To test the effect of -003, -005 and -024 on the enzymatic activity of CD38, recombinant His-CD38 protein was pre-incubated for 15 min at room temperature with various concentrations (30, 3, 0.3 and 0.03 µg/ml) of the different antibodies before adding the substrate NGD^+ .The production of cyclic GDP-ribose (cGDPR) was recorded at different time points after addition of antibodies (3, 6, 9, 12, 30, 45, 60, 75 and 90 min).

Fig 25B shows that -005 has a pronounced inhibitory effect on the production of cGDPR. After 90 minutes, addition of 30 and 3 µg/ml -005 resulted in a 32% and 34% reduced production of cGDPR (Table 9). Similar results were observed in independent experiments using different batches of -005.

No inhibitory effect on cGPDR production was observed after addition of -003 (Figure 25B, Table 9), -024 (Figure 25D, Table 9) or anti-KLH (Figure 25A, Table 9).

Based on these findings -005 is also expected to inhibit the synthesis of Cyclic ADP-ribose (cADPR) from NAD^+. Inhibition of the synthesis of cADPR can be determined according to the HPLC method described in Munshi et al., J. Biol. Chem. 275, 21566-21571 (2000).

Table 9. cGDPribose production in presence of CD38-specific antibodies or anti-KLH.

	Production (% of NGD control)			
	30 µg/ml	3 µg/ml	0.3 µg/ml	0.03 µg/ml
KLH	110	99	108	111
-003	99	100	107	107
-005	68	66	98	102
-024	99	100	104	105

EXAMPLE 24

Comparison of -003 and -005 with Morphosys antibody 3079.

Antibodies -003 and -005 were functionally compared to Morphosys antibody 3079 (TH-3079). Methods for cloning and expression of Morphosys antibody TH-3079 are described in Example 16. Methods for CDC are described in Example 6. Methods for ADCC are described in Example 5. Figure 26A shows that -005 and -003 and TH-3079 induce CDC-mediated lysis of CD38-transfected CHO cells, with similar maximal lysis. When EC_{50} values are compared, -005 antibody is better than TH3079 in inducing lysis of CHO-CD38 cells, with 2-times lower EC_{50} (see Table 10).

To test the effect of -003, -005 and -024 on the enzymatic activity of CD38, recombinant His-CD38 protein was pre-incubated for 15 min at room temperature with various concentrations (30, 3, 0.3 and 0.03 µg/ml) of the different antibodies before adding the substrate NGD^+.The production of cyclic GDP-ribose (cGDPR) was recorded at different time points after addition of antibodies (3, 6, 9, 12, 30, 45, 60, 75 and 90 min).

Fig 25C shows that -005 has a pronounced inhibitory effect on the production of cGDPR. After 90 minutes, addition of 30 and 3 µg/ml -005 resulted in a 32% and 34% reduced production of cGDPR (Table 9). Similar results were observed in independent experiments using different batches of -005.

No inhibitory effect on cGPDR production was observed after addition of -003 (Figure 25B, Table 9), -024 (Figure 25D, Table 9) or anti-KLH (Figure 25A, Table 9).

Based on these findings -005 is also expected to inhibit the synthesis of Cyclic ADP-ribose (cADPR) from NAD^+. Inhibition of the synthesis of cADPR can be determined according to the HPLC method described in Munshi et al., J. Biol. Chem. 275, 21566-21571 (2000).

Table 9. cGDPribose production in presence of CD38-specific antibodies or anti-KLH.

	Production (% of NGD control)			
	30 µg/ml	3 µg/ml	0.3 µg/ml	0.03 µg/ml
KLH	110	99	108	111
-003	99	100	107	107
-005	68	66	98	102
-024	99	100	104	105

EXAMPLE 24

Comparison of -003 and -005 with Morphosys antibody 3079.

Antibodies -003 and -005 were functionally compared to Morphosys antibody 3079 (TH-3079). Methods for cloning and expression of Morphosys antibody TH-3079 are described in Example 16. Methods for CDC are described in Example 6. Methods for ADCC are described in Example 5. Figure 26A shows that -005 and -003 and TH-3079 induce CDC-mediated lysis of CD38-transfected CHO cells, with similar maximal lysis. When EC_{50} values are compared, -005 antibody is better than TH3079 in inducing lysis of CHO-CD38 cells, with 2-times lower EC_{50} (see Table 10).

CLAIMS

1. An antibody binding to human CD38 encoded by

(i) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:1 and SEQ ID No:6, respectively;

(ii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:11 and SEQ ID No:16, respectively;

(iii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:21 and SEQ ID No:26, respectively; or

(iv) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions, which are conservative sequence modifications of the sequences as set forth in (i), (ii) or (iii).

