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(54) **ANTI-CD38 HUMAN ANTIBODIES AND USES THEREFOR**

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(57) **ABSTRACT**

The present invention provides recombinant antigen-binding regions and antibodies and functional fragments containing such antigen-binding regions that are specific for CD38, which plays an integral role in various disorders or conditions. These antibodies, accordingly, can be used to treat, for example, hematological malignancies such as multiple myeloma. Antibodies of the invention also can be used in the diagnostics field, as well as for investigating the role of CD38 in the progression of disorders associated with malignancies. The invention also provides nucleic acid sequences encoding the foregoing antibodies, vectors containing the same, pharmaceutical compositions and kits with instructions for use. The invention also provides isolated novel epitopes of CD38 and methods of use therefore.

## Figure 1a

### Variable Heavy Chain DNA

**3077_VH1B** (SEQ ID NO: 1):

```
(1)   CAGGTGCAAT TGGTTCAGAG CGGCGCGGAA GTGAAAAAAC CGGGCGCGAG
(51)  CGTGAAAGTG AGCTGCAAAG CCTCCGGATA TACCTTTACT TCTTATTCTA
(101) TTAATTGGGT CCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCTAT
(151) ATCGATCCGA ATCGTGGCAA TACGAATTAC GCGCAGAAGT TTCAGGGCCG
(201) GGTGACCATG ACCCGTGATA CCAGCATTAG CACCGCGTAT ATGGAACTGA
(251) GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTGAGTAT
(301) ATTTATTTTA TTCATGGTAT GCTTGATTTT TGGGGCCAAG GCACCCTGGT
(351) GACGGTTAGC TCA
```

**3079_VH3** (SEQ ID NO: 2):

```
(1)   CAGGTGCAAT TGGTGGAAAG CGGCGGCGGC CTGGTGCAAC CGGGCGGCAG
(51)  CCTGCGTCTG AGCTGCGCGG CCTCCGGATT TACCTTTTCT AATTATGGTA
(101) TGCATTGGGT GCGCCAAGCC CCTGGGAAGG GTCTCGAGTG GGTGAGCAAT
(151) ATCCGTTCTG ATGGTAGCTG GACCTATTAT GCGGATAGCG TGAAAGGCCG
(201) TTTTACCATT TCACGTGATA ATTCGAAAAA CACCCTGTAT CTGCAAATGA
(251) ACAGCCTGCG TGCGGAAGAT ACGGCCGTGT ATTATTGCGC GCGTCGTTAT
(301) TGGTCTAAGT CTCATGCTTC TGTTACTGAT TATTGGGGCC AAGGCACCCT
(351) GGTGACGGTT AGCTCA
```

**3080_ VH3** (SEQ ID NO: 3):

```
(1)   CAGGTGCAAT TGGTGGAAAG CGGCGGCGGC CTGGTGCAAC CGGGCGGCAG
(51)  CCTGCGTCTG AGCTGCGCGG CCTCCGGATT TACCTTTTCT TCTTATGGTA
(101) TGCATTGGGT GCGCCAAGCC CCTGGGAAGG GTCTCGAGTG GGTGAGCAAT
(151) ATCTATTCTG ATGGTAGCAA TACCTTTTAT GCGGATAGCG TGAAAGGCCG
(201) TTTTACCATT TCACGTGATA ATTCGAAAAA CACCCTGTAT CTGCAAATGA
(251) ACAGCCTGCG TGCGGAAGAT ACGGCCGTGT ATTATTGCGC GCGTAATATG
(301) TATCGTTGGC CTTTTCATTA TTTTTTTGAT TATTGGGGCC AAGGCACCCT
(351) GGTGACGGTT AGCTCA
```

**3100_VH 3** (SEQ ID NO: 4):

```
(1)   CAGGTGCAAT TGGTGGAAAG CGGCGGCGGC CTGGTGCAAC CGGGCGGCAG
(51)  CCTGCGTCTG AGCTGCGCGG CCTCCGGATT TACCTTTTCT TCTAATGGTA
(101) TGTCTTGGGT GCGCCAAGCC CCTGGGAAGG GTCTCGAGTG GGTGAGCAAT
(151) ATCTCTTATC TTTCTAGCTC TACCTATTAT GCGGATAGCG TGAAAGGCCG
(201) TTTTACCATT TCACGTGATA ATTCGAAAAA CACCCTGTAT CTGCAAATGA
(251) ACAGCCTGCG TGCGGAAGAT ACGGCCGTGT ATTATTGCGC GCGTTTTTAT
(301) GGTTATTTTA ATTATGCTGA TGTTTGGGGC CAAGGCACCC TGGTGACGGT
(351) TAGCTCA
```

**3077_1_VH1B** (SEQ ID NO: 31):

```
(1)   CAGGTGCAAT TAGTCCAAAG TGGTGCGGAA GTGAAAAAAC CGGGCGCGAG
(51)  CGTGAAAGTG AGCTGCAAAG CCTCCGGATA TACCTTTACT TCTTATTCTA
(101) TTAATTGGGT CCGCCAAGCC CCTGGGCAGG GTCTCGAGTG GATGGGCTAT
(151) ATCGATCCGA ATCGTGGCAA TACGAATTAC GCGCAGAAGT TTCAGGGCCG
```

**Figure 1a (Continued)**

```
(201) GGTGACCATG ACCCGTGATA CCAGCATTAG CACCGCGTAT ATGGAACTGA
(251) GCAGCCTGCG TAGCGAAGAT ACGGCCGTGT ATTATTGCGC GCGTGAGTAT
(301) ATTTATTTTA TTCATGGTAT GCTTGATTTT TGGGGCCAAG GCACCCTGGT
(351) GACGGTTAGC TCA
```

**Figure 1b**

**Variable Heavy Chain Peptide**

(CDR Regions in **Bold**)

**3077_VH1B** (SEQ ID NO: 5):

(1) QVQLVQSGAE VKKPGASVKV SCKAS**GYTFT SYSIN**WVRQA PGQGLEWMG**Y**
(51) **IDPNRGNTNY AQKFQG**RVTM TRDTSISTAY MELSSLRSED TAVYYCAR**EY**
(101) **IYFIHGMLDF** WGQGTLVTVS S

**3079_VH3** (SEQ ID NO: 6):
(1) QVQLVESGGG LVQPGGSLRL SCAAS**GFTFS NYGMH**WVRQA PGKGLEWVS**N**
(51) **IRSDGSWTYY ADSVKG**RFTI SRDNSKNTLY LQMNSLRAED TAVYYCAR**RY**
(101) **WSKSHASVTD Y**WGQGTLVTV SS

**3080_ VH3** (SEQ ID NO: 7):
(1) QVQLVESGGG LVQPGGSLRL SCAAS**GFTFS SYGMH**WVRQA PGKGLEWVS**N**
(51) **IYSDGSNTFY ADSVKG**RFTI SRDNSKNTLY LQMNSLRAED TAVYYCAR**NM**
(101) **YRWPFHYFFD Y**WGQGTLVTV SS

**3100_VH 3** (SEQ ID NO: 8):
(1) QVQLVESGGG LVQPGGSLRL SCAAS**GFTFS SNGMS**WVRQA PGKGLEWVS**N**
(51) **ISYLSSSTYY ADSVKG**RFTI SRDNSKNTLY LQMNSLRAED TAVYYCAR**FY**
(101) **GYFNYADV**WG QGTLVTVSS

# Figure 2a

## Variable Light Chain DNA

**3077_Vk kappa 2** (SEQ ID NO: 9):

```
(1)   GATATCGTGA TGACCCAGAG CCCACTGAGC CTGCCAGTGA CTCCGGGCGA
(51)  GCCTGCGAGC ATTAGCTGCA GAAGCAGCCA AAGCCTGCTT TTTATTGATG
(101) GCAATAATTA TCTGAATTGG TACCTTCAAA AACCAGGTCA AAGCCCGCAG
(151) CTATTAATTT ATCTTGGTTC TAATCGTGCC AGTGGGGTCC CGGATCGTTT
(201) TAGCGGCTCT GGATCCGGCA CCGATTTTAC CCTGAAAATT AGCCGTGTGG
(251) AAGCTGAAGA CGTGGGCGTG TATTATTGCC AGCAGTATTC TTCTAAGTCT
(301) GCTACCTTTG GCCAGGGTAC GAAAGTTGAA ATTAAACGTA CG
```

**3079_Vk kappa 1** (SEQ ID NO: 10):

```
(1)   GATATCCAGA TGACCCAGAG CCCGTCTAGC CTGAGCGCGA GCGTGGGTGA
(51)  TCGTGTGACC ATTACCTGCA GAGCGAGCCA GGATATTTCT GCTTTTCTGA
(101) ATTGGTACCA GCAGAAACCA GGTAAAGCAC CGAAACTATT AATTTATAAG
(151) GTTTCTAATT TGCAAAGCGG GGTCCCGTCC CGTTTTAGCG GCTCTGGATC
(201) CGGCACTGAT TTTACCCTGA CCATTAGCAG CCTGCAACCT GAAGACTTTG
(251) CGACTTATTA TTGCCAGCAG GCTTATTCTG GTTCTATTAC CTTTGGCCAG
(301) GGTACGAAAG TTGAAATTAA ACGTACG
```

**3080_Vl lambda 3** (SEQ ID NO: 11):

```
(1)   GATATCGAAC TGACCCAGCC GCCTTCAGTG AGCGTTGCAC CAGGTCAGAC
(51)  CGCGCGTATC TCGTGTAGCG GCGATAATAT TGGTAATAAG TATGTTTCTT
(101) GGTACCAGCA GAAACCCGGG CAGGCGCCAG TTGTTGTGAT TTATGGTGAT
(151) AATAATCGTC CCTCAGGCAT CCCGGAACGC TTTAGCGGAT CCAACAGCGG
(201) CAACACCGCG ACCCTGACCA TTAGCGGCAC TCAGGCGGAA GACGAAGCGG
(251) ATTATTATTG CTCTTCTTAT GATTCTTCTT ATTTTGTGTT TGGCGGCGGC
(301) ACGAAGTTAA CCGTTCTTGG CCAG
```

**3100_Vl lambda 3** (SEQ ID NO: 12):

```
(1)   GATATCGAAC TGACCCAGCC GCCTTCAGTG AGCGTTGCAC CAGGTCAGAC
(51)  CGCGCGTATC TCGTGTAGCG GCGATAATAT TGGTCATTAT TATGCTTCTT
(101) GGTACCAGCA GAAACCCGGG CAGGCGCCAG TTCTTGTGAT TTATCGTGAT
(151) AATGATCGTC CCTCAGGCAT CCCGGAACGC TTTAGCGGAT CCAACAGCGG
(201) CAACACCGCG ACCCTGACCA TTAGCGGCAC TCAGGCGGAA GACGAAGCGG
(251) ATTATTATTG CCAGTCTTAT GATTATCTTC ATGATTTTGT GTTTGGCGGC
(301) GGCACGAAGT TAACCGTTCT TGGCCAG
```

## Figure 2b

### Variable Light Chain Peptide

(CDR Regions in **Bold**)

**3077_Vk kappa 2** (SEQ ID NO: 13):

(1) DIVMTQSPLS LPVTPGEPAS ISC**RSSQSLL FIDGNNYLN**W YLQKPGQSPQ
(51) LLI**YLGSNRA S**GVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYC**QQYSSKS**
(101) **A**TFGQGTKVE IKRT

**3079_Vk kappa 1** (SEQ ID NO: 14):

(1) DIQMTQSPSS LSASVGDRVT ITC**RASQDIS AFLN**WYQQKP GKAPKLLI**YK**
(51) **VSNLQS**GVPS RFSGSGSGTD FTLTISSLQP EDFATYYC**QQ AYSGSI**TFGQ
(101) GTKVEIKRT

**3080_Vl lambda 3** (SEQ ID NO: 15):

(1) DIELTQPPSV SVAPGQTARI SC**SGDNIGNK YVS**WYQQKPG QAPVVVIY**GD**
(51) **NNRPS**GIPER FSGSNSGNTA TLTISGTQAE DEADYYC**SSY DSSYF**VFGGG
(101) TKLTVLGQ

**3100_Vl lambda 3** (SEQ ID NO: 16):

(1) DIELTQPPSV SVAPGQTARI SC**SGDNIGHY YAS**WYQQKPG QAPVLVIY**RD**
(51) **NDRPS**GIPER FSGSNSGNTA TLTISGTQAE DEADYYC**QSY DYLHDF**VFGG
(101) GTKLTVLGQ

**Figure 3**

**Variable Heavy Chain Consensus Sequences**

(CDR Regions in **Bold**)

**VH1B Consensus** (SEQ ID NO: 17):

(1) QVQLVQSGAE VKKPGASVKV SCKAS**GYTFT SYYMH**WVRQA PGQGLEWMG**W**
(51) **INPNSGGTNY AQKFQG**RVTM TRDTSISTAY MELSSLRSED TAVYYCAR**WG**
(101) **GDGFYAMDY**W GQGTLVTVSS

**VH3 Consensus** (SEQ ID NO: 18):

(1) QVQLVESGGG LVQPGGSLRL SCAAS**GFTFS SYAMS**WVRQA PGKGLEWVS**A**
(51) **ISGSGGSTYY ADSVKG**RFTI SRDNSKNTLY LQMNSLRAED TAVYYCAR**WG**
(101) **GDGFYAMDY**W GQGTLVTVS S

## Figure 4

### Variable Light Chain Consensus Sequences

(CDR Regions in **Bold**)

**VL_λ3 Consensus** (SEQ ID NO: 19):

(1) SYELTQPPSV SVAPGQTARI SC**SGDALGDK YAS**WYQQKPG QAPVLVIY**DD**
(51) **SDRPS**GIPER FSGSNSGNTA TLTISGTQAE DEADYYC**QQH YTTPP**VFGGG
(101) TKLTVLG

**VL_k1 Consensus** (SEQ ID NO: 20):

(1) DIQMTQSPSS LSASVGDRVT ITC**RASQGIS SYLA**WYQQKP GKAPKLLIY**A**
(51) **ASSLQS**GVPS RFSGSGSGTD FTLTISSLQP EDFATYYC**QQ HYTTP**PTFGQ
(101) GTKVEIKR

**VL_k2 Consensus** (SEQ ID NO: 21):

(1) DIVMTQSPLS LPVTPGEPAS ISC**RSSQSLL HSNGYNYLD**W YLQKPGQSPQ
(51) LLIY**LGSNRA S**GVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYC**QQHYTTP**
(101) PTFGQGTKVE IKR

**Figure 5**

**Peptide Sequence of CD38**

(SEQ ID NO: 22):

```
1    mancefspvs gdkpccrlsr raqlclgvsi lvlilvvvla vvvprwrqqw sgpgttkrfp
61   etvlarcvky teihpemrhv dcqsvwdafk gafiskhpcn iteedyqplm klgtqtvpcn
121  killwsrikd lahqftqvqr dmftledtll gyladdltwc gefntskiny qscpdwrkdc
181  snnpvsvfwk tvsrrfaeaa cdvvhvmlng srskifdkns tfgsvevhnl qpekvqtlea
241  wvihggreds rdlcqdptik elesiiskrn iqfsckniyr pdkflqcvkn pedssctsei
```

## Figure 6

## Nucleotide Sequence of Chimeric OKT10

Heavy Chain (SEQ ID NO: 23):

caggtggaat tggtggaatc tggaggatcc ctgaaactct cctgtgcagc ctcaggattc
gattttagta gatcctggat gaattgggtc cggcaggctc caggaaaagg gctagaatgg
attggagaaa ttaatccaga tagcagtacg ataaactata cgacatctct aaaggataaa
ttcatcatct ccagagacaa cgccaaaaat acgctgtacc tgcaaatgac caaagtgaga
tctgaggaca cagccctttta ttactgtgca agatatggta actggtttcc ttattggggc
caagggactc tggtcactgt cagctcagcc tccaccaagg gtccatcggt cttccccctg
gcaccctcct ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac
tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac
accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg
ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac
accaaggtgg acaagaaagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg
tgcccagcac ctgaactcct ggggggaccg tcagtcttcc tcttcccccc aaaacccaag
gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac
gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag
acaaagccgc gggaggagca gtacaacagc acgtaccggg tggtcagcgt cctcaccgtc
ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc
ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg
tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg
gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag
aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc
aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg
catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaa

Light Chain (SEQ ID NO: 24):

gatatcctga tgacccagtc tcaaaaaatc atgcccacat cagtgggaga cagggtcagc
gtcacctgca aggccagtca aaatgtggat actaatgtag cctggtatca acagaaacca

**Figure 6 (Continued)**

ggacagtctc ctaaagcact gatttactcg gcatcctacc gatacagtgg agtccctgat

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcaccaa tgtgcagtct

gaggacttgg cagagtattt ctgtcagcaa tatgacagct atcctctcac gttcggtgct

gggaccaagc tggacctgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt

Fig.7: Schematic Overview of Epitopes

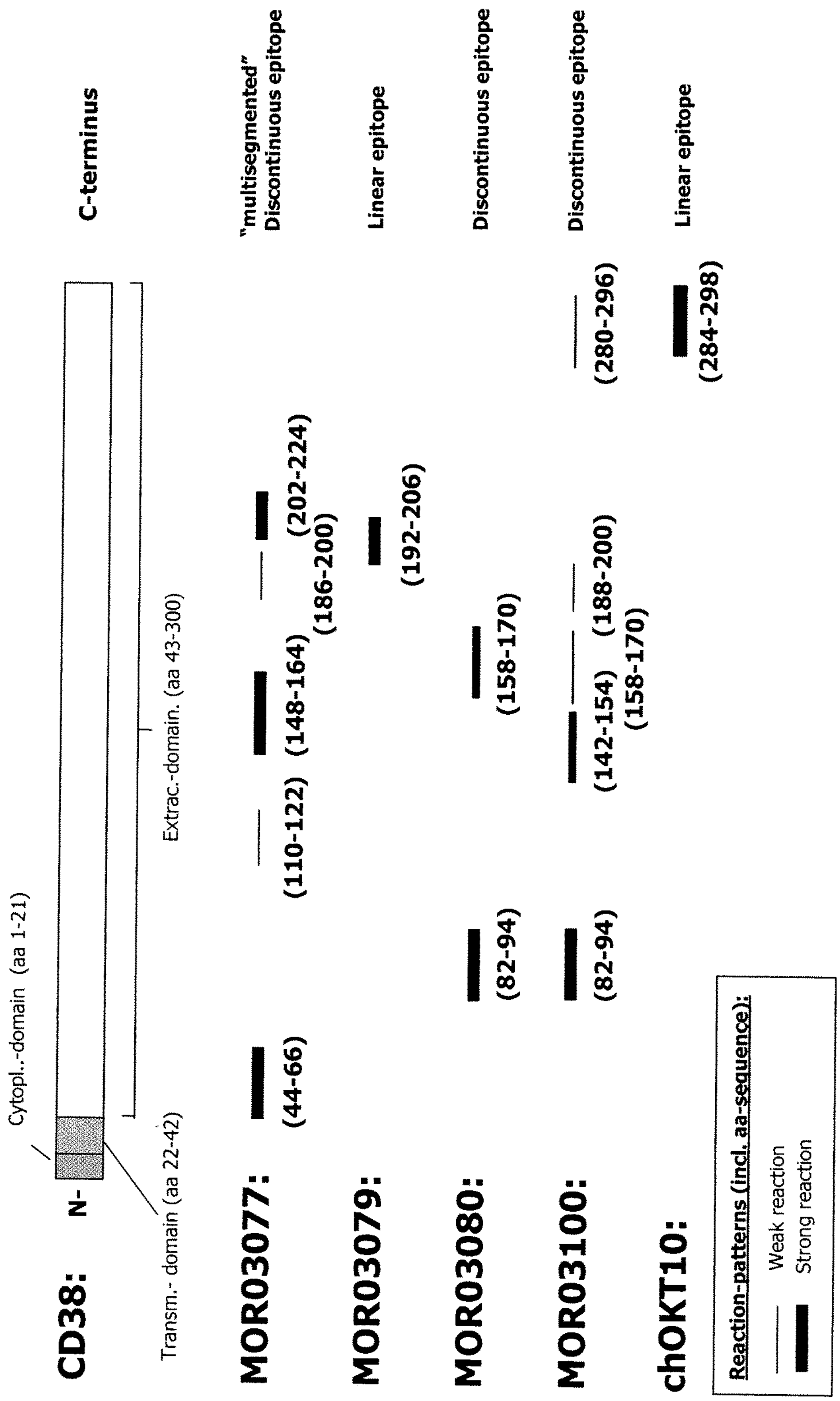


**Figure 8: DNA sequence of pMOPRH®_h_IgG1_1**

```
                 StyI
                ~~~~~~~
 601    TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA
        AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

                                                    AatII
                                                    ~~~~~~
 651    TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
        ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

 701    TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
        ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

 751    ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
        TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

 801    GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA CTGCTTACTG
        CAGATATATT CGTCTCGAGA GACCGATTGA TCTCTTGGGT GACGAATGAC

                     pMORPH®_Ig_FOR 100.0%             NheI
                     ~~~~~~~~~~~~~~~~~~~~~~           ~~~~~~
 851    GCTTATCGAA ATTAATACGA CTCACTATAG GGAGACCCAA GCTGGCTAGC
        CGAATAGCTT TAATTATGCT GAGTGATATC CCTCTGGGTT CGACCGATCG

               M  K   H  L  W   F  F  L   L  L  V  A   A  P  R ·
 901    GCCACCATGA AACACCTGTG GTTCTTCCTC CTGCTGGTGG CAGCTCCCAG
        CGGTGGTACT TTGTGGACAC CAAGAAGGAG GACGACCACC GTCGAGGGTC

                           EcoRI                BlpI          StyI
                          ~~~~~~~             ~~~~~~~~         ~
                                                            A  S  T ·
        · W  V  L   S  Q  V  E   F  C  R   R  L  A   Q
 951    ATGGGTCCTG TCCCAGGTGG AATTCTGCAG GCGGTTAGCT CAGCCTCCAC
        TACCCAGGAC AGGGTCCACC TTAAGACGTC CGCCAATCGA GTCGGAGGTG

        StyI          BbsI
        ~~~~~         ~~~~~~
        · K  G  P   S  V  F  P   L  A  P   S  S  K   S  T  S  G ·
1001    CAAGGGTCCA TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG
        GTTCCCAGGT AGCCAGAAGG GGGACCGTGG GAGGAGGTTC TCGTGGAGAC

        ·  G  T  A   A  L  G   C  L  V  K   D  Y  F   P  E  P
1051    GGGGCACAGC GGCCCTGGGC TGCCTGGTCA AGGACTACTT CCCCGAACCG
        CCCCGTGTCG CCGGGACCCG ACGGACCAGT TCCTGATGAA GGGGCTTGGC
```

