leukemia, a Hodgkin's leukemia, a non-Hodgkin's leukemia, a lymphoma, a Hodgkin's lymphoma, and a non-Hodgkin's lymphomas.

186. The method according to Claim 177, wherein the ocular neovascularization is selected from the group consisting of diabetic blindness, a retinopathy, an age-induced macular degeneration, and a rubeosis.

187. A method of treating a patient suffering from a disorder in which DLL4 is detrimental comprising the step of administering the binding protein of any one of claims 94-137 before, concurrent with, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an antibody or fragment thereof capable of binding human VEGFR2; methotrexate; an antibody, or fragment thereof, capable of binding human TNF; corticosteroids, cyclosporine, rapamycin, FK506, and non-steroidal anti-inflammatory agents.

WE CLAIM:

1. A binding protein comprising an antigen binding domain, said binding protein being capable of binding human DLL4, said antigen binding domain comprising six CDRs: CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3, wherein:
CDR-H1 is selected from the group consisting of:
residues 31-37 of SEQ ID NO:1;
SEQ ID NO:117;
SEQ ID NO:121;
SEQ ID NO:125;
SEQ ID NO:129;
SEQ ID NO:133;
SEQ ID NO:137;
SEQ ID NO:141;
SEQ ID NO:145;
SEQ ID NO:149;
SEQ ID NO:153;
SEQ ID NO:157;
SEQ ID NO:161;
SEQ ID NO:165;
SEQ ID NO:169;
SEQ ID NO:173;
SEQ ID NO:177;
SEQ ID NO:181;
SEQ ID NO:185;
SEQ ID NO:189;
SEQ ID NO:193;
SEQ ID NO:197;
SEQ ID NO:201;
SEQ ID NO:205;
SEQ ID NO:209;
SEQ ID NO:213;
residues 31-37 of SEQ ID NO:334;
residues 31-37 of SEQ ID NO:336;
residues 31-37 of SEQ ID NO:338;
residues 31-37 of SEQ ID NO:340;
residues 31-37 of SEQ ID NO:342;

residues 31-37 of SEQ ID NO:344;
residues 31-37 of SEQ ID NO:346;
residues 31-37 of SEQ ID NO:348;
residues 31-37 of SEQ ID NO:350;
residues 31-37 of SEQ ID NO:352;
residues 31-37 of SEQ ID NO:354;
residues 31-37 of SEQ ID NO:356;
residues 31-37 of SEQ ID NO:358; and
residues 31-37 of SEQ ID NO:360;

CDR-H2, selected from the group consisting of:

residues 52-67 of SEQ ID NO:1;
SEQ ID NO:118;
SEQ ID NO:122;
SEQ ID NO:126;
SEQ ID NO:130;
SEQ ID NO:134;
SEQ ID NO:138;
SEQ ID NO:142;
SEQ ID NO:146;
SEQ ID NO:150;
SEQ ID NO:154;
SEQ ID NO:158;
SEQ ID NO:162;
SEQ ID NO:166;
SEQ ID NO:170;
SEQ ID NO:174;
SEQ ID NO:178;
SEQ ID NO:182;
SEQ ID NO:186;
SEQ ID NO:190;
SEQ ID NO:194;
SEQ ID NO:198;
SEQ ID NO:202;
SEQ ID NO:206;
SEQ ID NO:210;
SEQ ID NO:214;
residues 52-67 of SEQ ID NO:334;

residues 52-67 of SEQ ID NO:336;
residues 52-67 of SEQ ID NO:338;
residues 52-67 of SEQ ID NO:340;
residues 52-67 of SEQ ID NO:342;
residues 52-67 of SEQ ID NO:344;
residues 52-67 of SEQ ID NO:346;
residues 52-67 of SEQ ID NO:348;
residues 52-67 of SEQ ID NO:350;
residues 52-67 of SEQ ID NO:352;
residues 52-67 of SEQ ID NO:354;
residues 52-67 of SEQ ID NO:356;
residues 52-67 of SEQ ID NO:358; and
residues 52-67 of SEQ ID NO:360;

CDR-H3 is selected from the group consisting of:

residues 100-110 of SEQ ID NO:1;
SEQ ID NO:119;
SEQ ID NO:123;
SEQ ID NO:127;
SEQ ID NO:131;
SEQ ID NO:135;
SEQ ID NO:139;
SEQ ID NO:143;
SEQ ID NO:147;
SEQ ID NO:151;
SEQ ID NO:155;
SEQ ID NO:159;
SEQ ID NO:163;
SEQ ID NO:167;
SEQ ID NO:171;
SEQ ID NO:175;
SEQ ID NO:179;
SEQ ID NO:183;
SEQ ID NO:187;
SEQ ID NO:191;
SEQ ID NO:195;
SEQ ID NO:199;
SEQ ID NO:203;

SEQ ID NO:207;
SEQ ID NO:211;
SEQ ID NO:215;
residues 100-110 of SEQ ID NO:334;
residues 100-110 of SEQ ID NO:336;
residues 100-110 of SEQ ID NO:338;
residues 100-110 of SEQ ID NO:340;
residues 100-110 of SEQ ID NO:342;
residues 100-110 of SEQ ID NO:344;
residues 100-110 of SEQ ID NO:346;
residues 100-110 of SEQ ID NO:348;
residues 100-110 of SEQ ID NO:350;
residues 100-110 of SEQ ID NO:352;
residues 100-110 of SEQ ID NO:354;
residues 100-110 of SEQ ID NO:356;
residues 100-110 of SEQ ID NO:358; and
residues 100-110 of SEQ ID NO:360;