2. An antibody comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID No:3, a V_L CDR2 having the sequence as set forth in SEQ ID No:4 and a V_L CDR3 having the sequence as set forth in SEQ ID No:5, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID No:8, a V_H CDR2 having the sequence as set forth in SEQ ID No:9 and a V_H CDR3 having the sequence as set forth in SEQ ID No:10.

3. An antibody binding to human CD38, comprising a V_L region having the amino acid sequence as set forth in SEQ ID No:2.

4. An antibody according to claim 2, comprising a V_L region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:2.

5. An antibody binding to human CD38, comprising a V_H region having the amino acid sequence as set forth in SEQ ID No:7.

6. An antibody according to claim 2, comprising a V_H region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:7.

7. An antibody according to claim 2, comprising a V_H region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:7.

8. An antibody binding to human CD38, comprising a V_L region as defined in claim 3 and a V_H region as defined in claim 5.

9. An antibody binding to human CD38, comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID

No:13, a V_L CDR2 having the sequence as set forth in SEQ ID No:14 and a V_L CDR3 having the sequence as set forth in SEQ ID No:15, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID No:18, a V_H CDR2 having the sequence as set forth in SEQ ID No:19 and a V_H CDR3 having the sequence as set forth in SEQ ID No:20.

10. An antibody binding to human CD38, comprising a V_L region having the amino acid sequence as set forth in SEQ ID No:12.

11. An antibody according to claim 9, comprising a V_L region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:12.

12. An antibody binding to human CD38, comprising a V_H region having the amino acid sequence as set forth in SEQ ID No:17.

13. An antibody according to claim 9, comprising a V_H region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:17.

14. An antibody according to claim 9, comprising a V_H region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:17.

15. An antibody binding to human CD38, comprising a V_L region as defined in claim 10 and a V_H region as defined in claim 12.

16. An antibody binding to human CD38, comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID No:23, a V_L CDR2 having the sequence as set forth in SEQ ID No:24 and a V_L CDR3 having the sequence as set forth in SEQ ID No:25, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID No:28, a V_H CDR2 having the sequence as set forth in SEQ ID No:29 and a V_H CDR3 having the sequence as set forth in SEQ ID No:30.

17. An antibody binding to human CD38, comprising a V_L region having the amino acid sequence as set forth in SEQ ID No:22.

18. An antibody according to claim 16, comprising a V_L region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:22.

19. An antibody binding to human CD38, comprising a V_H region having the amino acid sequence as set forth in SEQ ID No:27.

20. An antibody according to claim 16, comprising a V_H region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:27.

21. An antibody according to claim 16, comprising a V_H region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:27.

22. An antibody binding to human CD38, comprising a V_L region as defined in claim 17 and a V_H region as defined in claim 19.

23. An antibody which binds to human CD38 (SEQ ID No:31), and which does not bind to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), to the same degree that it binds to human CD38 (SEQ ID No:31).

23. An antibody according to claim 23, wherein the EC_{50} of the binding of the antibody to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), is less than 50%, such as less than 10%, less than 5% or less than 1% of the EC_{50} of the binding of the antibody to human CD38 (SEQ ID No:31).

24. An antibody which binds to human CD38 (SEQ ID No:31), and which does not bind to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), to the same degree that it binds to human CD38 (SEQ ID No:31).

25. An antibody according to claim 24, wherein the EC_{50} of the binding of the antibody to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), is less than 50%, such as less than 10%, less than 5% or less than 1% of the EC_{50} of the binding of the antibody to human CD38 (SEQ ID No:31).

26. An antibody according to any one of claims 23 to 25, wherein said antibody binds to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32), to the same degree that it binds to human CD38 (SEQ ID No:31).

27. An antibody according to claim 26, wherein the EC_{50} of the binding of the antibody to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32) corresponds to 75% - 125% of the EC_{50} of the binding of the antibody to human CD38 (SEQ ID No:31).

28. An antibody which binds to human CD38 (SEQ ID No:31), wherein the antibody possesses the following binding characteristics: (i) binds to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), to the same degree that it binds to human

CD38 (SEQ ID No:31), (ii) binds to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), to the same degree that it binds to human CD38 (SEQ ID No:31), and (iii) binds to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32), to the same degree that it binds to human CD38 (SEQ ID No:31).

29. An antibody which binds to human CD38 (SEQ ID No:31), wherein the antibody possesses the following binding characteristics: (i) does not bind to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), to the same degree that it binds to human CD38 (SEQ ID No:31), (ii) does not bind to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), to the same degree that it binds to human CD38 (SEQ ID No:31), (iii) binds to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32), to the same degree that it binds to human CD38 (SEQ ID No:31).

30. An antibody according to any one of claims 33, 35 or 37, wherein the EC_{50} is determined by use of an ELISA as described in Example 17 of the specification.