**Figure 8 (Continued)**

```
           V  T  V  S   W  N  S   G  A  L   T  S  G  V   H  T  F ·
1101      GTGACGGTGT CGTGGAACTC AGGCGCCCTG ACCAGCGGCG TGCACACCTT
          CACTGCCACA GCACCTTGAG TCCGCGGGAC TGGTCGCCGC ACGTGTGGAA

          · P  A  V   L  Q  S  S   G  L  Y   S  L  S   S  V  V  T ·
1151      CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCCTCAGC AGCGTGGTGA
          GGGCCGACAG GATGTCAGGA GTCCTGAGAT GAGGGAGTCG TCGCACCACT

          ·  V  P  S   S  S  L   G  T  Q  T   Y  I  C   N  V  N
1201      CCGTGCCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT
          GGCACGGGAG GTCGTCGAAC CCGTGGGTCT GGATGTAGAC GTTGCACTTA

                                StyI
                               ~~~~~~~
           H  K  P  S   N  T  K   V  D  K   K  V  E  P   K  S  C ·
1251      CACAAGCCCA GCAACACCAA GGTGGACAAG AAAGTTGAGC CCAAATCTTG
          GTGTTCGGGT CGTTGTGGTT CCACCTGTTC TTTCAACTCG GGTTTAGAAC

          · D  K  T   H  T  C  P   P  C  P   A  P  E   L  L  G  G ·
1301      TGACAAAACT CACACATGCC CACCGTGCCC AGCACCTGAA CTCCTGGGGG
          ACTGTTTTGA GTGTGTACGG GTGGCACGGG TCGTGGACTT GAGGACCCCC

                  BbsI                          StyI
                 ~~~~~~~                       ~~~~~~
          ·  P  S  V   F  L  F   P  P  K  P   K  D  T   L  M  I
1351      GACCGTCAGT CTTCCTCTTC CCCCCAAAAC CCAAGGACAC CCTCATGATC
          CTGGCAGTCA GAAGGAGAAG GGGGGTTTTG GGTTCCTGTG GGAGTACTAG

                                                           BbsI
                                                          ~~~~~
           S  R  T  P   E  V  T   C  V  V   V  D  V  S   H  E  D ·
1401      TCCCGGACCC CTGAGGTCAC ATGCGTGGTG GTGGACGTGA GCCACGAAGA
          AGGGCCTGGG GACTCCAGTG TACGCACCAC CACCTGCACT CGGTGCTTCT

          BbsI
          ~
          · P  E  V   K  F  N  W   Y  V  D   G  V  E   V  H  N  A ·
1451      CCCTGAGGTC AAGTTCAACT GGTACGTGGA CGGCGTGGAG GTGCATAATG
          GGGACTCCAG TTCAAGTTGA CCATGCACCT GCCGCACCTC CACGTATTAC

          ·  K  T  K   P  R  E   E  Q  Y  N   S  T  Y   R  V  V
1501      CCAAGACAAA GCCGCGGGAG GAGCAGTACA ACAGCACGTA CCGGGTGGTC
          GGTTCTGTTT CGGCGCCCTC CTCGTCATGT TGTCGTGCAT GGCCCACCAG

           S  V  L  T   V  L  H   Q  D  W   L  N  G  K   E  Y  K ·
1551      AGCGTCCTCA CCGTCCTGCA CCAGGACTGG CTGAATGGCA AGGAGTACAA
          TCGCAGGAGT GGCAGGACGT GGTCCTGACC GACTTACCGT TCCTCATGTT

          · C  K  V   S  N  K  A   L  P  A   P  I  E   K  T  I  S ·
1601      GTGCAAGGTC TCCAACAAAG CCCTCCCAGC CCCCATCGAG AAAACCATCT
          CACGTTCCAG AGGTTGTTTC GGGAGGGTCG GGGGTAGCTC TTTTGGTAGA

                                                 BsrGI
                                                ~~~~~~
          ·  K  A  K   G  Q  P   R  E  P  Q   V  Y  T   L  P  P
1651      CCAAAGCCAA AGGGCAGCCC CGAGAACCAC AGGTGTACAC CCTGCCCCCA
          GGTTTCGGTT TCCCGTCGGG GCTCTTGGTG TCCACATGTG GGACGGGGGT
```

**Figure 8 (Continued)**

```
        S  R  D  E   L  T  K   N  Q  V   S  L  T  C   L  V  K ·
1701   TCCCGGGATG AGCTGACCAA GAACCAGGTC AGCCTGACCT GCCTGGTCAA
       AGGGCCCTAC TCGACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT

       · G  F  Y   P  S  D  I   A  V  E   W  E  S   N  G  Q  P ·
1751   AGGCTTCTAT CCCAGCGACA TCGCCGTGGA GTGGGAGAGC AATGGGCAGC
       TCCGAAGATA GGGTCGCTGT AGCGGCACCT CACCCTCTCG TTACCCGTCG

       ·  E  N  N   Y  K  T   T  P  P  V   L  D  S   D  G  S
1801   CGGAGAACAA CTACAAGACC ACGCCTCCCG TGCTGGACTC CGACGGCTCC
       GCCTCTTGTT GATGTTCTGG TGCGGAGGGC ACGACCTGAG GCTGCCGAGG

        F  F  L  Y   S  K  L   T  V  D   K  S  R  W   Q  Q  G ·
1851   TTCTTCCTCT ACAGCAAGCT CACCGTGGAC AAGAGCAGGT GGCAGCAGGG
       AAGAAGGAGA TGTCGTTCGA GTGGCACCTG TTCTCGTCCA CCGTCGTCCC

          BbsI              NsiI
         ~~~~~~~           ~~~~~~
       · N  V  F   S  C  S  V   M  H  E   A  L  H   N  H  Y  T ·
1901   GAACGTCTTC TCATGCTCCG TGATGCATGA GGCTCTGCAC AACCACTACA
       CTTGCAGAAG AGTACGAGGC ACTACGTACT CCGAGACGTG TTGGTGATGT

          SapI                                        PmeI
         ~~~~~~~~                                   ~~~~~~~~
       ·  Q  K  S   L  S  L   S  P  G  K   *
1951   CGCAGAAGAG CCTCTCCCTG TCTCCGGGTA AATGAGGGCC CGTTTAAACC
       GCGTCTTCTC GGAGAGGGAC AGAGGCCCAT TTACTCCCGG GCAAATTTGG

2001   CGCTGATCAG CCTCGACTGT GCCTTCTAGT TGCCAGCCAT CTGTTGTTTG
       GCGACTAGTC GGAGCTGACA CGGAAGATCA ACGGTCGGTA GACAACAAAC

                  ~~~~~~~~~~~~~~~~~~~
                  pMORPH®_Ig_REV 100.0%
2051   CCCCTCCCCC GTGCCTTCCT TGACCCTGGA AGGTGCCACT CCCACTGTCC
       GGGGAGGGGG CACGGAAGGA ACTGGGACCT TCCACGGTGA GGGTGACAGG
```

**Figure 9: DNA Sequence of Ig kappy light chain expression vector pMORPH®_h_Igκ_1**

```
                 StyI
               ~~~~~~~
601   TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA
      AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

651   TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
      ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

701   TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
      ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

751   ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
      TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

801   GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA CTGCTTACTG
      CAGATATATT CGTCTCGAGA GACCGATTGA TCTCTTGGGT GACGAATGAC

                    pMORPH®_Ig_FOR 100%                NheI
                  =====================               ~~~~~~
851   GCTTATCGAA ATTAATACGA CTCACTATAG GGAGACCCAA GCTGGCTAGC
      CGAATAGCTT TAATTATGCT GAGTGATATC CCTCTGGGTT CGACCGATCG

 +1           M  V   L  Q  T   Q  V  F   I  S  L  L   L  W  I
         StyI
       ~~~~~~
901   GCCACCATGG TGTTGCAGAC CCAGGTCTTC ATTTCTCTGT TGCTCTGGAT
      CGGTGGTACC ACAACGTCTG GGTCCAGAAG TAAAGAGACA ACGAGACCTA
                                BbsI
                               ~~~~~~

 +1    S  G  A   Y  G  D  I   V  M  I   K  R  T   V  A  A
                     EcoRV              BsiWI
                    ~~~~~~~            ~~~~~~
951   CTCTGGTGCC TACGGGGATA TCGTGATGAT TAAACGTACG GTGGCTGCAC
      GAGACCACGG ATGCCCCTAT AGCACTACTA ATTTGCATGC CACCGACGTG

 +1 P  S  V  F   I  F  P   P  S  D  E   Q  L  K   S  G  T
1001  CATCTGTCTT CATCTTCCCG CCATCTGATG AGCAGTTGAA ATCTGGAACT
      GTAGACAGAA GTAGAAGGGC GGTAGACTAC TCGTCAACTT TAGACCTTGA
         BbsI
        ~~~~~~~
```

**Figure 9 (Continued)**

```
   +1  A  S  V  V   C  L  L   N  N  F   Y  P  R  E   A  K  V
1051  GCCTCTGTTG TGTGCCTGCT GAATAACTTC TATCCCAGAG AGGCCAAAGT
      CGGAGACAAC ACACGGACGA CTTATTGAAG ATAGGGTCTC TCCGGTTTCA

   +1   Q  W  K   V  D  N  A   L  Q  S   G  N  S   Q  E  S
1101  ACAGTGGAAG GTGGATAACG CCCTCCAATC GGGTAACTCC CAGGAGAGTG
      TGTCACCTTC CACCTATTGC GGGAGGTTAG CCCATTGAGG GTCCTCTCAC

   +1 V  T  E  Q   D  S  K   D  S  T  Y   S  L  S   S  T  L
1151  TCACAGAGCA GGACAGCAAG GACAGCACCT ACAGCCTCAG CAGCACCCTG
      AGTGTCTCGT CCTGTCGTTC CTGTCGTGGA TGTCGGAGTC GTCGTGGGAC

   +1  T  L  S  K   A  D  Y   E  K  H   K  V  Y  A   C  E  V
        BlpI
       ~~~~~~~
1201  ACGCTGAGCA AAGCAGACTA CGAGAAACAC AAAGTCTACG CCTGCGAAGT
      TGCGACTCGT TTCGTCTGAT GCTCTTTGTG TTTCAGATGC GGACGCTTCA

   +1   T  H  Q   G  L  S  S   P  V  T   K  S  F   N  R  G
1251  CACCCATCAG GGCCTGAGCT CGCCCGTCAC AAAGAGCTTC AACAGGGGAG
      GTGGGTAGTC CCGGACTCGA GCGGGCAGTG TTTCTCGAAG TTGTCCCCTC

   +1 E  C  *
                         PmeI                 pMORPH®_Ig_REV 100%
                      ~~~~~~~~~~              =================
1301  AGTGTTAGGG GCCCGTTTAA ACCCGCTGAT CAGCCTCGAC TGTGCCTTCT
      TCACAATCCC CGGGCAAATT TGGGCGACTA GTCGGAGCTG ACACGGAAGA


      =
1351  AGTTGCCAGC CATCTGTTGT TTGCCCCTCC CCCGTGCCTT CCTTGACCCT
      TCAACGGTCG GTAGACAACA AACGGGGAGG GGGCACGGAA GGAACTGGGA
```

**Figure 10: DNA Sequence of HuCAL® Ig lambda light chain vector pMORPH®_h_Ig□□1**

```
                StyI
              ~~~~~~~
 601  TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA
      AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

 651  TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA
      ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

 701  TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA
      ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

 751  ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG
      TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

 801  GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA CTGCTTACTG
      CAGATATATT CGTCTCGAGA GACCGATTGA TCTCTTGGGT GACGAATGAC

                  pM_Ig_FOR  100.0%                NheI
                ======================             ~~~~~~
 851  GCTTATCGAA ATTAATACGA CTCACTATAG GGAGACCCAA GCTGGCTAGC
      CGAATAGCTT TAATTATGCT GAGTGATATC CCTCTGGGTT CGACCGATCG

  +1        M  A   W  A  L   L  L  L   T  L  L  T   Q  G  T
          StyI
         ~~~~~~
 901  GCCACCATGG CCTGGGCTCT GCTGCTCCTC ACCCTCCTCA CTCAGGGCAC
      CGGTGGTACC GGACCCGAGA CGACGAGGAG TGGGAGGAGT GAGTCCCGTG

  +2                                            T  V   L  G  Q
  +1    G  S  W   A  D  I  V   M  H  E   V
       BamHI        EcoRV              HpaI       StyI
      ~~~~~~      ~~~~~~             ~~~~~~     ~~~~~~
 951  AGGATCCTGG GCTGATATCG TGATGCACGA AGTTAACCGT CCTAGGTCAG
      TCCTAGGACC CGACTATAGC ACTACGTGCT TCAATTGGCA GGATCCAGTC

  +2  P  K  A  A   P  S  V   T  L  F   P  P  S  S   E  E  L
       StyI
      ~~~~~~
1001  CCCAAGGCTG CCCCCTCGGT CACTCTGTTC CCGCCCTCCT CTGAGGAGCT
      GGGTTCCGAC GGGGGAGCCA GTGAGACAAG GGCGGGAGGA GACTCCTCGA

  +2    Q  A  N   K  A  T  L   V  C  L   I  S  D   F  Y  P
1051  TCAAGCCAAC AAGGCCACAC TGGTGTGTCT CATAAGTGAC TTCTACCCGG
      AGTTCGGTTG TTCCGGTGTG ACCACACAGA GTATTCACTG AAGATGGGCC
```

**Figure 10 (Continued)**

```
   +2 G  A  V  T   V  A  W   K  G  D  S   S  P  V   K  A  G
1101  GAGCCGTGAC AGTGGCCTGG AAGGGAGATA GCAGCCCCGT CAAGGCGGGA
      CTCGGCACTG TCACCGGACC TTCCCTCTAT CGTCGGGGCA GTTCCGCCCT

   +2  V  E  T  T   T  P  S   K  Q  S   N  N  K  Y   A  A  S
1151  GTGGAGACCA CCACACCCTC CAAACAAAGC AACAACAAGT ACGCGGCCAG
      CACCTCTGGT GGTGTGGGAG GTTTGTTTCG TTGTTGTTCA TGCGCCGGTC

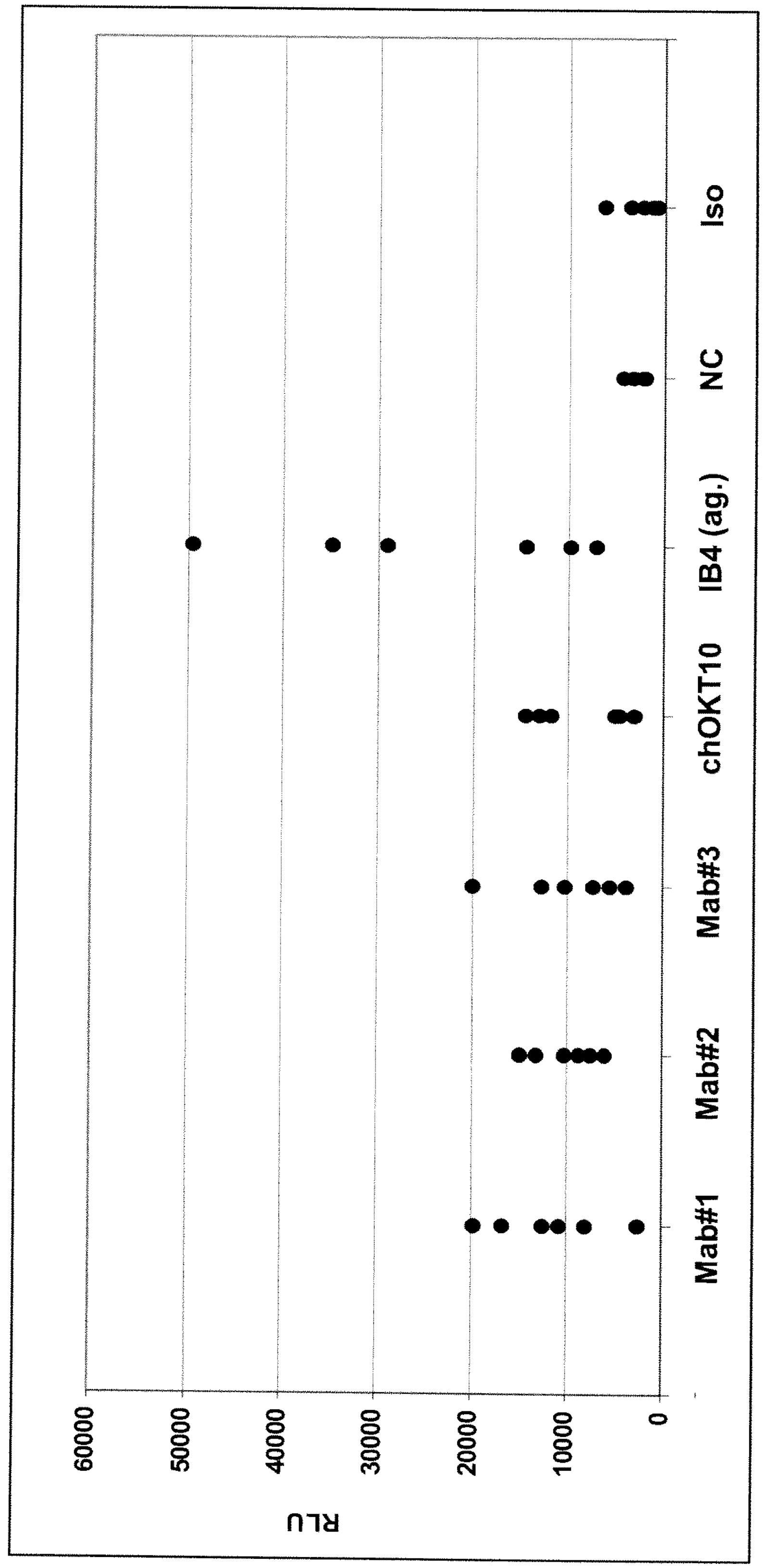
   +2  S  Y  L   S  L  T  P   E  Q  W   K  S  H   R  S  Y
1201  CAGCTATCTG AGCCTGACGC CTGAGCAGTG GAAGTCCCAC AGAAGCTACA
      GTCGATAGAC TCGGACTGCG GACTCGTCAC CTTCAGGGTG TCTTCGATGT

   +2 S  C  Q  V   T  H  E   G  S  T  V   E  K  T   V  A  P
                                           BbsI
                                          ~~~~~~
1251  GCTGCCAGGT CACGCATGAA GGGAGCACCG TGGAGAAGAC AGTGGCCCCT
      CGACGGTCCA GTGCGTACTT CCCTCGTGGC ACCTCTTCTG TCACCGGGGA

   +2  T  E  C  S   *
                              PmeI
                            ~~~~~~~~
1301  ACAGAATGTT CATAGGGGCC CGTTTAAACC CGCTGATCAG CCTCGACTGT
      TGTCTTACAA GTATCCCCGG GCAAATTTGG GCGACTAGTC GGAGCTGACA
                                          pM_Ig_REV 100%
                                             ==========

1351  GCCTTCTAGT TGCCAGCCAT CTGTTGTTTG CCCCTCCCCC GTGCCTTCCT
      CGGAAGATCA ACGGTCGGTA GACAACAAAC GGGGAGGGGG CACGGAAGGA
      pM_Ig_REV  100.0%
      ========
```