CDR-L1 is selected from the group consisting of:
residues 23-33 of SEQ ID NO:111;
SEQ ID NO:217;
SEQ ID NO:221;
SEQ ID NO:225;
SEQ ID NO:229;
SEQ ID NO:233;
SEQ ID NO:237;
SEQ ID NO:241;
SEQ ID NO:245;
SEQ ID NO:249;
SEQ ID NO:253;
SEQ ID NO:257;
SEQ ID NO:261;
SEQ ID NO:265;
SEQ ID NO:269;
SEQ ID NO:273;
SEQ ID NO:277;
SEQ ID NO:281;
SEQ ID NO:285;

SEQ ID NO:289;
SEQ ID NO:293;
SEQ ID NO:297;
SEQ ID NO:301;
SEQ ID NO:305;
SEQ ID NO:309;
SEQ ID NO:313;
residues 23-33 of SEQ ID NO:335;
residues 23-33 of SEQ ID NO:337;
residues 23-33 of SEQ ID NO:339;
residues 23-33 of SEQ ID NO:341;
residues 23-33 of SEQ ID NO:343;
residues 24-34 of SEQ ID NO:345;
residues 23-33 of SEQ ID NO:347;
residues 24-34 of SEQ ID NO:349;
residues 24-34 of SEQ ID NO:351;
residues 24-34 of SEQ ID NO:353;
residues 24-34 of SEQ ID NO:355;
residues 23-33 of SEQ ID NO:357;
residues 23-33 of SEQ ID NO:359; and
residues 23-33 of SEQ ID NO:361;

CDR-L2 is selected from the group consisting of:
residues 49-55 of SEQ ID NO:111;
SEQ ID NO:230;
SEQ ID NO:234;
SEQ ID NO:238;
SEQ ID NO:242;
SEQ ID NO:246;
SEQ ID NO:250;
SEQ ID NO:254;
SEQ ID NO:258;
SEQ ID NO:262;
SEQ ID NO:266;
SEQ ID NO:270;
SEQ ID NO:218;
SEQ ID NO:222;
SEQ ID NO:226;

SEQ ID NO:274;
SEQ ID NO:278;
SEQ ID NO:302;
SEQ ID NO:294;
SEQ ID NO:282;
SEQ ID NO:290;
SEQ ID NO:298;
SEQ ID NO:286;
SEQ ID NO:306;
SEQ ID NO:310;
SEQ ID NO:314;
residues 49-55 of SEQ ID NO:335;
residues 49-55 of SEQ ID NO:337;
residues 49-55 of SEQ ID NO:339;
residues 49-55 of SEQ ID NO:341;
residues 49-55 of SEQ ID NO:343;
residues 50-56 of SEQ ID NO:345;
residues 49-55 of SEQ ID NO:347;
residues 50-56 of SEQ ID NO:349;
residues 50-56 of SEQ ID NO:351;
residues 50-56 of SEQ ID NO:353;
residues 50-56 of SEQ ID NO:355;
residues 49-55 of SEQ ID NO:357;
residues 49-55 of SEQ ID NO:359; and
residues 49-55 of SEQ ID NO:361;

and

CDR-L3 is selected from the group consisting of:

residues 88-96 of SEQ ID NO:111;
SEQ ID NO:231;
SEQ ID NO:235;
SEQ ID NO:239;
SEQ ID NO:243;
SEQ ID NO:247;
SEQ ID NO:251;
SEQ ID NO:255;
SEQ ID NO:259;
SEQ ID NO:263;

SEQ ID NO:267;
SEQ ID NO:271;
SEQ ID NO:219;
SEQ ID NO:223;
SEQ ID NO:227;
SEQ ID NO:275;
SEQ ID NO:279;
SEQ ID NO:303;
SEQ ID NO:295;
SEQ ID NO:283;
SEQ ID NO:291;
SEQ ID NO:299;
SEQ ID NO:287;
SEQ ID NO:307;
SEQ ID NO:311;
SEQ ID NO:315;
residues 88-96 of SEQ ID NO:335;
residues 88-96 of SEQ ID NO:337;
residues 88-96 of SEQ ID NO:339;
residues 88-96 of SEQ ID NO:341;
residues 88-96 of SEQ ID NO:343;
residues 89-97 of SEQ ID NO:345;
residues 88-96 of SEQ ID NO:347;
residues 89-97 of SEQ ID NO:349;
residues 89-97 of SEQ ID NO:351;
residues 89-97 of SEQ ID NO:353;
residues 89-97 of SEQ ID NO:355;
residues 88-96 of SEQ ID NO:357;
residues 88-96 of SEQ ID NO:359; and
residues 88-96 of SEQ ID NO:361.

2. The binding protein according to claim 1, wherein said binding protein comprises at least 3 CDRs selected from the group of variable domain CDR sets consisting of:

VH E9 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:1

CDR-H2: residues 52-67 of SEQ ID NO:1

CDR-H3 residues 100-110 of SEQ ID NO:1

VL E9 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:111

CDR-L2: residues 49-55 of SEQ ID NO:111

CDR-L3: residues 88-96 of SEQ ID NO:111

VH E9.4 CDR Set

CDR-H1: SEQ ID NO:117

CDR-H2: SEQ ID NO:118

CDR-H3: SEQ ID NO:119

VL E9.4 CDR Set

CDR-L1: SEQ ID NO:229

CDR-L2: SEQ ID NO:230

CDR-L3: SEQ ID NO:231

VH E9.11 CDR Set

CDR-H1: SEQ ID NO:121

CDR-H2: SEQ ID NO:122

CDR-H3: SEQ ID NO:123

VL E9.11 CDR Set

CDR-L1: SEQ ID NO:233

CDR-L2: SEQ ID NO:234

CDR-L3: SEQ ID NO:235

VH E9.14 CDR Set

CDR-H1: SEQ ID NO:125

CDR-H2: SEQ ID NO:126

CDR-H3: SEQ ID NO:127

VL E9.14 CDR Set

CDR-L1: SEQ ID NO:237

CDR-L2: SEQ ID NO:238

CDR-L3: SEQ ID NO:239

VH E9.17 CDR Set

CDR-H1: SEQ ID NO:129

CDR-H2: SEQ ID NO:130

CDR-H3: SEQ ID NO:131

VL E9.17 CDR Set

CDR-L1: SEQ ID NO:241

CDR-L2: SEQ ID NO:242

CDR-L3: SEQ ID NO:243

VH E9.18 CDR Set

CDR-H1: SEQ ID NO:133

CDR-H2: SEQ ID NO:134

CDR-H3: SEQ ID NO:135

VL E9.18 CDR Set

CDR-L1: SEQ ID NO:245

CDR-L2: SEQ ID NO:246

CDR-L3: SEQ ID NO:247

VH E9.19 CDR Set

CDR-H1: SEQ ID NO:137

CDR-H2: SEQ ID NO:138

CDR-H3: SEQ ID NO:139

VL E9.19 CDR Set

CDR-L1: SEQ ID NO:249

CDR-L2: SEQ ID NO:250

CDR-L3: SEQ ID NO:251

VH E9.22 CDR Set

CDR-H1: SEQ ID NO:141

CDR-H2: SEQ ID NO:142

CDR-H3: SEQ ID NO:143

VL E9.22 CDR Set

CDR-L1: SEQ ID NO:253

CDR-L2: SEQ ID NO:254

CDR-L3: SEQ ID NO:255

VH E9.48 CDR Set

CDR-H1: SEQ ID NO:145

CDR-H2: SEQ ID NO:146

CDR-H3: SEQ ID NO:147

VL E9.48 CDR Set

CDR-L1: SEQ ID NO:257

CDR-L2: SEQ ID NO:258

CDR-L3: SEQ ID NO:259

VH E9.65 CDR Set

CDR-H1: SEQ ID NO:149

CDR-H2: SEQ ID NO:150

CDR-H3: SEQ ID NO:151

VL E9.65 CDR Set

CDR-L1: SEQ ID NO:261

CDR-L2: SEQ ID NO:262

CDR-L3: SEQ ID NO:263

VH E9.66 CDR Set

CDR-H1: SEQ ID NO:153

CDR-H2: SEQ ID NO:154

CDR-H3: SEQ ID NO:155

VL E9.66 CDR Set

CDR-L1: SEQ ID NO:265

CDR-L2: SEQ ID NO:266

CDR-L3: SEQ ID NO:267

VH E9.71 CDR Set

CDR-H1: SEQ ID NO:157

CDR-H2: SEQ ID NO:158

CDR-H3: SEQ ID NO:159

VL E9.71 CDR Set

CDR-L1: SEQ ID NO:269

CDR-L2: SEQ ID NO:270

CDR-L3: SEQ ID NO:271

VH E9.13 CDR Set

CDR-H1: SEQ ID NO:161

CDR-H2: SEQ ID NO:162

CDR-H3: SEQ ID NO:163

VL E9.13 CDR Set

CDR-L1: SEQ ID NO:217

CDR-L2: SEQ ID NO:218

CDR-L3: SEQ ID NO:219

VH E9.16 CDR Set

CDR-H1: SEQ ID NO:165

CDR-H2: SEQ ID NO:166

CDR-H3: SEQ ID NO:167

VL E9.16 CDR Set

CDR-L1: SEQ ID NO:221

CDR-L2: SEQ ID NO:222

CDR-L3: SEQ ID NO:223

VH E9.38 CDR Set

CDR-H1: SEQ ID NO:169

CDR-H2: SEQ ID NO:170

CDR-H3: SEQ ID NO:171

VL E9.38 CDR Set

CDR-L1: SEQ ID NO:225

CDR-L2: SEQ ID NO:226

CDR-L3: SEQ ID NO:227

VH E9.2B CDR Set

CDR-H1: SEQ ID NO:173

CDR-H2: SEQ ID NO:174

CDR-H3: SEQ ID NO:175

VL E9.2B CDR Set

CDR-L1: SEQ ID NO:273

CDR-L2: SEQ ID NO:274

CDR-L3: SEQ ID NO:275

VH E9.1F CDR Set

CDR-H1: SEQ ID NO:177

CDR-H2: SEQ ID NO:178

CDR-H3: SEQ ID NO:179

VL E9.1F CDR Set

CDR-L1: SEQ ID NO:277

CDR-L2: SEQ ID NO:278

CDR-L3: SEQ ID NO:279

VH E9.10H CDR Set

CDR-H1: SEQ ID NO:181

CDR-H2: SEQ ID NO:182

CDR-H3: SEQ ID NO:183

VL E9.10H CDR Set

CDR-L1: SEQ ID NO:301

CDR-L2: SEQ ID NO:302

CDR-L3: SEQ ID NO:303

VH E9.5E CDR Set

CDR-H1: SEQ ID NO:185

CDR-H2: SEQ ID NO:186

CDR-H3: SEQ ID NO:187

VL E9.5E CDR Set

CDR-L1: SEQ ID NO:293

CDR-L2: SEQ ID NO:294

CDR-L3: SEQ ID NO:295

VH E9.10C CDR Set

CDR-H1: SEQ ID NO:189

CDR-H2: SEQ ID NO:190

CDR-H3: SEQ ID NO:191

VL E9.10C CDR Set

CDR-L1: SEQ ID NO:281

CDR-L2: SEQ ID NO:282

CDR-L3: SEQ ID NO:283

VH E9.7E CDR Set

CDR-H1: SEQ ID NO:193