31. An antibody that specifically binds to a CD38 epitope, which epitope is also specifically bound by an antibody according to any one of claims 1, 8, 15 and 22.

32. An antibody that specifically binds to the region SKRNIQFSCKNIYR and the region EKVQTLEAWVIHGG of human CD38 (SEQ ID No:31).

33. An antibody according to any of claims 1-32, which antibody possesses one or more of the following characteristics:

(i) acts as an antagonist of CD38;

(ii) does not induce significant proliferation of peripheral blood mononuclear cells as determined by the method described in Example 18 of the specification;

(iii) does not induce release of significant IL-6 by human monocytes or peripheral blood mononuclear cells as determined by the method described in Example 19 of the specification;

(iv) does not induce release of detectable IFN-γ by human T cells or peripheral blood mononuclear cells as determined by the method described in Example 20 of the specification;

(v) is internalized by CD38 expressing cells; such as internalized by CHO-CD38 cells within 5 to 15 minutes at 37°C by the method as described in Example 12 of the specification;

(vi) induces ADCC; such as with an EC_{50} value of below 15 ng/ml, such as below 10 ng/ml in Daudi-luc cells and with an EC_{50} value of below 75 ng/ml, such as below 50 ng/ml, 30 ng/ml or 10 ng/ml in MM cells as determined by the method described in example 5 of the specification;
(vii) induces CDC in the presence of complement; such as with an EC_{50} value of below 5 µg/ml, such as below 1 µg/ml in daudi-luc or CD38-CHO cells by the method described in Example 6 of the specification;
(viii) inhibits the synthesis of cGDPR;
(ix) inhibits the synthesis of cADPR;
(x) binds to human CD38 with an affinity (K_D) of below 10^{-8} M, such as in the range of from 10^{-8} M to -10^{-11} M, for example in the range of from 7×10^{-9} M to -10^{-10} M, as determined by surface plasmon resonance as described in Example 20 of the specification.

34. An antibody according to claim 33, wich inhibits the synthesis of cGDPR by at least 25%, such as at least 30% after 90 minutes at a concentration of 3 µg/ml as determined by spectophotometric method described in Example 24 of the specification.

35. An antibody according to claim 33, wich inhibits the synthesis of cADPR by at least 25%, such as at least 30% after 90 minutes at a concentration of 3 µg/ml as determined by the HPLC method described in Munshi et al., J. Biol. Chem. 275, 21566-21571 (2000).

36. An antibody according to any one of claims 23 to 35, which is a human monoclonal antibody.

37. An antibody according to any one of claims 1 to 36, characterized in that it is a full length IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody, such as an IgG1 antibody, preferably an IgG1,κ antibody or an IgM antibody, preferably an IgM,κ antibody.

38. An antibody according to any one of claims 1 to 37, wherein the antibody is glycosylated in a eukaryotic cell.

39. An antibody according to any one of claims 1 to 38, which is an antibody fragment or a single chain antibody.

40. An antibody according to any one of claims 1 to 39, further comprising a chelator linker for attaching a radioisotope.

41. An antibody according to any one of claims 1 to 40, which is in a substantially isolated form.

42. An isolated nucleic acid encoding an antibody according to any one of claims 1 to 41.

43. An expression vector comprising a nucleic acid sequence encoding an antibody according to any one of claims 1 to 42.

44. An expression vector comprising
(i) a V_L nucleotide sequence of SEQ ID No:1,
(ii) a V_H nucleotide sequence of SEQ ID No:6,
(iii) a V_L nucleotide sequence of SEQ ID No:1 and a V_H nucleotide sequence of SEQ ID No:6;
(iv) a V_L nucleotide sequence of SEQ ID No:11;
(v) a V_H nucleotide sequence of SEQ ID No:16;
(vi) a V_L nucleotide sequence of SEQ ID No:11 and a V_H nucleotide sequence of SEQ ID No:16;
(vii) a V_L nucleotide sequence of SEQ ID No:21;
(viii) a V_H nucleotide sequence of SEQ ID No:26; or
(ix) a V_L nucleotide sequence of SEQ ID No:21 and a V_H nucleotide sequence of SEQ ID No:26.

45. An expression vector according to claim 43 or 44, further comprising a nucleotide sequence encoding the constant region of a light chain, a heavy chain or both light and heavy chains of a human antibody.

46. An expression vector according to claim 45, wherein the nucleotide sequence encoding the constant region of a light chain, a heavy chain or both light and heavy chains of a human antibody encodes an IgG1 antibody.

47. A hybridoma which produces a human monoclonal anti-CD38 antibody encoded by human light chain and human heavy chain nucleic acids comprising

(i) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:1 and SEQ ID No:6, respectively;

(ii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:11 and SEQ ID No:16, respectively;

(iii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:21 and SEQ ID No:26, respectively; or

(iv) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions, which are conservative sequence modifications of the sequences set forth in (i), (ii) or (iii).