Fig. 11: Proliferation Assay



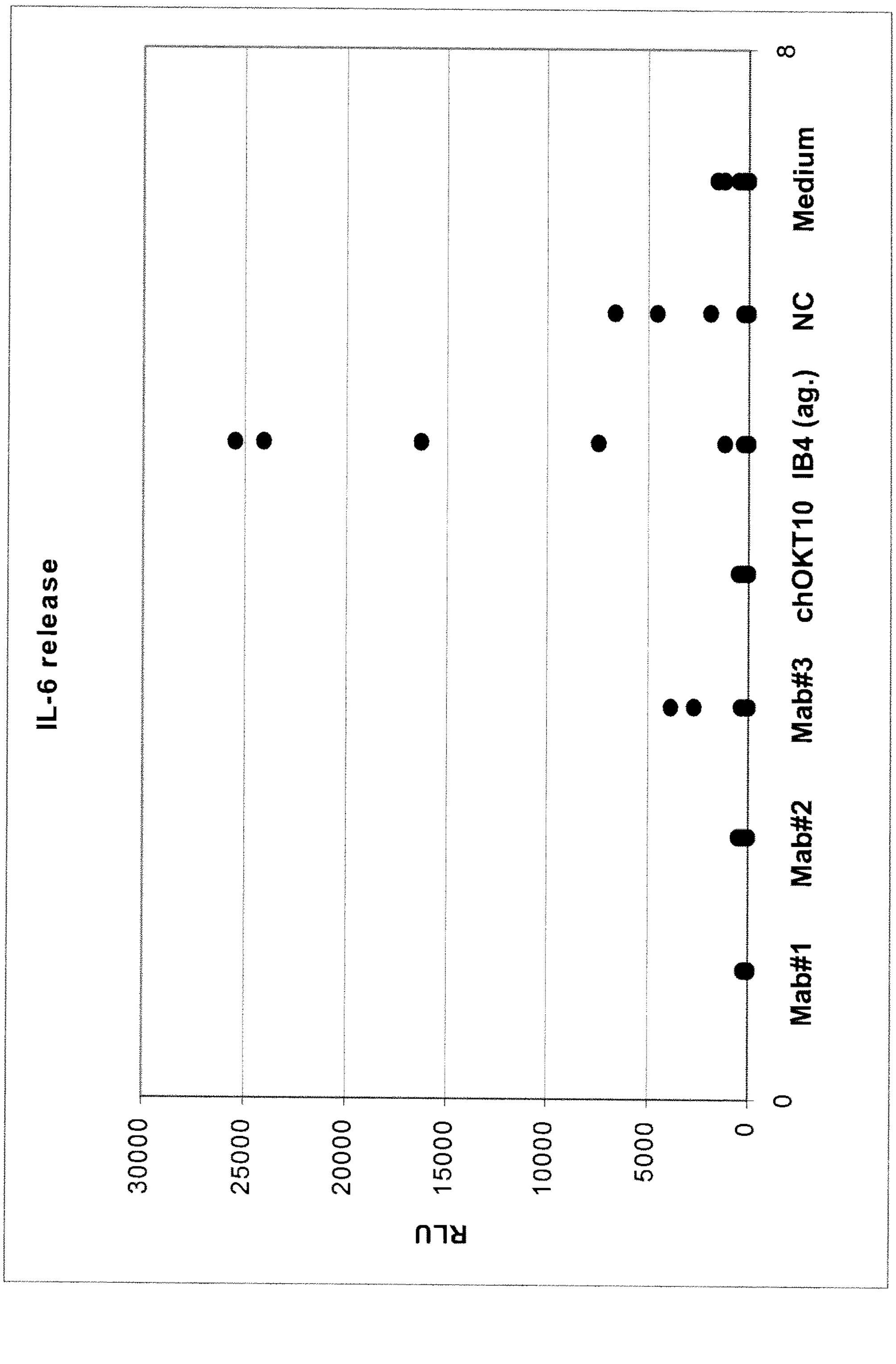



Fig. 12: IL-6 Release Assay

Fig. 13: Cytotoxicity towards CD34+/CD38+ progenitor cells

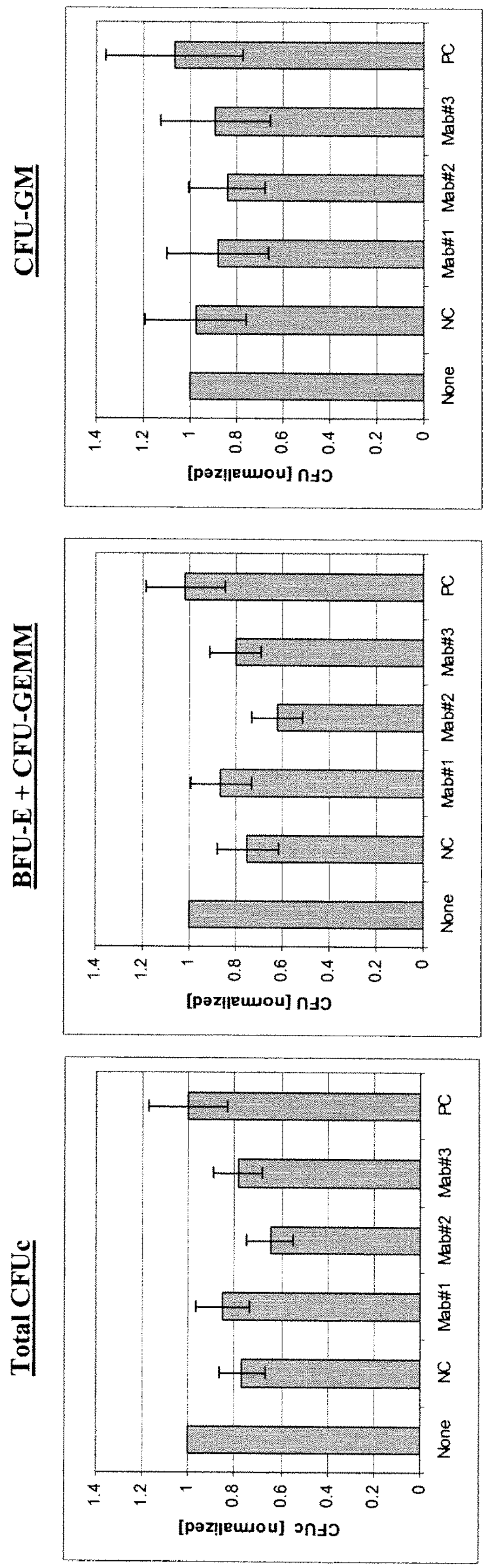


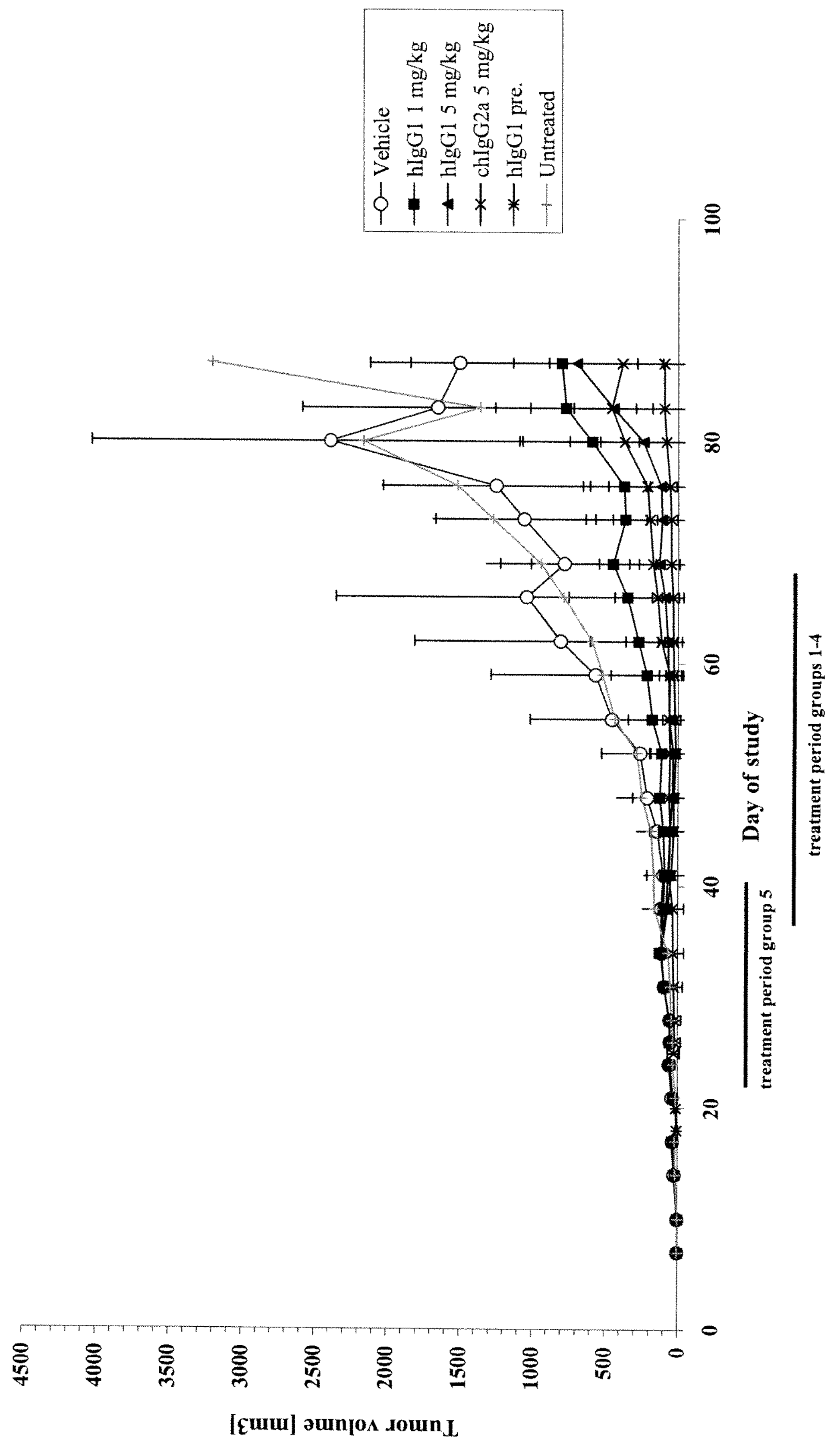
Fig. 14: ADCC with different cell-lines

| Cell line | Culture Collection | Origin | Expression [MFI] | Max. specific killing [%] in ADCC[a,c] | | | |
|---|---|---|---|---|---|---|---|
| | | | | Mab#1 | Mab#2 | Mab#3 | PC |
| RPMI 8226 | ATCC CCL-155 | MM | 405.71 | 56 | 58 | 54 | 46 |
| KMS-12-BM | DSMZ ACC551 | MM | 142.29 | 26 | 32 | 30 | 34 |
| NCI-H929 | ECACC95050415 | MM | 45.01 | 68 | 73 | 38 | 54 |
| OPM-2 | DSMZ ACC50 | MM | 37.99 | 6 | 13 | 3 | 7 |
| U-266 | ECACC85051003 | MM | 26.14 | 17 | 14 | 12 | 16 |
| KMS-11 | Namba *et al*., 1989[b] | MM | 26.81[d] | 22 | 30 | 26 | 28 |
| JVM-13 | DSMZACC19 | CLL | 463.93 | 11 | 20 | 12 | 15 |
| JVM-2 | DSMZACC12 | CLL | 140.84 | 22 | 28 | 10 | 24 |
| CCRF-CEM | ECACC85112105 | ALL | 301.46 | 24 | 29 | 20 | 22 |
| Jurkat | DSMZ ACC282 | ALL | 202.99 | 7 | 8 | 13 | 12 |
| AML-193 | DSMZ ACC549 | AML | 62.69[d] | 33 | 26 | 39 | 33 |
| OCI-AML5 | DSMZ ACC247 | AML | 207.55[d] | 20 | 21 | 16 | 26 |
| NB-4 | DSMZ ACC207 | AML | 164.7[d] | 36 | 38 | 32 | 37 |
| THP-1 | DSMZ ACC16 | AML | 34.41 | 64 | 59 | 38 | 43 |
| HL-60[d] | DSMZ ACC3 | AML | 18.43[d] | 29 | 35 | 29 | 29 |
| Raji | Burkitt's Lymph. | Burkitt's lymph. | n.d. | 53 | 62 | 48 | n.d. |

Fig. 15: ADCC with MM-samples

| Antibodies / Parameters: | Mab#1 | Mab#2 | Mab#3 | PC |
|---|---|---|---|---|
| MM samples: EC50 [nM][a]: | 0.116-0.202 | 0.006-0.185 | 0.027-0.249 | 0.282-0.356 |
| MM samples: Max spec. killing [%] | 13.1 - 61.6 | 16.2 - 57.9 | 13.6 - 36.0 | 15.5 - 49.5 |

Fig. 16: Treatment of human myeloma xenograft with MOR03080



# ANTI-CD38 HUMAN ANTIBODIES AND USES THEREFOR

## RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. application Ser. No. 14/630,042 filed on Feb. 24, 2015, which is pending, which is a Continuation of U.S. application Ser. No. 13/427,305, filed Mar. 22, 2012, which is abandoned, which is a Divisional of U.S. application Ser. No. 10/588,568, which issued as U.S. Pat. No. 8,263,746, which is the U.S. National Stage application of PCT/IB05/002476, filed Feb. 7, 2005, which claims priority to U.S. provisional application numbers 60/541,911 filed Feb. 6, 2004, 60/547,584 filed Feb. 26, 2004, 60/553,948 filed Mar. 18, 2004, and 60/599,014 filed Aug. 6, 2004, and 60/614,471, filed Oct. 1, 2004, the contents of each of which are incorporated herein in their entireties.

## SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Dec. 28, 2017, is named 102977-000012_SL.txt and is 47,825 bytes in size.

## BACKGROUND OF THE INVENTION

[0003] CD38 is a type-II membrane glycoprotein and belongs to the family of ectoenzymes, due to its enzymatic activity as ADP ribosyl-cyclase and cADP—hydrolase. During ontogeny, CD38 appears on CD34+ committed stem cells and lineage-committed progenitors of lymphoid, erythroid and myeloid cells. It is understood that CD38 expression persists only in the lymphoid lineage, through the early stages of T- and B-cell development.

[0004] The up-regulation of CD38 serves as a marker for lymphocyte activation—in particular B-cell differentiation along the plasmacytoid pathway. (Co-)receptor functions of CD38 leading to intracellular signaling or intercellular communication via its ligand, CD31, are postulated, as well as its role as an intracellular regulator of a second messenger, cyclic ADPr, in a variety of signaling cascades. However, its physiological importance remains to be elucidated, since knock out of the murine analogue or anti-CD38 auto-antibodies in humans do not appear to be detrimental.

[0005] Apart from observing its expression in the hematopoetic system, researchers have noted the up-regulation of CD38 on various cell-lines derived from B-, T-, and myeloid/monocytic tumors, including B- or T-cell acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). In MM, for example, strong CD38 expression is witnessed in the majority of all patient samples.

[0006] Hence, over-expression of CD38 on malignant cells provides an attractive therapeutic target for immunotherapy. Of special attraction is the fact that the most primitive pluripotent stem cells of the hematopoietic system are CD38– negative and that the extent of cytotoxic effects by ADCC or CDC correlates well with the expression-levels of the respective target.

[0007] Current approaches of anti-CD38 therapies can be divided in two groups: in vivo and ex vivo approaches. In in vivo approaches, anti-CD38 antibodies are administered to a subject in need of therapy in order to cause the antibody-mediated depletion of CD38-overexpressing malignant cells. Depletion can either be achieved by antibody-mediated ADCC and/or CDC by effector cells, or by using the anti-CD38 antibodies as targeting moieties for the transport of cytotoxic substances, e.g. saporin, to the target cells, and subsequent internalization. In the ex vivo approach, cell population, e.g. bone marrow cells, comprising CD38 over-expressing malignant cells are removed from an individual in need of treatment and are contacted with anti-CD38 antibodies. The target cells are either destroyed by cytotoxic substances, e.g. saporin, as described for the in vivo approach, or are removed by contacting the cell population with immobilized anti-CD38 antibodies, thus removing CD38 overexpressing target cells from the mixture. Thereafter, the depleted cell population is reinserted into the patient.

[0008] Antibodies specific for CD38 can be divided in different groups, depending on various properties. Binding of some antibodies to the CD38 molecule (predominantly aa 220-300) can trigger activities within the target cell, such as Ca2+ release, cytokine release, phosphorylation events and growth stimulation based on the respective antibody specificity (Konopleva et al., 1998; Ausiello et al., 2000), but no clear correlation between the binding site of the various known antibodies and their (non-)agonistic properties could be seen (Funaro et al., 1990).

[0009] Relatively little is known about the efficacy of published anti-CD38 antibodies. What is known is that all known antibodies seem to exclusively recognize epitopes (amino acid residues 220 to 300) located in the C-terminal part of CD38. No antibodies are known so far that are specific for epitopes in the N-terminal part of CD38 distant from the active site in the primary protein sequence. However, we have found that OKT10, which has been in clinical testing, has a relatively low affinity and efficacy when analyzed as chimeric construct comprising a human Fc part. Furthermore, OKT10 is a murine antibody rendering it unsuitable for human administration. A human anti-CD38 scFv antibody fragment has recently been described (WO 02/06347). However, that antibody is specific for a selectively expressed CD38 epitope.

[0010] Correspondingly, in light of the great potential for anti-CD38 antibody therapy, there is a high need for human anti-CD38 antibodies with high affinity and with high efficacy in mediating killing of CD38 overexpressing malignant cells by ADCC and/or CDC.

[0011] The present invention satisfies these and other needs by providing fully human and highly efficacious anti-CD38 antibodies, which are described below.

## SUMMARY OF THE INVENTION

[0012] It is an object of the invention to provide human and humanized antibodies that can effectively mediate the killing of CD38-overexpressing cells.

[0013] It is another object of the invention to provide antibodies that are safe for human administration.

[0014] It is also an object of the present invention to provide methods for treating disease or and/or conditions associated with CD38 up-regulation by using one or more antibodies of the invention. These and other objects of the invention are more fully described herein.

[0015] In one aspect, the invention provides an isolated antibody or functional antibody fragment that contains an antigen-binding region that is specific for an epitope of

CD38, where the antibody or functional fragment thereof is able to mediate killing of a CD38+target cell (LP-1 (DSMZ: ACC41) and RPMI-8226 (ATCC: CCL-155)) by antibody-dependent cellular cytotoxicity ("ADCC") with an at least two- to five-fold better efficacy than the chimeric OKT10 antibody having SEQ ID NOS: 23 and 24 (under the same or substantially the same conditions), when a human PBMC cell is employed as an effector cell, and when the ratio of effector cells to target cells is between about 30:1 and about 50:1. Such an antibody or functional fragment thereof may contain an antigen-binding region that contains an H-CDR3 region depicted in SEQ ID NO: 5, 6, 7, or 8; the antigen-binding region may further include an H-CDR2 region depicted in SEQ ID NO: 5, 6, 7, or 8; and the antigen-binding region also may contain an H-CDR1 region depicted in SEQ ID NO: 5, 6, 7, or 8. Such a CD38-specific antibody of the invention may contain an antigen-binding region that contains an L-CDR3 region depicted in SEQ ID NO: 13, 14, 15, or 16; the antigen-binding region may further include an L-CDR1 region depicted in SEQ ID NO: 13, 14, 15, or 16; and the antigen-binding region also may contain an L-CDR2 region depicted in SEQ ID NO: 13, 14, 15, or 16.

**[0016]** In another aspect, the invention provides an isolated antibody or functional antibody fragment that contains an antigen-binding region that is specific for an epitope of CD38, where the antibody or functional fragment thereof is able to mediate killing of a CD38-transfected CHO cell by CDC with an at least two-fold better efficacy than chimeric OKT10 (SEQ ID NOS: 23 and 24) under the same or substantially the same conditions as in the previous paragraph. An antibody satisfying these criteria may contain an antigen-binding region that contains an H-CDR3 region depicted in SEQ ID NO: 5, 6, or 7; the antigen-binding region may further include an H-CDR2 region depicted in SEQ ID NO: 5, 6, or 7; and the antigen-binding region also may contain an H-CDR1 region depicted in SEQ ID NO: 5, 6, or 7. Such a CD38-specific antibody of the invention may contain an antigen-binding region that contains an L-CDR3 region depicted in SEQ ID NO: 13, 14, or 15; the antigen-binding region may further include an L-CDR1 region depicted in SEQ ID NO: 13, 14, or 15; and the antigen-binding region also may contain an L-CDR2 region depicted in SEQ ID NO: 13, 14, or 15.

**[0017]** Antibodies (and functional fragments thereof) of the invention may contain an antigen-binding region that is specific for an epitope of CD38, which epitope contains one or more amino acid residues of amino acid residues 43 to 215 of CD38, as depicted by SEQ ID NO: 22. More specifically, an epitope to which the antigen-binding region binds may contain one or more amino acid residues found in one or more of the amino acid stretches taken from the list of amino acid stretches 44-66, 82-94, 142-154, 148-164, 158-170, and 192-206. For certain antibodies, the epitope may be linear, whereas for others, it may be conformational (i.e., discontinuous). An antibody or functional fragment thereof having one or more of these properties may contain an antigen-binding region that contains an H-CDR3 region depicted in SEQ ID NO: 5, 6, 7, or 8; the antigen-binding region may further include an H-CDR2 region depicted in SEQ ID NO: 5, 6, 7, or 8; and the antigen-binding region also may contain an H-CDR1 region depicted in SEQ ID NO: 5, 6, 7, or 8. Such a CD38-specific antibody of the invention may contain an antigen-binding region that contains an L-CDR3 region depicted in SEQ ID NO: 13, 14, 15, or 16; the antigen-binding region may further include an L-CDR1 region depicted in SEQ ID NO: 13, 14, 15, or 16; and the antigen-binding region also may contain an L-CDR2 region depicted in SEQ ID NO: 13, 14, 15, or 16.

**[0018]** Peptide variants of the sequences disclosed herein are also embraced by the present invention. Accordingly, the invention includes anti-CD38 antibodies having a heavy chain amino acid sequence with: at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 5, 6, 7, or 8; and/or at least 80 percent sequence homology in the CDR regions with the CDR regions depicted in SEQ ID NO: 5, 6, 7, or 8. Further included are anti-CD38 antibodies having a light chain amino acid sequence with: at least 60 percent sequence identity in the CDR regions with the CDR regions depicted in SEQ ID NO: 13, 14, 15 or 16; and/or at least 80 percent sequence homology in the CDR regions with the CDR regions depicted in SEQ ID NO: 13, 14, 15 or 16.

**[0019]** An antibody of the invention may be an IgG (e.g., $IgG_1$), while an antibody fragment may be a Fab or scFv, for example. An inventive antibody fragment, accordingly, may be, or may contain, an antigen-binding region that behaves in one or more ways as described herein.

**[0020]** The invention also is related to isolated nucleic acid sequences, each of which can encode an antigen-binding region of a human antibody or functional fragment thereof that is specific for an epitope of CD38. Such a nucleic acid sequence may encode a variable heavy chain of an antibody and include a sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, or 4, or a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, or 4. The nucleic acid might encode a variable light chain of an isolated antibody or functional fragment thereof, and may contain a sequence selected from the group consisting of SEQ ID NOS: 9, 10, 11, or 12, or a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 9, 10, 11, or 12.

**[0021]** Nucleic acids of the invention are suitable for recombinant production. Thus, the invention also relates to vectors and host cells containing a nucleic acid sequence of the invention.

**[0022]** Compositions of the invention may be used for therapeutic or prophylactic applications. The invention, therefore, includes a pharmaceutical composition containing an inventive antibody (or functional antibody fragment) and a pharmaceutically acceptable carrier or excipient therefor. In a related aspect, the invention provides a method for treating a disorder or condition associated with the undesired presence of CD38 or CD38 expressing cells. Such method contains the steps of administering to a subject in need thereof an effective amount of the pharmaceutical composition that contains an inventive antibody as described or contemplated herein.

**[0023]** The invention also relates to isolated epitopes of CD38, either in linear or conformational form, and their use for the isolation of an antibody or functional fragment thereof, which antibody of antibody fragment comprises an antigen-binding region that is specific for said epitope. In this regard, a linear epitope may contain amino acid residues 192-206, while a conformational epitope may contain one or more amino acid residues selected from the group consisting of amino acids 44-66, 82-94, 142-154, 148-164, 158-170 and 202-224 of CD38. An epitope of CD38 can be used, for example, for the isolation of antibodies or functional fragments thereof (each of which antibodies or antibody fragments comprises an antigen-binding region that is specific for such epitope), comprising the steps of contacting said epitope of CD38 with an antibody library and isolating the antibody(ies) or functional fragment(s) thereof.

**[0024]** In another embodiment, the invention provides an isolated epitope of CD38, which consists essentially of an amino acid sequence selected from the group consisting of amino acids 44-66, 82-94, 142-154, 148-164, 158-170, 192-206 and 202-224 of CD38. As used herein, such an epitope "consists essentially of" one of the immediately preceding amino acid sequences plus additional features, provided that the additional features do not materially affect the basic and novel characteristics of the epitope.

**[0025]** In yet another embodiment, the invention provides an isolated epitope of CD38 that consists of an amino acid sequence selected from the group consisting of amino acids 44-66, 82-94, 142-154, 148-164, 158-170, 192-206 and 202-224 of CD38.

**[0026]** The invention also provides a kit containing (i) an isolated epitope of CD38 comprising one or more amino acid stretches taken from the list of 44-66, 82-94, 142-154, 148-164, 158-170, 192-206 and 202-224; (ii) an antibody library; and (iii) instructions for using the antibody library to isolate one or more members of such library that binds specifically to such epitope.

