In another embodiment, the isolated antibody or protein of the invention comprises heavy chain (V_H) and light chain (V_L) variable regions having at least 60, 70, 80, 90, 95, 96, 97, 98, 99 or 100 percent sequence identity to V_H of Chir12.12 (SEQ ID NO:9) and V_L of Chir12.12 antibody (SEQ ID NO:10) respectively.

Specific examples of the antibodies according to the invention are

- mAb1 comprising heavy chain amino acid sequence of SEQ ID NO: 11 and light chain amino acid sequence of SEQ ID NO:12,
- mAb2 comprising heavy chain amino acid sequence of SEQ ID NO: 13 and light chain amino acid sequence of SEQ ID NO:14, or,
- mAb3 comprising heavy chain amino acid sequence of SEQ ID NO: 15 and light chain amino acid sequence of SEQ ID NO:16.

Accordingly, in another embodiment, the invention provides an isolated antibody or antigen-binding portion thereof directed against a target CD40 polypeptide (SEQ ID NO:28), wherein said antibody or antigen-binding portion is selected from the group consisting of:

a. mAb1 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 11 and light chain amino acid sequence of SEQ ID NO:12, and

b. mAb2 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 13 and light chain amino acid sequence of SEQ ID NO:14.

The isolated antibody or protein according to the invention may be used as a medicament. In particular, they are suitable for use in the treatment of autoimmune disorders, inflammatory disorders and/or in preventing or reducing the risk of graft rejection in transplantation.

The isolated antibody or protein according to the invention may be used in particular in the treatment of Multiple Sclerosis, Systemic Lupus Erythematosus, Sjögren's syndrome, Rheumatoid Arthritis, transplant rejection and graft-versus-host disease.

The invention also relates to pharmaceutical compositions comprising the above antibodies or proteins according to the invention, in combination with at least a pharmaceutically

acceptable excipient, diluent or carrier. Said pharmaceutical compositions may additionally comprise other active ingredients.

The invention also relates to a lyophilisate or a liquid formulation of an antibody or protein according to the invention.

The invention further relates to the isolated nucleic acid encoding the antibody or protein according to the invention and the corresponding cloning or expression vector comprising at least one nucleic acid selected from the group consisting of SEQ ID NOs: 22 to 27.

The invention also relates to a host cell comprising one or more cloning or expression vectors as defined above.

Summary

Anti-CD40 antibodies have not been reported to induce hemostatic events in patients, however elevations in pancreatic enzymes in B cell lymphoma patients receiving the anti-CD40 Ab Chir12.12 and the possible risk of pancreatitis precludes the use of this Fc-competent anti-CD40 antibody in chronic autoimmune disease and transplantation for safety reasons. We therefore generated Fc-silent IgG1 anti-CD40 antibodies (mAb1, mAb2, and mAb3) unable to mediate antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) both *in vitro* and *in vivo*. mAb1 was able to prolong non-human primate renal allograft survival in combination with sub-therapeutic doses of cyclosporine. In addition, mAb1 was able to completely suppress primary and secondary antibody responses to immunization with a T cell-dependent antigen. Crucially, there was no evidence of hemostatic events or abnormal pancreatic histology in either the transplant or immunization study. Collectively these results suggest mAb1 would be a safe and efficacious therapeutic, and could be used to treat patients suffering from B lymphocyte and antigen presenting cell driven autoimmune disease or undergoing allograft transplant where CD40-CD154 interactions are involved in contributing to pathology.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

CLAIMS

1. An isolated antibody or a protein comprising an antigen-binding portion of an antibody directed against a target CD40 polypeptide (SEQ ID NO:28), characterized in that said antibody or protein
   a. binds to CD40 polypeptide with a K_D of 10nM or less, and,
   b. comprises a silent IgG Fc region.

2. The isolated antibody or protein of Claim 1, wherein said antibody or protein inhibits CD40L induced signalling with an IC50 of 50ng/ml or less.

3. The isolated antibody or protein of any one of Claims 1 or 2, wherein said antibody of protein has no or low agonist activity with respect to CD40 signalling.