48. A hybridoma which produces a human monoclonal anti-CD38 antibody having human heavy chain and light chain variable regions which comprise

(i) the human light chain variable amino acid sequence as set forth in SEQ ID No:2, and the human heavy chain variable amino sequence as set forth in SEQ ID No:7;

(ii) the human light chain variable amino acid sequence as set forth in SEQ ID No:12, and the human heavy chain variable amino sequence as set forth in SEQ ID No:17;

(iii) the human light chain variable amino acid sequence as set forth in SEQ ID No:22, and the human heavy chain variable amino sequence as set forth in SEQ ID No:27; or

(iv) conservative sequences modifications of the human light chain and human heavy chain variable amino acid sequences as set forth in (i), (ii) or (iii).

49. A tranfectoma which produces a human monoclonal anti-CD38 antibody encoded by human light chain and human heavy chain nucleic acids comprising

(i) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:1 and SEQ ID No:6, respectively;

(ii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:11 and SEQ ID No:16, respectively;

(iii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:21 and SEQ ID No:26, respectively; or

(iv) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions, which are conservative sequence modifications of the sequences set forth in (i), (ii) or (iii).

50. A transfectoma which produces a human monoclonal anti-CD38 antibody having human heavy chain and light chain variable regions which comprise

(i) the human light chain variable amino acid sequence as set forth in SEQ ID No:2, and the human heavy chain variable amino sequence as set forth in SEQ ID No:7;

(ii) the human light chain variable amino acid sequence as set forth in SEQ ID No:12, and the human heavy chain variable amino sequence as set forth in SEQ ID No:17;

(iii) the human light chain variable amino acid sequence as set forth in SEQ ID No:22, and the human heavy chain variable amino sequence as set forth in SEQ ID No:27; or

(iv) conservative sequences modifications of the human light chain and human heavy chain variable amino acid sequences as set forth in (i), (ii) or (iii).

51. A eukaryotic or prokaryotic host cell which produces an antibody according to any one of claims 1 to 41.

52. A eukaryotic or prokaryotic host cell containing an expression vector according to any one of caims 43 to 46.

53. A transgenic nonhuman animal or plant comprising nucleic acids encoding a human heavy chain and a human light chain, wherein the animal or plant produces a detectable amount of an antibody according to any one of claims 1 to 41.

54. An immunoconjugate comprising an antibody according to any one of claims 1 to 41 linked to a cytotoxic agent, a radioisotope, or a drug.

55. An immunoconjugate comprising an antibody according to any one of claims 1 to 41, wherein the antibody is a monomeric IgM antibody linked to a cytotoxic agent, a radioisotope, or a drug.

56. A bispecific or multispecific molecule comprising an antibody according to any one of claims 1 to 41 and a binding specificity for a human effector cell.

57. A bispecific or multispecific molecule comprising an antibody according to any one of claims 1 to 41 and a binding specificity for CD3, CD4, CD138, IL-15R, membrane bound or receptor bound TNF-σ, a human Fc receptor, or membrane bound or receptor bound IL-15.

58. A pharmaceutical composition comprising an antibody according to any one of claims 1 to 41 or an immunoconjugate according to claim 54 or 55 and a pharmaceutically acceptable carrier.

59. A pharmaceutical composition according to claim 58 comprising one or more further therapeutic agents.

60. A method of inhibiting growth and/or proliferation of a cell expressing CD38, comprising administration of an antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46, such that the growth and/or proliferation of the cell is inhibited.

61. A method of treating a disease or disorder involving cells expressing CD38 in a subject, which method comprises administration of an antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46 to a subject in need thereof.

62. A method of preventing a disease or disorder involving cells expressing CD38 in a subject, which method comprises a administration of an antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46 to a subject in need thereof.

63. A method according to claim 61 or 62, wherein the disease or disorder is rheumatoid arthritis.

64. A method according to claim 61 or 62, wherein the disease or disorder is multiple myeloma.

65. A method according to any one of claims 60 to 64, wherein the method comprises administration of one or more further therapeutic agents to the subject.

66. A method according to claim 65, wherein the one or more further therapeutic agents are selected from a chemotherapeutic agent, an anti-inflammatory agent, or an immunosuppressive and/or immunomodulatory agent.

67. A method according to claim 65, wherein the one or more further therapeutic agents are selected from a group consisting of cisplatin, gefitinib, cetuximab, rituximab, bevacizumab, erlotinib, bortezomib, thalidomide, pamidronate, zoledronic acid, clodronate, risendronate, ibandronate, etidronate, alendronate, tiludronate, arsenic trioxide, lenalidomide, filgrastim, pegfilgrastim, sargramostim, suberoylanilide hydroxamic acid, and SCIO-469.