## BRIEF DESCRIPTION OF THE FIGURES

**[0027]** FIG. **1***a* provides nucleic acid sequences of various novel antibody variable heavy regions.

**[0028]** FIG. **1***b* provides amino acid sequences of various novel antibody variable heavy regions. CDR regions HCDR1, HCDR2 and HCDR3 are designated from N- to C-terminus in boldface.

**[0029]** FIG. **2***a* provides nucleic acid sequences of various novel antibody variable light regions.

**[0030]** FIG. **2***b* provides amino acid sequences of various novel antibody variable light regions. CDR regions LCDR1, LCDR2 and LCDR3 are designated from N- to C-terminus in boldface.

**[0031]** FIG. **3** provides amino acid sequences of variable heavy regions of various consensus-based HUCAL® (human combinatorial monoclonal antibody library) antibody master gene sequences. CDR regions HCDR1, HCDR2 and HCDR3 are designated from N- to C-terminus in boldface.

**[0032]** FIG. **4** provides amino acid sequences of variable light regions of various consensus-based HuCAL antibody master gene sequences. CDR regions LCDR1, LCDR2 and LCDR3 are designated from N- to C-terminus in boldface.

**[0033]** FIG. **5** provides the amino acid sequence of CD38 (SWISS-PROT primary accession number P28907).

**[0034]** FIG. **6** provides the nucleotide sequences of the heavy and light chains of chimeric OKT10.

**[0035]** FIG. **7** provides a schematic overview of epitopes of representative antibodies of the present invention.

**[0036]** FIG. **8** provides the DNA sequence of pMORPH®_h_IgG1_1 (bp 601-2100) (SEQ ID NO: 32): The vector is based on the pcDNA3.1+ vectors (Invitrogen). The amino acid sequence encoded by the DNA sequence is presented (SEQ ID NO: 35), and the amino acid sequence of the VH-stuffer sequence is indicated in bold, whereas the final reading frames of the VH-leader sequence and the constant region gene are printed in non-bold. Restriction sites are indicated above the sequence. The priming sites of the sequencing primers are underlined. The antisense strand of the DNA sequence is presented in SEQ ID NO: 44.

**[0037]** FIG. **9** provides the DNA sequence of Ig kappa light chain expression vector pMORPH®_h_1 (bp 601-1400) (SEQ ID NO: 33): The vector is based on the pcDNA3.1+ vectors (Invitrogen). The amino acid sequences encoded by the DNA sequence is presented (SEQ ID NO: 36), and the amino acid sequence of the Vκ-stuffer sequence is indicated in bold, whereas the final reading frames of the Vκ-leader sequence and of the constant region gene are printed in non-bold. Restriction sites are indicated above the sequence. The priming sites of the sequencing primers are underlined. The antisense strand of the DNA sequence is presented in SEQ ID NO: 45.

**[0038]** FIG. **10** provides the DNA sequence of HUCAL® Ig lambda light chain vector pMORPH®_h_Igλ_t (bp 601-1400) (SEQ ID NO: 34): The amino acid sequence encoded by the DNA sequence is presented (SEQ ID NO: 37), and the amino acid sequence of the Vλ-stuffer sequence is indicated in bold, whereas the final reading frames of the Vλ-leader sequence and of the constant region gene are printed in non-bold. Restriction sites are indicated above the sequence. The priming sites of the sequencing primers are underlined. The antisense strand of the DNA sequence is presented in SEQ ID NO: 46.

**[0039]** FIG. **11** provides the results of the proliferation assay: PBMCs from 6 different healthy donors (as indicated by individual dots) were cultured for 3 days in the presence of HUCAL® (human combinatorial monoclonal antibody library) antibodies Mab#1 (=MOR03077), Mab#2 (=MOR03079), and Mab#3 (=MOR03080), the reference antibody chOKT10, the agonistic (ag.) control IB4, an irrelevant HUCAL® negative control IgG1 (NC) and a murine IgG2a (Iso) as matched isotype control for IB4. A standard labeling with BrdU was used to measure proliferation activity and its incorporation (as RLU =relative light units) analyzed via a chemiluminescence-based ELISA.

**[0040]** FIG. **12** provides the results of the IL-6 Release Assay: PBMCs from 4-8 different healthy donors (as indicated by individual dots) were cultured for 24 hrs in the presence of HuCAL® antibodies Mab#1 (=MOR03077), Mab#2 (=MOR03079), and Mab#3 (=MOR03080), the reference antibody chOKT10, the agonistic (ag.) control IB4, an irrelevant HuCAL® negative control (NC) and medium only (Medium). IL-6 content in relative light units (RLU) was analyzed from culture supernatants via a chemiluminescence based ELISA.

**[0041]** FIG. **13** provides data about the cytotoxicity towards CD34+/CD38+ progenitor cells: PBMCs from healthy donors harboring autologous CD34+/CD38+ progenitor cells were incubated with HUCAL® Mab#1 (=MOR03077), Mab#2 (=MOR03079), and Mab#3 (=MOR03080), the positive control (PC=chOKT10) and an irrelevant HUCAL® negative control for 4 hours, respectively. Afterwards, the cell suspension was mixed with conditioned methyl-cellulose medium and incubated for 2 weeks. Colony forming units (CFU) derived from erythroid burst forming units (BFU-E; panel B) and granulocyte/erythroid/macrophage/ megakaryocyte stem cells (CFU-GEMM; panels B) and granulocyte/macrophage stem cells (CFU-GM; panel C) were counted and normalized against the medium control ("none"=medium). Panel A represents the total number of CFU (Total CFUc) for all progenitors.

Mean values from at least 10 different PBMC donors are given. Error bars represent standard error of the mean.

**[0042]** FIG. **14** provides data about ADCC with different cell-lines:

**[0043]** a: Single measurements (except for RPMI8226: average from 4 indiv. Assays); E:T -ratio: 30:1

**[0044]** b: Namba et al., 1989

**[0045]** c: 5 μg/ml used for antibody conc. (except for Raji with 0.1 μg/ml)

**[0046]** d: addition of retinoic assay for stimulation of CD38-expression specific killing [%]=[(exp. killing−medium killing)/(1−medium killing)]*100

**[0047]** PC: Positive control (=chOKT10)

**[0048]** MM: Multiple myeloma

**[0049]** CLL: Chronic B-cell leukemia

**[0050]** ALL: Acute lymphoblastic leukemia

**[0051]** AML: Acute myeloid leukemia

**[0052]** DSMZ: Deutsche Sammlung für Mikroorganismen and Zellkulturen GmbH

**[0053]** ATCC: American type culture collection

**[0054]** ECACC: European collection of cell cultures

**[0055]** MFI: Mean fluorescence intensities.

**[0056]** FIG. **15** provides data about ADCC with MM-samples:

**[0057]** [a]: 2-4 individual analyses

**[0058]** FIG. **16** provides the experimental results of mean tumor volumes after treatment of human myeloma xenograft with MOR03080: group 1: vehicle; group 2: MOR03080 as hIgG1 1mg/kg 32-68 days every second day; group 3: MOR03080 as hIgG1 5 mg/kg 32-68 days every second day; group 4: MOR03080 as chIgG2a 5 mg/kg 32-68 days every second day; group 5: MOR03080 as hIgG1 1 mg/kg, 14-36 days every second day; group 6: untreated

## DETAILED DESCRIPTION OF THE INVENTION

**[0059]** The present invention is based on the discovery of novel antibodies that are specific to or have a high affinity for CD38 and can deliver a therapeutic benefit to a subject. The antibodies of the invention, which may be human or humanized, can be used in many contexts, which are more fully described herein.

**[0060]** A "human" antibody or functional human antibody fragment is hereby defined as one that is not chimeric (e.g., not "humanized") and not from (either in whole or in part) a non-human species. A human antibody or functional antibody fragment can be derived from a human or can be a synthetic human antibody. A "synthetic human antibody" is defined herein as an antibody having a sequence derived, in whole or in part, in silico from synthetic sequences that are based on the analysis of known human antibody sequences. In silico design of a human antibody sequence or fragment thereof can be achieved, for example, by analyzing a database of human antibody or antibody fragment sequences and devising a polypeptide sequence utilizing the data obtained therefrom. Another example of a human antibody or functional antibody fragment, is one that is encoded by a nucleic acid isolated from a library of antibody sequences of human origin (i.e., such library being based on antibodies taken from a human natural source).

**[0061]** A "humanized antibody" or functional humanized antibody fragment is defined herein as one that is (i) derived from a non-human source (e.g., a transgenic mouse which bears a heterologous immune system), which antibody is based on a human germline sequence; or (ii) chimeric, wherein the variable domain is derived from a non-human origin and the constant domain is derived from a human origin or (iii) CDR-grafted, wherein the CDRs of the variable domain are from a non-human origin, while one or more frameworks of the variable domain are of human origin and the constant domain (if any) is of human origin.

**[0062]** As used herein, an antibody "binds specifically to," is "specific to/for" or "specifically recognizes" an antigen (here, CD38) if such antibody is able to discriminate between such antigen and one or more reference antigen(s), since binding specificity is not an absolute, but a relative property. In its most general form (and when no defined reference is mentioned), "specific binding" is referring to the ability of the antibody to discriminate between the antigen of interest and an unrelated antigen, as determined, for example, in accordance with one of the following methods. Such methods comprise, but are not limited to Western blots, ELISA-, RIA-, ECL-, IRMA-tests and peptide scans. For example, a standard ELISA assay can be carried out. The scoring may be carried out by standard color development (e.g. secondary antibody with horseradish peroxide and tetramethyl benzidine with hydrogenperoxide). The reaction in certain wells is scored by the optical density, for example, at 450 nm. Typical background (=negative reaction) may be 0.1 OD; typical positive reaction may be 1 OD. This means the difference positive/negative can be more than 10-fold. Typically, determination of binding specificity is performed by using not a single reference antigen, but a set of about three to five unrelated antigens, such as milk powder, BSA, transferrin or the like.

**[0063]** However, "specific binding" also may refer to the ability of an antibody to discriminate between the target antigen and one or more closely related antigen(s), which are used as reference points, e.g. between CD38 and CD157. Additionally, "specific binding" may relate to the ability of an antibody to discriminate between different parts of its target antigen, e.g. different domains or regions of CD38, such as epitopes in the N-terminal or in the C-terminal region of CD38, or between one or more key amino acid residues or stretches of amino acid residues of CD38.

**[0064]** Also, as used herein, an "immunoglobulin" (Ig) hereby is defined as a protein belonging to the class IgG, IgM, IgE, IgA, or IgD (or any subclass thereof), and includes all conventionally known antibodies and functional fragments thereof. A "functional fragment" of an antibody/immunoglobulin hereby is defined as a fragment of an antibody/immunoglobulin (e.g., a variable region of an IgG) that retains the antigen-binding region. An "antigen-binding region" of an antibody typically is found in one or more hypervariable region(s) of an antibody, i.e., the CDR-1, -2, and/or -3 regions; however, the variable "framework" regions can also play an important role in antigen binding, such as by providing a scaffold for the CDRs. Preferably, the "antigen-binding region" comprises at least amino acid residues 4 to 103 of the variable light (VL) chain and 5 to 109 of the variable heavy (VH) chain, more preferably amino acid residues 3 to 107 of VL and 4 to 111 of VH, and particularly preferred are the complete VL and VH chains (amino acid positions 1 to 109 of VL and 1 to 113 of VH;

numbering according to WO 97/08320). A preferred class of immunoglobulins for use in the present invention is IgG. "Functional fragments" of the invention include the domain of a $F(ab')_2$ fragment, a Fab fragment and scFv. The $F(ab')_2$ or Fab may be engineered to minimize or completely remove the intermolecular disulphide interactions that occur between the Cm and CL domains.

**[0065]** An antibody of the invention may be derived from a recombinant antibody library that is based on amino acid sequences that have been designed in silico and encoded by nucleic acids that are synthetically created. In silico design of an antibody sequence is achieved, for example, by analyzing a database of human sequences and devising a polypeptide sequence utilizing the data obtained therefrom. Methods for designing and obtaining in silico-created sequences are described, for example, in Knappik et al., J. Mol. Biol. (2000) 296:57; Krebs et al., J. Immunol. Methods. (2001) 254:67; and U.S. Patent No. 6,300,064 issued to Knappik et al., which hereby are incorporated by reference in their entirety.

Antibodies of the Invention

**[0066]** Throughout this document, reference is made to the following representative antibodies of the invention: "antibody nos." or "LACS" or "MOR" 3077, 3079, 3080 and 3100. LAC 3077 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 1 (DNA)/SEQ ID NO: 5 (protein) and a variable light region corresponding to SEQ ID NO: 9 (DNA)/SEQ ID NO: 13 (protein). LAC 3079 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 2 (DNA)/SEQ ID NO: 6 (protein) and a variable light region corresponding to SEQ ID NO: 10 (DNA)/SEQ ID NO: 14 (protein). LAC 3080 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 3 (DNA)/SEQ ID NO: 7 (protein) and a variable light region corresponding to SEQ ID NO: 11 (DNA)/SEQ ID NO: 15 (protein). LAC 3100 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 4 (DNA)/SEQ ID NO: 8 (protein) and a variable light region corresponding to SEQ ID NO: 12 (DNA)/SEQ ID NO: 16 (protein).

**[0067]** In one aspect, the invention provides antibodies having an antigen-binding region that can bind specifically to or has a high affinity for one or more regions of CD38, whose amino acid sequence is depicted by SEQ ID NO: 22. An antibody is said to have a "high affinity" for an antigen if the affinity measurement is at least 100 nM (monovalent affinity of Fab fragment). An inventive antibody or antigen-binding region preferably can bind to CD38 with an affinity of about less than 100 nM, more preferably less than about 60 nM, and still more preferably less than about 30 nM. Further preferred are antibodies that bind to CD38 with an affinity of less than about 10 nM, and more preferably less than 3 about nM. For instance, the affinity of an antibody of the invention against CD38 may be about 10.0 nM or 2.4 nM (monovalent affinity of Fab fragment).

**[0068]** Table 1 provides a summary of affinities of representative antibodies of the invention, as determined by surface plasmon resonance (BIACORE) and FACS Scatchard analysis:

TABLE 1

Antibody Affinities

| Antibody (Fab or IgG1) | BIACORE (Fab) $K_D$ [nM][a] | FACS Scatchard (IgG1)[b] $K_D$ [nM][a] |
|---|---|---|
| MOR03077 | 56.0 | 0.89 |
| MOR03079 | 2.4 | 0.60 |
| MOR03080 | 27.5 | 0.47 |
| MOR03100 | 10.0 | 6.31 |
| Chimeric OKT10 | not determined | 8.28 |

[a]mean from at least 2 different affinity determinations
[b]RPMI8226 MM cell-line used for FACS-Scatchards

**[0069]** With reference to Table 1, the affinity of LACs 3077, 3079, 3080 and 3100 was measured by surface plasmon resonance (BIACORE) on immobilized recombinant CD38 and by a flow cytometry procedure utilizing the CD38-expressing human RPMI8226 cell line. The BIACORE studies were performed on directly immobilized antigen (CD38-Fc fusion protein). The Fab format of LACs 3077, 3079, 3080 and 3100 exhibit an monovalent affinity range between about 2.4 and 56 nM on immobilized CD38-Fc fusion protein with LAC 3079 showing the highest affinity, followed by Fabs 3100, 3080 and 3077.

**[0070]** The IgG1 format was used for the cell-based affinity determination (FACS Scatchard). The right column of Table 1 denotes the binding strength of the LACS in this format. LAC 3080 showed the strongest binding, which is slightly stronger than LACS 3079 and 3077.

**[0071]** Another preferred feature of preferred antibodies of the invention is their specificity for an area within the N-terminal region of CD38. For example, LACs 3077, 3079, 3080, and 3100 of the invention can bind specifically to the N-terminal region of CD38.

**[0072]** The type of epitope to which an antibody of the invention binds may be linear (i.e. one consecutive stretch of amino acids) or conformational (i.e. multiple stretches of amino acids). In order to determine whether the epitope of a particular antibody is linear or conformational, the skilled worker can analyze the binding of antibodies to overlapping peptides (e.g., 13-mer peptides with an overlap of 11 amino acids) covering different domains of CD38. Using this analysis, the inventors have discovered that LACS 3077, 3080, and 3100 recognize discontinuous epitopes in the N-terminal region of CD38, whereas the epitope of LAC 3079 can be described as linear (see FIG. **7**). Combined with the knowledge provided herein, the skilled worker in the art will know how to use one or more isolated epitopes of CD38 for generating antibodies having an antigen-binding region that is specific for said epitopes (e.g. using synthetic peptides of epitopes of CD38 or cells expressing epitopes of CD38).

**[0073]** An antibody of the invention preferably is species cross-reactive with humans and at least one other species, which may be a rodent species or a non-human primate. The non-human primate can be rhesus, baboon and/or cynomolgus. The rodent species can be mouse, rat and/or hamster. An antibody that is cross reactive with at least one rodent species, for example, can provide greater flexibility and benefits over known anti-CD38 antibodies, for purposes of conducting in vivo studies in multiple species with the same antibody. Preferably, an antibody of the invention not only is able to bind to CD38, but also is able to mediate killing of a cell expressing CD38. More specifically, an antibody of the invention can mediate its therapeutic effect by depleting CD38-positive (e.g., malignant) cells via antibody-effector functions. These functions include antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

**[0074]** Table 2 provides a summary of the determination of EC50 values of representative antibodies of the invention in both ADCC and CDC:

TABLE 2

EC50 Values of Antibodies

| | ADCC EC50 [nM] | | CDC EC50 [nM] |
|---|---|---|---|
| Antibody (IgG1) | LP-1 | RPMI8226 | CHO-transfectants |
| MOR03077 | 0.60[a] | 0.08[a] | 0.8[c]; 0.94[d] |
| MOR03079 | 0.09[a] | 0.04[a] | 0.41[c] |
| MOR03080 | 0.17[b] | 0.05[a] | 3.2[c]; 2.93[d] |
| MOR03100 | 1.00[b] | 0.28[a] | 10.9[c]; 13.61[e] |
| Chimeric OKT10 | 5.23[a] | 4.10[a] | 9.30[c] |

[a]mean from at least 2 EC50 determinations
[b]single determination
[c]mean from 2 EC50 determinations
[d]mean from 3 EC50 determinations
[e]mean from 4 EC50 determinations

**[0075]** CD38-expression, however, is not only found on immune cells within the myeloid (e.g. monocytes, granulocytes) and lymphoid lineage (e.g. activated B and T-cells; plasma cells), but also on the respective precursor cells. Since it is important that those cells are not affected by antibody-mediated killing of malignant cells, the antibodies of the present invention are preferably not cytotoxic to precursor cells.

**[0076]** In addition to its catalytic activities as a cyclic ADP-ribose cyclase and hydrolase, CD38 displays the ability to transduce signals of biological relevance (Hoshino et al., 1997; Ausiello et al., 2000). Those functions can be induced in vivo by, e.g. receptor-ligand interactions or by cross-linking with agonistic anti-CD38 antibodies, leading, e.g. to calcium mobilization, lymphocyte proliferation and release of cytokines. Preferably, the antibodies of the present invention are non-agonistic antibodies.

Peptide Variants

**[0077]** Antibodies of the invention are not limited to the specific peptide sequences provided herein. Rather, the invention also embodies variants of these polypeptides. With reference to the instant disclosure and conventionally available technologies and references, the skilled worker will be able to prepare, test and utilize functional variants of the antibodies disclosed herein, while appreciating that variants having the ability to mediate killing of a CD38+ target cell fall within the scope of the present invention. As used in this context, "ability to mediate killing of a CD38+ target cell" means a functional characteristic ascribed to an anti-CD38 antibody of the invention. Ability to mediate killing of a CD38+ target cell, thus, includes the ability to mediate killing of a CD38+ target cell, e.g. by ADCC and/or CDC, or by toxin constructs conjugated to an antibody of the invention.

**[0078]** A variant can include, for example, an antibody that has at least one altered complementarity determining region (CDR) (hyper-variable) and/or framework (FR) (variable) domain/position, vis-à-vis a peptide sequence disclosed herein. To better illustrate this concept, a brief description of antibody structure follows.

**[0079]** An antibody is composed of two peptide chains, each containing one (light chain) or three (heavy chain) constant domains and a variable region (VL, VH), the latter of which is in each case made up of four FR regions and three interspaced CDRs. The antigen-binding site is formed by one or more CDRs, yet the FR regions provide the structural framework for the CDRs and, hence, play an important role in antigen binding. By altering one or more amino acid residues in a CDR or FR region, the skilled worker routinely can generate mutated or diversified antibody sequences, which can be screened against the antigen, for new or improved properties, for example.