CDR-H2: SEQ ID NO:194

CDR-H3: SEQ ID NO:195

VL E9.7E CDR Set

CDR-L1: SEQ ID NO:289

CDR-L2: SEQ ID NO:290

CDR-L3: SEQ ID NO:291

VH E9.12B CDR Set

CDR-H1: SEQ ID NO:197

CDR-H2: SEQ ID NO:198

CDR-H3: SEQ ID NO:199

VL E9.12B CDR Set

CDR-L1: SEQ ID NO:297

CDR-L2: SEQ ID NO:298

CDR-L3: SEQ ID NO:299

VH E9.10E CDR Set

CDR-H1: SEQ ID NO:201

CDR-H2: SEQ ID NO:202

CDR-H3: SEQ ID NO:203

VL E9.10E CDR Set

CDR-L1: SEQ ID NO:285

CDR-L2: SEQ ID NO:286

CDR-L3: SEQ ID NO:287

VH E9.6A CDR Set

CDR-H1: SEQ ID NO:205

CDR-H2: SEQ ID NO:206

CDR-H3: SEQ ID NO:207

VL E9.6A CDR Set

CDR-L1: SEQ ID NO:305

CDR-L2: SEQ ID NO:306

CDR-L3: SEQ ID NO:307

VH E9.7A CDR Set

CDR-H1: SEQ ID NO:209

CDR-H2: SEQ ID NO:210

CDR-H3: SEQ ID NO:211

VL E9.7A CDR Set

CDR-L1: SEQ ID NO:309

CDR-L2: SEQ ID NO:310

CDR-L3: SEQ ID NO:311

VH E9.8H CDR Set

CDR-H1: SEQ ID NO:213

CDR-H2: SEQ ID NO:214

CDR-H3: SEQ ID NO:215

VL E9.8H CDR Set

CDR-L1: SEQ ID NO:313

CDR-L2: SEQ ID NO:314

CDR-L3: SEQ ID NO:315

VH E9.1 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:334

CDR-H2: residues 52-67 of SEQ ID NO:334

CDR-H3: residues 100-110 of SEQ ID NO:334

VL E9.1 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:335

CDR-L2: residues 49-55 of SEQ ID NO:335

CDR-L3: residues 88-96 of SEQ ID NO:335

VH E9-SE1 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:336

CDR-H2: residues 52-67 of SEQ ID NO:336

CDR-H3: residues 100-110 of SEQ ID NO:336

VL E9-SE1 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:337

CDR-L2: residues 49-55 of SEQ ID NO:337

CDR-L3: residues 88-96 of SEQ ID NO:337

VH E9-SE2 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:338

CDR-H2: residues 52-67 of SEQ ID NO:338

CDR-H3: residues 100-110 of SEQ ID NO:338

VL E9-SE2 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:339

CDR-L2: residues 49-55 of SEQ ID NO:339

CDR-L3: residues 88-96 of SEQ ID NO:339

VH E9-SE3 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:340

CDR-H2: residues 52-67 of SEQ ID NO:340

CDR-H3: residues 100-110 of SEQ ID NO:340

VL E9-SE3 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:341

CDR-L2: residues 49-55 of SEQ ID NO:341

CDR-L3: residues 88-96 of SEQ ID NO:341

VH E9-SE4 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:342

CDR-H2: residues 52-67 of SEQ ID NO:342

CDR-H3: residues 100-110 of SEQ ID NO:342

VL E9-SE4 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:343

CDR-L2: residues 49-55 of SEQ ID NO:343

CDR-L3: residues 88-96 of SEQ ID NO:343

VH E9-SE5 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:344

CDR-H2: residues 52-67 of SEQ ID NO:344

CDR-H3: residues 100-110 of SEQ ID NO:344

VL E9-SE5 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:345

CDR-L2: residues 50-56 of SEQ ID NO:345

CDR-L3: residues 89-97 of SEQ ID NO:345

VH E9-SE6 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:346

CDR-H2: residues 52-67 of SEQ ID NO:346

CDR-H3: residues 100-110 of SEQ ID NO:346

VL E9-SE6 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:347

CDR-L2: residues 49-55 of SEQ ID NO:347

CDR-L3: residues 88-96 of SEQ ID NO:347

VH E9-SE7 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:348

CDR-H2: residues 52-67 of SEQ ID NO:348

CDR-H3: residues 100-110 of SEQ ID NO:348

VL E9-SE7 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:349

CDR-L2: residues 50-56 of SEQ ID NO:349

CDR-L3: residues 89-97 of SEQ ID NO:349

VH E9-SE8 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:350

CDR-H2: residues 52-67 of SEQ ID NO:350

CDR-H3: residues 100-110 of SEQ ID NO:350

VL E9-SE8 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:351