68. An *in vitro* method for detecting the presence of CD38 antigen, or a cell expressing CD38, in a sample comprising:

a) contacting the sample with an antibody according to any one of claims 1 to 41 under conditions that allow for formation of a complex between the antibody and CD38; and

b) detecting the formation of a complex.

69. A kit for detecting the presence of CD38 antigen, or a cell expressing CD38, in a sample comprising an antibody according to any one of claims 1 to 41.

70. An *in vivo* method for detecting CD38 antigen, or a cell expressing CD38, in a subject comprising:

a) administering antibody according to any one of claims 1 to 41 under conditions that allow for formation of a complex between the antibody and CD38; and

b) detecting the formed complex.

71. An anti-idiotypic antibody binding to an antibody according to any one of claims 1 to 22, 36 to 37 or 39.

72. Use of an anti-idiotypic antibody according to claim 71 for detecting the level of an antibody according to any one of claims 1 to 22, 36 to 37 or 39 in a sample.

73. Use of an anti-idiotypic antibody according to claim 71 for detecting the level of human monoclonal antibody against CD38 in a sample.

CLAIMS

1. An antibody binding to human CD38 encoded by

(i) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:1 and SEQ ID No:6, respectively;

(ii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:11 and SEQ ID No:16, respectively; or

(iii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:21 and SEQ ID No:26, respectively.

2. An antibody binding to human CD38, comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID No:3, a V_L CDR2 having the sequence as set forth in SEQ ID No:4 and a V_L CDR3 having the sequence as set forth in SEQ ID No:5, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID No:8, a V_H CDR2 having the sequence as set forth in SEQ ID No:9 and a V_H CDR3 having the sequence as set forth in SEQ ID No:10.

3. An antibody according to claim 2, comprising a V_L region having the amino acid sequence as set forth in SEQ ID No:2.

4. An antibody according to claim 2, comprising a V_L region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:2.

5. An antibody according to claim 2, binding to human CD38, comprising a V_H region having the amino acid sequence as set forth in SEQ ID No:7.

6. An antibody according to claim 2, comprising a V_H region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:7.

7. An antibody according to claim 2, comprising a V_H region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:7.

8. An antibody binding to human CD38, comprising a V_L region as defined in claim 3 and a V_H region as defined in claim 5.

9. An antibody binding to human CD38, comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID No:13, a V_L CDR2 having the sequence as set forth in SEQ ID No:14 and a V_L CDR3 having the sequence as set forth in SEQ ID No:15, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID No:18, a V_H CDR2 having the sequence as set forth in SEQ ID No:19 and a V_H CDR3 having the sequence as set forth in SEQ ID No:20.

10. An antibody according to claim 9, comprising a V_L region having the amino acid sequence as set forth in SEQ ID No:12.

11. An antibody according to claim 9, comprising a V_L region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:12.

12. An antibody according to claim 9, comprising a V_H region having the amino acid sequence as set forth in SEQ ID No:17.

13. An antibody according to claim 9, comprising a V_H region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence as set forth in SEQ ID No:17.

14. An antibody according to claim 9, comprising a V_H region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:17.

15. An antibody binding to human CD38, comprising a V_L region as defined in claim 10 and a V_H region as defined in claim 12.

16. An antibody binding to human CD38, comprising human light chain and human heavy variable regions, wherein the light chain variable region comprises a V_L CDR1 having the sequence as set forth in SEQ ID No:23, a V_L CDR2 having the sequence as set forth in SEQ ID No:24 and a V_L CDR3 having the sequence as set forth in SEQ ID No:25, and the heavy chain variable region comprises a V_H CDR1 having the sequence as set forth in SEQ ID No:28, a V_H CDR2 having the sequence as set forth in SEQ ID No:29 and a V_H CDR3 having the sequence as set forth in SEQ ID No:30.

17. An antibody according to claim 16, comprising a V_L region having the amino acid sequence as set forth in SEQ ID No:22.

18. An antibody according to claim 16, comprising a V_L region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:22.

19. An antibody according to claim 16, comprising a V_H region having the amino acid sequence as set forth in SEQ ID No:27.

20. An antibody according to claim 16, comprising a V_H region having at least about 90%, such as at least about 95% amino acid sequence identity to the sequence according to SEQ ID No:27.

21. An antibody according to claim 16, comprising a V_H region having 1-5, such as 1-3 amino acid substitutions, deletions or additions compared to the sequence as set forth in SEQ ID No:27.

22. An antibody binding to human CD38, comprising a V_L region as defined in claim 17 and a V_H region as defined in claim 19.