**[0080]** Tables 3a (VH) and 3b (VL) delineate the CDR and FR regions for certain antibodies of the invention and compare amino acids at a given position to each other and to corresponding consensus or "master gene" sequences (as described in U.S. Pat. No. 6,300,064):

Table 3a: VH Sequences

VH

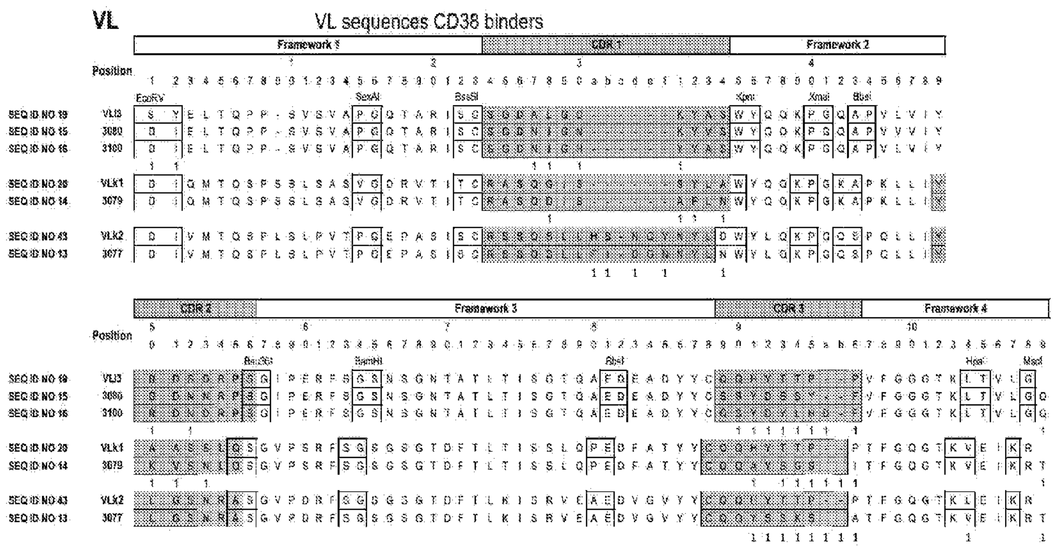
VH sequences CD38 binders

| | | Framework 1 | | | | | | | | | | | | | | | | | | | | | | | | CDR 1 | | | | | | | | | | | | Framework 2 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | 1 | | | | | | | | | | 2 | | | | | | | | | | 3 | | | | | | | | | | | | 4 | | | | | | | | | |
| Position | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | a | b | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| | | | | MfeI | | | | | | | | | | | | | | | | | | | | | | BspEI | | | | | | | | | | | | | | | | | BstXI | | | | | XhoI | | | | |
| SEQ ID NO: 17 | VH1B | Q | V | Q | L | V | Q | S | G | A | E | V | K | K | P | G | A | S | V | K | V | S | C | K | A | S | G | Y | T | F | T | S | - | - | Y | Y | M | H | W | V | R | Q | A | P | G | Q | G | L | E | W | M | G |
| SEQ ID NO: 5 | 3077 | Q | V | Q | L | V | Q | S | G | A | E | V | K | K | P | G | A | S | V | K | V | S | C | K | A | S | G | Y | T | F | T | S | | | Y | S | I | N | W | V | R | Q | A | P | G | Q | G | L | E | W | M | G |
| SEQ ID NO: 42 | VH3 | E | V | Q | L | V | E | S | G | G | G | L | V | Q | P | G | G | S | L | R | L | S | C | A | A | S | G | F | T | F | S | S | - | - | Y | A | M | S | W | V | R | Q | A | P | G | K | G | L | E | W | V | S |
| SEQ ID NO: 6 | 3079 | Q | V | Q | L | V | E | S | G | G | G | L | V | Q | P | G | G | S | L | R | L | S | C | A | A | S | G | F | T | F | S | N | | | Y | G | M | H | W | V | R | Q | A | P | G | K | G | L | E | W | V | S |
| SEQ ID NO: 7 | 3080 | Q | V | Q | L | V | E | S | G | G | G | L | V | Q | P | G | G | S | L | R | L | S | C | A | A | S | G | F | T | F | S | S | | | Y | G | M | H | W | V | R | Q | A | P | G | K | G | L | E | W | V | S |
| SEQ ID NO: 8 | 3100 | Q | V | Q | L | V | E | S | G | G | G | L | V | Q | P | G | G | S | L | R | L | S | C | A | A | S | G | F | T | F | S | S | | | V | G | M | S | W | V | R | Q | A | P | G | K | G | L | E | W | V | S |

| | | CDR 2 | | | | | | | | | | | | | | | | | | | Framework 3 | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 | | | | | | | | | | | | | 6 | | | | | | | | | | 7 | | | | | | | | | | 8 | | | | | | | | | | | | | 9 | | | | |
| Position | | 0 | 1 | 2 | a | b | c | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | a | b | c | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 |
| | | | | | | | | | | | | | | | | | | | | | | BstEII | | | | | | | | | | | | | | | | | | | | | | | | EagI | | | | BssHII | | |
| SEQ ID NO: 17 | VH1B | W | I | N | P | - | - | N | S | G | G | T | N | Y | A | Q | K | F | Q | G | R | V | T | M | T | R | D | T | S | I | S | T | A | Y | M | E | L | S | S | L | R | S | E | D | T | A | V | Y | Y | C | A | R |
| SEQ ID NO: 5 | 3077 | Y | I | D | P | | | N | R | G | N | T | N | Y | A | Q | K | F | Q | G | R | V | T | M | T | R | D | T | S | I | S | T | A | Y | M | E | L | S | S | L | R | S | E | D | T | A | V | Y | Y | C | A | R |
| SEQ ID NO: 42 | VH3 | A | I | S | G | - | - | S | G | G | S | T | Y | Y | A | D | S | V | K | G | R | F | T | I | S | R | D | N | S | K | N | T | L | Y | L | Q | M | N | S | L | R | A | E | D | T | A | V | Y | Y | C | A | R |
| SEQ ID NO: 6 | 3079 | N | I | R | S | | | D | G | S | W | T | Y | Y | A | D | S | V | K | G | R | F | T | I | S | R | D | N | S | K | N | T | L | Y | L | Q | M | N | S | L | R | A | E | D | T | A | V | Y | Y | C | A | R |
| SEQ ID NO: 7 | 3080 | N | I | Y | S | | | D | G | S | N | T | F | Y | A | D | S | V | K | G | R | F | T | I | S | R | D | N | S | K | N | T | L | Y | L | Q | M | N | S | L | R | A | E | D | T | A | V | Y | Y | C | A | R |
| SEQ ID NO: 8 | 3100 | N | I | S | Y | | | L | S | S | S | T | Y | Y | A | D | S | V | K | G | R | F | T | I | S | R | D | N | S | K | N | T | L | Y | L | Q | M | N | S | L | R | A | E | D | T | A | V | Y | Y | C | A | R |

| | | CDR 3 | | | | | | | | | | | | | | | | | | Framework 4 | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 10 | | | | | | | | | | | | | | | | | | | | 11 | | | |
| Position | | 5 | 6 | 7 | 8 | 9 | 0 | a | b | c | d | e | f | g | h | i | j | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 |
| | | | | | | | | | | | | | | | | | | | | | | StyI | | | | | | | BlpI | |
| SEQ ID NO: 17 | VH1B | W | G | G | D | G | F | Y | A | - | - | - | - | - | - | - | M | D | Y | W | G | Q | G | T | L | V | T | V | S | S |
| SEQ ID NO: 5 | 3077 | E | Y | I | Y | F | I | H | G | M | - | - | - | - | - | - | L | D | F | W | G | Q | G | T | L | V | T | V | S | S |
| SEQ ID NO: 42 | VH3 | W | G | G | D | G | F | Y | A | - | - | - | - | - | - | - | M | D | Y | W | G | Q | G | T | L | V | T | V | S | S |
| SEQ ID NO: 6 | 3079 | R | Y | W | S | K | S | H | A | S | V | - | - | - | - | - | T | D | Y | W | G | Q | G | T | L | V | T | V | S | S |
| SEQ ID NO: 7 | 3080 | N | M | Y | R | W | P | F | H | Y | F | - | - | - | - | - | F | D | Y | W | G | Q | G | T | L | V | T | V | S | S |
| SEQ ID NO: 8 | 3100 | F | Y | G | Y | F | N | Y | - | - | - | - | - | - | - | - | A | D | V | W | G | Q | G | T | L | V | T | V | S | S |

Table 3b: VL Sequences



[0081] The skilled worker can use the data in Tables 3a and 3b to design peptide variants that are within the scope of the present invention. It is preferred that variants are constructed by changing amino acids within one or more CDR regions; a variant might also have one or more altered framework regions. With reference to a comparison of the novel antibodies to each other, candidate residues that can be changed include e.g. residues 4 or 37 of the variable light and e.g. residues 13 or 43 of the variable heavy chains of LACs 3080 and 3077, since these are positions of variance vis-à-vis each other. Alterations also may be made in the framework regions. For example, a peptide FR domain might be altered where there is a deviation in a residue compared to a germline sequence.

[0082] With reference to a comparison of the novel antibodies to the corresponding consensus or "master gene" sequence, candidate residues that can be changed include e.g. residues 27, 50 or 90 of the variable light chain of LAC 3080 compared to VLX3 and e.g. residues 33, 52 and 97 of the variable heavy chain of LAC 3080 compared to VH3. Alternatively, the skilled worker could make the same analysis by comparing the amino acid sequences disclosed herein to known sequences of the same class of such antibodies, using, for example, the procedure described by Knappik et al., 2000 and U.S. Pat. No. 6,300,064 issued to Knappik et al.

[0083] Furthermore, variants may be obtained by using one LAC as starting point for optimization by diversifying one or more amino acid residues in the LAC, preferably amino acid residues in one or more CDRs, and by screening the resulting collection of antibody variants for variants with improved properties. Particularly preferred is diversification of one or more amino acid residues in CDR-3 of VL, CDR-3 of VH, CDR-1 of VL and/or CDR-2 of VH. Diversification can be done by synthesizing a collection of DNA molecules using trinucleotide mutagenesis (TRIM) technology (Virnekäs, B., Ge, L., Plückthun, A., Schneider, K. C., Wellnhofer, G., and Moroney S. E. (1994) Trinucleotide phosphoramidites: ideal reagents for the synthesis of mixed oligonucleotides for random mutagenesis. Nucl. Acids Res. 22, 5600.).

Conservative Amino Acid Variants

[0084] Polypeptide variants may be made that conserve the overall molecular structure of an antibody peptide sequence described herein. Given the properties of the individual amino acids, some rational substitutions will be recognized by the skilled worker. Amino acid substitutions, i.e., "conservative substitutions," may be made, for instance, on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues involved.

[0085] For example, (a) nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; (b) polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine; (c) positively charged (basic) amino acids include arginine, lysine, and histidine; and (d) negatively charged (acidic) amino acids include aspartic acid and glutamic acid. Substitutions typically may be made within groups (a)-(d). In addition, glycine and proline may be substituted for one another based on their ability to disrupt a-helices. Similarly, certain amino acids, such as alanine, cysteine, leucine, methionine, glutamic acid, glutamine, histidine and lysine are more commonly found in a-helices, while valine, isoleucine, phenylalanine, tyrosine, tryptophan and threonine are more commonly found in β-pleated sheets. Glycine, serine, aspartic acid, asparagine, and proline are commonly found in turns. Some preferred substitutions may be made among the following groups: (i) S and T; (ii) P and G; and (iii) A, V, L and I. Given the known genetic code, and recombinant and synthetic DNA techniques, the skilled scientist readily can construct DNAs encoding the conservative amino acid variants. In one particular example, amino acid position 3 in SEQ ID NOS: 5, 6, 7, and/or 8 can be changed from a Q to an E.

[0086] As used herein, "sequence identity" between two polypeptide sequences indicates the percentage of amino acids that are identical between the sequences. "Sequence similarity" indicates the percentage of amino acids that either are identical or that represent conservative amino acid substitutions. Preferred polypeptide sequences of the invention have a sequence identity in the CDR regions of at least 60%, more preferably, at least 70% or 80%, still more preferably at least 90% and most preferably at least 95%. Preferred antibodies also have a sequence similarity in the CDR regions of at least 80%, more preferably 90% and most preferably 95%.

DNA Molecules of the Invention

[0087] The present invention also relates to the DNA molecules that encode an antibody of the invention. These sequences include, but are not limited to, those DNA molecules set forth in FIGS. **1***a* and **2***a*.

[0088] DNA molecules of the invention are not limited to the sequences disclosed herein, but also include variants thereof. DNA variants within the invention may be described by reference to their physical properties in hybridization. The skilled worker will recognize that DNA can be used to identify its complement and, since DNA is double stranded, its equivalent or homolog, using nucleic acid hybridization techniques. It also will be recognized that hybridization can occur with less than 100% complementarity. However, given appropriate choice of conditions, hybridization techniques can be used to differentiate among DNA sequences based on their structural relatedness to a particular probe. For guidance regarding such conditions see, Sambrook et al., 1989 (Sambrook, J., Fritsch, E. F. and Maniatis, T. (1989) Molecular Cloning: A laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, USA) and Ausubel et al., 1995 (Ausubel, F. M., Brent, R., Kingston, R. E., Moore, D. D., Sedman, J. G., Smith, J. A., & Struhl, K. eds. (1995). Current Protocols in Molecular Biology. New York: John Wiley and Sons).

[0089] Structural similarity between two polynucleotide sequences can be expressed as a function of "stringency" of the conditions under which the two sequences will hybridize with one another. As used herein, the term "stringency" refers to the extent that the conditions disfavor hybridization. Stringent conditions strongly disfavor hybridization, and only the most structurally related molecules will hybridize to one another under such conditions. Conversely, non-stringent conditions favor hybridization of molecules displaying a lesser degree of structural relatedness. Hybridization stringency, therefore, directly correlates with the structural relationships of two nucleic acid sequences.

The following relationships are useful in correlating hybridization and relatedness (where $T_m$ is the melting temperature of a nucleic acid duplex):

a. $T_m=69.3+0.41(G+C)\%$

b. The $T_m$ of a duplex DNA decreases by 1° C. with every increase of 1% in the number of mismatched base pairs.

c. $(T_m)_{\mu 2}-(T_m)_{\mu 1}=18.5\ \log_{10}\mu 2/\mu 1$

where μ**1** and μ2 are the ionic strengths of two solutions.

**[0090]** Hybridization stringency is a function of many factors, including overall DNA concentration, ionic strength, temperature, probe size and the presence of agents which disrupt hydrogen bonding. Factors promoting hybridization include high DNA concentrations, high ionic strengths, low temperatures, longer probe size and the absence of agents that disrupt hydrogen bonding. Hybridization typically is performed in two phases: the "binding" phase and the "washing" phase.

**[0091]** First, in the binding phase, the probe is bound to the target under conditions favoring hybridization. Stringency is usually controlled at this stage by altering the temperature. For high stringency, the temperature is usually between 65° C. and 70° C., unless short (<20 nt) oligonucleotide probes are used. A representative hybridization solution comprises 6× SSC, 0.5% SDS, 5× Denhardt's solution and 100 μg of nonspecific carrier DNA. See Ausubel et al., section 2.9, supplement 27 (1994). Of course, many different, yet functionally equivalent, buffer conditions are known. Where the degree of relatedness is lower, a lower temperature may be chosen. Low stringency binding temperatures are between about 25° C. and 40° C. Medium stringency is between at least about 40° C. to less than about 65° C. High stringency is at least about 65° C.

**[0092]** Second, the excess probe is removed by washing. It is at this phase that more stringent conditions usually are applied. Hence, it is this "washing" stage that is most important in determining relatedness via hybridization. Washing solutions typically contain lower salt concentrations. One exemplary medium stringency solution contains 2× SSC and 0.1% SDS. A high stringency wash solution contains the equivalent (in ionic strength) of less than about 0.2× SSC, with a preferred stringent solution containing about 0.1× SSC. The temperatures associated with various stringencies are the same as discussed above for "binding." The washing solution also typically is replaced a number of times during washing. For example, typical high stringency washing conditions comprise washing twice for 30 minutes at 55° C. and three times for 15 minutes at 60° C.

**[0093]** Accordingly, the present invention includes nucleic acid molecules that hybridize to the molecules of set forth in Figures la and 2a under high stringency binding and washing conditions, where such nucleic molecules encode an antibody or functional fragment thereof having properties as described herein. Preferred molecules (from an mRNA perspective) are those that have at least 75% or 80% (preferably at least 85%, more preferably at least 90% and most preferably at least 95%) homology or sequence identity with one of the DNA molecules described herein. In one particular example of a variant of the invention, nucleic acid position 7 in SEQ ID NOS: 1, 2, 3 and/or 4 can be substituted from a C to a G, thereby changing the codon from CAA to GAA.

Functionally Equivalent Variants

**[0094]** Yet another class of DNA variants within the scope of the invention may be described with reference to the product they encode (see the peptides listed in FIGS. **1***b* and **2***b*). These functionally equivalent genes are characterized by the fact that they encode the same peptide sequences found in FIG. **1***b* and **2***b* due to the degeneracy of the genetic code. SEQ ID NOS: 1 and 31 are an example of functionally equivalent variants, as their nucleic acid sequences are different, yet they encode the same polypeptide, i.e. SEQ ID NO: 5.

**[0095]** It is recognized that variants of DNA molecules provided herein can be constructed in several different ways. For example, they may be constructed as completely synthetic DNAs. Methods of efficiently synthesizing oligonucleotides in the range of 20 to about 150 nucleotides are widely available. See Ausubel et al., section 2.11, Supplement 21 (1993). Overlapping oligonucleotides may be synthesized and assembled in a fashion first reported by Khorana et al., J. Mol. Biol. 72:209-217 (1971); see also Ausubel et al., supra, Section 8.2. Synthetic DNAs preferably are designed with convenient restriction sites engineered at the 5' and 3' ends of the gene to facilitate cloning into an appropriate vector.

**[0096]** As indicated, a method of generating variants is to start with one of the DNAs disclosed herein and then to conduct site-directed mutagenesis. See Ausubel et al., supra, chapter 8, Supplement 37 (1997). In a typical method, a target DNA is cloned into a single-stranded DNA bacteriophage vehicle. Single-stranded DNA is isolated and hybridized with an oligonucleotide containing the desired nucleotide alteration(s). The complementary strand is synthesized and the double stranded phage is introduced into a host. Some of the resulting progeny will contain the desired mutant, which can be confirmed using DNA sequencing. In addition, various methods are available that increase the probability that the progeny phage will be the desired mutant. These methods are well known to those in the field and kits are commercially available for generating such mutants.

Recombinant DNA Constructs and Expression

**[0097]** The present invention further provides recombinant DNA constructs comprising one or more of the nucleotide sequences of the present invention. The recombinant constructs of the present invention are used in connection with a vector, such as a plasmid or viral vector, into which a DNA molecule encoding an antibody of the invention is inserted.

**[0098]** The encoded gene may be produced by techniques described in Sambrook et al., 1989, and Ausubel et al., 1989. Alternatively, the DNA sequences may be chemically synthesized using, for example, synthesizers. See, for example, the techniques described in OLIGONUCLEOTIDE SYNTHESIS (1984, Gait, ed., IRL Press, Oxford), which is incorporated by reference herein in its entirety. Recombinant constructs of the invention are comprised with expression vectors that are capable of expressing the RNA and/or protein products of the encoded DNA(s). The vector may further comprise regulatory sequences, including a promoter operably linked to the open reading frame (ORF). The vector may further comprise a selectable marker sequence. Specific initiation and bacterial secretory signals also may be required for efficient translation of inserted target gene coding sequences.

**[0099]** The present invention further provides host cells containing at least one of the DNAs of the present invention. The host cell can be virtually any cell for which expression vectors are available. It may be, for example, a higher eukaryotic host cell, such as a mammalian cell, a lower eukaryotic host cell, such as a yeast cell, but preferably is a prokaryotic cell, such as a bacterial cell. Introduction of the recombinant construct into the host cell can be effected by calcium phosphate transfection, DEAE, dextran mediated transfection, electroporation or phage infection.

Bacterial Expression

**[0100]** Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and, if desirable, to provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli, Bacillus subtilis, Salmonella typhimurium* and various species within the genera *Pseudomonas, Streptomyces*, and *Staphylococcus.*

**[0101]** Bacterial vectors may be, for example, bacteriophage-, plasmid- or phagemid-based. These vectors can contain a selectable marker and bacterial origin of replication derived from commercially available plasmids typically containing elements of the well known cloning vector pBR322 (ATCC 37017). Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is de-repressed/induced by appropriate means (e.g., temperature shift or chemical induction) and cells are cultured for an additional period. Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

**[0102]** In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the protein being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of antibodies or to screen peptide libraries, for example, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable.

Therapeutic Methods

**[0103]** Therapeutic methods involve administering to a subject in need of treatment a therapeutically effective amount of an antibody contemplated by the invention. A "therapeutically effective" amount hereby is defined as the amount of an antibody that is of sufficient quantity to deplete CD38-positive cells in a treated area of a subject—either as a single dose or according to a multiple dose regimen, alone or in combination with other agents, which leads to the alleviation of an adverse condition, yet which amount is toxicologically tolerable. The subject may be a human or non-human animal (e.g., rabbit, rat, mouse, monkey or other lower-order primate).

**[0104]** An antibody of the invention might be co-administered with known medicaments, and in some instances the antibody might itself be modified. For example, an antibody could be conjugated to an immunotoxin or radioisotope to potentially further increase efficacy.

**[0105]** The inventive antibodies can be used as a therapeutic or a diagnostic tool in a variety of situations where CD38 is undesirably expressed or found. Disorders and conditions particularly suitable for treatment with an antibody of the inventions are multiple myeloma (MM) and other haematological diseases, such as chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML), and acute lymphocytic leukemia (ALL). An antibody of the invention also might be used to treat inflammatory disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).

**[0106]** To treat any of the foregoing disorders, pharmaceutical compositions for use in accordance with the present invention may be formulated in a conventional manner using one or more physiologically acceptable carriers or excipients. An antibody of the invention can be administered by any suitable means, which can vary, depending on the type of disorder being treated. Possible administration routes include parenteral (e.g., intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous), intrapulmonary and intranasal, and, if desired for local immunosuppressive treatment, intralesional administration. In addition, an antibody of the invention might be administered by pulse infusion, with, e.g., declining doses of the antibody. Preferably, the dosing is given by injections, most preferably intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. The amount to be administered will depend on a variety of factors such as the clinical symptoms, weight of the individual, whether other drugs are administered. The skilled artisan will recognize that the route of administration will vary depending on the disorder or condition to be treated.

**[0107]** Determining a therapeutically effective amount of the novel polypeptide, according to this invention, largely will depend on particular patient characteristics, route of administration, and the nature of the disorder being treated. General guidance can be found, for example, in the publications of the International Conference on Harmonisation and in REMINGTON'S PHARMACEUTICAL SCIENCES, chapters 27 and 28, pp. 484-528 (18th ed., Alfonso R. Gennaro, Ed., Easton, Pa.: Mack Pub. Co., 1990). More specifically, determining a therapeutically effective amount will depend on such factors as toxicity and efficacy of the medicament. Toxicity may be determined using methods well known in the art and found in the foregoing references. Efficacy may be determined utilizing the same guidance in conjunction with the methods described below in the Examples.

Diagnostic Methods

**[0108]** CD38 is highly expressed on hematological cells in certain malignancies; thus, an anti-CD38 antibody of the invention may be employed in order to image or visualize a site of possible accumulation of malignant cells in a patient. In this regard, an antibody can be detectably labeled, through the use of radioisotopes, affinity labels (such as biotin, avidin, etc.) fluorescent labels, paramagnetic atoms, etc. Procedures for accomplishing such labeling are well known to the art. Clinical application of antibodies in diagnostic imaging are reviewed by Grossman, H. B., Urol. Clin. North Amer. 13:465-474 (1986)), Unger, E. C. et al., Invest. Radiol. 20:693-700 (1985)), and Khaw, B. A. et al., Science 209:295-297 (1980)).

**[0109]** The detection of foci of such detectably labeled antibodies might be indicative of a site of tumor development, for example. In one embodiment, this examination is done by removing samples of tissue or blood and incubating such samples in the presence of the detectably labeled antibodies. In a preferred embodiment, this technique is done in a non-invasive manner through the use of magnetic imaging, fluorography, etc. Such a diagnostic test may be employed in monitoring the success of treatment of diseases, where presence or absence of CD38-positive cells is a relevant indicator. The invention also contemplates the use of an anti-CD38 antibody, as described herein for diagnostics in an ex vivo setting.

