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(54) **GENERATION AND PROFILING OF FULLY HUMAN GOLD-DERIVED THERAPEUTIC ANTIBODIES SPECIFIC FOR HUMAN CD38**

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(57) **ABSTRACT**

The present invention provides novel antibodies and methods for using 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 methods take advantage of newly discovered antibodies and surprising properties of such antibodies, such as the ability to bind CD38 of minipig origin and the ability to induce, by cross-linking, specific killing of cells that express CD38. These antibodies as well as the novel methods for using those antibodies can be used to treat, for example, hematological malignancies such as multiple myeloma.

CD38 expression analysis of Lymphocytes and Erythrocytes

MOR 03087:

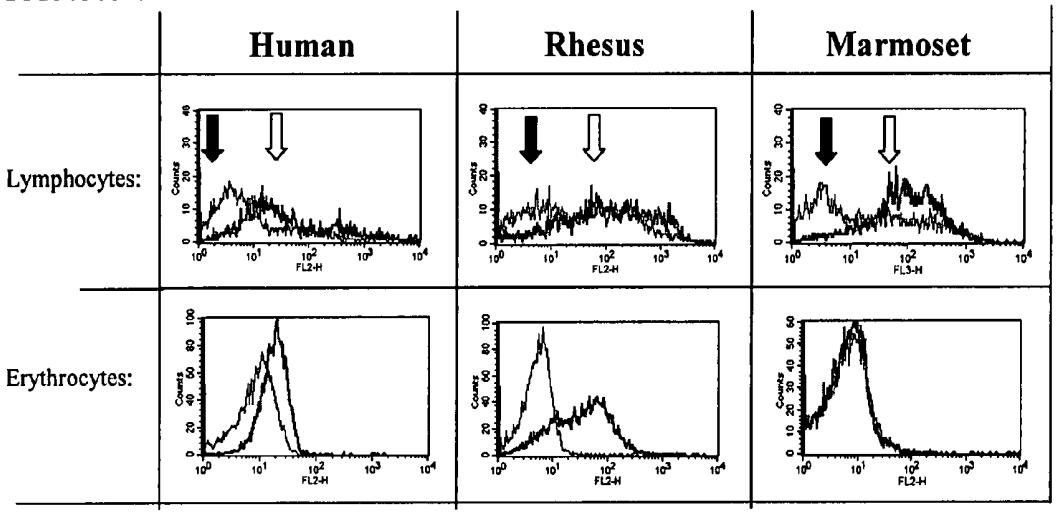

Figure 1a

Variable Heavy Chain DNA

3076_VH1A (SEQ ID NO: 1):
CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGC
AAAGCCTCCGGAGGCACTTTTTCTTCTAATGCTATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTC
TCGAGTGGATGGGCAATATCTGGCCGATTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCC
GGGTGACCATTACCGCGGATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCG
AAGATACGGCCGTGTATTATTGCGCGCGTAATGGTTATCTTGATACTAATACTTATATTGATTATTGG
GGCCAAGGCACCCTGGTGACGGTTAGCTCA

3078_VH3 (SEQ ID NO: 2):
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTGATTATGCTATGTCTTGGGTGCGCCAAGCCCCTGGGAAGG
GTCTCGAGTGGGTGAGCGCTATCCGTTATGATGGTAGCAATACCTATTATGCGGATAGCGTGAAAGG
CCGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGG
AAGATACGGCCGTGTATTATTGCGCGCGTTATTATTCTGGTATTTATCAGCATATTGATTATTGGGGC
CAAGGCACCCTGGTGACGGTTAGCTCA

3081_ VH3 (SEQ ID NO: 3):
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTTCTTATGCTCTTCATTGGGTGCGCCAAGCCCCTGGGAAGGG
TCTCGAGTGGGTGAGCTCTATCTCTGGTCTTGGTAGCACTACCTATTATGCGGATAGCGTGAAAGGC
CGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGA
AGATACGGCCGTGTATTATTGCGCGCGTTATCATTATGAGTATCATTATTTTTCTTCTGGTTTTGATAA
TTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

3085_ VH1A (SEQ ID NO: 4):
CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGCGAGCGTGAAAGTGAGCTG
CAAAGCCTCCGGATATACCTTTACTGGTTATTATATTAATTGGGTCCGCCAAGCCCCTGGGCAGGGT
CTCGAGTGGATGGGCTGGATCTTTCCGAATGGTGGCTCTACGGGTTACGCGCAGAAGTTTCAGGGC
CGGGTGACCATGACCCGTGATACCAGCATTAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGC
GAAGATACGGCCGTGTATTATTGCGCGCGTGGTAATATTTTTATTTTTGATTATTGGGGCCAAGGCAC
CCTGGTGACGGTTAGCTCA

3086_VH3 (SEQ ID NO: 5):
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTACTTCTTATTATATGCATTGGGTGCGCCAAGCCCCTGGGAAGGG
TCTCGAGTGGGTGAGCTATATCGATTCTTCTGGTAGCTCTACCTATTATGCGGATAGCGTGAAAGGC
CGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGA
AGATACGGCCGTGTATTATTGCGCGCGTCAGCTTATGCCTTTTGGTGGTTATTTTGATGTTTGGGGC
CAAGGCACCCTGGTGACGGTTAGCTCA

3087_ VH3 (SEQ ID NO: 6):
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTTCTTATTATATGAATTGGGTGCGCCAAGCCCCTGGGAAGGG

TCTCGAGTGGGTGAGCGGTATCTCTGGTGATCCTAGCAATACCTATTATGCGGATAGCGTGAAAGGC
CGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGA
AGATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCC
AAGGCACCCTGGTGACGGTTAGCTCA

3088_ VH3 (SEQ ID NO: 7):
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTTCTTATGCTATGAATTGGGTGCGCCAAGCCCCTGGGAAGG
GTCTCGAGTGGGTGAGCGGTATCTCTTCTTGGGGTAGCTCTACCTATTATGCGGATAGCGTGAAAGG
CCGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGG
AAGATACGGCCGTGTATTATTGCGCGCGTGAGGATGGTTCTTATATGACTGATTATTTTGCTTATTGG
GGCCAAGGCACCCTGGTGACGGTTAGCTCA

3089_ VH2 (SEQ ID NO: 8):
CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGT
ACCTTTTCCGGATTTAGCCTGTCTTCTGATGGTATGGGTGTGGGTTGGATTCGCCAGCCGCCTGGGA
AAGCCCTCGAGTGGCTGGCTCTTATCGATTGGGATGATGATAAGCGTTATAGCACCAGCCTGAAAAC
GCGTCTGACCATTAGCAAAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCG
GTGGATACGGCCACCTATTATTGCGCGCGTTTTAATTGGTTTTATCGTCTTGCTTTTGTTAATCCTGAT
GTTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

3101_ VH2 (SEQ ID NO: 9):
CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGT
ACCTTTTCCGGATTTAGCCTGTCTACTTCTCGTGTTGGTGTGTCTTGGATTCGCCAGCCGCCTGGGA
AAGCCCTCGAGTGGCTGGCTCATATCGATTGGAATGATGATAAGTATTATAGCACCAGCCTGAAAAC
GCGTCTGACCATTAGCAAAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCG
GTGGATACGGCCACCTATTATTGCGCGCGTGAGGATCGTCTTCTTGGTGGTTATGGTTATGATGTTT
GGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

3102_ VH4 (SEQ ID NO: 10):
CAGGTGCAATTGCAAGAAAGTGGTCCGGGCCTGGTGAAACCGGGCGAAACCCTGAGCCTGACCTG
CACCGTTTCCGGAGGCAGCATTTCTGGTAATTATTGGTCTTGGATTCGCCAGGCCCCTGGGAAGGG
TCTCGAGTGGATTGGCGATTATCATGGCTCTACCTATTATAATCCGAGCCTGAAAGGCCGGGTGACC
ATTAGCGTTGATACTTCGAAAAACCAGTTTAGCCTGAAACTGAGCAGCGTGACGGCGGAAGATACGG
CCGTGTATTATTGCGCGCGTGAGCAGTATCATTGGGGTCTTGCTTGGACTGGTTTTGATAATTGGGG
CCAAGGCACCCTGGTGACGGTTAGCTCA

3127_ VH5 (SEQ ID NO: 11):
CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGC
AAAGGTTCCGGATATTCCTTTTCTACTTCTTGGGTTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTC
TCGAGTGGATGGGCATTATCGATCCGGATATTAGCTATACCTCTTATTCTCCGAGCTTTCAGGGCCA
GGTGACCATTAGCGCGGATAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAG
CGATACGGCCATGTATTATTGCGCGCGTTATCTTATGGGTCTTGGTTATGATGTTTGGGGCCAAGGC
ACCCTGGTGACGGTTAGCTCA

3128_ VH2 (SEQ ID NO: 12):
CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGT
ACCTTTTCCGGATTTAGCCTGTCTTCTTCTGGTATGTCTGTGTCTTGGATTCGCCAGCCGCCTGGGA
AAGCCCTCGAGTGGCTGGCTCGTATCTATTCTGATGATTCTAAGTCTTATAGCACCAGCCTGAAAAC
GCGTCTGACCATTAGCAAAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCG
GTGGATACGGCCACCTATTATTGCGCGCGTGCTGCTCATTGGAATGGTCCTCTTTTTGATGTTTGGG
GCCAAGGCACCCTGGTGACGGTTAGCTCA

3129_ VH3 (SEQ ID NO: 13):
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTAATTATTCTATGAATTGGGTGCGCCAAGCCCCTGGGAAGGG
TCTCGAGTGGGTGAGCTATATCTATGGTGGTGGTAGCTATACCTATTATGCGGATAGCGTGAAAGGC
CGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGA
AGATACGGCCGTGTATTATTGCGCGCGTCAGGCTGGTATGTATTTTGATGTTTGGGGCCAAGGCACC
CTGGTGACGGTTAGCTCA

3130_ VH4 (SEQ ID NO: 14):
CAGGTGCAATTGCAAGAAAGTGGTCCGGGCCTGGTGAAACCGGGCGAAACCCTGAGCCTGACCTG
CACCGTTTCCGGAGGCAGCATTGGTTATTATTGGAATTGGATTCGCCAGGCCCCTGGGAAGGGTCT
CGAGTGGATTGGCCATATCTCTCGTTTTGGCTCTACCAATTATAATCCGAGCCTGAAAGGCCGGGTG
ACCATTAGCGTTGATACTTCGAAAAACCAGTTTAGCCTGAAACTGAGCAGCGTGACGGCGGAAGATA
CGGCCGTGTATTATTGCGCGCGGGAGTATACTGGTAATGATTGGTATCGTCAGCAGGGTCAGCATG
CTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

3131_ VH2 (SEQ ID NO: 15):
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ACCTTTTCCGGATTTAGCCTGTCTAATTCTGGTGTTGGTGTGGGTTGGATTCGCCAGCCGCCTGGGA
AAGCCCTCGAGTGGCTGGCTGATATCTATTCTGATACTACTAAGCGTTATAGCACCAGCCTGAAAAC
GCGTCTGACCATTAGCAAAGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCG
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CCCTGGTGACGGTTAGCTCA

6183_VH3 (SEQ ID NO: 77)
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GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6184_VH3 (SEQ ID NO: 78)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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TCTCGAGTGGGTGAGCGCTATTTCTCATGATGGTAATGTTAAGTATTATGCTGATTCTGTTAAGGGTC
GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6185_VH3 (SEQ ID NO: 79)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6186_VH3 (SEQ ID NO: 80)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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TCTCGAGTGGGTGAGCGCTATTAATCTTTCTGGTTCTGCTAAGTATTATGCTGATTCTGTTAAGGGTC
GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6187_VH3 (SEQ ID NO: 81)
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GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6188_VH3 (SEQ ID NO: 82)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6189_VH3 (SEQ ID NO: 83)
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AGGCACCCTGGTGACGGTTAGCTCA

6190_VH3 (SEQ ID NO: 84)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6192_VH3 (SEQ ID NO: 85)
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CGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGA
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AAGGCACCCTGGTGACGGTTAGCTCA

6195_VH3 (SEQ ID NO: 86)
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GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6197_VH3 (SEQ ID NO: 87)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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AGGCACCCTGGTGACGGTTAGCTCA

6200_VH3 (SEQ ID NO: 88)
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GCGCGGCCTCCGGATTTACCTTTTCTTCTTATTATATGAATTGGGTGCGCCAAGCCCCTGGGAAGGG
TCTCGAGTGGGTGAGCGCTATTTCTAATAATGGTAATGTTACTTATTATGCTGATTCTGTTAAGGGTC
GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6201_VH3 (SEQ ID NO: 89)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
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GTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAA
GATACGGCCGTGTATTATTGCGCGCGTGATCTTCCTCTTGTTTATACTGGTTTTGCTTATTGGGGCCA
AGGCACCCTGGTGACGGTTAGCTCA

6204_VH3 (SEQ ID NO: 90)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTTCTTATGCTATGAATTGGGTGCGCCAAGCCCCTGGGAAGG
GTCTCGAGTGGGTGAGCCATATTCGTAAGAAGAATACTTCTTATACTACTGAGTATGCTGCTTCTGTT
AAGGGTCGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCG

TGCGGAAGATACGGCCGTGTATTATTGCGCGCGTGAGGATGGTTCTTATATGACTGATTATTTTGCTT
ATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

6214_VH3 (SEQ ID NO: 91)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTTCTTATGCTATGAATTGGGTGCGCCAAGCCCCTGGGAAGG
GTCTCGAGTGGGTGAGCAATATTCAGCGTGTTGGTTCTACTTATTATGCTGATTCTGTTAAGGGTCGT
TTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGGAAGA
TACGGCCGTGTATTATTGCGCGCGTGAGGATGGTTCTTATATGACTGATTATTTTGCTTATTGGGGCC
AAGGCACCCTGGTGACGGTTAGCTCA

3077_VH1B (SEQ ID NO: 111)
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CAAAGCCTCCGGATATACCTTTACTTCTTATTCTATTAATTGGGTCCGCCAAGCCCCTGGGCAGGGT
CTCGAGTGGATGGGCTATATCGATCCGAATCGTGGCAATACGAATTACGCGCAGAAGTTTCAGGGC
CGGGTGACCATGACCCGTGATACCAGCATTAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGC
GAAGATACGGCCGTGTATTATTGCGCGCGTGAGTATATTTATTTTATTCATGGTATGCTTGATTTTTG
GGGCCAAGGCACCCTGGTGACGGTTAGCTCA

3079_VH3 (SEQ ID NO: 112)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGG
GTCTCGAGTGGGTGAGCAATATCCGTTCTGATGGTAGCTGGACCTATTATGCGGATAGCGTGAAAG
GCCGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCG
GAAGATACGGCCGTGTATTATTGCGCGCGTCGTTATTGGTCTAAGTCTCATGCTTCTGTTACTGATTA
TTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

3080_ VH3 (SEQ ID NO: 113)
CAGGTGCAATTGGTGGAAAGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCT
GCGCGGCCTCCGGATTTACCTTTTCTTCTTATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGG
GTCTCGAGTGGGTGAGCAATATCTATTCTGATGGTAGCAATACCTTTTATGCGGATAGCGTGAAAGG
CCGTTTTACCATTTCACGTGATAATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCGG
AAGATACGGCCGTGTATTATTGCGCGCGTAATATGTATCGTTGGCCTTTTCATTATTTTTTTGATTATT
GGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

Figure 1b

Variable Heavy Chain Peptide

(CDR Regions in **Bold** or underlined)