23. An antibody that specifically binds to a CD38 epitope, which epitope is also specifically bound by an antibody according to any one of claims 1, 8, 15 and 22.

24. An antibody that specifically binds to the region SKRNIQFSCKNIYR and the region EKVQTLEAWVIHGG of human CD38 (SEQ ID No:31).

25. An antibody according to claim 24, which does not bind to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), to the same degree that it binds to human CD38 (SEQ ID No:31).

26. An antibody according to claim 24, which does not bind to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), to the same degree that it binds to human CD38 (SEQ ID No:31).

27. An antibody according to any one of claims 25 to 26, wherein said antibody binds to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32), to the same degree that it binds to human CD38 (SEQ ID No:31).

28. An antibody according to claim 24, wherein the antibody possesses the following binding characteristics: (i) binds to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), to the same degree that it binds to human CD38 (SEQ ID No:31), (ii) binds to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), to the same degree that it binds to human CD38 (SEQ ID No:31), and (iii) binds to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32), to the same degree that it binds to human CD38 (SEQ ID No:31).

29. An antibody according to claim 24, wherein the antibody possesses the following binding characteristics: (i) does not bind to a mutant human CD38, wherein the serine residue in position 274 has been substituted with a phenylalanine residue (SEQ ID No:34), to the same degree that it binds to human CD38 (SEQ ID No:31), (ii) does not bind to a mutant human CD38, wherein the glutamine residue in position 272 has been substituted with an arginine residue (SEQ ID No:33), to the same degree that it binds to human CD38 (SEQ ID No:31), (iii) binds to a mutant human CD38, wherein the threonine residue in position 237 has been substituted with an alanine residue (SEQ ID No:32), to the same degree that it binds to human CD38 (SEQ ID No:31).

30. An antibody according to any of claims 1-29, which antibody possesses one or more of the following characteristics:

(i) acts as an antagonist of CD38;

(ii) does not induce significant proliferation of peripheral blood mononuclear cells as determined by the method described in Example 18 of the specification;

(iii) does not induce release of significant IL-6 by human monocytes or peripheral blood mononuclear cells as determined by the method described in Example 19 of the specification;

(iv) does not induce release of detectable IFN-γ by human T cells or peripheral blood mononuclear cells as determined by the method described in Example 20 of the specification;

(v) is internalized by CD38 expressing cells; such as internalized by CHO-CD38 cells within 5 to 15 minutes at 37°C by the method as described in Example 12 of the specification;

(vi) induces ADCC; such as with an EC_{50} value of below 15 ng/ml, such as below 10 ng/ml in Daudi-luc cells and with an EC_{50} value of below 75 ng/ml, such as below 50 ng/ml, 30

ng/ml or 10 ng/ml in MM cells as determined by the method described in example 5 of the specification;

(vii) induces CDC in the presence of complement; such as with an EC_{50} value of below 5 µg/ml, such as below 1 µg/ml in daudi-luc or CD38-CHO cells by the method described in Example 6 of the specification;

(viii) inhibits the synthesis of cGDPR;

(ix) inhibits the synthesis of cADPR;

(x) binds to human CD38 with an affinity (K_D) of below 10^{-8} M, such as in the range of from 10^{-8} M to – 10^{-11} M, for example in the range of from 7 x 10^{-9} M to – 10^{-10} M, as determined by surface plasmon resonance as described in Example 20 of the specification.

31. An antibody according to claim 30, which inhibits the synthesis of cGDPR by at least 25%, such as at least 30% after 90 minutes at a concentration of 3 µg/ml as determined by spectophotometric method described in Example 24 of the specification.

32. An antibody according to claim 31, which inhibits the synthesis of cGDPR by at least 30%, after 90 minutes at a concentration of 3 µg/ml as determined by spectophotometric method described in Example 24 of the specification.

33. An antibody according to claim 30, which inhibits the synthesis of cADPR by at least 25%, such as at least 30% after 90 minutes at a concentration of 3 µg/ml as determined by the HPLC method described in Munshi et al., J. Biol. Chem. 275, 21566-21571 (2000).

34. An antibody according to any one of claims 23 to 33, which is a human monoclonal antibody.

35. An antibody according to any one of claims 1 to 34, characterized in that it is a full length IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody.

36. An antibody according to claim 35, characterized in that it is a full-length IgG1 antibody, preferably an IgG1,κ antibody.

37. An antibody according to claim 35, characterized in that it is a full-length IgM antibody, preferably an IgM,κ antibody.

38. An antibody according to any one of claims 1 to 37, wherein the antibody is glycosylated in a eukaryotic cell.

39. An antibody according to any one of claims 1 to 38, which is an antibody fragment or a single chain antibody.

40. An antibody according to any one of claims 1 to 39, further comprising a chelator linker for attaching a radioisotope.