CDR-L2: residues 50-56 of SEQ ID NO:351

CDR-L3: residues 89-97 of SEQ ID NO:351

VH E9-FR1 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:352

CDR-H2: residues 52-67 of SEQ ID NO:352

CDR-H3: residues 100-110 of SEQ ID NO:352

VL E9-FR1 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:353

CDR-L2: residues 50-56 of SEQ ID NO:353

CDR-L3: residues 89-97 of SEQ ID NO:353

VH E9-FR2 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:354

CDR-H2: residues 52-67 of SEQ ID NO:354

CDR-H3: residues 100-110 of SEQ ID NO:354

VL E9-FR2 CDR Set

CDR-L1: residues 24-34 of SEQ ID NO:355

CDR-L2: residues 50-56 of SEQ ID NO:355

CDR-L3: residues 89-97 of SEQ ID NO:355

VH E9.71 CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:356

CDR-H2: residues 52-67 of SEQ ID NO:356

CDR-H3: residues 100-110 of SEQ ID NO:356

VL E9.71 CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:357

CDR-L2: residues 49-55 of SEQ ID NO:357

CDR-L3: residues 88-96 of SEQ ID NO:357

VH E9.71 (M) CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:358

CDR-H2: residues 52-67 of SEQ ID NO:358

CDR-H3: residues 100-110 of SEQ ID NO:358

VL E9.71 (M) CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:359

CDR-L2: residues 49-55 of SEQ ID NO:359

CDR-L3: residues 88-96 of SEQ ID NO:359

VH E9.71 (L) CDR Set

CDR-H1: residues 31-37 of SEQ ID NO:360

CDR-H2: residues 52-67 of SEQ ID NO:360

CDR-H3: residues 100-110 of SEQ ID NO:360

VL E9.71 (L) CDR Set

CDR-L1: residues 23-33 of SEQ ID NO:361

CDR-L2: residues 49-55 of SEQ ID NO:361

CDR-L3: residues 88-96 of SEQ ID NO:361

3. The binding protein according to claim 2, comprising at least two variable domain CDR sets.

4. The binding protein according to claim 3, wherein said at least two variable domain CDR sets are selected from a group consisting of:

VH E9 CDR Set and VL E9 CDR Set,

VH E9.4 CDR Set and VL E9.4 CDR Set,

VH E9.11 CDR Set and VL E9.11 CDR Set,

VH E9.14 CDR Set and VL E9.14 CDR Set,

VH E9.17 CDR Set and VL E9.17 CDR Set,

VH E9.18 CDR Set and VL E9.18 CDR Set,

VH E9.19 CDR Set and VL E9.19 CDR Set,

VH E9.22 CDR Set and VL E9.22 CDR Set,

VH E9.48 CDR Set and VL E9.48 CDR Set,

VH E9.65 CDR Set and VL E9.65 CDR Set,
VH E9.66 CDR Set and VL E9.66 CDR Set,
VH E9.71 CDR Set and VL E9.71 CDR Set,
VH E9.13 CDR Set and VL E9.13 CDR Set,
VH E9.16 CDR Set and VL E9.16 CDR Set,
VH E9.38 CDR Set and VL E9.38 CDR Set,
VH E9.2B CDR Set and VL E9.2B CDR Set,
VH E9.1F CDR Set and VL E9.1F CDR Set,
VH E9.10H CDR Set and VL E9.10H CDR Set,
VH E9.5E CDR Set and VL E9.5E CDR Set,
VH E9.10C CDR Set and VL E9.10C CDR Set,
VH E9.7E CDR Set and VL E9.7E CDR Set,
VH E9.12B CDR Set and VL E9.12B CDR Set,
VH E9.10E CDR Set and VL E9.10E CDR Set,
VH E9.6A CDR Set and VL E9.6A CDR Set,
VH E9.7A CDR Set and VL E9.7A CDR Set,
VH E9.8H CDR Set and VL E9.8H CDR Set,
VH E9-SE1 CDR Set and VL E9-SE1 CDR Set,
VH E9-SE2 CDR Set and VL E9-SE2 CDR Set,
VH E9-SE3 CDR Set and VL E9-SE3 CDR Set,
VH E9-SE4 CDR Set and VL E9-SE4 CDR Set,
VH E9-SE5 CDR Set and VL E9-SE5 CDR Set,
VH E9-SE6 CDR Set and VL E9-SE6 CDR Set,
VH E9-SE7 CDR Set and VL E9-SE7 CDR Set,
VH E9-SE8 CDR Set and VL E9-SE8 CDR Set,
VH E9-FR1 CDR Set and VL E9-FR1 CDR Set,
VH E9-FR2 CDR Set and VL E9-FR2 CDR Set,
VH E9.71 CDR Set and VL E9.71 CDR Set,
VH E9.71(M) CDR Set and VL E9.71(M) CDR Set, and
VH E9.71(L) CDR Set and VL E9.71(L) CDR Set.

5. The binding protein according to any one of Claims 1-4, further comprising a human acceptor framework.

6. The binding protein according to claim 4, wherein said human acceptor framework comprises an amino acid sequence selected from the group consisting of:

| | | | |
|---|---|---|---|
| SEQ ID NO.: 6, | SEQ ID NO.: 7, | SEQ ID NO.: 8, | SEQ ID NO.: 9, |
| SEQ ID NO.: 10, | SEQ ID NO.: 11, | SEQ ID NO.: 12, | SEQ ID NO.: 13, |
| SEQ ID NO.: 14, | SEQ ID NO.: 15, | SEQ ID NO.: 16, | SEQ ID NO.: 17, |
| SEQ ID NO.: 18, | SEQ ID NO.: 19 | SEQ ID NO.: 20, | SEQ ID NO.: 21, |
| SEQ ID NO.: 22, | SEQ ID NO.: 35, | SEQ ID NO.: 36, | SEQ ID NO.: 37, |
| SEQ ID NO.: 38, | SEQ ID NO.: 39, | SEQ ID NO.: 40, | SEQ ID NO.: 41, |
| SEQ ID NO.: 42, | SEQ ID NO.: 43, | SEQ ID NO.: 44, | SEQ ID NO.: 45, |
| SEQ ID NO.: 46, | SEQ ID NO.: 47, | SEQ ID NO.: 48, | SEQ ID NO.: 49, |
| SEQ ID NO.: 50, | SEQ ID NO.: 51, | SEQ ID NO.: 52, | SEQ ID NO.: 53, |
| SEQ ID NO.: 54, | SEQ ID NO.: 55, | SEQ ID NO.: 56, | SEQ ID NO.: 57, |
| SEQ ID NO.: 58, | SEQ ID NO.: 59, | SEQ ID NO.: 60, | SEQ ID NO.: 61, |
| SEQ ID NO.: 62, | | | |
| SEQ ID NO.: 23, | SEQ ID NO.: 24, | SEQ ID NO.: 25, | SEQ ID NO.: 26, |
| SEQ ID NO.: 27, | SEQ ID NO.: 28, | SEQ ID NO.: 29, | SEQ ID NO.: 30, |
| SEQ ID NO.: 31, | SEQ ID NO.: 32, | SEQ ID NO.: 33, | SEQ ID NO.: 34, |
| SEQ ID NO.: 63, | SEQ ID NO.: 64, | SEQ ID NO.: 65, | SEQ ID NO.: 66, |
| SEQ ID NO.: 67, | SEQ ID NO.: 68, | SEQ ID NO.: 69, | SEQ ID NO.: 70, |
| SEQ ID NO.: 71, | SEQ ID NO.: 72, | SEQ ID NO.: 73, | SEQ ID NO.: 74, |
| SEQ ID NO.: 75, | SEQ ID NO.: 76, | SEQ ID NO.: 77, | SEQ ID NO.: 78, |

SEQ ID NO.: 79, SEQ ID NO.: 80, SEQ ID NO.: 81, SEQ ID NO.: 82,

SEQ ID NO.: 83, SEQ ID NO.: 84, SEQ ID NO.: 85, SEQ ID NO.: 86,

SEQ ID NO.: 87, SEQ ID NO.: 88, SEQ ID NO.: 89, SEQ ID NO.: 90,

SEQ ID NO.: 91, SEQ ID NO.: 92, SEQ ID NO.: 93, SEQ ID NO.: 94,

SEQ ID NO.: 95, SEQ ID NO.: 96, SEQ ID NO.: 97, and SEQ ID NO.: 98.

7. The binding protein according to claim 6, wherein said human acceptor framework comprises at least one framework region amino acid substitution at a key residue, said key residue selected from the group consisting of:

a residue adjacent to a CDR;
a glycosylation site residue;
a rare residue;
a residue capable of interacting with human DLL4
a canonical residue;
a contact residue between heavy chain variable region and light chain variable region;
a residue within a Vernier zone; and
a residue in a region that overlaps between a Chothia-defined variable heavy chain CDR1 and a Kabat-defined first heavy chain framework.

8. The binding protein according to claim 7, wherein said key residue is selected from the group consisting of: 2H, 4H, 24H, 26H, 27H, 29H, 34H, 35H, 37H, 39H, 44H, 45H, 47H, 48H, 49H, 50H, 51H, 58H, 59H, 60H, 63H, 67H, 69H, 71H, 73H, 76H, 78H, 91H, 93H, 94H, 2L, 4L, 25L, 29L, 27bL, 33L, 34L, 36L, 38L, 43L, 44L, 46L, 47L, 48L, 49L, 55L, 58L, 62L, 64L, 71L, 87L, 89L, 90L, 91L, 94L, and 95L.

9. The binding protein according to claim 1, wherein said binding protein comprises at least one variable domain having amino acid sequence selected from the group consisting of:

SEQ ID NOS:1, 111, 116, 228, 120, 232, 124, 236, 128, 240, 132, 244, 136, 248, 140, 252, 144, 256, 148, 260, 152, 264, 156, 268, 160, 216, 164, 220, 168, 224, 172, 272, 176, 276, 180, 300, 184, 292, 188, 280, 192, 288, 196, 296, 200, 284, 204, 304,

208, 308, 212, 312, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, and 361.

10. The binding protein according to claim 9, wherein said binding protein comprises two variable domains, wherein said two variable domains have amino acid sequences selected from the group consisting of: SEQ ID NOS:1 and 111, SEQ ID NOS:116 and 228, SEQ ID NOS:120 and 232, SEQ ID NOS:124 and 236, SEQ ID NOS:128 and 240, SEQ ID NOS:132 and 244, SEQ ID NOS:136 and 248, SEQ ID NOS:140 and 252, SEQ ID NOS:144 and 256, SEQ ID NOS:148 and 260, SEQ ID NOS:152 and 264, SEQ ID NOS:156 and 268, SEQ ID NOS: 160 and 216, SEQ ID NOS: 164 and 220, SEQ ID NOS:168 and 224, SEQ ID NOS:172 and 272, SEQ ID NOS:176 and 276, SEQ ID NOS:180 and 300, SEQ ID NOS:184 and 292, SEQ ID NOS:188 and 280, SEQ ID NOS:192 and 288, SEQ ID NOS:196 and 296, SEQ ID NOS:200 and 284, SEQ ID NOS:204 and 304, SEQ ID NOS:208 and 308, SEQ ID NOS:212 and 312, SEQ ID NOS:334 and 335, SEQ ID NOS:336 and 337, SEQ ID NOS:338 and 339, SEQ ID NOS:340 and 341, SEQ ID NOS:342 and 343, SEQ ID NOS:344 and 345, SEQ ID NOS:346 and 347, SEQ ID NOS:348 and 349, SEQ ID NOS:350 and 351, SEQ ID NOS:352 and 353, SEQ ID NOS:354 and 355, SEQ ID NOS:356 and 357, SEQ ID NOS:358 and 359, SEQ ID NOS:360 and 361.