Therapeutic And Diagnostic Compositions

**[0110]** The antibodies of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, wherein an antibody of the invention (including any functional fragment thereof) is combined in a mixture with a pharmaceutically acceptable carrier vehicle. Suitable vehicles and their formulation are described, for example, in REMINGTON'S PHARMACEUTICAL SCIENCES (18th ed., Alfonso R. Gennaro, Ed., Easton, Pa.: Mack Pub. Co., 1990). In order to form a pharmaceutically acceptable composition suitable for effective administration, such compositions will contain an effective amount of one or more of the antibodies of the present invention, together with a suitable amount of carrier vehicle.

**[0111]** Preparations may be suitably formulated to give controlled-release of the active compound. Controlled-release preparations may be achieved through the use of polymers to complex or absorb anti-CD38 antibody. The controlled delivery may be exercised by selecting appropriate macromolecules (for example polyesters, polyamino acids, polyvinyl, pyrrolidone, ethylenevinyl-acetate, methylcellulose, carboxymethylcellulose, or protamine, sulfate) and the concentration of macromolecules as well as the methods of incorporation in order to control release. Another possible method to control the duration of action by controlled release preparations is to incorporate anti-CD38 antibody into particles of a polymeric material such as polyesters, polyamino acids, hydrogels, poly(lactic acid) or ethylene vinylacetate copolymers. Alternatively, instead of incorporating these agents into polymeric particles, it is possible to entrap these materials in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatine-microcapsules and poly(methylmethacylate) microcapsules, respectively, or in colloidal drug delivery systems, for example, liposomes, albumin microspheres, microemulsions, nanoparticles, and nanocapsules or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences (1980).

**[0112]** The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules, or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

**[0113]** The compositions may, if desired, be presented in a pack or dispenser device, which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration.

**[0114]** The invention further is understood by reference to the following working examples, which are intended to illustrate and, hence, not limit the invention.

## EXAMPLES

Cell-Lines

**[0115]** The following cell-lines were obtained from the European Collection of Cell Cultures (ECACC), the German Collection of Microorganisms (DSMZ) or the American Type Culture collection (ATCC): hybridoma cell line producing the CD38 mouse IgG1 monoclonal antibody OKT10 (ECACC, #87021903), Jurkat cells (DSMZ, ACC282), LP-1 (DSMZ, ACC41), RPMI8226 (ATCC, CCL-155), HEK293 (ATCC, CRL-1573), CHO-Kl (ATCC, CRL-61) and Raji (ATCC, CCL-86)

Cells and Culture-Conditions

**[0116]** All cells were cultured under standardized conditions at 37° C. and 5% $CO_2$ in a humidified incubator. The cell-lines LP-1, RPMI8226, Jurkat and Raji were cultured in RPMI1640 (Pan biotech GmbH, #PO4-16500) supplemented with 10% FCS (PAN biotech GmbH, #P30-3302), 50 U/ml penicillin, 50 μg/m1 streptomycin (Gibco, #15140-122) and 2 mM glutamine (Gibco, #25030-024) and, in case of Jurkat- and Raji-cells, additionally 10 mM Hepes (Pan biotech GmbH, #P05-01100) and 1 mM sodium pyruvate (Pan biotech GmbH, # PO4-43100) had to be added.

**[0117]** CHO-Kl and HEK293 were grown in DMEM (Gibco, #10938-025) supplemented with 2 mM glutamine and 10% FCS. Stable CD38 CHO-Kl transfectants were maintained in the presence of G418 (PAA GmbH, P11-012) whereas for HEK293 the addition of 1 mM sodium-pyruvate was essential. After transient transfection of HEK293 the 10% FCS was replaced by Ultra low IgG FCS (Invitrogen, #16250-078). The cell-line OKT10 was cultured in IDMEM (Gibco, #31980-022), supplemented with 2 mM glutamine and 20% FCS.

Preparation of Single Cell Suspensions from Peripheral Blood

**[0118]** All blood samples were taken after informed consent. Peripheral blood mononuclear cells (PBMC) were isolated by HISTOPAQUE®-1077 (medium comprising polysucrose and sodium diatrizoate adjusted to density of 1.077 g/mL)(Sigma) according to the manufacturer's instructions from healthy donors. Red blood cells were depleted from these cell suspensions by incubation in ACK Lysis Buffer (0.15 M NH4Cl, 10 mM $KHCO_3$, 0.1 M EDTA) for 5 min at RT or a commercial derivative (Bioscience, #00-4333). Cells were washed twice with PBS and then further processed for flow cytometry or ADCC (see below).

Flow Cytometry ("FACS")

**[0119]** All stainings were performed in round bottom 96-well culture plates (Nalge Nunc) with $2\times10^5$ cells per well. Cells were incubated with Fab or IgG antibodies at the indicated concentrations in 50 μl FACS buffer (PBS, 3% FCS, 0.02% $NaN_3$) for 40 min at 4° C. Cells were washed twice and then incubated with R-Phycoerythrin (PE) conjugated goat-anti-human or goat-anti-mouse IgG (H+L) $F(ab')_2$ (Jackson Immuno Research), diluted 1:200 in FACS buffer, for 30 min at 4° C. Cells were again washed, resuspended in 0.3 ml FACS buffer and then analyzed by flow cytometry in a FACSCalibur (Becton Dickinson, San Diego, Calif.).

**[0120]** For FACS based Scatchard analyses RPMI8226 cells were stained with at 12 different dilutions (1:2k) starting at 12.5 μg/ml (IgG) final concentration. At least two independent measurements were used for each concentration and KD values extrapolated from median fluorescence intensities according to Chamow et al. (1994).

Surface Plasmon Resonance

**[0121]** The kinetic constants $k_{on}$ and $k_{off}$ were determined with serial dilutions of the respective Fab binding to covalently immobilized CD38-Fc fusion protein using the BIACORE 3000 instrument (BIACORE, Uppsala, Sweden). For covalent antigen immobilization standard EDC-NHS amine coupling chemistry was used. For direct coupling of CD38 Fc-fusion protein CMS senor chips (BIACORE) were coated with ~600-700 RU in 10 mM acetate buffer, pH 4.5. For the reference flow cell a respective amount of HSA (human serum albumin) was used. Kinetic measurements were done in PBS (136 mM NaCl, 2.7 mM KCl, 10 mM $Na_2HPO_4$, 1.76 mM $KH_2PO_4$ pH 7.4) at a flow rate of 20 μl/min using Fab concentration range from 1.5-500 nM. Injection time for each concentration was 1 min, followed by 2 min dissociation phase. For regeneration 5 μl 10 mM HCl was used. All sensograms were fitted locally using BIA evaluation software 3.1 (BIACORE).

Example 1

**[0122]** Antibody Generation from HUCAL®Libraries

**[0123]** For the generation of therapeutic antibodies against CD38, selections with the MorphoSys HUCAL GOLD® phage display library were carried out. HUCAL GOLD® is a Fab library based on the HUCAL® concept (Knappik et al., 2000; Krebs et al., 2001), in which all six CDRs are diversified, and which employs the CYSDISPLAY™ technology for linking Fab fragments to the phage surface (Lohning, 2001).

A. Phagemid Rescue, Phage Amplification and Purification

**[0124]** HUCAL GOLD® phagemid library was amplified in 2×TY medium containing 34 μg/ml chloramphenicol and 1% glucose (2×TY-CG). After helper phage infection (VCSM13) at an OD600 of 0.5 (30 min at 37° C. without shaking; 30 min at 37° C. shaking at 250 rpm), cells were spun down (4120 g; 5 min; 4° C.), resuspended in 2×TY/34 μg/ml chloramphenicol/50 μg/ml kanamycin and grown overnight at 22° C. Phages were PEG-precipitated from the supernatant, resuspended in PBS/20% glycerol and stored at −80° C. Phage amplification between two panning rounds was conducted as follows: mid-log phase TG1 cells were infected with eluted phages and plated onto LB-agar supplemented with 1% of glucose and 34 μg/ml of chloramphenicol (LB-CG). After overnight incubation at 30° C., colonies were scraped off, adjusted to an OD600 of 0.5 and helper phage added as described above.

B. Pannings with HUCAL GOLD®

**[0125]** For the selections HUCAL GOLD® antibody-phages were divided into three pools corresponding to different VH master genes (pool 1: VH1/5λκ, pool 2: VH3□ λκ, pool 3: VH2/4/6 λκ). These pools were individually subjected to 3 rounds of whole cell panning on CD38-expressing CHO-Kl cells followed by pH-elution and a post-adsorption step on CD38-negative CHO-Kl-cells for depletion of irrelevant antibody-phages. Finally, the remaining antibody phages were used to infect *E. coli* TG1 cells. After centrifugation the bacterial pellet was resuspended in 2×TY medium, plated on agar plates and incubated overnight at 30° C. The selected clones were then scraped from the plates, phages were rescued and amplified. The second and the third round of selections were performed as the initial one.

**[0126]** The Fab encoding inserts of the selected HUCAL GOLD® phages were subcloned into the expression vector pMORPH®×9 Fab FS (Rauchenberger et al., 2003) to facilitate rapid expression of soluble Fab. The DNA of the selected clones was digested with Xbal and EcoRI thereby cutting out the Fab encoding insert (ompA-VLCL and phoA-Fd), and cloned into the Xbal/EcoRI cut vector pMORPH®x9_Fab_FS. Fab expressed in this vector carry two C-terminal tags (FLAG™ (recognizing the FLAG octapeptide epitope, SIGMA) and STREP-TAG® II) (comprising eight amino acid residues binding specifically to the STREPTACTIN™ ligand) for detection and purification.

Example 2

Biological Assays

**[0127]** Antibody dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity was measured according to a published protocol based on flow-cytometry analysis (Naundorf et al., 2002) as follows:

ADCC:

**[0128]** For ADCC measurements, target cells (T) were adjusted to 2.0 E+05 cells/ml and labeled with 100 ng/ml Calcein AM (Molecular Probes, C-3099) in RPMI1640 medium (Pan biotech GmbH) for 2 minutes at room temperature. Residual calcein was removed by 3 washing steps in RPMI1640 medium. In parallel PBMC were prepared as source for (natural killer) effector cells (E), adjusted to 1.0 E+07 and mixed with the labeled target cells to yield a final E:T-ratio of 50:1 or less, depending on the assay conditions. Cells were washed once and the cell-mix resuspended in 200 μl RPMI1640 medium containing the respective antibody at different dilutions. The plate was incubated for 4 hrs under standardized conditions at 37° C. and 5% CO2 in a humidified incubator. Prior to FACS analysis cells were labeled with propidium-iodide (PI) and analyzed by flow-cytometry (Becton-Dickinson). Between 50.000 and 150.000 events were counted for each assay. The following equation gave rise to the killing activity [in %]:

$$\frac{ED^A}{EL^A + ED^A} \times 100$$

with $ED^A$=events dead cells (calcein +PI stained cells), and $EL^A$=events living cells (calcein stained cells)

CDC:

**[0129]** For CDC measurements, 5.0 E+04 CD38 CHO-K1 transfectants were added to a microtiter well plate (Nunc) together with a 1:4 dilution of human serum (Sigma, #S-1764) and the respective antibody. All reagents and cells were diluted in RPMI1640 medium (Pan biotech GmbH) supplemented with 10% FCS. The reaction-mix was incubated for 2 hrs under standardized conditions at 37° C. and 5% $CO_2$ in a humidified incubator. As negative controls served either heat-inactivated complement or CD38-transfectants without antibody. Cells were labeled with PI and subjected to FACS-analysis.

**[0130]** In total 5000 events were counted and the number of dead cells at different antibody concentrations used for the determination of EC50 values. The following equation gave rise to the killing activity [in %]:

$$\frac{ED^C}{EL^C + ED^C} \times 100$$

with $ED^C$=events dead cells (PI stained cells), and $EL^C$=events living cells (unstained)

**[0131]** Cytotoxicity values from a total of 12 different antibody-dilutions (1:2$^n$) in triplicates were used in ADCC and duplicates in CDC for each antibody in order obtain EC-50 values with a standard analysis software (PRISM®, Graph Pad Software).

Example 3

Generation of Stable CD38-Transfectants and CD38 Fe-Fusion Proteins

**[0132]** In order to generate CD38 protein for panning and screening two different expression systems had to be established. The first strategy included the generation of CD38-Fc-fusion protein, which was purified from supernatants after transient transfection of HEK293 cells. The second strategy involved the generation of a stable CHO-K1—cell line for high CD38 surface expression to be used for selection of antibody-phages via whole cell panning.

**[0133]** As an initial step Jurkat cells (DSMZ ACC282) were used for the generation of cDNA (Invitrogen) followed by amplification of the entire CD38-coding sequence using primers complementary to the first 7 and the last 9 codons of CD38, respectively (primer MTE001 & MTE002rev; Table 4). Sequence analysis of the CD38-insert confirmed the published amino acid sequence by Jackson et al. (1990) except for position 49 which revealed a glutamine instead of a tyrosine as described by Nata et al. (1997). For introduction of restriction endonuclease sites and cloning into different derivatives of expression vector pcDNA3.1 (Stratagene), the purified PCR-product served as a template for the re-amplification of the entire gene (primers MTE006 & MTE007rev, Table 4) or a part (primers MTE004 & MTE009rev, Table 4) of it. In the latter case a fragment encoding for the extracellular domain (aa 45 to 300) was amplified and cloned in frame between a human Vkappa leader sequence and a human Fc-gamma 1 sequence. This vector served as expression vector for the generation of soluble CD38-Fc fusion-protein. Another pcDNA3.1-derivative without leader-sequence was used for insertion of the CD38 full-length gene. In this case a stop codon in front of the Fc-coding region and the missing leader-sequence gave rise to CD38-surface expression. HEK293 cells were transiently transfected with the Fc-fusion protein vector for generation of soluble CD38 Fc-fusion protein and, in case of the full-length derivative, CHO-K1-cells were transfected for the generation of a stable CD38-expressing cell line.

TABLE 4

| Primer # | Sequence (5' - >3') |
|---|---|
| MTE001 | ATG GCC AAC TGC GAG TTC AGC (SEQ ID NO: 25) |
| MTE002rev | TCA GAT CTC AGA TGT GCA AGA TGA ATC (SEQ ID NO: 26) |
| MTE004 | TT GGT ACC AGG TGG CGC CAG CAG TG (SEQ ID NO: 27) |
| MTE006 | TT GGT ACC ATG GCC AAC TGC GAG (SEQ ID NO: 28) |
| MTE007rev | CCG ATA **TCA*** GAT CTC AGA TGT GCA AGA TG (SEQ ID NO: 29) |
| MTE009rev | CCG ATA TC GAT CTC AGA TGT GCA AGA TG (SEQ ID NO: 30) |

* leading to a stop codon (TGA) in the sense orientation.

Example 4

Cloning, Expression and Purification of HuCAL® IgG1:

**[0134]** In order to express full length IgG, variable domain fragments of heavy (VH) and light chains (VL) were subcloned from Fab expression vectors into appropriate AMORPH®_hIg vectors (see FIGS. **8** to **10**). Restriction endonuclease pairs BlpI/MfeI (insert-preparation) and BlpI/EcoRI (vector-preparation) were used for subcloning of the VH domain fragment into pMORPH® hIgG1. Enzyme-pairs EcoRV/HpaI (lambda-insert) and EcoRV/BsiWI (kappa-insert) were used for subcloning of the VL domain fragment into the respective pMORPH®_hIgκ_1 or pMORPH®_h_Igλ_1 vectors. Resulting IgG constructs were expressed in HEK293 cells (ATCC CRL-1573) by transient transfection using standard calcium phosphate —DNA coprecipitation technique.

**[0135]** IgGs were purified from cell culture supernatants by affinity chromatography via Protein A Sepharose column. Further down stream processing included a buffer exchange by gel filtration and sterile filtration of purified IgG. Quality control revealed a purity of >90% by reducing SDS-PAGE and >90% monomeric IgG as determined by analytical size exclusion chromatography. The endotoxin content of the material was determined by a kinetic LAL based assay (Cambrex European Endotoxin Testing Service, Belgium).

Example 5

**[0136]** Generation and Production of Chimeric OKT10 (chOKT10; SEQ ID NOS: 23 and 24)

**[0137]** For the construction of chOKT10 the mouse VH and VL regions were amplified by PCR using cDNA prepared from the murine OKT10 hybridoma cell line (ECACC

#87021903). A set of primers was used as published (Dattamajumdar et al., 1996; Zhou et al., 1994). PCR products were used for Topo-cloning (Invitrogen; pCRII-vector) and single colonies subjected to sequence analysis (M13 reverse primer) which revealed two different kappa light chain sequences and one heavy chain sequence. According to sequence alignments (EMBL-nucleotide sequence database) and literature (Krebber et al, 1997) one of the kappa-sequence belongs to the intrinsic repertoire of the tumor cell fusion partner X63Ag8.653 and hence does not belong to OKT10 antibody. Therefore, only the new kappa sequence and the single VH-fragment was used for further cloning. Both fragments were reamplified for the addition of restriction endonuclease sites followed by cloning into the respective pMORPH® IgG1-expression vectors. The sequences for the heavy chain (SEQ ID NO: 23) and light chain (SEQ ID NO: 24) are given in FIG. **6**. HEK293 cells were transfected transiently and the supernatant analyzed in FACS for the chimeric OKT10 antibody binding to the CD38 over-expressing Raji cell line (ATCC).

Example 6

Epitope Mapping

1. Materials and Methods:

Antibodies:

**[0138]** The following anti-CD38 IgGs were sent for epitope mappings:

| MOR# | Lot # | Format | Conc. [mg/ml]/ Vol.[μl] |
|---|---|---|---|
| MOR03077 | 2CHE106_030602 | human IgG1 | 0.44/1500 |
| MOR03079 | 2APO31 | human IgG1 | 0.38/500 |
| MOR03080 | 030116_4CUE16 | human IgG1 | 2.28/200 |
| MOR03100 | 030612_6SBA6 | human IgG1 | 0.39/500 |
| chim. OKT10* | 030603_2CHE111 | human IgG1 | 0.83/500 |

*chimeric OKT10 consisting of human Fc and mouse variable regions.

CD38-Sequence:

**[0139]** The amino acid (aa) sequence (position 44-300) is based on human CD38 taken from the published sequence under SWISS-PROT primary accession number P28907. At position 49 the aa Q (instead of T) has been used for the peptide-design.

PepSpot-Analysis:

**[0140]** The antigen peptides were synthesized on a cellulose membrane in a stepwise manner resulting in a defined arrangement (peptide array) and are covalently bound to the cellulose membrane. Binding assays were performed directly on the peptide array.

**[0141]** In general an antigen peptide array is incubated with blocking buffer for several hours to reduce non-specific binding of the antibodies. The incubation with the primary (antigen peptide-binding) antibody in blocking buffer occurs followed by the incubation with the peroxidase (POD)-labelled secondary antibody, which binds selectively the primary antibody. A short T (Tween)-TBS-buffer washing directly after the incubation of the antigen peptide array with the secondary antibody followed by the first chemiluminescence experiment is made to get a first overview which antigen peptides do bind the primary antibody. Several buffer washing steps follow (T-TBS- and TBS-buffer) to reduce false positive binding (unspecific antibody binding to the cellulose membrane itself). After these washing steps the final chemiluminescence analysis is performed. The data were analysed with an imaging system showing the signal intensity (Boehringer Light units, BLU) as single measurements for each peptide. In order to evaluate non-specific binding of the secondary antibodies (anti-human IgG), these antibodies were incubated with the peptide array in the absence of primary antibodies as the first step. If the primary antibody does not show any binding to the peptides it can be directly labelled with POD, which increases the sensitivity of the system (as performed for MOR3077). In this case a conventional coupling chemistry via free amino-groups is performed.

**[0142]** The antigen was scanned with 13-mer peptides (11 amino acids overlap). This resulted in arrays of 123 peptides. Binding assays were performed directly on the array. The peptide-bound antibodies MOR03077, MOR03079, MOR03080, MOR03100 and chimeric OKT10 were detected using a peroxidase-labelled secondary antibody (peroxidase conjugate-goat anti-human IgG, gamma chain specific, affinity isolated antibody; Sigma-Aldrich, A6029). The mappings were performed with a chemiluminescence substrate in combination with an imaging system. Additionally, a direct POD-labelling of MOR03077 was performed in order to increase the sensitivity of the system.

2. Summary and Conclusions:

**[0143]** All five antibodies showed different profiles in the PepSpot analysis. A schematic summary is given in FIG. **7**, which illustrates the different aa sequences of CD38 being recognized. The epitope for MOR03079 and chimeric OKT10 can clearly be considered as linear. The epitope for MOR03079 can be postulated within aa 192-206 (VSRRFAEAACDVVHV (SEQ ID NO:38)) of CD38 whereas for chimeric OKT10 a sequence between aa 284 and 298 (FLQCVKNPEDSSCTS (SEQ ID NO:39)) is recognized predominantly. The latter results confirm the published data for the parental murine OKT10 (Hoshino et al., 1997), which postulate its epitope between aa 280-298. Yet, for a more precise epitope definition and determination of key amino acids (main antigen-antibody interaction sites) a shortening of peptides VSRRFAEAACDVVHV (SEQ ID NO:38) and FLQCVKNPEDSSCTS (SEQ ID NO:39) and an alanine-scan of both should be envisaged.

**[0144]** The epitopes for MOR03080 and MOR03100 can be clearly considered as discontinuous since several peptides covering different sites of the protein sites were recognized. Those peptides comprise aa 82-94 and aa 158-170 for MOR03080 and aa 82-94, 142-154, 158-170, 188-200 and 280-296 for MOR03100. However, some overlaps between both epitopes can be postulated since two different sites residing within aa positions 82-94 (CQSVWDAFKGAFI (SEQ ID NO:40); peptide #20) and 158-170 (TWCGEFNTSKINY (SEQ ID NO:41); peptide #58) are recognized by both antibodies.

**[0145]** The epitope for MOR03077 can be considered as clearly different from the latter two and can be described as multisegmented discontinuous epitope. The epitope includes aa 44-66, 110-122, 148-164, 186-200 and 202-224.

