Patent Claims

1. A bispecific antibody for binding human CD20 and human transferrin receptor comprising

a) one antibody comprising two pairs each of an antibody light chain and an antibody heavy chain, wherein the binding sites formed by each of the pairs of the heavy chain and the light chain specifically bind to a first antigen, and

b) one additional Fab fragment, ~~wherein the additional Fab fragment is fused to the C-terminus of one of the heavy chains of the antibody,~~ wherein the binding site of the additional Fab fragment specifically binds to a second antigen,

~~wherein each of the antibody light chains comprises in the constant light chain domain (CL) at position 123 the amino acid residue arginine (instead of the wild-type glutamic acid residue; E123R mutation) and at position 124 the amino acid residue lysine (instead of the wild-type glutamine residue; Q124K mutation) (numbering according to Kabat),~~

~~wherein each of the antibody heavy chains comprises in the first constant heavy chain domain (CH1) at position 147 an glutamic acid residue (instead of the wild-type lysine residue; K147E mutation) and at position 213 an glutamic acid residue (instead of the wild-type lysine amino acid residue; K213E mutation) (numbering according to Kabat EU index),~~

~~wherein the additional Fab fragment specifically binding to the second antigen comprises a domain crossover such that the constant light chain domain (CL) and the constant heavy chain domain 1 (CH1) are replaced by each other, and~~

~~wherein the first antigen is human CD20 protein and the second antigen is human transferrin receptor~~said bispecific antibody comprising

- SEQ ID NO: 06 to 09, or

- SEQ ID NO: 11 to 13 and SEQ ID NO: 22, or

- SEQ ID NO: 14 to 17.

~~2. The antibody according to claim 1, wherein the additional Fab fragment is fused to the C-terminus of the heavy chain by a peptidic linker.~~

~~3~~2. The antibody according to ~~any one of claims 1 and 2~~claim 1, wherein

a) the heavy chain that is fused to the additional Fab fragments has as C-terminal heavy chain amino acid residues the tripeptide LSP wherein the proline thereof is directly fused to the first amino acid residue of the additional Fab fragment or of the peptidic linker via a peptide bond, and

b) the heavy chain that is not fused to the additional Fab fragments has as C-terminal heavy chain amino acid residues the tripeptide LSP, or SPG, or PGK.

~~4. The antibody according to anyone of claims 1 to 3, wherein the antibody is~~

~~a) a full length antibody of the human subclass IgG1, or~~

~~b) a full length antibody of the human subclass IgG4, or~~

~~c) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G,~~

~~d) a full length antibody of the human subclass IgG4 with the mutations S228P, L235E and P329G,~~

~~e) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain,~~

~~f) a full length antibody of the human subclass IgG4 with the mutations S228P and P329G in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain,~~

~~g) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, I253A, H310A and H435A in both heavy chains and the mutations T366W and S354C in one heavy chain and the~~

mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain,

h) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, M252Y, S254T and T256E in both heavy chains and the mutations T366W and S354C in one heavy chain and the mutations T366S, L368A, Y407V and Y349C in the respective other heavy chain, or

i) a full length antibody of the human subclass IgG1 with the mutations L234A, L235A, P329G, H310A, H433A and Y436A in both heavy chains and the mutations i) T366W, and ii) S354C or Y349C, in one heavy chain and the mutations i) T366S, L368A, and Y407V, and ii) Y349C or S354C, in the respective other heavy chain.

5. The antibody according to any one of claims 1 to 4, wherein the bispecific antibody comprises

i) a light chain that has a sequence identity to SEQ ID NO: 01 of 70 % or more,

ii) a heavy chain that has a sequence identity to SEQ ID NO: 02 of 70 % or more,

iii) a light chain that has a sequence identity to SEQ ID NO: 03 of 70 % or more, and

iv) a heavy chain Fab fragment that has a sequence identity to SEQ ID NO: 04 of 70 % or more.