3076_VH1A (SEQ ID NO: 16):
QVQLVQSGAEVKKPGSSVKVSCKAS**GGTFSSNAIS**WVRQAPGQGLEWMG**NIWPIFGTANYAQKFQG**R
VTITADESTSTAYMELSSLRSEDTAVYYCAR**NGYLDTNTYIDY**WGQGTLVTVSS

3078_VH3 (SEQ ID NO: 17):
QVQLVESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWVS**AIRYDGSNTYYADSVKG**R
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YYSGIYQHIDY**WGQGTLVTVSS

3081_ VH3 (SEQ ID NO: 18):
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFSSYALH**WVRQAPGKGLEWVS**SISGLGSTTYYADSVKG**RF
TISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YHYEYHYFSSGFDN**WGQGTLVTVSS

3085_ VH1A (SEQ ID NO: 19):
QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTGYYIN**WVRQAPGQGLEWMG**WIFPNGGSTGYAQKFQG**R
VTMTRDTSISTAYMELSSLRSEDTAVYYCAR**GNIFIFDY**WGQGTLVTVSS

3086_VH3 (SEQ ID NO: 20):
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFTSYYMH**WVRQAPGKGLEWVS**YIDSSGSSTYYADSVKG**R
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**QLMPFGGYFDV**WGQGTLVTVSS

3087_ VH3 (SEQ ID NO: 21):
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFSSYYMN**WVRQAPGKGLEWVS**GISGDPSNTYYADSVKG**R
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**DLPLVYTGFAY**WGQGTLVTVSS

3088_ VH3 (SEQ ID NO: 22):
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFSSYAMN**WVRQAPGKGLEWVS**GISSWGSSTYYADSVKG**R
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARE**DGSYMTDYFAY**WGQGTLVTVSS

3089_ VH2 (SEQ ID NO: 23):
QVQLKESGPALVKPTQTLTLTCTFS**GFSLSSDGMGVG**WIRQPPGKALEWLA**LIDWDDDKRYSTSLKT**RL
TISKDTSKNQVVLTMTNMDPVDTATYYCAR**FNWFYRLAFVNPDV**WGQGTLVTVSS

3101_ VH2 (SEQ ID NO: 24):
QVQLKESGPALVKPTQTLTLTCTFS**GFSLSTSRVGVS**WIRQPPGKALEWLA**HIDWNDDKYYSTSLKT**RLT
ISKDTSKNQVVLTMTNMDPVDTATYYCARE**DRLLGGYGYDV**WGQGTLVTVSS

3102_VH4 (SEQ ID NO: 25):
QVQLQESGPGLVKPGETLSLTCTVS**GGSISGNYWS**WIRQAPGKGLEWIG**DYHGSTYYNPSLKG**RVTISV
DTSKNQFSLKLSSVTAEDTAVYYCAR**EQYHWGLAWTGFDN**WGQGTLVTVSS

3127_VH5 (SEQ ID NO: 26):
QVQLVQSGAEVKKPGESLKISCKGS**GYSFSTSWVG**WVRQMPGKGLEWMGI**IDPDISYTSYSPSFQG**QV
TISADKSISTAYLQWSSLKASDTAMYYCAR**YLMGLGYDV**WGQGTLVTVSS

3128_VH2 (SEQ ID NO: 27):
QVQLKESGPALVKPTQTLTLTCTFS**GFSLSSSGMSVS**WIRQPPGKALEWLA**RIYSDDSKSYSTSLK**TRLTI
SKDTSKNQVVLTMTNMDPVDTATYYCAR**AAHWNGPLFDV**WGQGTLVTVSS

3129_VH3 (SEQ ID NO: 28):
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFSNYSMN**WVRQAPGKGLEWVS**YIYGGGSYTYYADSVKG**R
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**QAGMYFDV**WGQGTLVTVSS

3130_VH4 (SEQ ID NO: 29):
QVQLQESGPGLVKPGETLSLTCTVS**GGSIGYYWN**WIRQAPGKGLEWIG**HISRFGSTNYNPSLKG**RVTISV
DTSKNQFSLKLSSVTAEDTAVYYCAR**EYTGNDWYRQQGQHADY**WGQGTLVTVSS

3131_VH2 (SEQ ID NO: 30):
QVQLKESGPALVKPTQTLTLTCTFS**GFSLSNSGVGVG**WIRQPPGKALEWLA**DIYSDTTKRYSTSLKT**RLTI
SKDTSKNQVVLTMTNMDPVDTATYYCAR**YGEAYFDY**WGQGTLVTVSS

6183_VH3 (SEQ ID NO: 92)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSGINMESTRIYYADSVKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6184_VH3 (SEQ ID NO: 93)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISHDGNVKYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6185_VH3 (SEQ ID NO: 94)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISMNGDYISYADSVKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6186_VH3 (SEQ ID NO: 95)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAINLSGSAKYYADSVKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6187_VH3 (SEQ ID NO: 96)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISSNGDITYYADSVKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6188_VH3 (SEQ ID NO: 97)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISTNGWQTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6189_VH3 (SEQ ID NO: 98)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAINMIGNVTNYADSVKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6190_VH3 (SEQ ID NO: 99)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSYINPNGMMTNYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6192_VH3 (SEQ ID NO: 100)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSVISPGGEAKSYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6195_VH3 (SEQ ID NO: 101)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISGNGGHTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6197_VH3 (SEQ ID NO: 102)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISMDGVYKYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6200_VH3 (SEQ ID NO: 103)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISNNGNVTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6201_VH3 (SEQ ID NO: 104)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYYMNWVRQAPGKGLEWVSAISMHGDTTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARDLPLVYTGFAYWGQGTLVTVSS

6204_VH3 (SEQ ID NO: 105)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSHIRKKNTSYTTEYAASVKG
RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAREDGSYMTDYFAYWGQGTLVTVSS

6214_VH3 (SEQ ID NO: 106)
QVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMNWVRQAPGKGLEWVSNIQRVGSTYYADSVKGRF
TISRDNSKNTLYLQMNSLRAEDTAVYYCAREDGSYMTDYFAYWGQGTLVTVSS

3077_VH1B (SEQ ID NO: 114)
QVQLVQSGAEVKKPGASVKVSCKAS**GYTFTSYSIN**WVRQAPGQGLEWMGYI**DPNRGNTNYAQKFQG**R
VTMTRDTSISTAYMELSSLRSEDTAVYYCAR**EYIYFIHGMLDF**WGQGTLVTVSS

3079_VH3 (SEQ ID NO: 115)
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFSNYGMH**WVRQAPGKGLEWVS**NIRSDGSWTYYADSVKG**
RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**RYWSKSHASVTDY**WGQGTLVTVSS

3080_VH3 (SEQ ID NO: 116)
QVQLVESGGGLVQPGGSLRLSCAAS**GFTFSSYGMH**WVRQAPGKGLEWVS**NIYSDGSNTFYADSVKG**R
FTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**NMYRWPFHYFFDY**WGQGTLVTVSS

Figure 2a

Variable Light Chain DNA

3076_Vl lambda 2 (SEQ ID NO: 31):
GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGT
ACGGGTACTAGCAGCGATATTGGTGCTTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCG
AAACTTATGATTTATGAGGTTTCTTCTCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAG
CGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCTC
TTCTTATGATCTTACTCCTCCTGGTAAGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3078_Vl lambda 3 (SEQ ID NO: 32):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATATTGGTCATTATTATGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATGGTGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTTC
TGATGTTGGTTCTCTTGATGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3081_ Vk kappa 3 (SEQ ID NO: 33):
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAG
CTGCAGAGCGAGCCAGACTGGTTCTACTTCTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCA
CCGCGTCTATTAATTTATGATGCTTCTAAGCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTG
GATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGACTTATTATTG
CCATCAGTATTATAACGTTCCTCATACCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACG

3085_ Vl lambda 1 (SEQ ID NO: 34):
GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCATCTCGTGT
AGCGGCAGCAGCAGCAACATTGGTAATAATTATGTGTCTTGGTACCAGCAGTTGCCCGGGACGGCG
CCGAAACTTCTGATTTATGGTGATGATCAGCGTCCCTCAGGCGTGCCGGATCGTTTTAGCGGATCCA
AAAGCGGCACCAGCGCGAGCCTTGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGATTATTATT
GCCAGTCTTATGGTACTTTTTCTTCTTTTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3086_Vk kappa 1 (SEQ ID NO: 35):
GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACC
TGCAGAGCGAGCCAGAATATTTCTCAGTGGCTGAATTGGTACCAGCAGAAACCAGGTAAAGCACCG
AAACTATTAATTTATGGTGCTTCTAATTTGCAAAGCGGGGTCCCGTCCCGTTTTAGCGGCTCTGGATC
CGGCACTGATTTTACCCTGACCATTAGCAGCCTGCAACCTGAAGACTTTGCGACTTATTATTGCCAG
CAGTATTATGATCTTCCTAATACCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACG

3087_ Vl lambda 3 (SEQ ID NO: 36):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATCTTCGTCATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATGGTGATTCTAAGCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGAC
TTATACTGGTGGTGCTTCTCTTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3088_ Vl lambda 3 (SEQ ID NO: 37):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATATTGGTCATTATTATGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATTCTGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTC
TTATAATGGTACTTATGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3089_ Vk kappa 3 (SEQ ID NO: 38):
GATATCGTGCTGACCCAGAGCCCGGCGACCCTGAGCCTGTCTCCGGGCGAACGTGCGACCCTGAG
CTGCAGAGCGAGCCAGTCTGTTTCTTCTTCTTATCTGGCTTGGTACCAGCAGAAACCAGGTCAAGCA
CCGCGTCTATTAATTTATGGTGCTTCTTCTCGTGCAACTGGGGTCCCGGCGCGTTTTAGCGGCTCTG
GATCCGGCACGGATTTTACCCTGACCATTAGCAGCCTGGAACCTGAAGACTTTGCGGTTTATTATTG
CCAGCAGGGTTATAATTCTCCTTTTACCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACG

3101_ Vl lambda 3 (SEQ ID NO: 39):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATTCTCTTGGTTCTTATTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTGGTGATGATACTAAGCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCG
GCAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTT
CTCGTACTGGTTATAATAATTCTTTTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3102_ V'l lambda 3 (SEQ ID NO: 40):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATCTTGGTCATTATTATGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATGATGATTCTGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTGC
TTATGCTATGCATATGACTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3127_ Vl lambda 2 (SEQ ID NO: 41):
GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGT
ACGGGTACTAGCAGCGATGTTGGTGCTATTAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGG
CGCCGAAACTTATGATTTATGATGTTAATAAGCGTCCCTCAGGCGTGCCGGATCGTTTTAGCGGATC
CAAAAGCGGCAACACCGCGAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTA
TTGCGGTTCTTATACTATGCAGGTTGGTTCTTATGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTG
GCCAG

3128_ Vl lambda 3 (SEQ ID NO: 42):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATATTGGTCATTATTATGCTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTG
TTGTGATTTATGATGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGC
TTATACTGGTGATGGTGGTCGTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3129_ Vl lambda 3 (SEQ ID NO: 43):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATCTTGGTTCTAAGGTTGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTT

CTTGTGATTTATTATGATAATAAGCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCG
GCAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGT
CTTATACTTTTGAGTCTGGTTCTGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3130_ Vl lambda 3 (SEQ ID NO: 44):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATCTTGGTCATTATTATGTTGATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATGCTGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTTCT
TATTCTCAGCAGTCTATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

3131_ Vl lambda 3 (SEQ ID NO: 45):
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATCTTGGTAATTTTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATGAGGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTTCT
TGGGATATGTATCGTACTATTTTTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

6278_Vl lambda 3 (SEQ ID NO: 107)
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATATTGGTCATTATTATGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATTCTGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTC
TGCTGATAATTTTCCTTTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAG

6279_ Vl lambda 3 (SEQ ID NO: 108)
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATATTGGTCATTATTATGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTC
TTGTGATTTATTCTGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTC
TTATACTATGTCTGATGTTCTTGTTGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAG

3077_Vk kappa 2 (SEQ ID NO: 117)
GATATCGTGATGACCCAGAGCCCACTGAGCCTGCCAGTGACTCCGGGCGAGCCTGCGAGCATTAGC
TGCAGAAGCAGCCAAAGCCTGCTTTTTATTGATGGCAATAATTATCTGAATTGGTACCTTCAAAAACC
AGGTCAAAGCCCGCAGCTATTAATTT ATCTTGGTTCTAATCGTGCCAGTGGGGTCCCGGATCGTTT
TAGCGGCTCTGGATCCGGCACCGATTTTACCCTGAAAATTAGCCGTGTGGAAGCTGAAGACGTGGG
CGTGTATTATTGCCAGCAGTATTCTTCTAAGTCTGCTACCTTTGGCCAGGGTACGAAAGTTGAAATTA
AACGTACG

3079_Vk kappa 1 (SEQ ID NO: 118)
GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACC
TGCAGAGCGAGCCAGGATATTTCTGCTTTTCTGAATTGGTACCAGCAGAAACCAGGTAAAGCACCGA
AACTATTAATTTATAAGGTTTCTAATTTGCAAAGCGGGGTCCCGTCCCGTTTTAGCGGCTCTGGATCC
GGCACTGATTTTACCCTGACCATTAGCAGCCTGCAACCTGAAGACTTTGCGACTTATTATTGCCAGCA
GGCTTATTCTGGTTCTATTACCTTTGGCCAGGGTACGAAAGTTGAAATTAAACGTACG

3080_Vl lambda 3 (SEQ ID NO: 119)
GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGT
AGCGGCGATAATATTGGTAATAAGTATGTTTCTTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTG
TTGTGATTTATGGTGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGG
CAACACCGCGACCCTGACCATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTTCT
TATGATTCTTCTTATTTTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAG

Figure 2b

Variable Light Chain Peptide

(CDR Regions in **Bold** or underlined)

3076_Vl lambda 2 (SEQ ID NO: 46):
DIALTQPASVSGSPGQSITISCTGTSSDIGAYVSWYQQHPGKAPKLMIYEVSSRPSGVSNRFSGSKSGNT
ASLTISGLQAEDEADYYCSSYDLTPPGKVFGGGTKLTVLGQ

3078_Vl lambda 3 (SEQ ID NO: 47):
DIELTQPPSVSVAPGQTARISCSGDNIGHYYVSWYQQKPGQAPVLVIYGDNNRPSGIPERFSGSNSGNTA
TLTISGTQAEDEADYYCASDVGSLDVFGGGTKLTVLGQ

3081_ Vk kappa 3 (SEQ ID NO: 48):
DIVLTQSPATLSLSPGERATLSCRASQTGSTSYLAWYQQKPGQAPRLLIYDASKRATGVPARFSGSGSGT
DFTLTISSLEPEDFATYYCHQYYNVPHTFGQGTKVEIKRT

3085_ Vl lambda 1 (SEQ ID NO: 49):
DIVLTQPPSVSGAPGQRVTISC**SGSSSNIGNNYVS**WYQQLPGTAPKLLIY**GDDQRPS**GVPDRFSGSKSG
TSASLAITGLQSEDEADYYC**QSYGTFSSF**VFGGGTKLTVLGQ

3086_Vk kappa 1 (SEQ ID NO: 50):
DIQMTQSPSSLSASVGDRVTITCRASQNISQWLNWYQQKPGKAPKLLIYGASNLQSGVPSRFSGSGSGT
DFTLTISSLQPEDFATYYCQQYYDLPNTFGQGTKVEIKRT

3087_ Vl lambda 3 (SEQ ID NO: 51):
DIELTQPPSVSVAPGQTARISCSGDNLRHYYVYWYQQKPGQAPVLVIYGDSKRPSGIPERFSGSNSGNT
ATLTISGTQAEDEADYYCQTYTGGASLVFGGGTKLTVLGQ