4. The isolated antibody or protein of any one of Claims 1 to 3, wherein said antibody or protein comprises a silent IgG Fc region selected from the group consisting of the amino acid sequence of SEQ ID NO:17, SEQ ID NO:18 or SEQ ID NO:19.

5. The isolated antibody or protein according to any one of Claims 1 to 4, comprising heavy chain (V_H) and light chain (V_L) variable regions having at least 60, 70, 80, 90, 95, 96, 97, 98, 99 or 100 percent sequence identity to V_H of SEQ ID NO:9 and V_L of SEQ ID NO:10 respectively.

6. The isolated antibody or protein according to any one of Claims 1 to 5, selected from the group consisting of:
   a. mAb1 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 11 and light chain amino acid sequence of SEQ ID NO:12,
   b. mAb2 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 13 and light chain amino acid sequence of SEQ ID NO:14, and,
   c. mAb3 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 15 and light chain amino acid sequence of SEQ ID NO:16.

7. The isolated antibody or protein according to any one of Claims 1 to 6, for use as a medicament.

8. The isolated antibody or protein according to any one of Claims 1 to 7, for use in the treatment of autoimmune disorders and/or inflammatory disorders.

9. The isolated antibody or protein according to any one of Claims 1 to 8, for use in preventing or reducing the risk of graft rejection in transplantation.

10. The isolated antibody or protein according to Claim 7, for use in the treatment of Multiple Sclerosis, Systemic Lupus Erythematosus, Sjögren's syndrome, Rheumatoid Arthritis, transplant rejection and graft-versus-host disease.

11. A pharmaceutical composition, comprising an antibody or protein according to any one of Claims 1 to 6, in combination with at least a pharmaceutically acceptable excipient, diluent or carrier.

12. The pharmaceutical composition of Claim 11, additionally comprising other active ingredients.

13. A liquid pharmaceutical formulation comprising an antibody or protein according to any one of Claims 1 to 6 with at least a buffer.

14. An isolated nucleic acid encoding the antibody or protein according to any one of Claims 1 to 6.

15. A cloning or expression vector comprising one or more nucleic acids according to Claim 14.

16. A cloning or expression vector according to Claim 15 comprising at least one of the following coding sequences (a)-(c), operatively linked to suitable promoter sequences:

(a) SEQ ID NO:22 and SEQ ID NO:23;

(b) SEQ ID NO:24 and SEQ ID NO:25; or,

(c) SEQ ID NO:26 and SEQ ID NO:27.

17. A host cell comprising one or more cloning or expression vectors according to Claim 15 to 16.

18. A process for the production of an antibody or a protein of any one of Claims 1 to 6, comprising culturing the host cell of Claim 17, purifying and recovering said antibody or protein.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An isolated antibody or antigen-binding portion thereof, directed against a target CD40 polypeptide (SEQ ID NO:28), wherein said antibody or antigen-binding portion is selected from the group consisting of:
   a. mAb1 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 11 and light chain amino acid sequence of SEQ ID NO:12, and
   b. mAb2 antibody comprising heavy chain amino acid sequence of SEQ ID NO: 13 and light chain amino acid sequence of SEQ ID NO:14.

2. A pharmaceutical composition, comprising the antibody or antigen-binding portion according to claim 1, in combination with at least a pharmaceutically acceptable excipient, diluent or carrier.

3. A liquid pharmaceutical formulation comprising the antibody or antigen-binding portion according to claim 1 with at least a buffer.

4. Use of the isolated antibody or antigen-binding portion according to claim 1 in the manufacture of a medicament for inhibiting CD40L-mediated CD40 signaling in a subject.

5. Use of the isolated antibody or antigen-binding portion according to claim 1 in the manufacture of a medicament for the treatment of an autoimmune or inflammatory disorder.

6. Use of claim 5 wherein the autoimmune or inflammatory disorder is multiple sclerosis, systemic lupus erythematosus, lupus nephritis, inflammatory bowel disease, Crohn's disease, Sjögren's syndrome, myasthenia gravis, rheumatoid arthritis, atherosclerosis, transplant rejection or graft-versus hose disease.