CLAIMS

1. A polypeptide comprising at least one immunoglobulin single variable domain (ISVD) specifically binding CD40L, and optionally comprising an ISVD binding serum albumin and/or a C-terminal extension, wherein binding to CD40L modulates an activity of CD40L.

2. The polypeptide according to claim 1, wherein said ISVD specifically binding CD40L essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which
   (i) CDR1 is chosen from the group consisting of SEQ ID NOs: 33, 61, 40 and 68; and amino acid sequences that have 1, 2 or 3 amino acid difference(s) with SEQ ID NOs: 33, 61, 40 or 68;
   (ii) CDR2 is chosen from the group consisting of SEQ ID NOs: 35, 63, 42 and 70; and amino acid sequences that have 1, 2 or 3 amino acid difference(s) with SEQ ID NOs: 35, 63, 42 or 70; and
   (iii) CDR3 is chosen from the group consisting of SEQ ID NO: 37, 65, 44 and 72; and amino acid sequences that have 1, 2, 3 or 4 amino acid difference(s) with SEQ ID NOs: 37, 65, 44 or 72.

3. The polypeptide according to claim 2, in which CDR1 is chosen from the group consisting of
   (a) SEQ ID NO: 61 and
   (b) amino acid sequences that have 1, 2 or 3 amino acid difference(s) with SEQ ID NO: 61, wherein
      - at position 1 the G has been changed into E or R;
      - at position 2 the R has been changed into H or G;
      - at position 3 the T has been changed into I, A, S or P;
      - at position 4 the P has been changed into S;
      - at position 5 the L has been changed into P;
      - at position 6 the N has been changed into S, D or I;
      - at position 7 the Y has been changed into H;
      - at position 8 the H has been changed into N;
      - at position 9 the M has been changed into K, T or V; and/or
      - at position 10 the A has been changed into G, S or T;

   and/or

in which CDR2 is chosen from the group consisting of

(a) SEQ ID NO: 63; and

(b) amino acid sequences that have 1, 2 or 3 amino acid difference(s) with SEQ ID NO: 63, wherein

- at position 1 the A has been changed into G;
- at position 2 the I has been changed into V;
- at position 4 the S has been changed into N, R or G;
- at position 6 the L has been changed into I;
- at position 7 the G has been changed into S or D;
- at position 8 the S has been changed into G, I or F; and/or
- at position 9 the T has been changed into P or S;

and/or

in which CDR3 is chosen from the group consisting of

(a) SEQ ID NO: 65; and

(b) amino acid sequences that have 1, 2, 3 or 4 amino acid difference(s) with SEQ ID NO: 65, wherein

- at position 1 the R has been changed into Q or L;
- at position 2 the E has been changed into D or K;
- at position 3 the T has been changed into S, M, A or K;
- at position 4 the T has been changed into I, S, A or R;
- at position 5 the H has been changed into Y or N;
- at position 6 the Y has been changed into I, H or N;
- at position 7 the S has been changed into T, G, N or I;
- at position 8 the T has been changed into I or A;
- at position 9 the S has been changed into N or R;
- at position 10 the D has been changed into A;
- at position 11 the R has been changed into S or G;
- at position 13 the N has been changed into D, Y or S;
- at position 14 the E has been changed into V, A, D or N;
- at position 15 the M has been changed into I, V, K or T;
- at position 16 the R has been changed into K, S, W, M, G or T;
- at position 17 the H has been changed into N, L, Q, R or D;
- at position 19 the D has been changed into N; and/or
- at position 20 the Y has been changed into H, F or N.

4. The polypeptide according to any one of claims 2 to 3, in which

- CDR1 is SEQ ID NO: 33, CDR2 is SEQ ID NO: 35 and CDR3 is SEQ ID NO: 37; or
- CDR1 is SEQ ID NO: 61, CDR2 is SEQ ID NO: 63 and CDR3 is SEQ ID NO: 65.