3088_ Vl lambda 3 (SEQ ID NO: 52):
DIELTQPPSVSVAPGQTARISCSGDNIGHYYVSWYQQKPGQAPVLVIYSDSNRPSGIPERFSGSNSGNTA
TLTISGTQAEDEADYYCQSYNGTYVFGGGTKLTVLGQ

3089_ Vk kappa 3 (SEQ ID NO: 53):
DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGVPARFSGSGSGT
DFTLTISSLEPEDFAVYYCQQGYNSPFTFGQGTKVEIKRT

3101_ Vl lambda 3 (SEQ ID NO: 54):
DIELTQPPSVSVAPGQTARISCSGDSLGSYYVHWYQQKPGQAPVLVIGDDTKRPSGIPERFSGSNSGNT
ATLTISGTQAEDEADYYCGSRTGYNNSFVFGGGTKLTVLGQ

3102_ Vl lambda 3 (SEQ ID NO: 55):
DIELTQPPSVSVAPGQTARISCSGDNLGHYYVSWYQQKPGQAPVLVIYDDSDRPSGIPERFSGSNSGNT
ATLTISGTQAEDEADYYCGAYAMHMTVFGGGTKLTVLGQ

3127_ Vl lambda 2 (SEQ ID NO: 56):
DIALTQPASVSGSPGQSITISCTGTSSDVGAINYVSWYQQHPGKAPKLMIYDVNKRPSGVPDRFSGSKSG
NTASLTISGLQAEDEADYYCGSYTMQVGSYVFGGGTKLTVLGQ

3128_ Vl lambda 3 (SEQ ID NO: 57):
DIELTQPPSVSVAPGQTARISCSGDNIGHYYAHWYQQKPGQAPVVVIYDDNDRPSGIPERFSGSNSGNT
ATLTISGTQAEDEADYYCQAYTGDGGRVFGGGTKLTVLGQ

3129_ Vl lambda 3 (SEQ ID NO: 58):
DIELTQPPSVSVAPGQTARISCSGDNLGSKVVSWYQQKPGQAPVLVIYYDNKRPSGIPERFSGSNSGNTA
TLTISGTQAEDEADYYCQSYTFESGSVVFGGGTKLTVLGQ

3130_ Vl lambda 3 (SEQ ID NO: 59):
DIELTQPPSVSVAPGQTARISCSGDNLGHYYVDWYQQKPGQAPVLVIYADNNRPSGIPERFSGSNSGNT
ATLTISGTQAEDEADYYCSSYSQQSMVFGGGTKLTVLGQ

3131_ Vl lambda 3 (SEQ ID NO: 60):
DIELTQPPSVSVAPGQTARISCSGDNLGNFYVHWYQQKPGQAPVLVIYEDSNRPSGIPERFSGSNSGNT
ATLTISGTQAEDEADYYCSSWDMYRTIFVFGGGTKLTVLGQ

6278_ Vl lambda 3 (SEQ ID NO: 109)
DIELTQPPSVSVAPGQTARISCSGDNIGHYYVSWYQQKPGQAPVLVIYSDSNRPSGIPERFSGSNSGNTA
TLTISGTQAEDEADYYCQSADNFPFVFGGGTKLTVLGQ

6279_ Vl lambda 3 (SEQ ID NO: 110)
DIELTQPPSVSVAPGQTARISCSGDNIGHYYVSWYQQKPGQAPVLVIYSDSNRPSGIPERFSGSNSGNTA
TLTISGTQAEDEADYYCQSYTMSDVLVVFGGGTKLTVLGQ

3077_Vk kappa 2 (SEQ ID NO: 120)
DIVMTQSPLSLPVTPGEPASISC**RSSQSLLFIDGNNYLN**WYLQKPGQSPQLLI**YLGSNRAS**GVPDRFSGS
GSGTDFTLKISRVEAEDVGVYYC**QQYSSKSA**TFGQGTKVEIKRT

3079_Vk kappa 1 (SEQ ID NO: 121)
DIQMTQSPSSLSASVGDRVTITC**RASQDISAFLN**WYQQKPGKAPKLLI**YKVSNLQS**GVPSRFSGSGSGT
DFTLTISSLQPEDFATYYC**QQAYSGSI**TFGQGTKVEIKRT

3080_Vl lambda3 (SEQ ID NO: 122)
DIELTQPPSVSVAPGQTARISC**SGDNIGNKYVS**WYQQKPGQAPVVVIY**GDNNRPS**GIPERFSGSNSGNT
ATLTISGTQAEDEADYYC**SSYDSSYF**VFGGGTKLTVLGQ

Figure 3

Variable Heavy Chain Consensus Sequences

(CDR Regions in **Bold**)

VH1A Consensus (SEQ ID NO: 61):
QVQLVQSGAEVKKPGSSVKVSCKAS**GGTFSSYAIS**WVRQAPGQGLEWMG**GIIPIFGTANYAQKFQG**RVTI
TADESTSTAYMELSSLRSEDTAVYYCAR**WGGDGFYAMDY**WGQGTLVTVSS

VH2 Consensus (SEQ ID NO: 62)
QVQLKESGPALVKPTQTLTLTCTFS**GFSLSTSGVGVG**WIRQPPGKALEWLA**LIDWDDDKYYSTSLKT**RLT
ISKDTSKNQVVLTMTNMDPVDTATYYCAR**WGGDGFYAMDY**WGQGTLVTVSS

VH3 Consensus (SEQ ID NO: 63):

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

VH4 Consensus (SEQ ID NO: 64):
QVQLQESGPGLVKPSETLSLTCTVS**GGSISSYYWS**WIRQPPGKGLEWIG**YIYYSGSTNYNPSLKS**RVTIS
VDTSKNQFSLKLSSVTAADTAVYYCAR**WGGDGFYAMDY**WGQGTLVTVSS

VH5 Consensus (SEQ ID NO: 65):
QVQLVQSGAEVKKPGESLKISCKGS**GYSFTSYWIG**WVRQMPGKGLEWMG**IIYPGDSDTRYSPSFQGQ**VTI
SADKSISTAYLQWSSLKASDTAMYYCAR**WGGDGFYAMDY**WGQGTLVTVSS

Figure 4

Variable Light Chain Consensus Sequences

(CDR Regions in **Bold**)

Vl_λ1 Consensus (SEQ ID NO: 66):
DIVLTQPPSVSGAPGQRVTISC**SGSSSNIGSNYVS**WYQQLPGTAPKLLIY**DNNQRPS**GVPDRFSGSKSGT
SASLAITGLQSEDEADYYC**QQHYTTPP**VFGGGTKLTVLGQ

Vl_λ2 Consensus (SEQ ID NO: 67):
DIALTQPASVSGSPGQSITISC**TGTSSDVGGYNYVS**WYQQHPGKAPKLMIY**DVSNRPS**GVSNRFSGSKSG
NTASLTISGLQAEDEADYYC**QQHYTTPP**VFGGGTKLTVLGQ

Vl_λ3 Consensus (SEQ ID NO: 68):

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

Vl_k1 Consensus (SEQ ID NO: 69):

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

Vl_k3 Consensus (SEQ ID NO: 70):
DIVLTQSPATLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GVPARFSGSGSGT
DFTLTISSLEPEDFAVYYC**QQHYTTPP**TFGQGTKVEIKRT