11. The binding protein according to claim 8, wherein said binding protein comprises at least one variable domain having an amino acid sequence selected from the group consisting of: SEQ ID NOS:1, 111, 116, 228, 120, 232, 124, 236, 128, 240, 132, 244, 136, 248, 140, 252, 144, 256, 148, 260, 152, 264, 156, 268, 160, 216, 164, 220, 168, 224, 172, 272, 176, 276, 180, 300, 184, 292, 188, 280, 192, 288, 196, 296, 200, 284, 204, 304, 208, 308, 212, 312, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, and 361.

12. The binding protein according to claim 1, further comprising a heavy chain immunoglobulin constant domain selected from the group consisting of: a human IgM constant domain; a human IgG1 constant domain; a human IgG2 constant domain; a human IgG3 constant domain; a human IgG4 constant domain; a human IgE constant domain and a human IgA constant domain.

13. The binding protein according to claim 9, wherein said heavy chain immunoglobulin constant domain is a human IgG1 constant domain, said human IgG1 constant

domain comprising amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3.

14. The binding protein according to claim 1, further comprising a light chain immunoglobulin constant domain, wherein said light chain immunoglobulin constant domain is a human Ig kappa constant domain comprising amino acid sequence SEQ ID NO:4.

15. The binding protein according to claim 1, further comprising a light chain immunoglobulin constant domain, wherein said light chain immunoglobulin constant domain is a human Ig lambda constant domain comprising amino acid sequence SEQ ID NO:5.

16. The binding protein according to Claim 1 wherein said binding protein is selected from the group consisting of: an immunoglobulin molecule, an scFv, a monoclonal antibody, a human antibody, a chimeric antibody, a humanized antibody, a single domain antibody, a Fab fragment, a Fab' fragment, an $F(ab')_2$, an Fv, a disulfide linked Fv, a single domain antibody, a diabody, a multispecific antibody, a bispecific antibody, and a dual specific antibody.

17. The binding protein according to claim 16, wherein said binding protein is a human antibody.

18. A binding protein capable of binding human DLL-4, said binding protein comprising:
an Ig constant heavy region having an amino acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:3;
an Ig constant light region having an amino acid sequence selected from the group consisting of SEQ ID NO:4 and SEQ ID NO:5;
an Ig variable heavy region having an amino acid sequence selected from the group consisting:
SEQ ID NOS:1, 116, 120, 124, 128, 132, 136, 140, 144, 148, 152, 156, 160, 164, 168, 172, 176, 180, 184, 188, 192, 196, 200, 204, 208, 212, 334, 336, 338, 340, 342, 344, 346, 348, 350, 352, 354, 356, 358, and 360; and
an Ig variable light region having an amino acid sequence selected from the group consisting:

SEQ ID NOS:111, 228, 232, 236, 240, 244, 248, 252, 256, 260, 264, 268, 216, 220, 224, 272, 276, 300, 292, 280, 288, 296, 284, 304, 308, 312, 335, 337, 339, 341, 343, 345, 347, 349, 351, 353, 355, 357, 359, and 361.

19. The binding protein according to Claim 18, wherein the Ig constant light region is SEQ ID NO:5.

20. The binding protein according to any one of Claims 1 to 19, wherein the binding protein is capable of blocking DLL4 interaction with a Notch protein selected from the group consisting of Notch-1, Notch-2, Notch-3, Notch-4, and combinations thereof.

21. The binding protein according to Claim 20, wherein the binding protein is capable of blocking DLL4 interaction with Notch-1 and Notch-4.

22. The binding protein according to any one of Claims 1 to 21, wherein the binding protein is capable of modulating a biological function of DLL4.

23. The binding protein according to any one of Claims 1 to 21, wherein said binding protein is capable of neutralizing a DLL4.

24. The binding protein according to claim 23, wherein said DLL4 is selected from the group consisting of: human DLL4, mouse DLL4, cynomolgus DLL4, and rat DLL4.

25. The binding protein according to claim 23, wherein said binding protein is capable of reducing normal angiogenesis.

26. The binding protein according to claim 23, wherein said binding protein has a dissociation constant ($K_D$) selected from the group consisting of: at most about $10^{-7}$ M; at most about $10^{-8}$ M; at most about $10^{-9}$ M; at most about $10^{-10}$ M; at most about $10^{-11}$ M; at most about $10^{-12}$ M; and at most $10^{-13}$ M.

27. The binding protein according to claim 23, wherein said binding protein has an on rate selected from the group consisting of: at least about $10^2 M^{-1}s^{-1}$; at least about $10^3 M^{-1}s^{-1}$; at least about $10^4 M^{-1}s^{-1}$; at least about $10^5 M^{-1}s^{-1}$; and at least about $10^6 M^{-1}s^{-1}$.

28. The binding protein according to claim 23, wherein said binding protein has an off rate selected from the group consisting of: at most about $10^{-3}s^{-1}$; at most about $10^{-4}s^{-1}$; at most about $10^{-5}s^{-1}$; and at most about $10^{-6}s^{-1}$.