41. An antibody according to any one of claims 1 to 40, which is in a substantially isolated form.

42. An isolated nucleic acid encoding an antibody according to any one of claims 1 to 41.

43. An expression vector comprising a nucleic acid sequence encoding an antibody according to any one of claims 1 to 41.

44. An expression vector according to claim 43, comprising
(i) a V_L nucleotide sequence of SEQ ID No:1,
(ii) a V_H nucleotide sequence of SEQ ID No:6,
(iii) a V_L nucleotide sequence of SEQ ID No:1 and a V_H nucleotide sequence of SEQ ID No:6;
(iv) a V_L nucleotide sequence of SEQ ID No:11;
(v) a V_H nucleotide sequence of SEQ ID No:16;
(vi) a V_L nucleotide sequence of SEQ ID No:11 and a V_H nucleotide sequence of SEQ ID No:16;
(vii) a V_L nucleotide sequence of SEQ ID No:21;
(viii) a V_H nucleotide sequence of SEQ ID No:26; or
(ix) a V_L nucleotide sequence of SEQ ID No:21 and a V_H nucleotide sequence of SEQ ID No:26.

45. An expression vector according to claim 43 or 44, further comprising a nucleotide sequence encoding the constant region of a light chain, a heavy chain or both light and heavy chains of a human antibody.

46. An expression vector according to claim 45, wherein the nucleotide sequence encoding the constant region of a light chain, a heavy chain or both light and heavy chains of a human antibody encodes an IgG1 antibody.

47. A hybridoma which produces a human monoclonal anti-CD38 antibody encoded by human light chain and human heavy chain nucleic acids comprising

(i) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:1 and SEQ ID No:6, respectively;

(ii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:11 and SEQ ID No:16, respectively;

(iii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:21 and SEQ ID No:26.

48. A hybridoma which produces a human monoclonal anti-CD38 antibody having human heavy chain and light chain variable regions which comprise

(i) the human light chain variable amino acid sequence as set forth in SEQ ID No:2, and the human heavy chain variable amino sequence as set forth in SEQ ID No:7;

(ii) the human light chain variable amino acid sequence as set forth in SEQ ID No:12, and the human heavy chain variable amino sequence as set forth in SEQ ID No:17;

(iii) the human light chain variable amino acid sequence as set forth in SEQ ID No:22, and the human heavy chain variable amino sequence as set forth in SEQ ID No:27.

49. A transfectoma which produces a human monoclonal anti-CD38 antibody encoded by human light chain and human heavy chain nucleic acids comprising

(i) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:1 and SEQ ID No:6, respectively;

(ii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:11 and SEQ ID No:16, respectively;

(iii) human light chain and human heavy chain nucleic acids comprising nucleotide sequences in their variable regions as set forth in SEQ ID No:21 and SEQ ID No:26, respectively.

50. A transfectoma which produces a human monoclonal anti-CD38 antibody having human heavy chain and light chain variable regions which comprise

(i) the human light chain variable amino acid sequence as set forth in SEQ ID No:2, and the human heavy chain variable amino sequence as set forth in SEQ ID No:7;

(ii) the human light chain variable amino acid sequence as set forth in SEQ ID No:12, and the human heavy chain variable amino sequence as set forth in SEQ ID No:17;

(iii) the human light chain variable amino acid sequence as set forth in SEQ ID No:22, and the human heavy chain variable amino sequence as set forth in SEQ ID No:27.

51. A eukaryotic or prokaryotic host cell which produces an antibody according to any one of claims 1 to 41.

52. A eukaryotic or prokaryotic host cell containing an expression vector according to any one of claims 43 to 46.

53. A transgenic nonhuman animal or plant comprising nucleic acids encoding a human heavy chain and a human light chain, wherein the animal or plant produces a detectable amount of an antibody according to any one of claims 1 to 41.

54. An immunoconjugate comprising an antibody according to any one of claims 1 to 41 linked to a cytotoxic agent, a radioisotope, or a drug.

55. An immunoconjugate comprising an antibody according to any one of claims 1 to 41, wherein the antibody is a monomeric IgM antibody linked to a cytotoxic agent, a radioisotope, or a drug.

56. A bispecific or multispecific molecule comprising an antibody according to any one of claims 1 to 41 and a binding specificity for a human effector cell.

57. A bispecific or multispecific molecule comprising an antibody according to any one of claims 1 to 41 and a binding specificity for CD3, CD4, CD138, IL-15R, membrane bound or receptor bound TNF-α, a human Fc receptor, or membrane bound or receptor bound IL-15.

58. A pharmaceutical composition comprising an antibody according to any one of claims 1 to 41 or an immunoconjugate according to claim 54 or 55 and a pharmaceutically acceptable carrier.