5. The polypeptide according to any one of claims 2 to 4, in which said ISVD is SEQ ID NO: 8 or SEQ ID NO: 6.

6. The polypeptide according to claim 2, in which CDR1 is chosen from the group consisting of

(a) SEQ ID NO: 40; and

(b) amino acid sequences that have 1, 2 or 3 amino acid difference(s) with SEQ ID NO: 40, wherein

- at position 3 the T has been changed into S, N, A or I;
- at position 4 the L has been changed into Q, S, M or G;
- at position 8 the A has been changed into N or V;
- at position 9 the I has been changed into L or V; and/or
- at position 10 the G has been changed into A;

and/or

in which CDR2 is chosen from the group consisting of

(a) SEQ ID NO: 42; and

(b) amino acid sequences that have 1, 2 or 3 amino acid difference(s) with SEQ ID NO: 42, wherein

- at position 2 the I has been changed into V;
- at position 3 the S has been changed into G;
- at position 5 the E has been changed into G;
- at position 6 the G has been changed into S;
- at position 7 the S has been changed into G, N, T or I;
- at position 8 the T has been changed into A, P, I or S; and/or
- at position 9 the S has been changed into I, R or G;

and/or

in which CDR3 is chosen from the group consisting of

(a) SEQ ID NO: 44; and

(b) amino acid sequences that have 1, 2, 3 or 4 amino acid difference(s) with SEQ ID NO: 44, wherein

- at position 4 the R has been changed into S;
- at position 7 the L has been changed into F, M or W;

- at position 8 the G has been changed into D, A or S;
- at position 9 the S has been changed into G, N or R;
- at position 10 the S has been changed into G, N, T or R;
- at position 12 the D has been changed into G, N, E or V;
- at position 13 the T has been changed into N or A;
- at position 14 the Q has been changed into H, K, L or R;
- at position 15 the S has been changed into P or T;
- at position 16 the H has been changed into N or Y;
- at position 17 the Q has been changed into L, R or H;
- at position 18 the Y has been changed into F;
- at position 19 the D has been changed into G; and/or
- at position 20 the Y has been changed into F or N.

7. The polypeptide according to any one of claims 2 and 6, in which CDR1 is SEQ ID NO: 40, CDR2 is SEQ ID NO: 42 and CDR3 is SEQ ID NO: 44, preferably in which said ISVD is SEQ ID NO: 7 or SEQ ID NO: 3.

8. The polypeptide according to any one of claims 1 to 7, wherein said polypeptide binds to CD40L:
- with a KD between $1E^{-07}$ M and $1E^{-13}$ M, such as between $1E^{-08}$ M and $1E^{-12}$ M, preferably at most $1E^{-07}$ M, preferably lower than $1E^{-08}$ M or $1E^{-09}$ M, or even lower than $1E^{-10}$ M, such as $5E^{-11}$ M, $4E^{-11}$ M, $3E^{-11}$ M, $2E^{-11}$ M, $1.7E^{-11}$ M, $1E^{-11}$, or even $5E^{-12}$ M, $4E^{-12}$ M, $3E^{-12}$ M, $1E^{-12}$ M, for instance as determined by a KinExA;
- with an IC_{50} between $1E^{-07}$ M and $1E^{-12}$ M, such as between $1E^{-08}$ M and $1E^{-11}$ M, for instance as determined by a B-cell proliferation assay or as determined by a B-cell signaling assay; and/or
- with an IC_{50} of at most $1E^{-07}$ M, preferably $1E^{-08}$ M, $1E^{-09}$ M, or $5E^{-10}$ M, $4E^{-10}$ M, $3E^{-10}$ M, $2E^{-10}$ M, such as $1E^{-10}$ M; and/or
- with an off-rate of less than $5E^{-04}$ (s^{-1}), for instance as determined by SPR.

9. The polypeptide according to any one of claims 1 to 8, wherein said CD40L, is preferably human CD40L, preferably SEQ ID NO: 1.