29. A labeled binding protein comprising a binding protein of Claim 16, wherein said binding protein is conjugated to a detectable label.

30. An antibody construct comprising a binding protein described in Claim 1 and further comprising a linker polypeptide or an immunoglobulin constant domain.

31. The antibody construct according to claim 30, selected from the group consisting of:

an immunoglobulin molecule,
a monoclonal antibody,
a chimeric antibody,
a CDR-grafted antibody,
a humanized antibody,
a Fab,
a Fab',
a $F(ab')_2$,
a Fv,
a disulfide linked Fv,
a scFv,
a single domain antibody,
a diabody,
a multispecific antibody,
a dual specific antibody, and
a bispecific antibody.

32. The antibody construct according to claim 30, wherein said antibody construct comprises a heavy chain immunoglobulin constant domain selected from the group consisting of:

a human IgM constant domain,
a human IgG1 constant domain,
a human IgG2 constant domain,
a human IgG3 constant domain,
a human IgG4 constant domain,
a human IgE constant domain,

a human IgA constant domain,
and an IgG constant domain variant with one or more mutations altering binding strength to Fc neonatal receptor, Fc gamma receptors, or C1q.

33. An antibody conjugate comprising an antibody construct as described in Claim 30, wherein said antibody construct is conjugated to a therapeutic or cytotoxic agent.

34. The antibody conjugate of Claim 33, wherein said therapeutic or cytotoxic agent is selected from the group consisting of: an anti-metabolite, an alkylating agent, an antibiotic, a growth factor, a cytokine, an anti-angiogenic agent, an anti-mitotic agent, an anthracycline, toxin, and an apoptotic agent.

35. An isolated nucleic acid encoding a polypeptide selected from the group consisting of: a polypeptide comprising a heavy chain variable domain, wherein the heavy chain variable domain comprises one or more of CDR-H1, a CDR-H2, or a CDR-H3 as described in Claim 1; a polypeptide comprising a light chain variable domain, wherein the light chain variable domain comprises one or more of CDR-L1, a CDR-L2, or a CDR-L3 as described in Claim 1; or a combination of both polypeptides.

36. A vector comprising an isolated nucleic acid according to Claim 35.

37. A host cell comprising a vector according to Claim 36, wherein said cell is not a transformed host cell within a human.

38. The host cell according to claim 37, wherein said host cell is a eukaryotic cell selected from the group consisting of: a protist cell, an animal cell, a plant cell, and a fungal cell.

39. The host cell according to claim 38, wherein said eukaryotic cell is an animal cell selected from the group consisting of: a mammalian cell, an avian cell, and an insect cell.

40. The host cell according to claim 39, wherein said host cell is a CHO cell, a COS, a Sf9 cell, or a yeast cell.

41. A method of producing a binding protein that binds human DLL4, comprising culturing the host cell of Claim 37 in a culture medium under conditions sufficient to produce a binding protein that binds human DLL4.

42. A binding protein produced according to the method of claim 41.

43. A crystallized binding protein comprising a binding protein according to Claim 1, wherein said binding protein exists as a crystal.

44. A pharmaceutical composition comprising the binding protein of any one of Claims 1 to 19 or 42, and a pharmaceutically acceptable carrier, and optionally comprising an additional therapeutic agent.

45. The pharmaceutical composition of claim 44, wherein said additional agent is selected from the group consisting of: angiogenesis inhibitors; kinase inhibitors; co-stimulation molecule blockers; adhesion molecule blockers; anti-cytokine antibody or functional fragment thereof; methotrexate; corticosteroids; cyclosporine; rapamycin; FK506; and non-steroidal anti-inflammatory agents.

46. Use of the binding protein of any one of Claims 1 to 19, or 42, in the manufacture of a pharmaceutical composition for reducing human DLL4 activity.

47. Use of the binding protein of any one of Claims 1 to 19, or 42, in the manufacture of a pharmaceutical composition for reducing human DLL4 activity in a human subject suffering from a disorder in which DLL4 activity is detrimental.

48. The use of Claim 47, wherein said disorder is selected from the group consisting of: breast cancer, colon cancer, rectal cancer, lung cancer, oropharynx cancer, hypopharynx cancer, esophageal cancer, stomach cancer, pancreas cancer, liver cancer, gallbladder cancer, bile duct cancer, small intestine cancer, urinary tract cancer, female genital tract cancer, male genital tract cancer, endocrine gland cancer, skin cancer, hemangiomas, melanomas, sarcomas, brain tumor, nerve cancer, eye tumor, meninges cancer, solid tumors from hematopoietic malignancies, tumor metastases, ocular neovascularization, edema, rheumatoid arthritis, multiple sclerosis, atheroscleorotic plaques, Crohn's disease, inflammatory bowel disease, refractory ascites, psoriasis, sarcoidosis, arterial arteriosclerosis, sepsis, peptic ulcers, burns, and pancreatitis, polycystic ovarian disease (POD), endometriosis,

uterine fibroids, benign prostate hypertrophy, and other angiogenesis independent and dependent diseases characterized by abberant DLL4 activity.

49. Use of the binding protein of any one of Claims 1 to 19, or 42, in the manufacture of a pharmaceutical composition for treating a patient suffering from a disorder in which DLL4 is detrimental, wherein said composition is for administration before, concurrent with, or after the administration of a second agent, wherein the second agent is selected from the group consisting of an antibody or fragment thereof capable of binding human VEGFR2; methotrexate; an antibody, or fragment thereof, capable of binding human TNF; corticosteroids, cyclosporine, rapamycin, FK506, and non-steroidal anti-inflammatory agents.