59. A pharmaceutical composition according to claim 58 comprising one or more further therapeutic agents.

60. An antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46, for use in a method of inhibiting growth and/or proliferation of a cell expressing CD38.

61. An antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46, for use in a method of treating a disease or disorder involving cells expressing CD38 in a subject.

62. An antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46 for use in a method of preventing a disease or disorder involving cells expressing CD38 in a subject

63. An antibody, immunoconjugate, pharmaceutical composition or expression vector for the use in a method according to claim 61 or 62, wherein the disease or disorder is rheumatoid arthritis.

64. An antibody, immunoconjugate, pharmaceutical composition or expression vector for the use in a method according to claim 61 or 62, wherein the disease or disorder is multiple myeloma.

65. An antibody, immunoconjugate, pharmaceutical composition or expression vector for the use in a method according to any one of claims 60 to 64, wherein the method comprises administration of one or more further therapeutic agents to the subject.

66. An antibody, immunoconjugate, pharmaceutical composition or expression vector for the use in a method according to claim 65, wherein the one or more further therapeutic agents are selected from a chemotherapeutic agent, an anti-inflammatory agent, or an immunosuppressive and/or immunomodulatory agent.

67. An antibody, immunoconjugate, pharmaceutical composition or expression vector for the use in a method according to claim 65, wherein the one or more further therapeutic agents are selected from a group consisting of cisplatin, gefitinib, cetuximab, rituximab, bevacizumab, erlotinib, bortezomib, thalidomide, pamidronate, zoledronic acid, clodronate, risendronate, ibandronate, etidronate, alendronate, tiludronate, arsenic trioxide, lenalidomide, filgrastim, pegfilgrastim, sargramostim, suberoylanilide hydroxamic acid, and SCIO-469.

68. An *in vitro* method for detecting the presence of CD38 antigen, or a cell expressing CD38, in a sample comprising:

a) contacting the sample with an antibody according to any one of claims 1 to 41 under conditions that allow for formation of a complex between the antibody and CD38; and
b) detecting the formation of a complex.

69. A kit for detecting the presence of CD38 antigen, or a cell expressing CD38, in a sample comprising an antibody according to any one of claims 1 to 41.

70. An antibody according to any one of claims 1 to 41 for use *in vivo* to detect CD38 antigen, or a cell expressing CD38, comprising:
a) the administration of the antibody under conditions that allow for formation of a complex between the antibody and CD38; and
b) detecting the formed complex.

71. An anti-idiotypic antibody binding to an antibody according to any one of claims 1 to 22, 36 to 37 or 39.

72. Use of an anti-idiotypic antibody according to claim 71 for detecting the level of an antibody according to any one of claims 1 to 22, 36 to 37 or 39 in a sample.

73. Use of an anti-idiotypic antibody according to claim 71 for detecting the level of human monoclonal antibody against CD38 in a sample.

74. The use of an antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46, in the manufacture of a medicament for use in a method of inhibiting growth and/or proliferation of a cell expressing CD38.

75. The use of an antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression vector according to any one of claims 43 to 46, in the manufacture of a medicament for use in a method of treating a disease or disorder involving cells expressing CD38 in a subject.

76. The use of an antibody according to any one of claims 1 to 41, an immunoconjugate according to claim 54 or 55, a pharmaceutical composition according to claim 58 or 59, or an expression

vector according to any one of claims 43 to 46 in the manufacture of a medicament for use in a method of preventing a disease or disorder involving cells expressing CD38 in a subject

77. The use according to claim 75 or 76, wherein the disease or disorder is rheumatoid arthritis.

78. The use according to claim 75 or 76, wherein the disease or disorder is multiple myeloma.

79. The use according to any one of claims 74 to 78, wherein the method comprises administration of one or more further therapeutic agents to the subject.

80. The use according to claim 79, wherein the one or more further therapeutic agents are selected from a chemotherapeutic agent, an anti-inflammatory agent, or an immunosuppressive and/or immunomodulatory agent.

81. The use according to claim 79, wherein the one or more further therapeutic agents are selected from a group consisting of cisplatin, gefitinib, cetuximab, rituximab, bevacizumab, erlotinib, bortezomib, thalidomide, pamidronate, zoledronic acid, clodronate, risendronate, ibandronate, etidronate, alendronate, tiludronate, arsenic trioxide, lenalidomide, filgrastim, pegfilgrastim, sargramostim, suberoylanilide hydroxamic acid, and SCIO-469.

82. The use of an antibody according to any one of claims 1 to 41 in the manufacture of a medicament for use *in vivo* to detect CD38 antigen, or a cell expressing CD38, in a method comprising:

a) the administration of the antibody under conditions that allow for formation of a complex between the antibody and CD38; and

b) detecting the formed complex.