Example 7

IL-6-Release/Proliferation Assay

1. Materials and Methods:

**[0146]** Proliferation- and a IL-6 release assays have been performed according to Ausiello et al. (2000) with the following modifications: PBMCs from different healthy donors (after obtaining informed consent) were purified by density gradient centrifugation using the HISTOPAQUE® (medium comprising polysucrose and sodium diatrizoate adjusted to density of 1.077 g/mL) cell separation system according to the instructions of the supplier (Sigma) and cultured under standard conditions (5% CO2, 37° C.) in RPMI1640 medium, supplemented with 10% FCS and glutamine ("complete RPMI1640"). For both assays the following antibodies were used: HuCAL® anti-CD38 IgGls Mabs MOR03077, MOR03079, and MOR03080, an agonistic murine IgG2a monoclonal antibody (IB4; Malavasi et al., 1984), an irrelevant HuCAL® IgG1 antibody, a matched isotype control (murine IgG2a: anti-trinitrophenol, hapten-specific antibody; cat.#: 555571, clone G155-178; Becton Dickinson) or a medium control. For the IL-6 release assay, 1.0 E+06 PBMCs in 0.5 ml complete RPMI1640 medium were incubated for 24 hrs in a 15 ml culture tube (Falcon) in the presence of 20 μg/ml antibodies. Cell culture supernatants were harvested and analysed for IL-6 release using the Quantikine kit according to the manufacturer's protocol (R&D systems). For the proliferation assay 2.0E+05 PBMCs were incubated for 3 days in a 96-well flat bottom plate (Nunc) in the presence of 20 pg/m1 antibodies. Each assay was carried out in duplicates. After 4 days BrdU was added to each well and cells incubated for an additional 24 hrs at 37° C. prior to cell fixation and DNA denaturation according to the protocol of the supplier (Roche). Incorporation of BrdU was measured via an anti-BrdU peroxidase-coupled antibody in a chemiluminescence-based setting.

2. Summary and Conclusions:

Proliferation Assay:

**[0147]** In addition to its catalytic activities as a cyclic ADP-ribose cyclase and hydrolase, CD38 displays the ability to transduce signals of biological relevance (Hoshino et al., 1997; Ausiello et al., 2000). Those functions can be induced in vivo by e.g. receptor-ligand interactions or by cross-linking with anti-CD38 antibodies. Those signalling events lead e.g. to calcium mobilization, lymphocyte proliferation and release of cytokines. However, this signalling is not only dependent on the antigenic epitope but might also vary from donor to donor (Ausiello et al., 2000). In the view of immunotherapy non-agonistic antibodies are preferable over agonistic antibodies. Therefore, HuCAL® anti-CD38 antibodies (Mabs MOR03077; MOR03079, MOR03080) were further characterized in a proliferation assay and IL-6-(important MM growth-factor) release assay in comparison to the reference antibody chOKT10 and the agonistic anti-CD38 monoclonal antibody IB4.

**[0148]** As demonstrated in FIG. **11** and FIG. **12** the HUCAL® anti-CD38 antibodies Mab#1, 2 and 3 as well as the reference antibody chOKT10 and corresponding negative controls showed no or only weak induction of proliferation and no IL-6-release as compared to the agonistic antibody IB4.

Example 8

Clonogenic Assay

1. Materials and Methods:

**[0149]** PBMCs harbouring autologous CD34+/CD38+precursor cells were isolated from healthy individuals (after obtaining informed consent) by density gradient centrifugation using the Histopaque cell separation system according to the instructions of the supplier (Sigma) and incubated with different HUCAL® IgGlanti-CD38 antibodies (Mabs MOR03077, MOR03079, and MOR03080) and the positive control (PC) chOKT10 at 10 μg/ml. Medium and an irrelevant HUCAL® IgG1 served as background control. Each ADCC-assay consisted of 4.0E+05 PBMCs which were incubated for 4 hrs at 37° C. in RPMI1640 medium supplemented with 10% FCS. For the clonogenic assay 2.50 ml "complete" methylcellulose (CellSystems) was inoculated with 2.5 E+05 cells from the ADCC-assay and incubated for colony-development for at least 14 days in a controlled environment (37° C.; 5% CO2). Colonies were analyzed by two independent operators and grouped into BFU-E +CFU-GEMM (erythroid burst forming units and granulocyte/erythroid/macrophage/megakaryocyte stem cells) and CFU-GM (granulocyte/macrophage stem cells).

2. Summary and Conclusions:

**[0150]** Since CD38-expression is not only found on immune cells within the myeloid (e.g. monocytes, granulocytes) and lymphoid lineage (e.g. activated B and T-cells; plasma cells) but also on the respective precursor cells (CD34+/CD38+), it is important that those cells are not affected by antibody-mediated killing. Therefore, a clonogenic assay was applied in order to analyse those effects on CD34+/CD38+progenitors.

**[0151]** PBMCs from healthy donors were incubated with HUCAL® anti-CD38 antibodies (Mab#1, Mab#2 and Mab#3) or several controls (irrelevant HUCAL® antibody, medium and reference antibody chOKT10 as positive control) according to a standard ADCC-protocol followed by further incubation in conditioned methylcellulose for colony-development. As shown in FIG. **13** no significant reduction of colony-forming units are shown for all HUCAL® anti-CD38 antibodies as compared to an irrelevant antibody or the reference antibody.

Example 9

**[0152]** ADCC Assays with Different Cell-Lines and Primary Multiple Myeloma Cells

1. Materials and Methods:

**[0153]** Isolation and ADCC of MM-patient samples: Bone marrow aspirates were obtained from multiple myeloma patients (after obtaining informed consent). Malignant cells were purified via a standard protocol using anti-CD138 magnetic beads (Milteny Biotec) after density gradient centrifugation (Sigma). An ADCC-assay was performed as described before.

2. Summary and Conclusions:

**[0154]** Several cell-lines derived from different malignancies were used in ADCC in order to show the cytotoxic effect of the HUCAL® anti-CD38 antibodies on a broader spectrum of cell-lines including different origins and CD38 expression-levels. As shown in FIG. **14**, all cells were killed in ADCC at constant antibody concentrations (5 μg/ml) and E:T ratios at 30:1.Cytotoxicity via ADCC was also shown for several multiple myeloma samples from patients. All HUCAL® anti-CD38 antibodies were able to perform a dose-dependent killing of MM-cells and the EC50-values varied between 0.006 and 0.249 nM (FIG. **15**).

Example 10

Cross-Reactivity Analysis by FACS and Immunohistochemistry (IHC)

1. Materials and Methods:

**[0155]** IHC with tonsils: For IHC HUCAL® anti-CD38 Mabs and an irrelevant negative control antibody were converted into the bivalent dHLX-format (Plückthun & Pack, 1997). 5 μm cryo sections from lymph nodes derived from Cynomolgus monkey, Rhesus monkey and humans (retrieved from the archives of the Institute of Pathology of the University of Graz/Austria) were cut with a Leica CM3050 cryostat. Sections were air-dried for 30 minutes to 1 hour and fixed in ice-cold methanol for 10 minutes and washed with PBS. For the detection of the dHLX-format a mouse anti-His antibody (Dianova) in combination with the Envision Kit (DAKO) was used. For the detection of the anti-CD38 mouse antibodies (e.g. reference mouse monoclonal OKT10) the Envison kit was used only.

**[0156]** FACS-analysis of lymphocytes: EDTA-treated blood samples were obtained from healthy humans (after obtaining informed consent), from Rhesus and Cynomolgus monkeys and subjected to density gradient centrifugation using the HISTOPAQUE® (medium comprising polysucrose and sodium diatrizoate adjusted to density of 1.077 g/mL)cell separation system according to the instructions of the supplier (Sigma). For FACS-analysis cells from the interphase were incubated with primary antibodies (HUCAL® anti-CD38 and negative control Mabs as murine IgG2a or Fab-format, the positive control murine antibody OKT10 and a matched isotype control) followed by incubation with anti-M2 Flag (Sigma; only for Fab-format) and a phycoerythrin (PE)-labeled anti-mouse conjugate (Jackson Research). FACS analysis was performed on the gated lymphocyte population.

2. Summary and Conclusions:

**[0157]** HUCAL® anti-CD38 were analyzed for inter-species CD38 cross-reactivity. Whereas all anti-CD38 Mabs were able to detect human CD38 on lymphocytes in FACS and IHC, only MOR03080 together with the positive control OKT10 showed an additional reactivity with Cynomolgus and Rhesus monkey CD38 (see Table 5: Cross-reactivity analysis).

TABLE 5

| | Lymphocytes (PACS) and lymph-nodes (IHC) from: | | |
|---|---|---|---|
| Antibody | Human | Cynomolgus Monkey | Rhesus Monkey |
| Mab#1 | ++ | – | – |
| Mab#2 | ++ | – | – |
| Mab#3 | ++ | ++ | ++ |
| PC | ++ | ++ | ++ |
| NC | – | – | – |

++: strong positive staining;
–: no staining;
NC: negative control;
PC: positive control (=reference cMAb)

Example 11

**[0158]** Treatment of Human Myeloma Xenografts in Mice (using the RPMI8226 Cell Line) with MOR03080

1. Establishment of subcutaneous mouse model:

**[0159]** A subcutaneous mouse model for the human myeloma-derived tumor cell line RPMI8226 in female C.B-17-SCID mice was established as follows by Aurigon Life Science GmbH (Tutzing, Germany): on day –1, 0, and 1, anti-asialo GM1 polyclonal antibodies (ASGM) (WAKO-Chemicals), which deplete the xenoreactive NK-cells in the SCID mice were applied intravenously in order to deactivate any residual specific immune reactivity in C.B-17-SCID mice. On day 0, either $5\times10^{6}$ or $1\times10^{7}$ RPMI8226 tumor cells in 50 μl PBS were inoculated subcutaneously into the right flank of mice either treated with ASGM (as described above) or untreated (each group consisting of five mice). Tumor development was similar in all 4 inoculated groups with no significant difference being found for treatment with or without anti-asialo GM1 antibodies or by inoculation of different cell numbers. Tumors appear to be slowly growing with the tendency of stagnation or oscillation in size for some days. Two tumors oscillated in size during the whole period of investigation, and one tumor even regarded and disappeared totally from a peak volume of 321 $mm^3$. A treatment study with this tumor model should include a high number of tumor-inoculated animals per group.

2. Treatment with MOR03080:

2.1 Study Objective

**[0160]** This study was performed by Aurigon Life Science GmbH (Tutzing, Germany) to compare the anti-tumor efficacy of intraperitoneally applied antibodies (HUCAL® anti-CD38) as compared to the vehicle treatment (PBS). The human antibody hMOR03080 (isotype IgG1) was tested in different amounts and treatment schedules. In addition the chimeric antibody chMOR03080 (isotype IgG2a: a chimeric antibody comprising the variable regions of MOR03080 and murine constant regions constructed in a similar way as described in Example 5 for chimeric OKT10 (murine VH/VL and human constant regions)) was tested. The RPMI8226 cancer cell line had been chosen as a model and was inoculated subcutaneously in female SCID mice as described above. The endpoints in the study were body weight (b.w.), tumor volume and clinical signs.

2.2 Antibodies and Vehicle

**[0161]** The antibodies were provided ready to use to Aurigon at concentrations of 2.13 mg/ml (MOR03080 hIgG1) and 1.73 mg/ml (MOR03080 chIgG2a, and stored at −80° C. until application. The antibodies were thawed and diluted with PBS to the respective end concentration. The vehicle (PBS) was provided ready to use to Aurigon and stored at 4° C. until application.

2.3 Animal Specification

**[0162]** Species: mouse

**[0163]** Strain: Fox chase C.B-17-scid (C.B-Igh-1b/IcrTac)

**[0164]** Number and sex: 75 females

**[0165]** Supplier: Taconic M&B, Bomholtvej 10, DK-8680 Ry

**[0166]** Health status: SPF

**[0167]** Weight ordered: appr. 18 g

**[0168]** Acclimatization: 9 days

2.4 Tumor Cell Line

**[0169]** The tumor cells (RPMI8226 cell line) were grown and transported to Aurigon Life Science GmbH, where the cells were splitted and grown for another cycle. Aurigon prepared the cells for injection on the day of inoculation. The culture medium used for cell propagation was RPMI 1640 supplemented with 5% FCS, 2 mM L-Glutamin and Pen-Strep. The cells showed no unexpected growth rate or behaviour.

**[0170]** For inoculation, tumor cells were suspended in PBS and adjusted to a final concentration of $1\times10^7$ cells/50 μl in PBS. The tumor cell suspension was mixed thoroughly before being injected.

2.5 Experimental Procedure

**[0171]** On day 0, $1\times10^7$ RPMI8226 tumor cells were inoculated subcutaneously into the right dorsal flank of 75 SCID mice. A first group was built with 15 randomly chosen animals (group 5) directly after inoculation. This group was treated with 1 mg/kg b.w. hIgGl-MOR03080 every second day between day 14 and 36. From all other 60 animals 4 groups were built with ten animals in each group on day 31 (tumor volume of about 92 $mm^3$). Groups 1-4 were built with comparable means tumor sizes and standard deviations. An additional group of 5 animals (group 6) was chosen showing relatively small tumor volumes (tumor volume of about 50 $mm^3$) for comparison with pre-treated group 5 (all but three mice showing tumor volumes of less than 10 $mm^3$, one with about 22 $mm^3$, one with about 44 $mm^3$ and one with about 119 $mm^3$). Groups 1 to 4 were treated every second day from day 32 to day 68 with either PBS (Vehicle; group 1), 1 mg/kg b.w. hIgG1-MOR03080 (group 2) or 5 mg/kg b.w.hIgGl-MOR03080 (group 3), or with 5 mg/kg b.w. chIgG2a-MOR03080 (group 4). Group 6 did not receive any treatment (see Table 6). Tumor volumes, body weight and clinical signs were measured two times a week until end of study.

TABLE 6

| Group | No. of animals | Type of application | Substance | Schedule | Treatment dose [mg/kg] | Appl. volume [μl/kg] |
|---|---|---|---|---|---|---|
| 1 | 10 | i.p. | vehicle (PBS) | every second day between day 32 and day 68 | — | 10 |
| 2 | 10 | i.p. | MOR03080 human IgG1 | every second day between day 32 and day 68 | 1 | 10 |
| 3 | 10 | i.p. | MOR03080 huma IgG1 | every second day between day 32 and day 68 | 5 | 10 |
| 4 | 10 | i.p. | MOR03080 chimeric IgG2a | every second day between day 32 and day 68 | 5 | 10 |
| 5 | 15 | i.p. | MOR03080 human IgG1 | every second day between day 14 and day 36 | 1 | 10 |
| 6 | 5 | — | — | — | — | — |

2.6 Results

**[0172]** Clinical Observations and Mortality

**[0173]** No specific tumor or substance related clinical findings or mortality were observed. In group 3 (hIgG1 5 mg/kg) four animals died during blood sampling (one on day 3, one on day 34; two on day 52). In group 4 (muIgG2a 1 mg/kg) a single animal died during blood sampling (day 34). All other animals, that died during the study have been euthanized because of the tumor size.

Body Weight Development

**[0174]** No drug related interference with weight development was observed in comparison to group 1 (vehicle). Body weight was markedly influenced by blood sampling in groups 3 (hIgG1 5 mg/kg) and 4 (muIgG2a 5 mg/kg). Despite such interruptions the mean weight gain of all groups was continuous.

Tumor development (see FIG. **16**)

**[0175]** In group 1 (vehicle) tumor growth was found in the expected rate with a slow progression. As this cell line has a pronounced standard deviation values for the largest and smallest tumor have been excluded from further statistical analysis. The tumor growth of animals in group 1 was comparable to the tumor growth in group 6 (untreated), although this group started with a lower mean tumor volume on day 31. Treatment might therefore have a slight influence on the tumor growth rate. In group 1, two mice had to be euthanized before day 83 because of the tumor size, and a further one before day 87, so that the mean value of tumor volume is no longer representative after day 80. In group 6, one mouse had to be euthanized before day 80 because of the tumor size, two mice before day 83, and a further one before day 87, so that the mean value of tumor volume is no longer representative after day 76.

**[0176]** In group 2, treated with 1 mg/kg b.w. of hIgG1, one animal has been excluded from further analysis, because the tumor grew into the muscular tissue and this usually enhances the speed of tumor growth. Compared with the control group 1 (vehicle) the mean tumor size started to differ significantly starting with day 45 until the end of the study. No enhanced tumor growth was observed after end of treatment (day 68).

**[0177]** Animals of group 3 (5 mg/kg b.w. hIgG1) revealed a marked decrease in tumor growth in comparison to group 1 (vehicle), getting statistically significant with day 38 until day 83. The mean tumor volume started to strongly regrow about two weeks after the end of treatment. One out of ten tumors disappeared at day 45 and did not regrow up to 19 days after end of treatment.

**[0178]** The best performance of all treatment groups starting with 92 $mm^3$ tumor volume was found in group 4 (5 mg/kg b.w. muIgG2a), where the mean tumor volume showed clear regression and tumors even disappeared in 4 animals until the end of the observation period. The difference to the mean tumor volume of group 1 (vehicle) was highly significant beginning from day 38 until the end of study.

**[0179]** The early treatment with 1 mg/kg b.w. hIgG1 between days 14 and 36 (group 5) revealed an early as well as long lasting effect on tumor development. One animal has been excluded from further analysis as the tumor grew into muscular tissue. On day 31, only five animals had a measurable tumor at the site of inoculation, in comparison to the rest of the inoculated animals, where only 2 out of 60 did not respond to tumor inoculation. The tumor progression was delayed of about 31 days (comparison of day 52 of control group 1 with day 83 of group 5). About 50% of the animals did not show tumors at the site of inoculation at the end of the study.

2.7 Conclusion

**[0180]** No specific tumor or substance related clinical findings or mortality were observed in comparison with group 1 (control).

**[0181]** No drug related interference with weight development was observed.

**[0182]** Tumor growth of RPMI8226 tumor cells after treatment was reduced in the order of efficiency: hIgG1 1 mg/kg, 14-36 days every second day (group 5)>muIgG2a 5 mg/kg 32-68 days every second day (group 4)>hIgG1 5 mg/kg 32-68 days every second day (group 3)>hIgG1 1mg/kg 32-68 days every second day (group 2). In groups 2 to 4, mean tumor volumes were again increased after end of treatment to varying extents.

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Gly Tyr Ile Asp Pro Asn Arg Gly Asn Thr Asn Tyr Ala Gln Lys Phe
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Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Asn Ile Tyr Ser Asp Gly Ser Asn Thr Phe Tyr Ala Asp Ser Val
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
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Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
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Tyr Lys Val Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
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Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
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Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
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<211> LENGTH: 300
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

Met Ala Asn Cys Glu Phe Ser Pro Val Ser Gly Asp Lys Pro Cys Cys
1               5                   10                  15

Arg Leu Ser Arg Arg Ala Gln Leu Cys Leu Gly Val Ser Ile Leu Val
            20                  25                  30

Leu Ile Leu Val Val Val Leu Ala Val Val Val Pro Arg Trp Arg Gln
```

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```
        35                  40                  45

Gln Trp Ser Gly Pro Gly Thr Thr Lys Arg Phe Pro Glu Thr Val Leu
    50                  55                  60

Ala Arg Cys Val Lys Tyr Thr Glu Ile His Pro Glu Met Arg His Val
65                  70                  75                  80

Asp Cys Gln Ser Val Trp Asp Ala Phe Lys Gly Ala Phe Ile Ser Lys
                85                  90                  95

His Pro Cys Asn Ile Thr Glu Glu Asp Tyr Gln Pro Leu Met Lys Leu
            100                 105                 110

Gly Thr Gln Thr Val Pro Cys Asn Lys Ile Leu Leu Trp Ser Arg Ile
        115                 120                 125

Lys Asp Leu Ala His Gln Phe Thr Gln Val Gln Arg Asp Met Phe Thr
    130                 135                 140

Leu Glu Asp Thr Leu Leu Gly Tyr Leu Ala Asp Asp Leu Thr Trp Cys
145                 150                 155                 160

Gly Glu Phe Asn Thr Ser Lys Ile Asn Tyr Gln Ser Cys Pro Asp Trp
                165                 170                 175

Arg Lys Asp Cys Ser Asn Asn Pro Val Ser Val Phe Trp Lys Thr Val
            180                 185                 190

Ser Arg Arg Phe Ala Glu Ala Ala Cys Asp Val Val His Val Met Leu
        195                 200                 205

Asn Gly Ser Arg Ser Lys Ile Phe Asp Lys Asn Ser Thr Phe Gly Ser
    210                 215                 220

Val Glu Val His Asn Leu Gln Pro Glu Lys Val Gln Thr Leu Glu Ala
225                 230                 235                 240

Trp Val Ile His Gly Gly Arg Glu Asp Ser Arg Asp Leu Cys Gln Asp
                245                 250                 255

Pro Thr Ile Lys Glu Leu Glu Ser Ile Ile Ser Lys Arg Asn Ile Gln
            260                 265                 270

Phe Ser Cys Lys Asn Ile Tyr Arg Pro Asp Lys Phe Leu Gln Cys Val
        275                 280                 285

Lys Asn Pro Glu Asp Ser Ser Cys Thr Ser Glu Ile
    290                 295                 300
```

<210> SEQ ID NO 23
<211> LENGTH: 1317
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

```
caggtggaat tggtggaatc tggaggatcc ctgaaactct cctgtgcagc ctcaggattc      60

gattttagta gatcctggat gaattgggtc cggcaggctc caggaaaagg gctagaatgg     120

attggagaaa ttaatccaga tagcagtacg ataaactata cgacatctct aaaggataaa     180

ttcatcatct ccagagacaa cgccaaaaat acgctgtacc tgcaaatgac caaagtgaga     240

tctgaggaca cagcccttta ttactgtgca agatatggta actggtttcc ttattggggc     300

caagggactc tggtcactgt cagctcagcc tccaccaagg gtccatcggt cttccccctg     360

gcaccctcct ccaagagcac ctctgggggc acagcggccc tgggctgcct ggtcaaggac     420

tacttccccg aaccggtgac ggtgtcgtgg aactcaggcg ccctgaccag cggcgtgcac     480

accttcccgg ctgtcctaca gtcctcagga ctctactccc tcagcagcgt ggtgaccgtg     540
```

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```
ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac    600

accaaggtgg acaagaaagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg    660

tgcccagcac ctgaactcct ggggggaccg tcagtcttcc tcttcccccc aaaacccaag    720

gacaccctca tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac    780

gaagaccctg aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag    840

acaaagccgc gggaggagca gtacaacagc acgtaccggg tggtcagcgt cctcaccgtc    900

ctgcaccagg actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc    960

ccagccccca tcgagaaaac catctccaaa gccaaagggc agccccgaga accacaggtg   1020

tacaccctgc ccccatcccg ggatgagctg accaagaacc aggtcagcct gacctgcctg   1080

gtcaaaggct tctatcccag cgacatcgcc gtggagtggg agagcaatgg gcagccggag   1140

aacaactaca agaccacgcc tcccgtgctg gactccgacg gctccttctt cctctacagc   1200

aagctcaccg tggacaagag caggtggcag caggggaacg tcttctcatg ctccgtgatg   1260

catgaggctc tgcacaacca ctacacgcag aagagcctct ccctgtctcc gggtaaa      1317
```

<210> SEQ ID NO 24
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