Figure 5

Peptide Sequence of CD38

(SEQ ID NO: 71):

```
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: 72):

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 cagcccttta 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 gggggggaccg 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: 73):

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

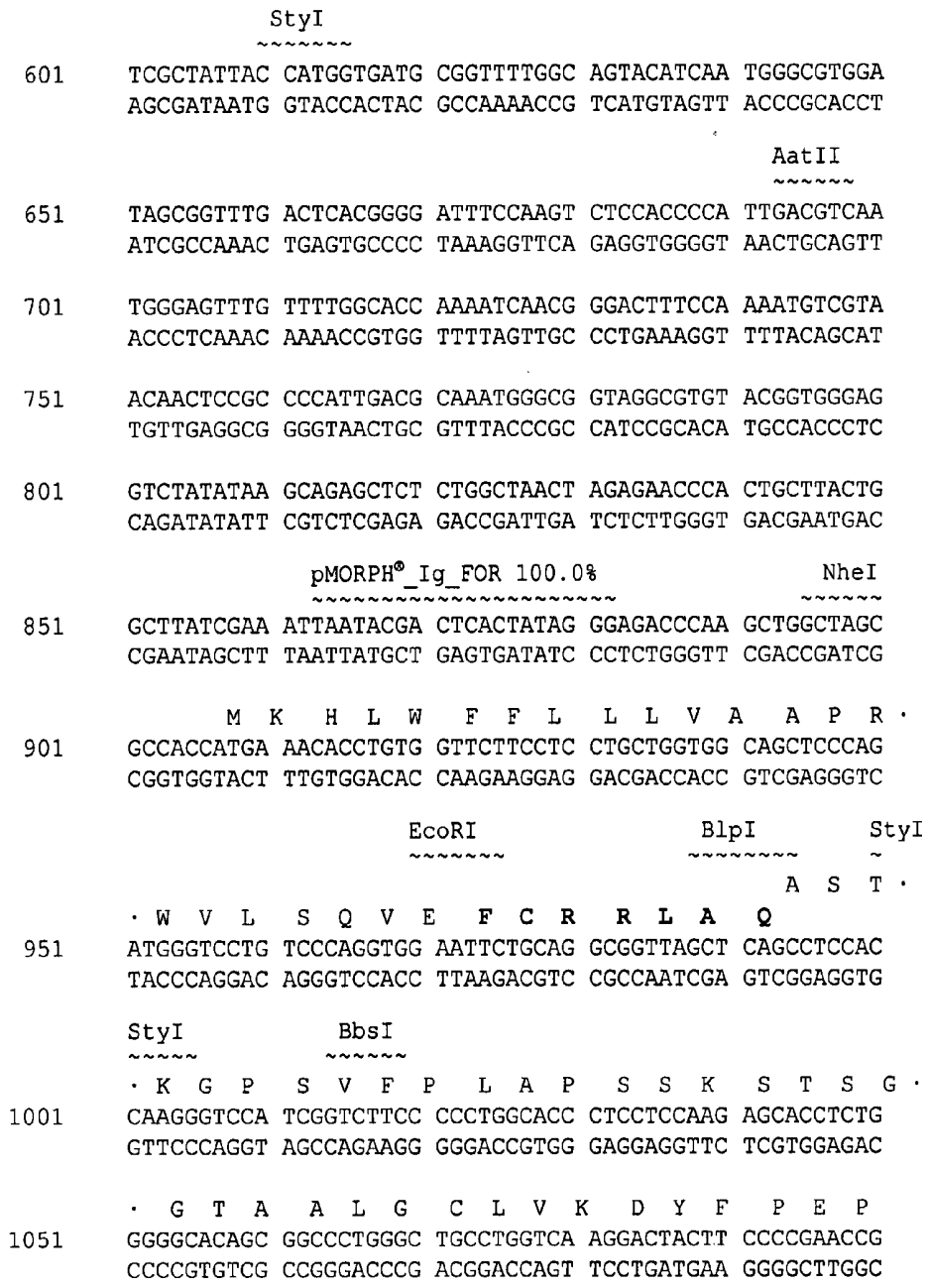
cccagagagg ccaaagtaca gtggaaggtg gataacgccc tccaatcggg taactcccag gagagtgtca

cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacg ctgagcaaag cagactacga

gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc ctgagctcgc ccgtcacaaa gagcttcaac

aggggagagt gt

Figure 7: DNA sequence of pMOPRH®_h_IgG1_1



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      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
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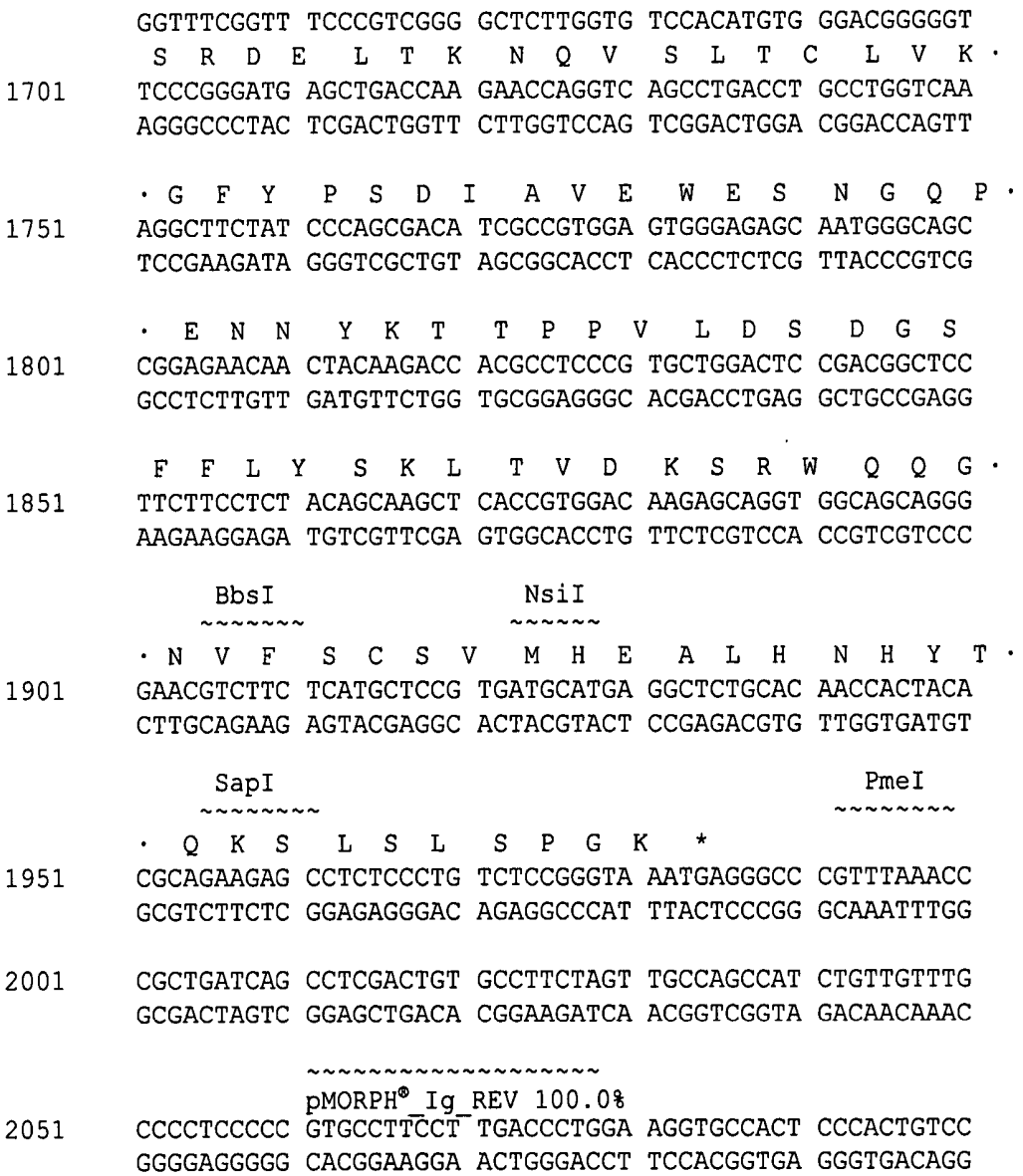
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S R D E L T K N Q V S L T C L V K ·
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AGGGCCCTAC TCGACTGGTT CTTGGTCCAG TCGGACTGGA CGGACCAGTT
· G F Y P S D I A V E W E S N G Q P ·
1751 AGGCTTCTAT CCCAGCGACA TCGCCGTGGA GTGGGAGAGC AATGGGCAGC
TCCGAAGATA 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
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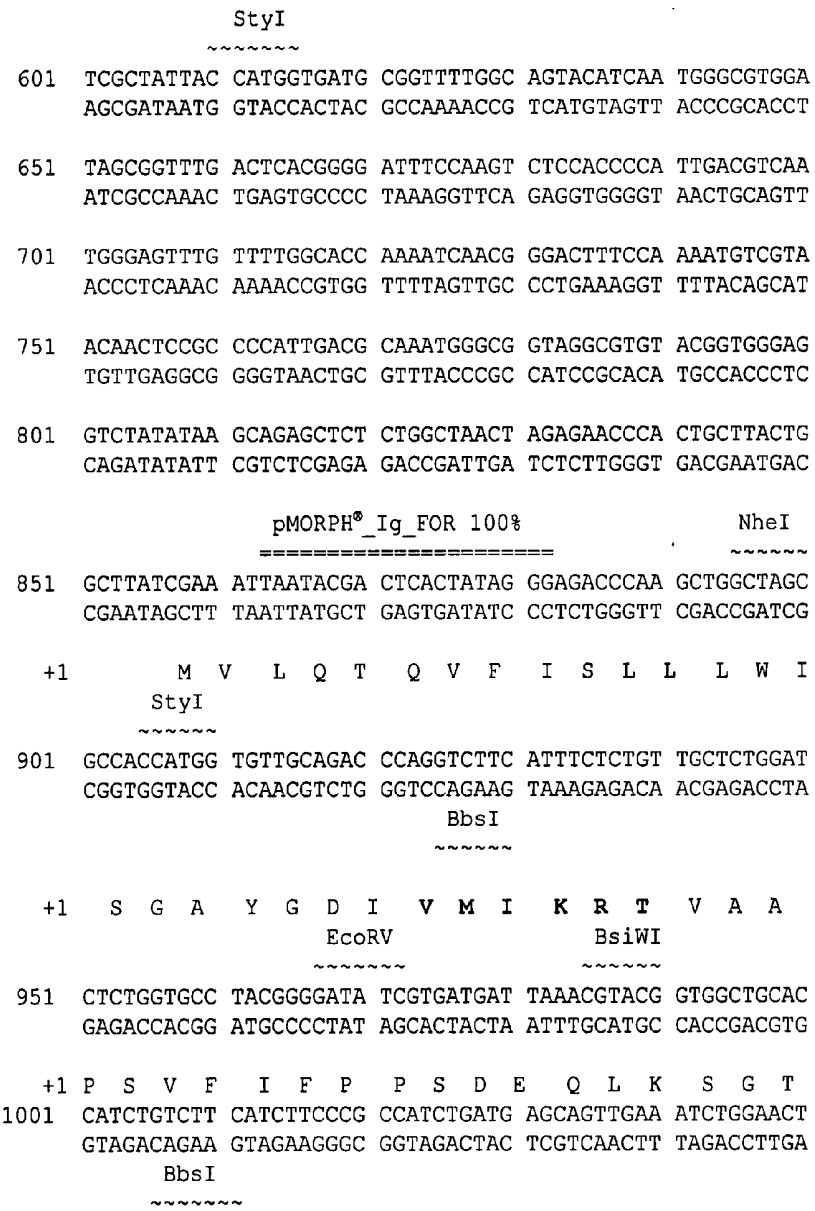
Figure 8: DNA Sequence of Ig kappa light chain expression vector pMORPH®_h_Igκ_1



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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 9: DNA Sequence of HuCAL® Ig lambda light chain vector pMORPH®_h_Igλ_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
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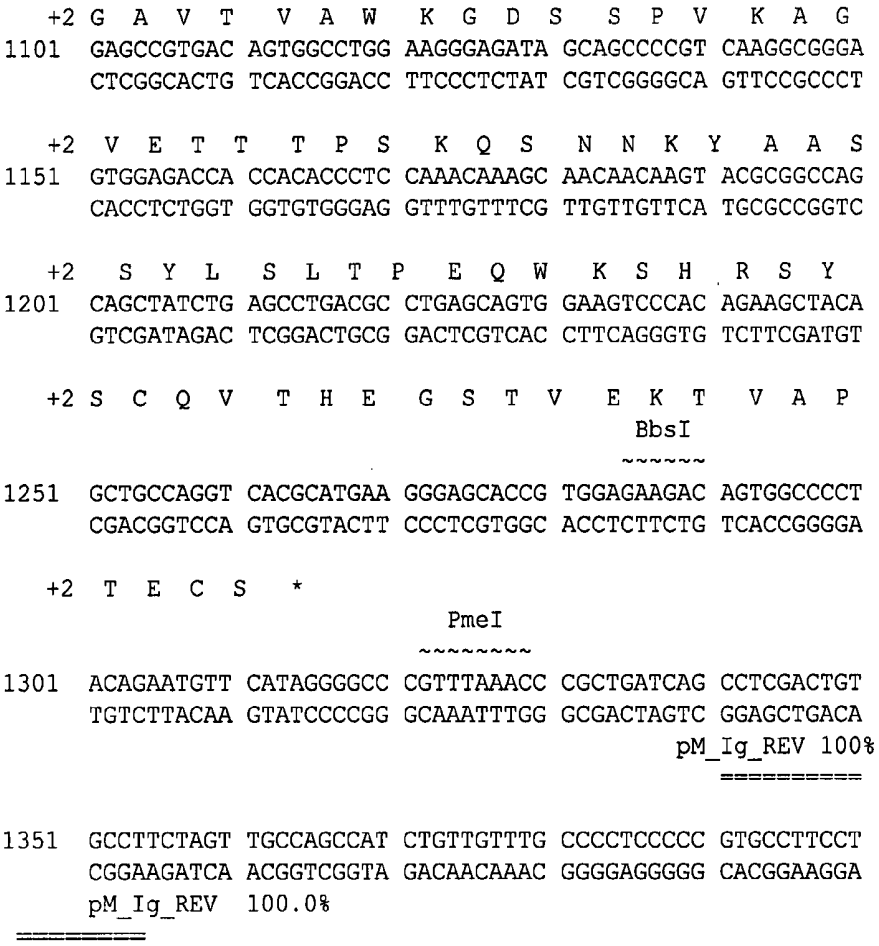
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CTCGGCACTG TCACCGGACC TTCCCTCTAT CGTCGGGGCA GTTCCGCCCT
+2 V E T T T P S K Q S N N K Y A A S
1151 GTGGAGACCA CCACACCCTC CAAACAAAGC AACAACAAGT ACGCGGCCAG
CACCTCTGGT GGTGTGGGAG GTTTGTTTCG TTGTTGTTCA TGCGCCGGTC
+2 S Y L S L T P E Q W K S H R S Y
1201 CAGCTATCTG 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%

Figure 10

Designation:	Format	Affinity Maturation	Heavy chain from:	Light chain from:
MOR06183	Fab/IgG1	new H-CDR2	MOR06183	MOR03087 (parental)
MOR06184	Fab/IgG1	new H-CDR2	MOR06184	MOR03087 (parental)
MOR06185	Fab/IgG1	new H-CDR2	MOR06185	MOR03087 (parental)
MOR06186	Fab/IgG1	new H-CDR2	MOR06186	MOR03087 (parental)
MOR06187	Fab/IgG1	new H-CDR2	MOR06187	MOR03087 (parental)
MOR06188	Fab/IgG1	new H-CDR2	MOR06188	MOR03087 (parental)
MOR06189	Fab/IgG1	new H-CDR2	MOR06189	MOR03087 (parental)
MOR06190	Fab/IgG1	new H-CDR2	MOR06190	MOR03087 (parental)
MOR06192	Fab/IgG1	new H-CDR2	MOR06192	MOR03087 (parental)
MOR06195	Fab/IgG1	new H-CDR2	MOR06195	MOR03087 (parental)
MOR06197	Fab/IgG1	new H-CDR2	MOR06197	MOR03087 (parental)
MOR06200	Fab/IgG1	new H-CDR2	MOR06200	MOR03087 (parental)
MOR06201	Fab/IgG1	new H-CDR2	MOR06201	MOR03087 (parental)
MOR06204	Fab/IgG1	new H-CDR2	MOR06204	MOR03088 (parental)
MOR06214	Fab/IgG1	new H-CDR2	MOR06214	MOR03088 (parental)
MOR06278	Fab	new L-CDR3	MOR03088 (parental)	MOR06278
MOR06279	Fab	new L-CDR3	MOR03088 (parental)	MOR06279
MOR06347	IgG1	new L-CDR3	MOR03088 (parental)	MOR06278
MOR06348	IgG1	new L-CDR3 & H-CDR2	MOR06214	MOR06278

FIGURE 11: CD38-expression analysis of Lymphocytes and Erythrocytes

A: MOR 3087

B: MOR 3088

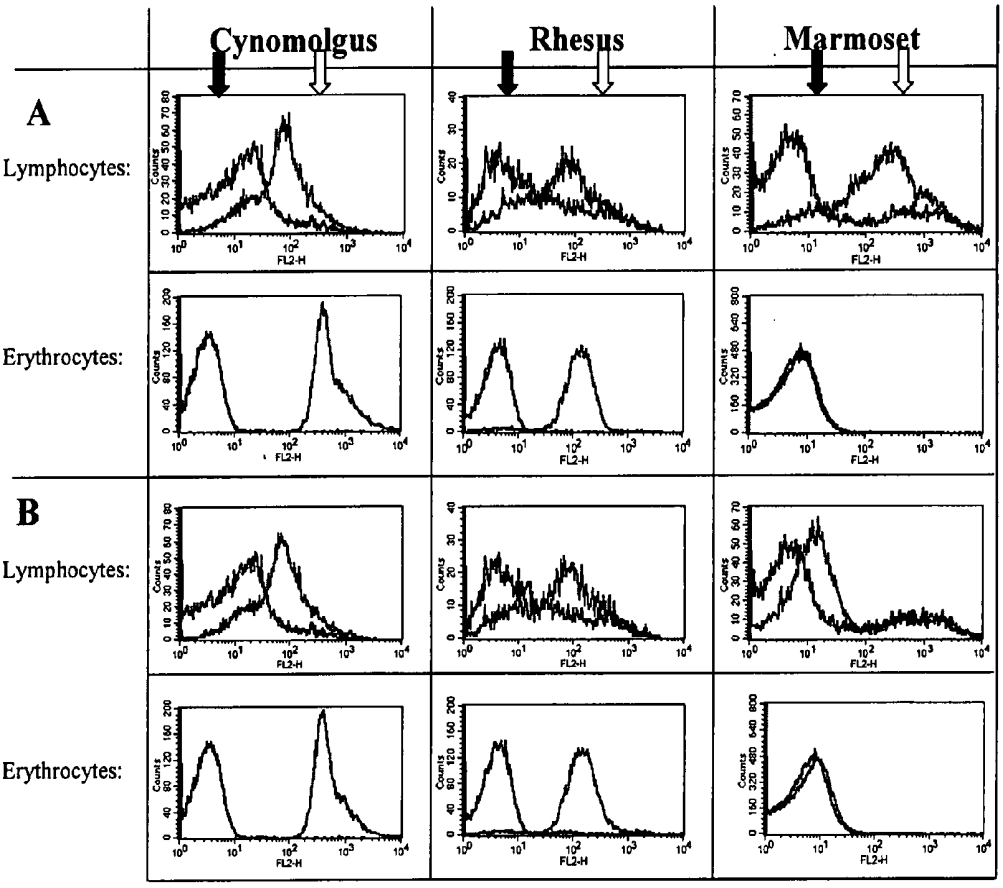


Figure 12: CD38 expression analysis of Lymphocytes and Erythrocytes

MOR 03087:

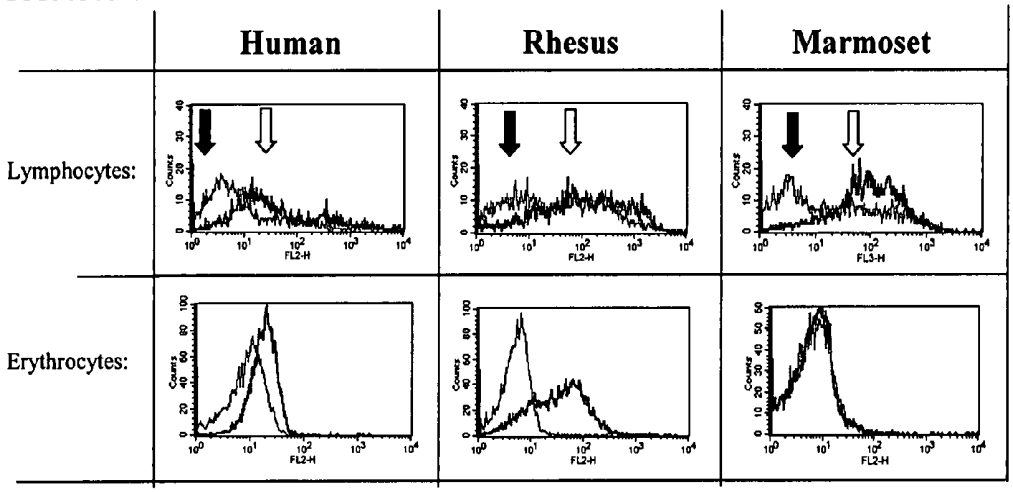
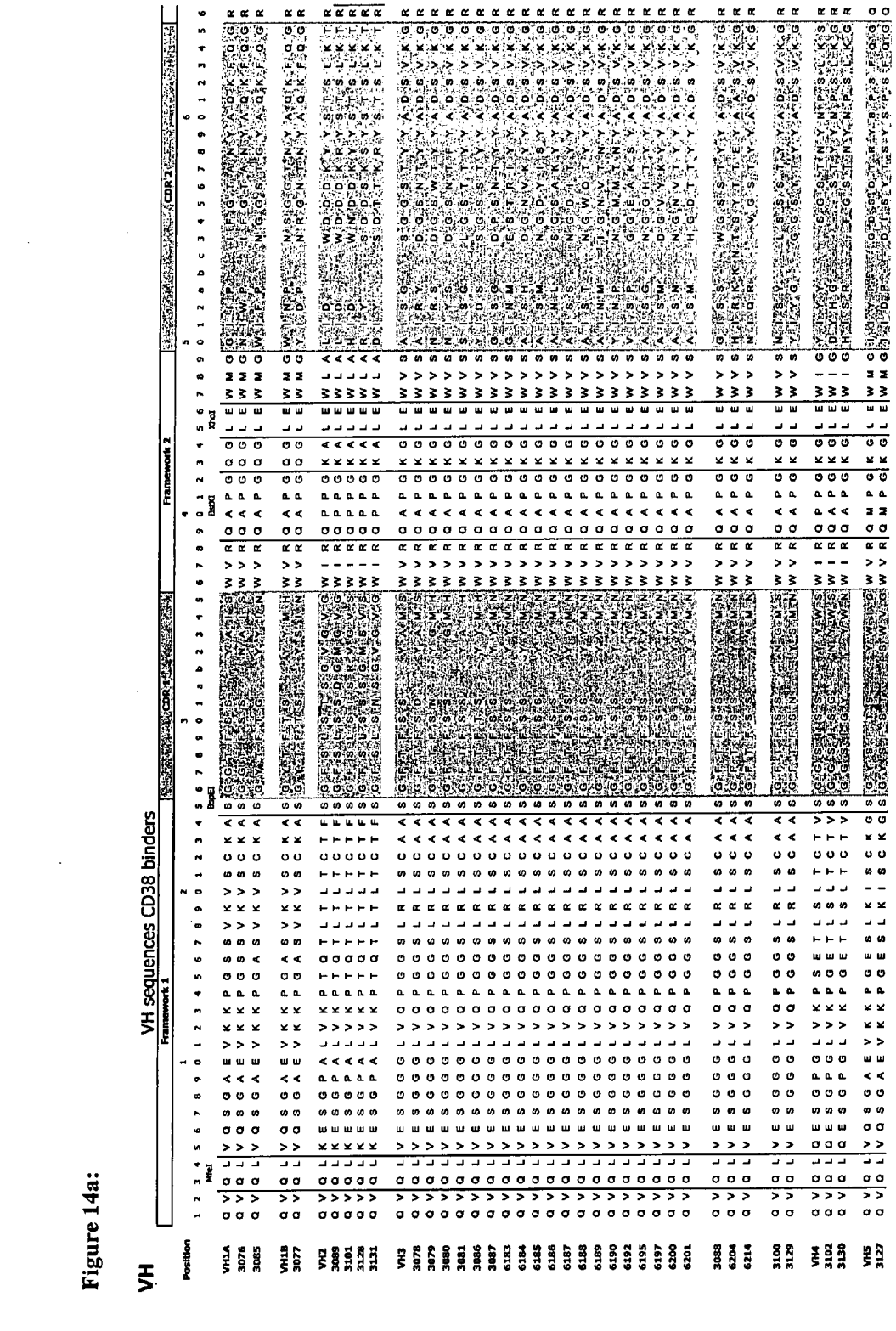


Figure 13: Overview Cross-Reactivity Anti-CD38 Antibodies

	Human		Rhesus		Cynomolgus		Marmoset	
Species/Tissue: / Anti-CD38 MAbs:	PBMCs	Erythr.	PBMCs	Erythr.	PBMCs	Erythr.	PBMCs	Erythr.
3076	+	n.d.	-	-	-	-	-	-
3077	+	-	-	-	-	-	-	-
3078	+	n.d.	-	-	-	-	-	-
3079	+	+	-	-	-	-	-	-
3080	+	+/-	+	-	+	-	-	-
3081	+	n.d.	-	-	-	-	-	-
3085	+	n.d.	-	-	-	-	-	-
3086	+	n.d.	-	-	-	-	-	-
3087	+	+/-	+	+	+	+	+	-
3088	+	-	+	+	+	+	+	-
3089	+	n.d.	-	-	-	-	-	-
3101	+	n.d.	-	-	-	-	-	-
3102	+	n.d.	-	-	-	-	-	-
3127	+	n.d.	-	-	-	-	-	-
3128	+	n.d.	-	-	-	-	-	-
3129	+	n.d.	-	-	-	-	-	-
3130	+	n.d.	-	-	-	-	-	-
3131	+	n.d.	-	-	-	-	-	-

+ : positive staining
+/-: weak positive staining
- : negative staining
n.d.: not determined

Figure 14a: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VH sequences CD38 binders
Framework 1
CDR1
Framework 2
CDR2
Position
VH1A
VH1B
VH2
VH3
VH4
VH5

Figure 14a to be continued :

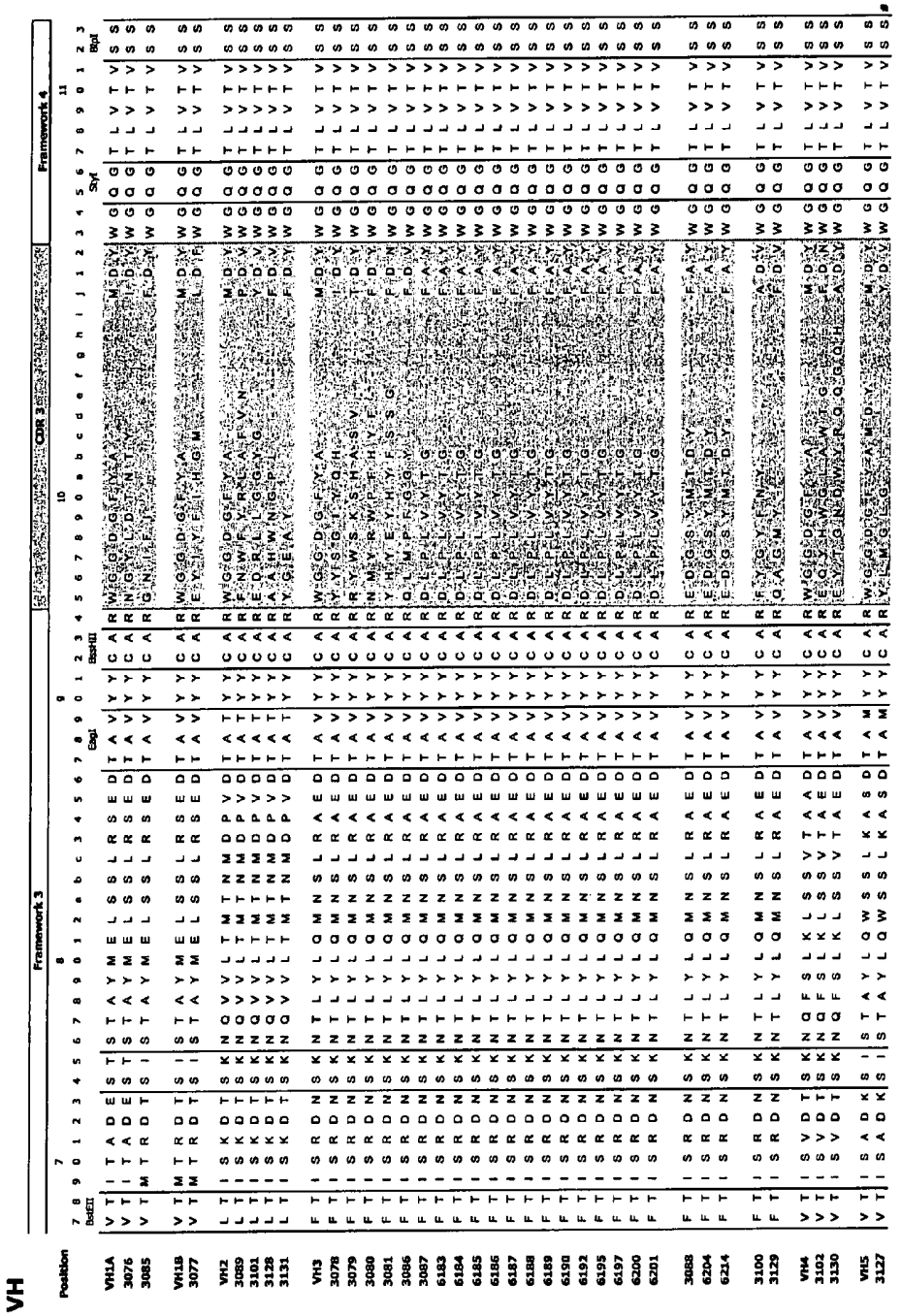
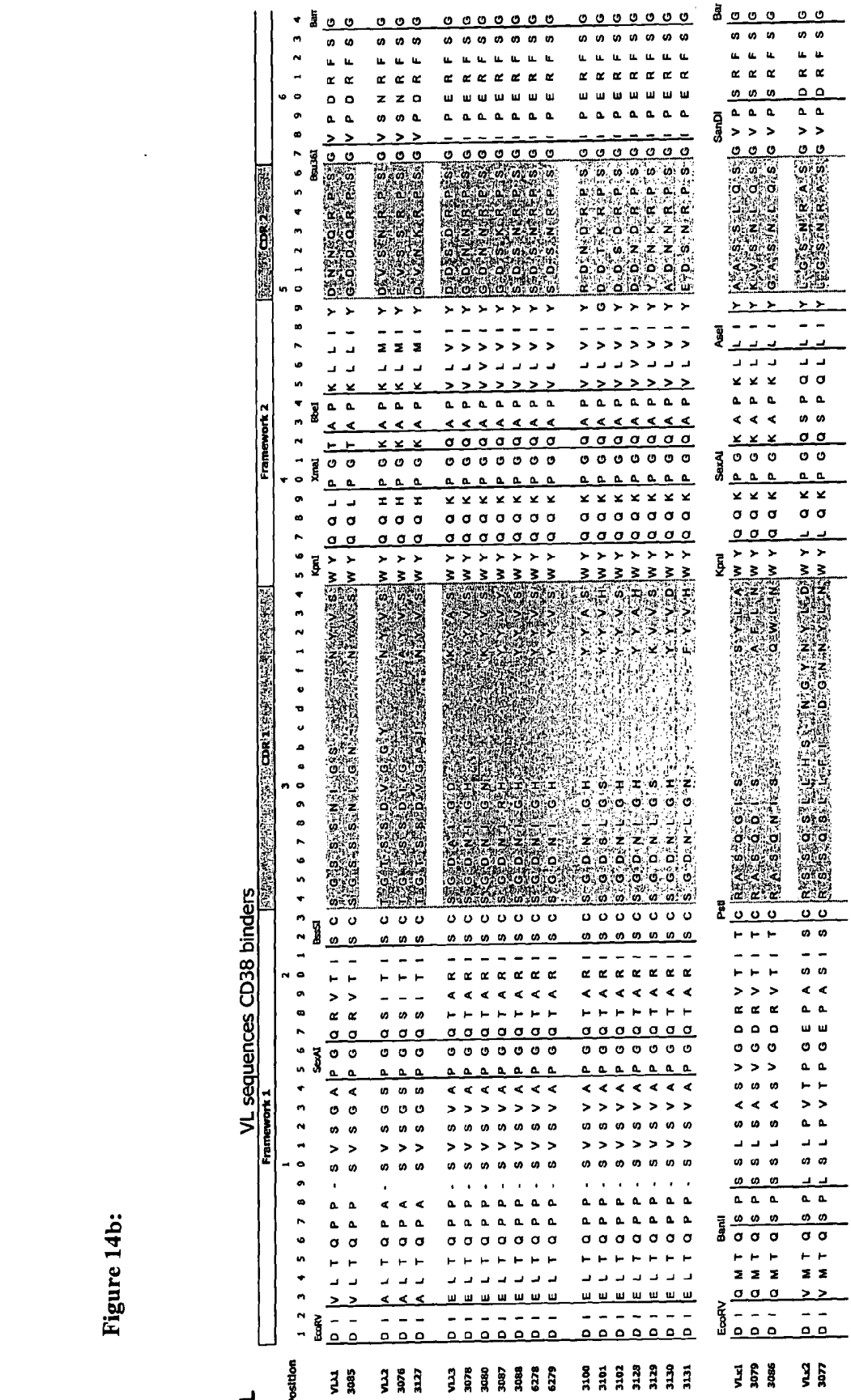


Figure 14b: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Framework 1
CDR 1
Framework 2
CDR 2
Position
VLk1
3085
VLk2
3076
3127
VL13
3078
3080
3087
3088
6278
6279
3100
3101
3102
3128
3129
3130
3131
VLk1
3079
3086
VLk2
3077

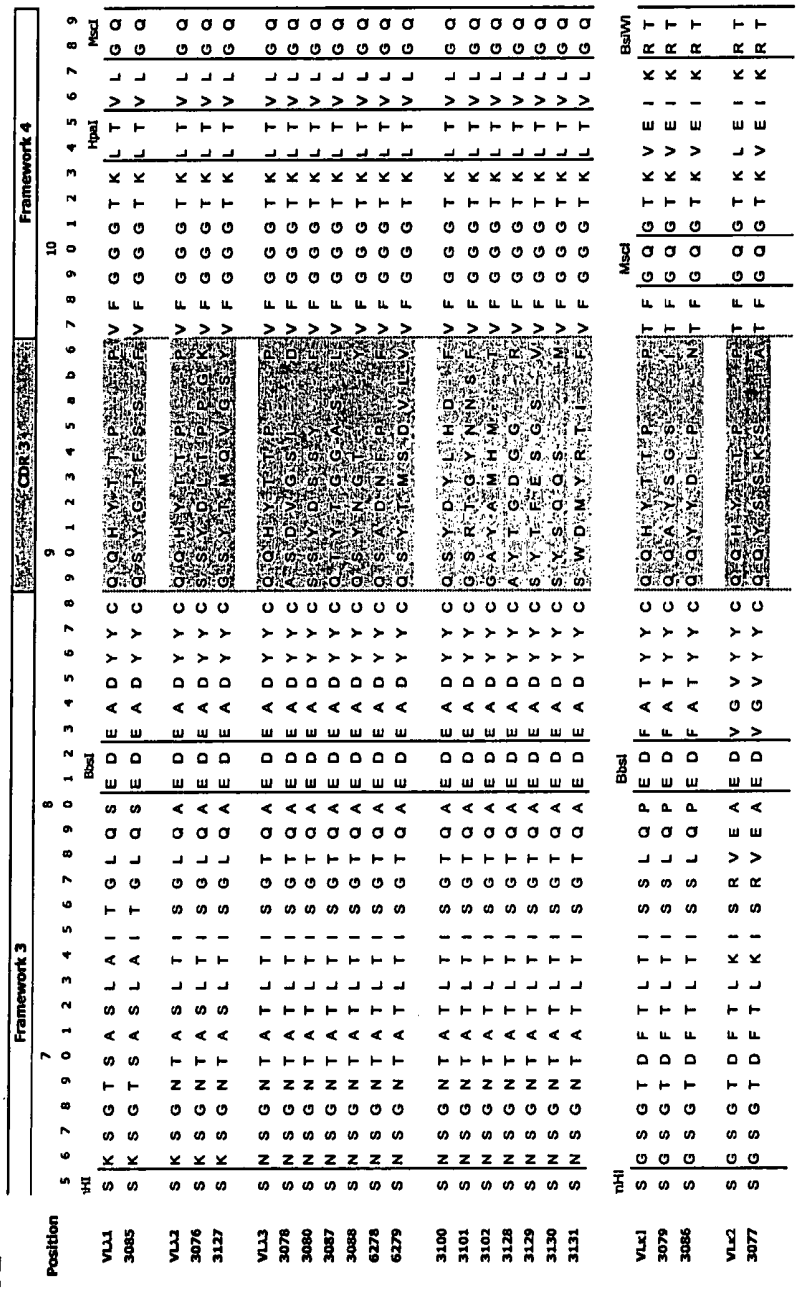

Figure 14b to be continued:

GENERATION AND PROFILING OF FULLY HUMAN GOLD-DERIVED THERAPEUTIC ANTIBODIES SPECIFIC FOR HUMAN CD38

SUMMARY OF THE INVENTION

[0001] The present invention relates to an isolated antigen-binding region that is specific for CD38, which comprises (i) an H-CDR3 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) an H-CDR3 region that has at least a sixty percent identity to an H-CDR3 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106

[0002] The present invention furthermore relates to an isolated antibody or functional fragment thereof that is specific for CD38, which comprises (i) a variable heavy chain depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) a variable heavy chain that has at least a sixty percent identity to a variable heavy chain depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

[0003] Additionally, the present invention relates to an isolated antigen-binding region that is specific for CD38, which comprises (i) an L-CDR3 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) an L-CDR3 region that has at least a sixty percent identity to an L-CDR3 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

[0004] Also, the present invention relates to an isolated antibody or functional fragment thereof, which comprises (i) a variable light chain depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) a variable light chain that has at least a sixty percent identity to a variable light chain depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

[0005] The present invention further relates to a variable heavy chain of an isolated antigen-binding region that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91, wherein said antigen-binding region is specific for CD38.

[0006] The present invention also relates to a variable light chain of an isolated antigen-binding region that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108, wherein said antibody or functional fragment thereof is specific for CD38.

[0007] Further, the present invention relates to an isolated nucleic acid sequence that encodes an antigen-binding region of a human antibody or functional fragment thereof that is specific for CD38.

[0008] Additionally, the invention relates to a nucleic acid sequence encoding a variable heavy chain of an isolated antigen-binding region, which comprises (i) a sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 and 91 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91, wherein said antigen-binding region is specific for CD38.

[0009] The present invention also relates to a nucleic acid sequence encoding a variable light chain of an isolated antigen-binding region, which comprises (i) a sequence selected from the group consisting of SEQ ID NOS: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 and 108 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 wherein said antigen-binding region is specific for CD38.

[0010] The present invention further relates to a method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody comprises (i) a nucleic acid sequence encoding a heavy chain depicted in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91, wherein said antibody or a functional fragment thereof is specific for CD38.

[0011] Additionally, the present invention relates to A method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody comprises (i) a nucleic acid sequence encoding a light chain depicted in SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108, wherein said antibody or a functional fragment thereof is specific for CD38.

[0012] Also, the present invention relates to a method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody or said functional fragment thereof comprises (i) a heavy chain amino acid sequence depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) a variable heavy chain that has at least a sixty percent identity to a variable heavy chain depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

[0013] Also, the present invention relates to a method of inducing specific killing of tumor cells that express CD38,

wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody comprises (i) and/or a light chain amino acid sequence depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) a variable light chain that has at least a sixty percent identity to a variable light chain depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

[0014] Furthermore, the present invention relates to a method of detecting specific killing of tumor cells that express CD38, by CD38 cross-linking, comprising the steps of:

[0015] (i) administering to a subject in need thereof an effective amount of a human or humanized anti-CD38 antibody or a functional fragment thereof, and

[0016] (ii) detecting the specific killing activity of said human or humanized anti-CD38 antibody or said functional fragment thereof.

[0017] Also, the present invention relates to a method of detecting the presence of CD38 in a tissue or a cell of minipig origin, comprising the steps of:

[0018] (i) allowing a human or humanized anti-CD38 antibody or a functional fragment thereof to come into contact with said CD38, and

[0019] (ii) detecting the specific binding of said human or humanized anti-CD38 antibody or functional fragment thereof to said CD38 minipig cells, wherein said antibody or functional fragment thereof is also able to specifically bind to CD38 of human origin.

[0020] Furthermore, the present invention relates to A method of detecting CD38 in a CD38-expressing erythrocyte, comprising the steps of:

[0021] (i) allowing a human or humanized anti-CD38 antibody or a functional fragment thereof to come into contact with said CD38-expressing erythrocyte, and

[0022] (ii) detecting the specific binding of said human or humanized anti-CD38 antibody or functional fragment thereof to said CD38-expressing erythrocytes, wherein said antibody or functional fragment thereof is also able to specifically bind to human CD38 from a cell or tissue other than human erythrocytes.

[0023] The present invention also relates to an isolated antibody or functional fragment thereof according to the present invention, which comprises (i) an H-CDR3 region depicted in SEQ ID NO: 21 or 22 or (ii) an H-CDR3 region at least a sixty percent identity thereto, and that is specific for human CD38 and marmoset CD38.

BRIEF DESCRIPTION OF THE FIGURES

[0024] FIG. **1***a* provides nucleic acid sequences of various antibody variable heavy regions for use in the present invention.