10. The polypeptide according to any one of claims 1 to 9, wherein said modulation of an activity is
- antagonizing an activity of CD40L;
- blocking the binding of CD40L to CD40 of at least 20%, such as at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or even more, for instance as determined by ligand competition, B-cell

activation assay, AlphaScreen, or competitive binding assays, such as competition ELISA or competition FACS);

- antagonizing CD40 mediated induction of T-cell costimulatory molecules, such as CD80 and CD86 and/or immunostimulatory molecules such as IL12;
- inhibiting B-cell activation, for instance as determined by a TT IgG assay;
- not substantially inducing JNK phosphorylation in Jurkat T cells;
- not substantially inducing IFNγ secretion by Jurkat T cells co-stimulated with anti-CD3 antibody;
- not substantially inducing activation of primary endothelial cells; and/or
- not substantially inducing platelet activation or platelet aggregation, for instance as determined by a platelet activation assay or platelet aggregation assay.

11. The polypeptide according to any of claims 1 to 10, wherein said ISVD binding serum albumin essentially consists of 4 framework regions (FR1 to FR4, respectively) and 3 complementarity determining regions (CDR1 to CDR3 respectively), in which CDR1 is SEQ ID NO: 74, CDR2 is SEQ ID NO: 75 CDR3 is SEQ ID NO: 76, preferably said ISVD binding serum albumin is chosen from the group consisting of ALB135 (SEQ ID NO: 15), ALB129 (SEQ ID NO: 13), ALB8 (SEQ ID NO: 11), ALB23 (SEQ ID NO: 12), and ALB132 (SEQ ID NO: 14).

12. The polypeptide according to any of claims 1 to 11, wherein said C-terminal extension is a C-terminal extension (X)n , in which n is 1 to 10, preferably 1 to 5, such as 1, 2, 3, 4 or 5 (and preferably 1 or 2, such as 1); and each X is an (preferably naturally occurring) amino acid residue that is independently chosen, and preferably independently chosen from the group consisting of alanine (A), glycine (G), valine (V), leucine (L) or isoleucine (I).

13. The polypeptide according to any one of claims 1 to 12, wherein said polypeptide has at least 80%, 90%, 95% or 100% sequence identity with C010003318 (SEQ ID NO: 9) or C010003313 (SEQ ID NO: 78).

14. The polypeptide according to any one of claims 1 to 13 for use as a medicament.

15. The polypeptide according to any one of claims 1 to 13 for use in treating or preventing a symptom of an autoimmune disease, Systemic Lupus Erythematosus (SLE), Lupus Nephritis, Immune Thrombocytopenic Purpura (ITP), transplant rejection, Crohn's Disease, Sjögren's Syndrome, Inflammatory Bowel Disease (IBD), colitis, asthma/allergy, atherosclerosis, Myasthenia Gravis, Multiple Sclerosis, Psoriasis, Rheumatoid Arthritis, Ankylosing Spondylitis,

Coronary Heart Disease, Type 1 Diabetes, amyotrophic lateral sclerosis (ALS) and/or immune response to recombinant drug products, e.g., factor VII in hemophilia.

16. The polypeptide according to any one of claims 1 to 13, wherein said polypeptide cross-blocks the binding to CD40L of at least one of the polypeptides 46B03 (SEQ ID NO: 6), 28B02 (SEQ ID NO: 3) C010003290 (SEQ ID NO: 8) and C010003318 (SEQ ID NO: 9) and/or is cross-blocked from binding to CD40L by at least one of the polypeptides 46B03 (SEQ ID NO: 6), 28B02 (SEQ ID NO: 3) C010003290 (SEQ ID NO: 8) and C010003318 (SEQ ID NO: 9).

17. A polypeptide cross-blocking binding to CD40L by at least one of 46B03 (SEQ ID NO: 6), 28B02 (SEQ ID NO: 3) C010003290 (SEQ ID NO: 8) and C010003318 (SEQ ID NO: 9) and/or is cross-blocked from binding to CD40L by at least one of 46B03 (SEQ ID NO: 6), 28B02 (SEQ ID NO: 3) C010003290 (SEQ ID NO: 8) and C010003318 (SEQ ID NO: 9), wherein said polypeptide comprises at least one VH, VL, dAb, immunoglobulin single variable domain (ISVD) specifically binding to CD40L, wherein binding to CD40L modulates an activity of CD40L.