6. The antibody according to any one of claims 1 to 4, wherein the bispecific antibody comprises a light chain that has the amino acid sequence of SEQ ID NO: 01, a heavy chain that has the amino acid sequence of SEQ ID NO: 02, a light chain that has the amino acid sequence of SEQ ID NO: 03, and an antibody Fab fragment comprising the amino acid sequences of SEQ ID NO: 04.

7<u>3</u>. The antibody according to any one of claims 1 to 6<u>claim 1</u>, wherein the antibody is monoclonal.

~~8~~4. A pharmaceutical formulation for binding human CD20 and human transferrin receptor comprising the antibody according to any one of claims 1 to ~~7~~ 3 and a pharmaceutically acceptable carrier.

~~9~~5. The antibody according to any one of claims 1 to ~~7~~ 3 for use as a medicament.

~~10. The antibody according to any one of claims 1 to 7 for the treatment of multiple sclerosis.~~

~~11. Use of the antibody according to any one of claims 1 to 7 in the manufacture of a medicament.~~

~~12. The use of claim 11, wherein the medicament is for treatment of multiple sclerosis.~~

~~13. The use of claim 11, wherein the medicament is for depleting brain sequestered B-cells expressing CD20.~~

~~14. A method of treating an individual having multiple sclerosis comprising administering to the individual an effective amount of the antibody according to any one of claims 1 to 7.~~

~~15. A method of depleting brain sequestered B-cells expressing CD20 in an individual comprising administering to the individual an effective amount of the antibody according to any one of claims 1 to 7 to deplete brain sequestered B-cells expressing CD20.~~

6. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a proliferative disease.

7. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a B-cell proliferative disease.

8. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a B-cell lymphoma.

9. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a primary central nervous system lymphoma.

10. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of a tumor.

11. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of human carcinoma.

12. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an autoimmune disease.

13. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an autoimmune disease selected from the group consisting of inflammatory responses such as inflammatory skin diseases including psoriasis and dermatitis (e.g. atopic dermatitis); systemic scleroderma and sclerosis; responses associated with inflammatory bowel disease (such as Crohn's disease and ulcerative colitis); respiratory distress syndrome (including adult respiratory distress syndrome; ARDS); dermatitis; meningitis; encephalitis; uveitis; colitis; glomerulonephritis; allergic conditions such as eczema and asthma and other conditions involving infiltration of T-cells and chronic inflammatory responses; atherosclerosis; leukocyte adhesion deficiency; rheumatoid arthritis; systemic lupus erythematosus (SLE); diabetes mellitus (e.g. Type I diabetes mellitus or insulin dependent diabetes mellitus); multiple sclerosis; Reynaud's syndrome; autoimmune thyroiditis; allergic encephalomyelitis; Sjogren's syndrome; juvenile onset diabetes; and immune responses associated with acute and delayed hypersensitivity mediated by cytokines and T-lymphocytes typically found in tuberculosis, sarcoidosis, polymyositis, granulomatosis and vasculitis; pernicious anemia (Addison's disease); diseases involving leukocyte diapedesis; central nervous system (CNS) inflammatory disorder; multiple organ injury syndrome; hemolytic anemia (including, but not limited to cryoglobinemia or Coombs positive anemia); myasthenia gravis; antigen-antibody complex mediated diseases; anti-glomerular basement membrane disease; anti-phospholipid syndrome; allergic neuritis; Graves' disease; Lambert-Eaton myasthenic syndrome; pemphigoid bullous; pemphigus; autoimmune polyendocrinopathies; Reiter's disease; stiff-man syndrome; Bechet disease; giant cell arteritis; immune complex nephritis; IgA nephropathy; IgM polyneuropathies; immune thrombocytopenic purpura (ITP) or autoimmune thrombocytopenia.

14. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of multiple sclerosis.

15. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the treatment of secondary progressive multiple sclerosis.

16. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of tumor cells expressing CD20.

17. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of tumor cells expressing CD20 in the brain.

18. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of circulating B-cells expressing CD20.

19. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of circulating B-cells expressing CD20 in the brain.

20. Use of the antibody according to any one of claims 1 to 3 in the manufacture of a medicament for the depletion of brain sequestered B-cells expressing CD20.