[0025] FIG. **1***b* provides amino acid sequences of various antibody variable heavy regions for use in the present invention. CDR regions HCDR1, HCDR2 and HCDR3 are designated from N- to C-terminus in boldface.

[0026] FIG. **2***a* provides nucleic acid sequences of various antibody variable light regions for use in the present invention.

[0027] FIG. **2***b* provides amino acid sequences of various antibody variable light regions for use in the present invention. CDR regions LCDR1, LCDR2 and LCDR3 are designated from N- to C-terminus in boldface.

[0028] FIG. **3** provides amino acid sequences of variable heavy regions of various consensus-based HuCAL antibody master gene sequences. CDR regions HCDR1, HCDR2 and HCDR3 are designated from N- to C-terminus in boldface.

[0029] 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.

[0030] FIG. **5** provides the amino acid sequence of CD38 (SWISS-PROT primary accession number P28907).

[0031] FIG. **6** provides the nucleotide sequences of the heavy and light chains of chimeric OKT10.

[0032] FIG. **7** provides the DNA sequence of pMORPH®_h_IgG1_1 (bp 601-2100) (SEQ ID NO: 74): The vector is based on the pcDNA3.1+ vectors (Invitrogen). 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.

[0033] FIG. **8** provides the DNA sequence of Ig kappa light chain expression vector pMORPH®_h_Igκ_1 (bp 601-1400) (SEQ ID NO: 75): The vector is based on the pcDNA3.1+ vectors (Invitrogen). The amino acid sequences 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.

[0034] FIG. **9** provides the DNA sequence of HuCAL Ig lambda light chain vector pMORPH®_h_Igλ_1 (bp 601-1400) (SEQ ID NO: 76): 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.

[0035] FIG. **10** provides different combinations of heavy and light chains in the Fab/IgG format for use in the present invention

[0036] FIG. **11** provides CD38-expression analysis of Lymphocytes and Erythrocytes obtained by FACS. PBMCs and Erythrocytes were isolated from whole blood of cynomolgus, rhesus and marmoset by density gradient centrifugation followed by FACS-analysis using anti-CD38 Fab antibodies MOR03087 (A, right histograms, light arrow) and MOR03088 (B, right histograms; light arrow). An irrelevant Fab-antibody (A & B, left histograms; black arrow) was used as a negative control.

[0037] FIG. **12** provides CD38 expression analysis of Lymphocytes and Erythrocytes obtained by FACS. PBMCs and Erythrocytes were isolated from whole blood of human, cynomolgus and marmoset by density gradient centrifugation followed by FACS-analysis using anti-CD38 IgG1 MOR03087 (right histograms; white arrow). An irrelevant IgG1 control antibody (A & B, left histograms; black arrow) was used as a negative control.

[0038] FIG. **13** provides a comparative overview of Cross-Reactivity of different anti-CD38 antibodies.

[0039] FIGS. **14**(*a*) and **14**(*b*) delineate the CDR and FR regions for certain antibodies for use in the invention and

compare amino acids at a given position to each other and to corresponding consensus sequences.

DETAILED DESCRIPTION OF THE INVENTION

[0040] The present invention is based on the discovery of novel antibodies and methods of using antibodies that are specific to or have a high affinity for CD38 and can deliver a therapeutic benefit to a subject. The antibodies, which may be human or humanized, can be used in many contexts, which are more fully described herein. Suitable antibodies for use in the present invention are disclosed in U.S. 60/614,471, which hereby is incorporated by reference.

[0041] 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).

[0042] 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.

[0043] 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, FACS, IHC 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 hydrogen peroxide). 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. It is possible for an antibody to be "specific to" or "specific for" an antigen of 2 or more cells/tissues and/or 2 or more species, provided that the antibody meets binding criteria for each of such cells/tissues and species, for example. Accordingly, an antibody may bind specifically to the target antigen CD38 on various cell types and/or tissues, e.g. erythrocytes, lymphocytes isolated from peripheral blood, spleen or lymph-nodes. In addition, an antibody may be specific to both CD38 of one species and CD38 of another species.

[0044] "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.

[0045] 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 C_{H1} and C_L domains.

[0046] The term "parental binder" as used in connection with the present invention denotes any binder which has not undergone the process of optimization. A process of optimization is described elsewhere in the present specification.

[0047] The term "binder" as used in connection with the present invention may be used in a synonymous manner as the term "immunoglobulin" or "antibody".

[0048] An antibody for use in 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. Pat. No. 6,300,064 issued to Knappik et al., which hereby are incorporated by reference in their entirety.

[0049] Antibodies for Use in the Invention

[0050] Throughout this document, reference is made to the following representative antibodies for use in the invention: "antibody nos." or "LACS" or "MOR" 3076 or 03076, 3078 or 03078, 3081 or 03081, 3085 or 03085, 3086 or 03086, 3087 or 03087, 3088 or 03088, 3089 or 03089, 3101 or 03101, 3102 or 03102, 3127 or 03127, 3128 or 03128, 3129 or 03129, 3130 or 03130, 3131 or 03131, 6183 or 06183, 6184 or 06184, 6185 or 06185, 6186 or 06186, 6187 or 06187, 6188 or 06188, 6189 or 06189, 6190 or 06190, 6192 or 06192, 6195 or 06195, 6197 or 06197, 6200 or 06200, 6201 or 06201, 6204 or 06204, 6214 or 06214, 6278 or 06278, 6279 or 06279. LAC 3076 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 1 (DNA)/SEQ ID NO: 16 (protein) and a variable light region corresponding to SEQ ID NO: 31 (DNA)/SEQ ID NO: 46 (protein). LAC 3078 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 2 (DNA)/SEQ ID NO: 17 (protein) and a variable light region corresponding to SEQ ID NO: 32 (DNA)/SEQ ID NO: 47 (protein). LAC 3081 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 3 (DNA)/SEQ ID NO: 18 (protein) and a variable light region corresponding to SEQ ID NO: 33 (DNA)/SEQ ID NO: 48 (protein). LAC 3085 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 4 (DNA)/SEQ ID NO: 19 (protein) and a variable light region corresponding to SEQ ID NO: 34 (DNA)/SEQ ID NO: 49 (protein). LAC 3086 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 5 (DNA)/SEQ ID NO: 20 (protein) and a variable light region corresponding to SEQ ID NO: 35 (DNA)/SEQ ID NO: 50 (protein). LAC 3087 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 6 (DNA)/SEQ ID NO: 21 (protein) and a variable light region corresponding to SEQ ID NO: 36 (DNA)/SEQ ID NO: 51 (protein). LAC 3088 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 7 (DNA)/SEQ ID NO: 22 (protein) and a variable light region corresponding to SEQ ID NO: 37 (DNA)/SEQ ID NO: 52 (protein). LAC 3089 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 8 (DNA)/SEQ ID NO: 23 (protein) and a variable light region corresponding to SEQ ID NO: 38 (DNA)/SEQ ID NO: 53 (protein). LAC 3101 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 9 (DNA)/SEQ ID NO: 24 (protein) and a variable light region corresponding to SEQ ID NO: 39 (DNA)/SEQ ID NO: 54 (protein). LAC 3102 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 10 (DNA)/SEQ ID NO: 25 (protein) and a variable light region corresponding to SEQ ID NO: 40 (DNA)/SEQ ID NO: 55 (protein). LAC 3127 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 11 (DNA)/SEQ ID NO: 26 (protein) and a variable light region corresponding to SEQ ID NO: 41 (DNA)/SEQ ID NO: 56 (protein). LAC 3128 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 12 (DNA)/SEQ ID NO: 27 (protein) and a variable light region corresponding to SEQ ID NO: 42 (DNA)/SEQ ID NO: 57 (protein). LAC 3129 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 13 (DNA)/SEQ ID NO: 28 (protein) and a variable light region corresponding to SEQ ID NO: 43 (DNA)/SEQ ID NO: 58 (protein). LAC 3130 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 14 (DNA)/SEQ ID NO: 29 (protein) and a variable light region corresponding to SEQ ID NO: 44 (DNA)/SEQ ID NO: 59 (protein). LAC 3131 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 15 (DNA)/SEQ ID NO: (protein) and a variable light region corresponding to SEQ ID NO: 45 (DNA)/SEQ ID NO: 60 (protein). Furthermore, optimized clones, which were derived from the parental binders MOR03087 and MOR03088, comprise the following: MOR06183 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 77 (DNA)/SEQ ID NO: 92 (protein). MOR06184 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 78 (DNA)/SEQ ID NO: 93 (protein). MOR06185 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 79 (DNA)/SEQ ID NO: 94 (protein). MOR06186 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 80 (DNA)/SEQ ID NO: 95 (protein). MOR06187 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 81 (DNA)/SEQ ID NO: 96 (protein). MOR06188 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 82 (DNA)/SEQ ID NO: 97. MOR06189 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 83 (DNA)/SEQ ID NO:98 (protein). MOR06190 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 84 (DNA)/SEQ ID NO: 99 (protein). MOR06192 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 85 (DNA)/SEQ ID NO: 100 (protein). MOR06195 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 86 (DNA)/SEQ ID NO: 101 (protein). MOR06197 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 87 (DNA)/SEQ ID NO: 102 (protein). MOR06200 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 88 (DNA)/SEQ ID NO: 103 (protein). MOR06201 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 89 (DNA)/SEQ ID NO: 104 (protein). MOR 06204 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 90 (DNA)/SEQ ID NO: 105 (protein). MOR06214 represents an antibody having a variable heavy region corresponding to SEQ ID NO: 91 (DNA)/SEQ ID NO: 106 (protein). MOR06278 represents an antibody having a variable light region corresponding to SEQ ID NO: 107 (DNA)/SEQ ID NO: 109 (protein). MOR 06279 represents an antibody having a variable light region corresponding to SEQ ID NO: 108 (DNA)/SEQ ID NO: 110 (protein).

[0051] Antibodies of the invention were characterized in Fab and/or IgG format and comprise various combinations of the light and heavy chains of optimized and parental binders. FIG. **10** shows several non-limiting combinations which can be used in connection with the present invention.

[0052] In one aspect, the invention provides methods for using 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: 71. 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 antibody or antigen-binding region for use in the present invention preferably can bind to CD38 with an affinity of about less than 600 nM. Preferably, the antibody or antigen-binding region for use in the present invention 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 uses of 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 for use in the invention against CD38 may be about 10.0 nM or 2.4 nM (monovalent affinity of Fab fragment).

[0053] Table 1 provides a summary of affinities of representative antibodies, 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]
MOR03076	440/596	n.d.