```
gatatcctga tgacccagtc tcaaaaaatc atgcccacat cagtgggaga cagggtcagc     60

gtcacctgca aggccagtca aaatgtggat actaatgtag cctggtatca acagaaacca    120

ggacagtctc ctaaagcact gatttactcg gcatcctacc gatacagtgg agtccctgat    180

cgcttcacag gcagtggatc tgggacagat ttcactctca ccatcaccaa tgtgcagtct    240

gaggacttgg cagagtattt ctgtcagcaa tatgacagct atcctctcac gttcggtgct    300

gggaccaagc tggacctgaa acgtacggtg gctgcaccat ctgtcttcat cttcccgcca    360

tctgatgagc agttgaaatc tggaactgcc tctgttgtgt gcctgctgaa taacttctat    420

cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag    480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg    540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc    600

ctgagctcgc ccgtcacaaa gagcttcaac aggggagagt gt                       642
```

<210> SEQ ID NO 25
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 25

```
atggccaact gcgagttcag c                                               21
```

<210> SEQ ID NO 26
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

-continued

primer

<400> SEQUENCE: 26

tcagatctca gatgtgcaag atgaatc 27

<210> SEQ ID NO 27
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 27

ttggtaccag gtggcgccag cagtg 25

<210> SEQ ID NO 28
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 28

ttggtaccat ggccaactgc gag 23

<210> SEQ ID NO 29
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 29

ccgatatcag atctcagatg tgcaagatg 29

<210> SEQ ID NO 30
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
primer

<400> SEQUENCE: 30

ccgatatcga tctcagatgt gcaagatg 28

<210> SEQ ID NO 31
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

caggtgcaat tagtccaaag tggtgcggaa gtgaaaaaac cgggcgcgag cgtgaaagtg 60

agctgcaaag cctccggata tacctttact tcttattcta ttaattgggt ccgccaagcc 120

cctgggcagg gtctcgagtg gatgggctat atcgatccga atcgtggcaa tacgaattac 180

gcgcagaagt ttcagggccg ggtgaccatg acccgtgata ccagcattag caccgcgtat 240

atggaactga gcagcctgcg tagcgaagat acggccgtgt attattgcgc gcgtgagtat 300

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```
atttatttta ttcatggtat gcttgatttt tggggccaag gcaccctggt gacggttagc    360

tca                                                                  363


<210> SEQ ID NO 32
<211> LENGTH: 1500
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide construct

<400> SEQUENCE: 32

tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg     60

actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc    120

aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg    180

gtaggcgtgt acggtgggag gtctatataa gcagagctct ctggctaact agagaaccca    240

ctgcttactg gcttatcgaa attaatacga ctcactatag ggagacccaa gctggctagc    300

gccaccatga aacacctgtg gttcttcctc ctgctggtgg cagctcccag atgggtcctg    360

tcccaggtgg aattctgcag gcggttagct cagcctccac caagggtcca tcggtcttcc    420

ccctggcacc ctcctccaag agcacctctg ggggcacagc ggccctgggc tgcctggtca    480

aggactactt ccccgaaccg gtgacggtgt cgtggaactc aggcgccctg accagcggcg    540

tgcacacctt cccggctgtc ctacagtcct caggactcta ctccctcagc agcgtggtga    600

ccgtgccctc cagcagcttg ggcacccaga cctacatctg caacgtgaat cacaagccca    660

gcaacaccaa ggtggacaag aaagttgagc ccaaatcttg tgacaaaact cacacatgcc    720

caccgtgccc agcacctgaa ctcctggggg gaccgtcagt cttcctcttc cccccaaaac    780

ccaaggacac cctcatgatc tcccggaccc ctgaggtcac atgcgtggtg gtggacgtga    840

gccacgaaga ccctgaggtc aagttcaact ggtacgtgga cggcgtggag gtgcataatg    900

ccaagacaaa gccgcgggag gagcagtaca acagcacgta ccgggtggtc agcgtcctca    960

ccgtcctgca ccaggactgg ctgaatggca aggagtacaa gtgcaaggtc tccaacaaag   1020

ccctcccagc ccccatcgag aaaaccatct ccaaagccaa agggcagccc cgagaaccac   1080

aggtgtacac cctgccccca tcccgggatg agctgaccaa gaaccaggtc agcctgacct   1140

gcctggtcaa aggcttctat cccagcgaca tcgccgtgga gtgggagagc aatgggcagc   1200

cggagaacaa ctacaagacc acgcctcccg tgctggactc cgacggctcc ttcttcctct   1260

acagcaagct caccgtggac aagagcaggt ggcagcaggg gaacgtcttc tcatgctccg   1320

tgatgcatga ggctctgcac aaccactaca cgcagaagag cctctccctg tctccgggta   1380

aatgagggcc cgtttaaacc cgctgatcag cctcgactgt gccttctagt tgccagccat   1440

ctgttgtttg cccctccccc gtgccttcct tgaccctgga aggtgccact cccactgtcc   1500


<210> SEQ ID NO 33
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide construct

<400> SEQUENCE: 33
```

-continued

```
tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg     60
actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc    120
aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg    180
gtaggcgtgt acggtgggag gtctatataa gcagagctct ctggctaact agagaaccca    240
ctgcttactg gcttatcgaa attaatacga ctcactatag ggagacccaa gctggctagc    300
gccaccatgg tgttgcagac ccaggtcttc atttctctgt tgctctggat ctctggtgcc    360
tacggggata tcgtgatgat taaacgtacg gtggctgcac catctgtctt catcttcccg    420
ccatctgatg agcagttgaa atctggaact gcctctgttg tgtgcctgct gaataacttc    480
tatcccagag aggccaaagt acagtggaag gtggataacg ccctccaatc gggtaactcc    540
caggagagtg tcacagagca ggacagcaag gacagcacct acagcctcag cagcaccctg    600
acgctgagca aagcagacta cgagaaacac aaagtctacg cctgcgaagt cacccatcag    660
ggcctgagct cgcccgtcac aaagagcttc aacaggggag agtgttaggg gcccgtttaa    720
acccgctgat cagcctcgac tgtgccttct agttgccagc catctgttgt ttgcccctcc    780
cccgtgcctt ccttgaccct                                                800
```

<210> SEQ ID NO 34
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide construct

<400> SEQUENCE: 34

```
tcgctattac catggtgatg cggttttggc agtacatcaa tgggcgtgga tagcggtttg     60
actcacgggg atttccaagt ctccacccca ttgacgtcaa tgggagtttg ttttggcacc    120
aaaatcaacg ggactttcca aaatgtcgta acaactccgc cccattgacg caaatgggcg    180
gtaggcgtgt acggtgggag gtctatataa gcagagctct ctggctaact agagaaccca    240
ctgcttactg gcttatcgaa attaatacga ctcactatag ggagacccaa gctggctagc    300
gccaccatgg cctgggctct gctgctcctc accctcctca ctcagggcac aggatcctgg    360
gctgatatcg tgatgcacga agttaaccgt cctaggtcag cccaaggctg ccccctcggt    420
cactctgttc ccgccctcct ctgaggagct tcaagccaac aaggccacac tggtgtgtct    480
cataagtgac ttctacccgg gagccgtgac agtggcctgg aagggagata gcagccccgt    540
caaggcggga gtggagacca ccacaccctc caaacaaagc aacaacaagt acgcggccag    600
cagctatctg agcctgacgc ctgagcagtg gaagtcccac agaagctaca gctgccaggt    660
cacgcatgaa gggagcaccg tggagaagac agtggcccct acagaatgtt catagggggcc   720
cgtttaaacc cgctgatcag cctcgactgt gccttctagt tgccagccat ctgttgtttg    780
cccctccccc gtgccttcct                                                800
```

<210> SEQ ID NO 35
<211> LENGTH: 359
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
protein construct

-continued

```
<400> SEQUENCE: 35

Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro Arg Trp
1               5                   10                  15

Val Leu Ser Gln Val Glu Phe Cys Arg Arg Leu Ala Gln Ala Ser Thr
            20                  25                  30

Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser
        35                  40                  45

Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu
    50                  55                  60

Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His
65                  70                  75                  80

Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser
                85                  90                  95

Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys
            100                 105                 110

Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu
        115                 120                 125

Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro
    130                 135                 140

Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
145                 150                 155                 160

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
                165                 170                 175

Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp
            180                 185                 190

Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr
        195                 200                 205

Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
    210                 215                 220

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu
225                 230                 235                 240

Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
                245                 250                 255

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys
            260                 265                 270

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
        275                 280                 285

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
    290                 295                 300

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
305                 310                 315                 320

Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser
                325                 330                 335

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
            340                 345                 350

Leu Ser Leu Ser Pro Gly Lys
        355


<210> SEQ ID NO 36
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
```

-continued

```
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein construct

<400> SEQUENCE: 36

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1               5                   10                  15

Gly Ala Tyr Gly Asp Ile Val Met Ile Lys Arg Thr Val Ala Ala Pro
            20                  25                  30

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        35                  40                  45

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    50                  55                  60

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
65                  70                  75                  80

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                85                  90                  95

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            100                 105                 110

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        115                 120                 125

Asn Arg Gly Glu Cys
    130


<210> SEQ ID NO 37
<211> LENGTH: 135
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      protein construct

<400> SEQUENCE: 37

Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly Thr Gly
1               5                   10                  15

Ser Trp Ala Asp Ile Val Met His Glu Val Thr Val Leu Gly Gln Pro
            20                  25                  30

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        35                  40                  45

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    50                  55                  60

Gly Ala Val Thr Val Ala Trp Lys Gly Asp Ser Ser Pro Val Lys Ala
65                  70                  75                  80

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                85                  90                  95

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            100                 105                 110

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        115                 120                 125

Val Ala Pro Thr Glu Cys Ser
    130                 135


<210> SEQ ID NO 38
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
```

-continued

```
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 38

Val Ser Arg Arg Phe Ala Glu Ala Ala Cys Asp Val Val His Val
1               5                   10                  15


<210> SEQ ID NO 39
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 39

Phe Leu Gln Cys Val Lys Asn Pro Glu Asp Ser Ser Cys Thr Ser
1               5                   10                  15


<210> SEQ ID NO 40
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 40

Cys Gln Ser Val Trp Asp Ala Phe Lys Gly Ala Phe Ile
1               5                   10


<210> SEQ ID NO 41
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 41

Thr Trp Cys Gly Glu Phe Asn Thr Ser Lys Ile Asn Tyr
1               5                   10


<210> SEQ ID NO 42
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
```

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Ala Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 43
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Gln Gln His
85 90 95

Tyr Thr Thr Pro Pro Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

Arg

<210> SEQ ID NO 44
<211> LENGTH: 1500
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

<400> SEQUENCE: 44

ggacagtggg agtggcacct tccagggtca aggaaggcac gggggagggg caaacaacag 60

atggctggca actagaaggc acagtcgagg ctgatcagcg ggtttaaacg ggccctcatt 120

tacccggaga cagggagagg ctcttctgcg tgtagtggtt gtgcagagcc tcatgcatca 180

cggagcatga gaagacgttc ccctgctgcc acctgctctt gtccacggtg agcttgctgt 240

agaggaagaa ggagccgtcg gagtccagca cgggaggcgt ggtcttgtag ttgttctccg 300

gctgcccatt gctctcccac tccacggcga tgtcgctggg atagaagcct ttgaccaggc 360

aggtcaggct gacctggttc ttggtcagct catcccggga tgggggcagg gtgtacacct 420

gtggttctcg ggctgccct ttggctttgg agatggtttt ctcgatgggg gctgggaggg 480

ctttgttgga gaccttgcac ttgtactcct tgccattcag ccagtcctgg tgcaggacgg 540

tgaggacgct gaccacccgg tacgtgctgt tgtactgctc ctcccgcggc tttgtcttgg 600

cattatgcac ctccacgccg tccacgtacc agttgaactt gacctcaggg tcttcgtggc 660

tcacgtccac caccacgcat gtgacctcag gggtccggga gatcatgagg gtgtccttgg 720

gttttggggg gaagaggaag actgacggtc cccccaggag ttcaggtgct gggcacggtg 780

ggcatgtgtg agttttgtca caagatttgg gctcaacttt cttgtccacc ttggtgttgc 840

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```
tgggcttgtg attcacgttg cagatgtagg tctgggtgcc caagctgctg gagggcacgg    900

tcaccacgct gctgagggag tagagtcctg aggactgtag gacagccggg aaggtgtgca    960

cgccgctggt cagggcgcct gagttccacg acaccgtcac cggttcgggg aagtagtcct   1020

tgaccaggca gcccagggcc gctgtgcccc cagaggtgct cttggaggag ggtgccaggg   1080

ggaagaccga tggacccttg gtggaggctg agctaaccgc ctgcagaatt ccacctggga   1140

caggacccat ctgggagctg ccaccagcag gaggaagaac cacaggtgtt tcatggtggc   1200

gctagccagc ttgggtctcc ctatagtgag tcgtattaat ttcgataagc cagtaagcag   1260

tgggttctct agttagccag agagctctgc ttatatagac ctcccaccgt acacgcctac   1320

cgcccatttg cgtcaatggg gcggagttgt tacgacattt tggaaagtcc cgttgatttt   1380

ggtgccaaaa caaactccca ttgacgtcaa tggggtggag acttggaaat ccccgtgagt   1440

caaaccgcta tccacgccca ttgatgtact gccaaaaccg catcaccatg gtaatagcga   1500
```

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<210> SEQ ID NO 45
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
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<400> SEQUENCE: 45

agggtcaagg aaggcacggg ggaggggcaa acaacagatg gctggcaact agaaggcaca     60

gtcgaggctg atcagcgggt ttaaacgggc cctaacact ctcccctgtt gaagctcttt    120

gtgacgggcg agctcaggcc ctgatgggtg acttcgcagg cgtagacttt gtgtttctcg    180

tagtctgctt tgctcagcgt cagggtgctg ctgaggctgt aggtgctgtc cttgctgtcc    240

tgctctgtga cactctcctg ggagttaccc gattggaggg cgttatccac cttccactgt    300

actttggcct ctctgggata gaagttattc agcaggcaca caacagaggc agttccagat    360

ttcaactgct catcagatgg cgggaagatg aagacagatg gtgcagccac cgtacgttta    420

atcatcacga tatccccgta ggcaccagag atccagagca acagagaaat gaagacctgg    480

gtctgcaaca ccatggtggc gctagccagc ttgggtctcc ctatagtgag tcgtattaat    540

ttcgataagc cagtaagcag tgggttctct agttagccag agagctctgc ttatatagac    600

ctcccaccgt acacgcctac cgcccatttg cgtcaatggg gcggagttgt tacgacattt    660

tggaaagtcc cgttgatttt ggtgccaaaa caaactccca ttgacgtcaa tggggtggag    720

acttggaaat ccccgtgagt caaaccgcta tccacgccca ttgatgtact gccaaaaccg    780

catcaccatg gtaatagcga                                                800
```

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<210> SEQ ID NO 46
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

<400> SEQUENCE: 46

aggaaggcac gggggagggg caaacaacag atggctggca actagaaggc acagtcgagg     60

ctgatcagcg ggtttaaacg ggcccctatg aacattctgt aggggccact gtcttctcca    120
```

-continued

```
cggtgctccc ttcatgcgtg acctggcagc tgtagcttct gtgggacttc cactgctcag    180

gcgtcaggct cagatagctg ctggccgcgt acttgttgtt gctttgtttg gagggtgtgg    240

tggtctccac tcccgccttg acggggctgc tatctccctt ccaggccact gtcacggctc    300

ccgggtagaa gtcacttatg agacacacca gtgtggcctt gttggcttga agctcctcag    360

aggagggcgg gaacagagtg accgaggggg cagccttggg ctgacctagg acggttaact    420

tcgtgcatca cgatatcagc ccaggatcct gtgccctgag tgaggagggt gaggagcagc    480

agagcccagg ccatggtggc gctagccagc ttgggtctcc ctatagtgag tcgtattaat    540

ttcgataagc cagtaagcag tggttctct agttagccag agagctctgc ttatatagac    600

ctcccaccgt acacgcctac cgcccatttg cgtcaatggg gcggagttgt tacgacattt    660

tggaaagtcc cgttgatttt ggtgccaaaa caaactccca ttgacgtcaa tggggtggag    720

acttggaaat ccccgtgagt caaaccgcta tccacgccca ttgatgtact gccaaaaccg    780

catcaccatg gtaatagcga                                                800
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<210> SEQ ID NO 47
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 47

```
Asp Val Val His Val Met Leu Asn Gly Ser Arg Ser Lys Ile Phe Asp
1               5                   10                  15

Lys Asn Ser Thr Phe Gly Ser
            20
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<210> SEQ ID NO 48
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 48

```
Asp Val Val His Val Met Leu Asn Gly Ser Arg Ser Lys
1               5                   10
```

<210> SEQ ID NO 49
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 49

```
Val Val His Val Met Leu Asn Gly Ser Arg Ser Lys Ile
1               5                   10
```

<210> SEQ ID NO 50
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 50

Val His Val Met Leu Asn Gly Ser Arg Ser Lys Ile Phe
1               5                   10

<210> SEQ ID NO 51
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 51

His Val Met Leu Asn Gly Ser Arg Ser Lys Ile Phe Asp
1               5                   10

<210> SEQ ID NO 52
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 52

Val Met Leu Asn Gly Ser Arg Ser Lys Ile Phe Asp Lys
1               5                   10

<210> SEQ ID NO 53
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 53

Met Leu Asn Gly Ser Arg Ser Lys Ile Phe Asp Lys Asn
1               5                   10

<210> SEQ ID NO 54
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 54

Leu Asn Gly Ser Arg Ser Lys Ile Phe Asp Lys Asn Ser
1               5                   10

<210> SEQ ID NO 55
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 55

Asn Gly Ser Arg Ser Lys Ile Phe Asp Lys Asn Ser Thr

-continued

```
1               5                   10


<210> SEQ ID NO 56
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 56

Gly Ser Arg Ser Lys Ile Phe Asp Lys Asn Ser Thr Phe
1               5                   10


<210> SEQ ID NO 57
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 57

Ser Arg Ser Lys Ile Phe Asp Lys Asn Ser Thr Phe Gly
1               5                   10


<210> SEQ ID NO 58
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide

<400> SEQUENCE: 58

Arg Ser Lys Ile Phe Asp Lys Asn Ser Thr Phe Gly Ser
1               5                   10
```

**1-84**. (canceled)

**85**. An isolated human monoclonal antibody comprising six complementarity determining regions that binds a peptide consisting of the amino acid sequence DVVHVMLNGSRSKIFDKNSTFGS (SEQ ID NO: 47).

**86**. A composition comprising the isolated human monoclonal antibody of claim **85** and a pharmaceutically acceptable carrier.

**87**. An isolated human monoclonal antibody comprising six complementarity determining regions that binds a peptide consisting of the amino acid sequence, DVVHVMLNGSRSKIFDKNSTFGS (SEQ ID NO: 47), or that binds a 13-amino acid sequence subset thereof.

**88**. The antibody of claim **87**, wherein the peptide consists of the amino acid sequence selected from the group consisting of DVVHVMLNGSRSKIFDKNSTFGS (SEQ ID NO: 47), DVVHVMLNGSRSK (SEQ ID NO: 48), VVHVMLNGSRSKI (SEQ ID NO: 49), VHVMLNGSRSKIF (SEQ ID NO: 50), HVMLNGSRSKIFD (SEQ ID NO: 51), VMLNGSRSKIFDK (SEQ ID NO: 52), MLNGSRSKIFDKN (SEQ ID NO: 53), LNGSRSKIFDKNS (SEQ ID NO: 54), NGSRSKIFDKNST (SEQ ID NO: 55), GSRSKIFDKNSTF (SEQ ID NO: 56), SRSKIFDKNSTFG (SEQ ID NO: 57), and RSKIFDKNSTFGS (SEQ ID NO: 58).

**89**. The antibody of claim **88**, wherein the peptide consists of the amino acid sequence selected from the group consisting of DVVHVMLNGSRSK (SEQ ID NO: 48), VHVMLNGSRSKIF (SEQ ID NO: 50), VMLNGSRSKIFDK (SEQ ID NO: 52), LNGSRSKIFDKNS (SEQ ID NO: 54), and RSKIFDKNSTFGS (SEQ ID NO: 58).

**90**. The antibody of claim **89**, wherein the peptide consists of the amino acid sequence, VHVMLNGSRSKIF (SEQ ID NO: 50).

**91**. A composition comprising the isolated human monoclonal antibody of claim **87** and a pharmaceutically acceptable carrier.

**92**. A composition comprising the isolated human monoclonal antibody of claim **90** and a pharmaceutically acceptable carrier.

**93**. A method of treating the overexpression of CD38 in a patient in need thereof of a therapeutically effective amount of the antibody of claim **85**.

**94**. The method of claim **93**, wherein the patient has multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, or acute lymphocytic leukemia.

**95**. The method of claim **94**, wherein the patient has rheumatoid arthritis or systemic lupus erythematosus.

**96**. A method of treating the overexpression of CD38 in a patient in need thereof with a therapeutically effective amount of the antibody of claim **87**.

**97**. The method of claim **96**, wherein the patient has multiple myeloma, chronic lyphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, or acute lymphocytic leukemia.

**98**. The method of claim **97**, wherein the patient has rheumatoid arthritis or systemic lupus erythematosus.

**99**. A method of treating the overexpression of CD38 in a patient in need thereof with a therapeutically effective amount of the antibody of claim **90**.

**100**. The method of claim **99**, wherein the patient has multiple myeloma, chronic lyphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, or acute lymphocytic leukemia.

**101**. A method of treating cancer in a subject in need thereof, wherein the cancer comprises cells that overexpress CD38, comprising administering to the subject a therapeutically effective amount of the antibody of claim **85**.

**102**. The method of claim **101**, wherein the patient has multiple myeloma, chronic lyphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, or acute lymphocytic leukemia.

**103**. A method of treating the cancer in a subject in need thereof, wherein the cancer comprises cells that overexpress CD38 in a patient in need thereof with a therapeutically effective amount of the antibody of claim **90**.

**104**. The method of claim **103**, wherein the patient has multiple myeloma, chronic lyphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, or acute lymphocytic leukemia.

* * * * *