MOR03078	n.d.	n.d.
MOR03081	416/450	2.5
MOR03085	122	10
MOR03086	30	n.d.
MOR03087	17/38	5
MOR03088	95	n.d.
MOR03089	340	n.d.
MOR03101	314	n.d.
MOR03102	64	5
MOR03127	168 (54)[c]	n.d.
MOR03128	117/84[d]	n.d.
MOR03129	43	n.d.
MOR03130	n.d.	n.d.
MOR03131	451	n.d.
Chimeric OKT10	n.d.	8.28

[a]Fab format; analysis on human CD38 Fc-fusion aa 45-300
[b]IgG1 format; analysis with Raji cells
[c]standard deviation (n = 3)
[d]standard deviation (n = 4)

[0054] With reference to Table 1, the affinity of LACs was measured by surface plasmon resonance (Biacore) on human CD38 Fc-fusion and by a flow cytometry procedure utilizing the CD38-expressing human Raji cell line. The Biacore studies were performed on directly immobilized antigen (CD38-Fc fusion protein). The Fab format of LACs exhibit an monovalent affinity range between about 30 and 596 nM on immobilized CD38-Fc fusion protein.

[0055] 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.

[0056] Another preferred feature of preferred antibodies for use in the invention is their specificity for an area within the N-terminal region of CD38. For example, LACs of the invention can bind specifically to the N-terminal region of CD38.

[0057] Optimized antibodies of the present invention were further characterized as shown in Tables 2 and 3. Summaries are provided of affinities as determined by surface plasmon resonance (Biacore) and FACS Scatchard analysis. Additionally, FACS-binding to human erythrocytes and ELISA binding studies to CD38 Fc-Fusion protein have also been determined. The characterizations show that several optimized binders show a reduced binding to human erythrocytes and a higher ELISA signal as compared to the parental clone. In addition derivatives of MOR03088 have an improved affinity as shown by FACS Scatchards and affinity determinations.

TABLE 2

		Overview characterizations of affinity-matured clones:						
		Affinities		Scatchards [EC_{50}s]		FACS anal. FACS-Binding to human	Efficacy ELISA	
MOR#	Optimization	KDs (Biacore)[a] [nM]	KDs (Bioveris)[a] [pM]	RPMI8226[a] [nM]	OPM2[b] [nM]	Erythrocytes[b] (Compared to MOR03087)	ADCC[b,c]	CD38 Fc-Fusion protein[b] (% Reactivity of MOR03087)
03087	Parental	5.68	48.77	5.37	17.4*/5.7	=MOR03087	+	100
6183	H-CDR2	13.47	25.98	28.06	8.91	<MOR03087	+	106
6184	H-CDR2	9.68	66.22	4.01	10.58	~MOR03087	n.d.	150
6185	H-CDR2	4.39	13.69	7.30	11.50	<MOR03087	+	142
6186	H-CDR2	4.62	5.09	6.47	15.57	<MOR03087	n.d.	117
6187	H-CDR2	12.46	45.38	16.85	9.37	~MOR03087	n.d.	145
6188	H-CDR2	3.96	59.32	22.71	20.15	<MOR03087	n.d.	140
6189	H-CDR2	4.95	24.69	9.41	n.e.	~MOR03087	n.d.	126
6190	H-CDR2	15.65	48.85	11.66	n.e.	<MOR03087	n.d.	125
6192	H-CDR2	5.01	74.73	7.07	n.e.	~MOR03087	n.d.	111
6195	H-CDR2	4.52	55.73	5.60	n.e.	~MOR03087	n.d.	155
6197	H-CDR2	4.81	12.74	6.92	n.e.	<MOR03087	n.d.	138
6200	H-CDR2	7.92	59.91	5.02	7.15	>MOR03087	n.d.	144
6201	H-CDR2	6.81	18.59	9.00	n.e.	~MOR03087	n.d.	137
03088	Parental	41.40	2149.92	24.6*	15.3*	no binding	+	18
6204	H-CDR2	22.72	58.51	6.36	n.e.	<MOR03087	n.d.	56
6214	H-CDR2	5.26	93.65	5.32	n.e.	<MOR03087	n.d.	109
6347	L-CDR3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
6348	L-CDR3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

[a]Fab-format
[b]IgG-format
[c]Human Effector cells & RPMI8226 Target cells (E:T ratio = 30:1)
+: Killing of RPMI8226 cells in ADCC
n.d.: not determined
*different experiment

TABLE 3

EC_{50} in FACS-Scatchard, ADCC and CDC

	Characterizations				
	FACS-Scatchard				CDC
Anti-CD38 MAbs:	RPMI8226 EC_{50} [nM][a]	CCRF-CEM EC_{50} [nM][a]	OPM2 EC_{50} [nM][b]	ADCC RPMI8226 EC_{50} [nM][b]	CHO EC_{50} [nM][a]
MOR03087	6.3	14.7	17.54	0.14	3.4
MOR03088	24.6	25.5	2.6	n.e.	n.e.
MOR03080	1.8	2.6	1.9	0.13	1.9

[a]single measurement
[b]mean from 2 measurements

[0058] The type of epitope to which an antibody for use in 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. LACS may recognize discontinuous or linear epitopes in the N-terminal region of CD38. 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).

[0059] An antibody for use in the invention preferably is species cross-reactive with humans and at least one other non-human species. The non-human species can be non-human primate, e.g. rhesus, baboon and/or cynomolgus. Other non-human species can be minipig, rabbit, mouse, rat and/or hamster. An antibody that is cross reactive with at least one other species beside human 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. An antibody that is cross reactive with minipig and/or rabbit, for example, can be a candidate for toxicology and safety studies.

[0060] Preferably, an antibody for use in 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 for use in 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).

[0061] 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.

[0062] 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

[0063] Antibodies for use in the invention are not limited to the specific peptide sequences provided herein. Rather, the invention also embodies the use of 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 for use in 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 for use in the invention.

[0064] 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.

[0065] 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.

[0066] FIGS. **14** *a* (VH) and **14** *b* (VL) delineate the CDR and FR regions for certain antibodies for use in 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).

[0067] The skilled worker will be able to design peptide variants, the use of which is 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. 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.

[0068] 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 (Virnekas, 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

[0069] 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.

[0070] 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 α-helices. Similarly, certain amino acids, such as alanine, cysteine, leucine, methionine, glutamic acid, glutamine, histidine and lysine are more commonly found in α-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.

[0071] 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%. Preferred polypeptide sequences of the invention have a sequence identity in the variable 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 variable regions of at least 80%, more preferably 90% and most preferably 95%.

DNA Molecules of the Invention

[0072] The present invention also relates to uses of DNA molecules that encode an antibody for use in the invention. These sequences include, but are not limited to, those DNA molecules set forth in FIGS. **1***a* and **2***a*.

[0073] 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).

[0074] 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):

[0075] a. $T_m=69.3+0.41(G+C)\%$

[0076] b. The T_m of a duplex DNA decreases by 1° C. with every increase of 1% in the number of mismatched base pairs.

[0077] c. $(T_m)_{\mu 2}-(T_m)_{\mu 1}=18.5 \log_{10} \mu 2/\mu 1$

[0078] where μ1 and μ2 are the ionic strengths of two solutions.

[0079] 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.

[0080] 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.

[0081] 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 O.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.

[0082] Accordingly, the present invention includes the use of nucleic acid molecules that hybridize to the molecules of set forth in FIGS. **1***a* and **2***a* under high stringency binding and washing conditions, where such nucleic molecules encode an antibody or functional fragment thereof for uses 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.

Functionally Equivalent Variants

[0083] Yet another class of DNA variants the use of which is 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 FIGS. **1***b* and **2***b* due to the degeneracy of the genetic code.

[0084] 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.

[0085] 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

[0086] The present invention further provides for the use of recombinant DNA constructs comprising one or more of the nucleotide sequences of the present invention. The recombinant constructs are used in connection with a vector, such as a plasmid or viral vector, into which a DNA molecule encoding an antibody for use in the invention is inserted.

[0087] 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.

[0088] The present invention further provides for uses of host cells containing at least one of the DNAs disclosed herein. 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

[0089] 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.*

[0090] 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.

[0091] 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

[0092] 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).

[0093] An antibody for use in 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.

[0094] Disorders and conditions particularly suitable for treatment with an antibody 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 also might be used to treat inflammatory disease such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).

[0095] 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 for use in 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 for use in 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.

[0096] 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

[0097] CD38 is highly expressed on hematological cells in certain malignancies; thus, an anti-CD38 antibody for use in 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)). Preferred antibodies or antigen-binding regions of the invention for use as a diagnostic compound comprise a variable heavy chain sequence selected from the group consisting of SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 and 106 and/or a variable light chain sequence selected from the group consisting of SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 and 110.

[0098] 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

[0099] The antibodies for use in the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, wherein an antibody for use in 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 for use in the present invention, together with a suitable amount of carrier vehicle. Preferred antibodies or antigen-binding regions of the invention for use as a diagnostic compound comprise a variable heavy chain sequence selected from the group consisting of SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 and 106 and/or a variable light chain sequence selected from the group consisting of SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 and 110.

[0100] 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).

[0101] 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.

[0102] 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.

[0103] 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

[0104] 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-K1 (ATCC, CRL-61), Raji (ATCC, CCL-86), and OPM2 (DSMZ, ACC50).

Cells and Culture-Conditions

[0105] 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, #P04-16500) supplemented with 10% FCS (PAN biotech GmbH, #P30-3302), 50 U/ml penicillin, 50 µg/ml 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, #P04-43100) had to be added.

[0106] CHO-K1 and HEK293 were grown in DMEM (Gibco, #10938-025) supplemented with 2 mM glutamine and 10% FCS. Stable CD38 CHO-K1 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

[0107] All blood samples were taken after informed consent. Peripheral blood mononuclear cells (PBMC) were isolated by Histopaque®-1077 (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")

[0108] All stainings were performed in round bottom 96-well culture plates (Nalge Nunc) with 2×10^5 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.).

[0109] For FACS based Scatchard analyses RPMI8226 cells were stained with at 12 different dilutions ($1:2^n$) starting at 12.5 µg/ml (IgG) final concentration. At least two independent measurements were used for each concentration and K_D values extrapolated from median fluorescence intensities according to Chamow et al. (1994).

Surface Plasmon Resonance

[0110] 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 CM5 sensor 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

Antibody Generation from HuCAL Libraries

[0111] 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 (Löhning, 2001).

A. Phagemid Rescue, Phage Amplification and Purification

[0112] 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®

[0113] For the selections HuCAL GOLD® antibody-phages were divided into three pools corresponding to different VH master genes (pool 1: VH1/5λκ, pool 2: VH3λκ, pool 3: VH2/4/6λκ). These pools were individually subjected to 3 rounds of whole cell panning on CD38-expressing CHO-K1 cells followed by pH-elution and a post-adsorption step on CD38-negative CHO-K1-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.

[0114] The Fab encoding inserts of the selected HuCAL GOLD® phages were subcloned into the expression vector pMORPH®x9_Fab_FS (Rauchenberger et al., 2003) to facilitate rapid expression of soluble Fab. The DNA of the selected clones was digested with XbaI and EcoRI thereby cutting out the Fab encoding insert (ompA-VLCL and phoA-Fd), and cloned into the XbaI/EcoRI cut vector pMORPH®x9_Fab_FS. Fab expressed in this vector carry two C-terminal tags (FLAG™ and Strep-tag® II) for detection and purification.

Example 2

Biological Assays

[0115] 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:

[0116] For ADCC measurements, target cells (T) were adjusted to 2.0E+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 1.0E+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% CO_2 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.

[0117] 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:

[0118] For CDC measurements, 5.0E+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.

[0119] 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)

[0120] 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 Fc-Fusion Proteins

[0121] In order to generate CD38 protein for panning and screening two different expression systems had to be estab-

lished. 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.

[0122] 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: 123)
MTE002rev	TCA GAT CTC AGA TGT GCA AGA TGA ATC (SEQ ID NO: 124)
MTE004	TT GGT ACC AGG TGG CGC CAG CAG TG (SEQ ID NO: 125)
MTE006	TT GGT ACC ATG GCC AAC TGC GAG (SEQ ID NO: 126)
MTE007rev	CCG ATA **TCA*** GAT CTC AGA TGT GCA AGA TG (SEQ ID NO: 127)
MTE009rev	CCG ATA TC GAT CTC AGA TGT GCA AGA TG (SEQ ID NO: 128)

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

Example 4

Cloning, Expression and Purification of HuCAL® IgG1

[0123] 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 pMORPH®_hIg vectors (see FIGS. **7** to **9**). 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®hIgκ1 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.

[0124] 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

Generation and Production of Chimeric OKT10 (chOKT10; SEQ ID NOS: 72 and 73)

[0125] 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: 72) and light chain (SEQ ID NO: 73) 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

Cross Reactivity Analysis by FACS (MOR 03087 and MOR 03088)

1. Materials and Methods:

[0126] FIGS. **11** and **12** show FACS analyses of lymphocytes and erythrocytes: EDTA-treated blood samples were obtained from healthy humans (after obtaining informed consent) and from non human primates (Rhesus, Cynomolgus and Marmoset) and were subjected to density gradient centrifugation using the Histopaque cell separation system according to the instructions of the supplier (Sigma). For FACS-analysis, cells from the interphase (PBMC-fraction) and pellet (Erythrocyte-fraction) were incubated with anti-CD38 HuCAL® antibodies in different formats

[0127] An overview of cross reactivity profiles of different anti CD38 antibodies is shown in FIG. **13**

2. Summary and Conclusion:

[0128] The results show that among all CD38 antibodies only MOR03087 and MOR03088 showed cross-reactivity to marmoset PBMCs. Surprisingly, CD38-expression on marmoset erythrocytes is almost not detectable as compared to the strong expression on cynomolgus and rhesus erythrocytes. Thus, the CD38 expression on marmoset erythrocytes and PBMCs is more reflecting the human situation, where CD38 expression is low on erythrocytes and moderate to high on PBMCs. Marmoset is therefore considered to be suited as a model to study toxicity of molecules binding to CD38.

[0129] Based on the above study, it was decided to further optimize the binders MOR 03087 and MOR 03088, as described elsewhere in the specification, see e.g. paragraph relating to "Antibodies for use in the invention". A person skilled in the art would expect that also the derivative antibodies of the parentals would show a comparable cross reactivity profile.

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agctgcgcgg cctccggatt tacctttact tcttattata tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagctat atcgattctt ctggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcagctt 300

atgccttttg gtggttattt tgatgtttgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 6
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

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agctgcgcgg cctccggatt tacctttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcggt atctctggtg atcctagcaa tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 7
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttct tcttatgcta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcggt atctcttctt ggggtagctc tacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgaggat 300

ggttcttata tgactgatta ttttgcttat tggggccaag gcaccctggt gacggttagc 360

tca 363

<210> SEQ ID NO 8
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct tctgatggta tgggtgtggg ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcttatcg attgggatga tgataagcgt 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtttt 300

aattggtttt atcgtcttgc ttttgttaat cctgatgttt ggggccaagg caccctggtg 360

acggttagct ca 372

<210> SEQ ID NO 9
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct acttctcgtg ttggtgtgtc ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcatatcg attggaatga tgataagtat 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtgag 300

gatcgtcttc ttggtggtta tggttatgat gtttggggcc aaggcaccct ggtgacggtt 360

agctca 366

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<210> SEQ ID NO 10
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

caggtgcaat tgcaagaaag tggtccgggc ctggtgaaac cgggcgaaac cctgagcctg 60

acctgcaccg tttccggagg cagcatttct ggtaattatt ggtcttggat tcgccaggcc 120

cctgggaagg gtctcgagtg gattggcgat tatcatggct ctacctatta taatccgagc 180

ctgaaaggcc gggtgaccat tagcgttgat acttcgaaaa accagtttag cctgaaactg 240

agcagcgtga cggcggaaga tacggccgtg tattattgcg cgcgtgagca gtatcattgg 300

ggtcttgctt ggactggttt tgataattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 11
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

caggtgcaat tggttcagag cggcgcggaa gtgaaaaaac cgggcgaaag cctgaaaatt 60

agctgcaaag gttccggata ttccttttct acttcttggg ttggttgggt gcgccagatg 120

cctgggaagg gtctcgagtg gatgggcatt atcgatccgg atattagcta tacctcttat 180

tctccgagct ttcagggcca ggtgaccatt agcgcggata aaagcattag caccgcgtat 240

cttcaatgga gcagcctgaa agcgagcgat acggccatgt attattgcgc gcgttatctt 300

atgggtcttg gttatgatgt ttggggccaa ggcaccctgg tgacggttag ctca 354

<210> SEQ ID NO 12
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct tcttctggta tgtctgtgtc ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctcgtatct attctgatga ttctaagtct 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtgct 300

gctcattgga atggtcctct ttttgatgtt tggggccaag gcaccctggt gacggttagc 360

tca 363

<210> SEQ ID NO 13
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct aattattcta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagctat atctatggtg gtggtagcta tacctattat 180

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gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcaggct 300

ggtatgtatt ttgatgtttg gggccaaggc accctggtga cggttagctc a 351

<210> SEQ ID NO 14
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 14

caggtgcaat tgcaagaaag tggtccgggc ctggtgaaac cgggcgaaac cctgagcctg 60

acctgcaccg tttccggagg cagcattggt tattattgga attggattcg ccaggccccct 120

gggaagggtc tcgagtggat tggccatatc tctcgttttg gctctaccaa ttataatccg 180

agcctgaaag gccgggtgac cattagcgtt gatacttcga aaaaccagtt tagcctgaaa 240

ctgagcagcg tgacggcgga agatacggcc gtgtattatt gcgcgcggga gtatactggt 300

aatgattggt atcgtcagca gggtcagcat gctgattatt ggggccaagg caccctggtg 360

acggttagct ca 372

<210> SEQ ID NO 15
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 15

caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60

acctgtacct tttccggatt tagcctgtct aattctggtg ttggtgtggg ttggattcgc 120

cagccgcctg ggaaagccct cgagtggctg gctgatatct attctgatac tactaagcgt 180

tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240

gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgttat 300

ggtgaggctt attttgatta ttggggccaa ggcaccctgg tgacggttag ctca 354

<210> SEQ ID NO 16
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Asn
20 25 30

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

Gly Asn Ile Trp Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Asn Gly Tyr Leu Asp Thr Asn Thr Tyr Ile Asp Tyr Trp Gly
100 105 110

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Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 17
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

Gln 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 Asp 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 Arg Tyr Asp Gly Ser Asn 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

Ala Arg Tyr Tyr Ser Gly Ile Tyr Gln His Ile Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 18
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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

Ser Ser Ile Ser Gly Leu Gly Ser Thr 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

Ala Arg Tyr His Tyr Glu Tyr His Tyr Phe Ser Ser Gly Phe Asp Asn
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 19
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19
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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Gly Tyr
            20                  25                  30

Tyr Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Phe Pro Asn Gly Gly Ser Thr Gly Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Gly Asn Ile Phe Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> SEQ ID NO 20
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

```
Gln 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 Thr Ser Tyr
            20                  25                  30

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

Ser Tyr Ile Asp Ser Ser Gly Ser 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

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

Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> SEQ ID NO 21
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

```
Gln 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

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

Ser Gly Ile Ser Gly Asp Pro Ser Asn Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60
```

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```
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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 22
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

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

Ser Gly Ile Ser Ser Trp Gly Ser 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

Ala Arg Glu Asp Gly Ser Tyr Met Thr Asp Tyr Phe Ala Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 23
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Ser Asp
            20                  25                  30

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

Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys Arg Tyr Ser Thr Ser
    50                  55                  60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Phe Asn Trp Phe Tyr Arg Leu Ala Phe Val Asn Pro Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

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<210> SEQ ID NO 24
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30

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

Trp Leu Ala His Ile Asp Trp Asn Asp Asp Lys Tyr Tyr Ser Thr Ser
50 55 60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Glu Asp Arg Leu Leu Gly Gly Tyr Gly Tyr Asp Val Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 25
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Gly Asn
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Asp Tyr His Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Gly Arg
50 55 60

Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys Leu
65 70 75 80

Ser Ser Val Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Glu
85 90 95

Gln Tyr His Trp Gly Leu Ala Trp Thr Gly Phe Asp Asn Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 26
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

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

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Ser Thr Ser

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            20                  25                  30

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

Gly Ile Ile Asp Pro Asp Ile Ser Tyr Thr Ser Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

Ala Arg Tyr Leu Met Gly Leu Gly Tyr Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115
```

<210> SEQ ID NO 27
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

```
Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Ser Ser
            20                  25                  30

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

Trp Leu Ala Arg Ile Tyr Ser Asp Asp Ser Lys Ser Tyr Ser Thr Ser
    50                  55                  60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Ala Ala His Trp Asn Gly Pro Leu Phe Asp Val Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

<210> SEQ ID NO 28
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

```
Gln 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 Asn Tyr
            20                  25                  30

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

Ser Tyr Ile Tyr Gly Gly Gly Ser Tyr 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
```

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```
                85                  90                  95

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

Val Thr Val Ser Ser
        115


<210> SEQ ID NO 29
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Gly Tyr Tyr
            20                  25                  30

Trp Asn Trp Ile Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Ile Gly
        35                  40                  45

His Ile Ser Arg Phe Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Gly
    50                  55                  60

Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu Lys
65                  70                  75                  80

Leu Ser Ser Val Thr Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg
                85                  90                  95

Glu Tyr Thr Gly Asn Asp Trp Tyr Arg Gln Gln Gly Gln His Ala Asp
            100                 105                 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 30
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 30

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Asn Ser
            20                  25                  30

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

Trp Leu Ala Asp Ile Tyr Ser Asp Thr Thr Lys Arg Tyr Ser Thr Ser
    50                  55                  60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Tyr Gly Glu Ala Tyr Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 31
<211> LENGTH: 333
<212> TYPE: DNA
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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatattggt gcttatgtgt cttggtacca gcagcatccc 120

gggaaggcgc cgaaacttat gatttatgag gtttcttctc gtccctcagg cgtgagcaac 180

cgttttagcg gatccaaaag cggcaacacc gcgagcctga ccattagcgg cctgcaagcg 240

gaagacgaag cggattatta ttgctcttct tatgatctta ctcctcctgg taaggtgttt 300

ggcggcggca cgaagttaac cgttcttggc cag 333

<210> SEQ ID NO 32
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtcattat tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cgcttctgat gttggttctc ttgatgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccag 324

<210> SEQ ID NO 33
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60

ctgagctgca gagcgagcca gactggttct acttcttatc tggcttggta ccagcagaaa 120

ccaggtcaag caccgcgtct attaatttat gatgcttcta agcgtgcaac tggggtcccg 180

gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240

cctgaagact ttgcgactta ttattgccat cagtattata acgttcctca tacctttggc 300

cagggtacga aagttgaaat taaacgtacg 330

<210> SEQ ID NO 34
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

gatatcgtgc tgacccagcc gccttcagtg agtggcgcac caggtcagcg tgtgaccatc 60

tcgtgtagcg gcagcagcag caacattggt aataattatg tgtcttggta ccagcagttg 120

cccgggacgg cgccgaaact tctgatttat ggtgatgatc agcgtccctc aggcgtgccg 180

gatcgtttta gcggatccaa aagcggcacc agcgcgagcc ttgcgattac gggcctgcaa 240

agcgaagacg aagcggatta ttattgccag tcttatggta ctttttcttc ttttgtgttt 300

ggcggcggca cgaagttaac cgttcttggc cag 333

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<210> SEQ ID NO 35
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca gaatatttct cagtggctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttatggt gcttctaatt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat tttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag tattatgatc ttcctaatac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 36
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tcgtcattat tatgtttatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatggtgat tctaagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagacttat actggtggtg cttctcttgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 37
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtcattat tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttattctgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat aatggtactt atgtgtttgg cggcggcacg 300

aagttaaccg ttcttggcca g 321

<210> SEQ ID NO 38
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

gatatcgtgc tgacccagag cccggcgacc ctgagcctgt ctccgggcga acgtgcgacc 60

ctgagctgca gagcgagcca gtctgtttct tcttcttatc tggcttggta ccagcagaaa 120

ccaggtcaag caccgcgtct attaatttat ggtgcttctt ctcgtgcaac tggggtcccg 180

gcgcgtttta gcggctctgg atccggcacg gattttaccc tgaccattag cagcctggaa 240

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cctgaagact ttgcggttta ttattgccag cagggttata attctccttt tacctttggc 300

cagggtacga aagttgaaat taaacgtacg 330

<210> SEQ ID NO 39
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgattctct tggttcttat tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat tggtgatgat actaagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggttctcgt actggttata ataattcttt tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag 330

<210> SEQ ID NO 40
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tggtcattat tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgatgat tctgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg cggtgcttat gctatgcata tgactgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccag 324

<210> SEQ ID NO 41
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

gatatcgcac tgacccagcc agcttcagtg agcggctcac caggtcagag cattaccatc 60

tcgtgtacgg gtactagcag cgatgttggt gctattaatt atgtgtcttg gtaccagcag 120

catcccggga aggcgccgaa acttatgatt tatgatgtta ataagcgtcc ctcaggcgtg 180

ccggatcgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240

caagcggaag acgaagcgga ttattattgc ggttcttata ctatgcaggt tggttcttat 300

gtgtttggcg gcggcacgaa gttaaccgtt cttggccag 339

<210> SEQ ID NO 42
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtcattat tatgctcatt ggtaccagca gaaacccggg 120

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caggcgccag ttgttgtgat ttatgatgat aatgatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccaggcttat actggtgatg gtggtcgtgt gtttggcggc 300

ggcacgaagt taaccgttct tggccag 327

<210> SEQ ID NO 43
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tggttctaag gttgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttattatgat aataagcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat acttttgagt ctggttctgt tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag 330

<210> SEQ ID NO 44
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tggtcattat tatgttgatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgctgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctcttcttat tctcagcagt ctatggtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccag 324

<210> SEQ ID NO 45
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatct tggtaatttt tatgttcatt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttatgaggat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctcttcttgg gatatgtatc gtactatttt tgtgtttggc 300

ggcggcacga agttaaccgt tcttggccag 330

<210> SEQ ID NO 46
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Ile Gly Ala Tyr
            20                  25                  30

Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile
        35                  40                  45

Tyr Glu Val Ser Ser Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly
    50                  55                  60

Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala
65                  70                  75                  80

Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Leu Thr Pro Pro
                85                  90                  95

Gly Lys Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 47
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly His Tyr Tyr Val
            20                  25                  30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Gly Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Ala Ser Asp Val Gly Ser Leu Asp Val
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 48
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Gly Ser Thr Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Asp Ala Ser Lys Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Thr Tyr Tyr Cys His Gln Tyr Tyr Asn Val Pro
                85                  90                  95
```

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```
His Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210> SEQ ID NO 49
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Gly Asp Asp Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Gly Thr Phe Ser
                85                  90                  95

Ser Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 50
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Ser Gln Trp
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asp Leu Pro Asn
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105


<210> SEQ ID NO 51
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Arg His Tyr Tyr Val
            20                  25                  30

Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
```

-continued

```
        35                  40                  45

Gly Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Thr Tyr Thr Gly Gly Ala Ser Leu
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 52
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly His Tyr Tyr Val
            20                  25                  30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Ser Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asn Gly Thr Tyr Val Phe
                85                  90                  95

Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 53
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

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

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Gly Tyr Asn Ser Pro
                85                  90                  95

Phe Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210> SEQ ID NO 54
<211> LENGTH: 110
<212> TYPE: PRT
```

-continued

<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Ser Tyr Tyr Val
20 25 30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Gly
35 40 45

Asp Asp Thr Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Arg Thr Gly Tyr Asn Asn Ser
85 90 95

Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 55
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly His Tyr Tyr Val
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gly Ala Tyr Ala Met His Met Thr Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 56
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Ile
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

-continued

```
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Met Gln
                85                  90                  95

Val Gly Ser Tyr Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
            100                 105                 110

Gln
```

<210> SEQ ID NO 57
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

```
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1               5                   10                  15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly His Tyr Tyr Ala
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr
        35                  40                  45

Asp Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Tyr Thr Gly Asp Gly Gly Arg
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105
```

<210> SEQ ID NO 58
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

```
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
1               5                   10                  15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Ser Lys Val Val
            20                  25                  30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Tyr Asp Asn Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Thr Phe Glu Ser Gly Ser
                85                  90                  95

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110
```

<210> SEQ ID NO 59
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

```
Asp Ile Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln
```

-continued

```
1               5                   10                  15

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly His Tyr Tyr Val
            20                  25                  30

Asp Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Ala Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ser Gln Gln Ser Met Val
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 60
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Leu Gly Asn Phe Tyr Val
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Glu Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Trp Asp Met Tyr Arg Thr Ile
                85                  90                  95

Phe Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110


<210> SEQ ID NO 61
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 61

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
            20                  25                  30

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

Gly Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe
    50                  55                  60

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln
```

-continued

```
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 62
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Gln Val Gln Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1               5                   10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

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

Trp Leu Ala Leu Ile Asp Trp Asp Asp Asp Lys Tyr Tyr Ser Thr Ser
    50                  55                  60

Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

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

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 63
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Gln 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

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 64
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64
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```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Tyr
            20                  25                  30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

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

Thr Leu Val Thr Val Ser Ser
        115
```

<210> SEQ ID NO 65
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

```
Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1               5                   10                  15

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr
            20                  25                  30

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

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
    50                  55                  60

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95

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 66
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

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

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Asp Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60
```

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Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro
85 90 95

Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 67
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

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

Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30

Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
35 40 45

Met Ile Tyr Asp Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr
85 90 95

Pro Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 68
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Ala Leu Gly Asp Lys Tyr Ala
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
35 40 45

Asp Asp Ser Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly
100 105

<210> SEQ ID NO 69
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
            100                 105


<210> SEQ ID NO 70
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

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

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro
                85                  90                  95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210> SEQ ID NO 71
<211> LENGTH: 300
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

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
        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
```

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```
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 72
<211> LENGTH: 1317
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

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

ccctccagca gcttgggcac ccagacctac atctgcaacg tgaatcacaa gcccagcaac    600

accaaggtgg acaagaaagt tgagcccaaa tcttgtgaca aaactcacac atgcccaccg    660

tgcccagcac ctgaactcct gggggggaccg 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
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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 73
<211> LENGTH: 642
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

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 74
<211> LENGTH: 1500
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (307)..(393)

<400> SEQUENCE: 74

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

gccacc atg aaa cac ctg tgg ttc ttc ctc ctg ctg gtg gca gct ccc 348
Met Lys His Leu Trp Phe Phe Leu Leu Leu Val Ala Ala Pro
1 5 10

aga tgg gtc ctg tcc cag gtg gaa ttc tgc agg cgg tta gct cag 393
Arg Trp Val Leu Ser Gln Val Glu Phe Cys Arg Arg Leu Ala Gln
15 20 25

cctccaccaa gggtccatcg gtcttccccc tggcaccctc ctccaagagc acctctgggg 453

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```
gcacagcggc cctgggctgc ctggtcaagg actacttccc cgaaccggtg acggtgtcgt    513

ggaactcagg cgccctgacc agcggcgtgc acaccttccc ggctgtccta cagtcctcag    573

gactctactc cctcagcagc gtggtgaccg tgccctccag cagcttgggc acccagacct    633

acatctgcaa cgtgaatcac aagcccagca acaccaaggt ggacaagaaa gttgagccca    693

aatcttgtga caaaactcac acatgcccac cgtgcccagc acctgaactc ctggggggac    753

cgtcagtctt cctcttcccc ccaaaaccca aggacaccct catgatctcc cggacccctg    813

aggtcacatg cgtggtggtg gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt    873

acgtggacgg cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagtacaaca    933

gcacgtaccg ggtggtcagc gtcctcaccg tcctgcacca ggactggctg aatggcaagg    993

agtacaagtg caaggtctcc aacaaagccc tcccagcccc catcgagaaa accatctcca   1053

aagccaaagg gcagccccga gaaccacagg tgtacaccct gcccccatcc cgggatgagc   1113

tgaccaagaa ccaggtcagc ctgacctgcc tggtcaaagg cttctatccc agcgacatcg   1173

ccgtggagtg ggagagcaat gggcagccgg agaacaacta caagaccacg cctcccgtgc   1233

tggactccga cggctccttc ttcctctaca gcaagctcac cgtggacaag agcaggtggc   1293

agcaggggaa cgtcttctca tgctccgtga tgcatgaggc tctgcacaac cactacacgc   1353

agaagagcct ctccctgtct ccgggtaaat gagggcccgt ttaaacccgc tgatcagcct   1413

cgactgtgcc ttctagttgc cagccatctg ttgtttgccc ctcccccgtg ccttccttga   1473

ccctggaagg tgccactccc actgtcc                                       1500
```

<210> SEQ ID NO 75
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (307)..(705)

<400> SEQUENCE: 75

```
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

gccacc atg gtg ttg cag acc cag gtc ttc att tct ctg ttg ctc tgg       348
       Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp
       1               5                   10

atc tct ggt gcc tac ggg gat atc gtg atg att aaa cgt acg gtg gct      396
Ile Ser Gly Ala Tyr Gly Asp Ile Val Met Ile Lys Arg Thr Val Ala
15                  20                  25                  30

gca cca tct gtc ttc atc ttc ccg cca tct gat gag cag ttg aaa tct      444
Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
                35                  40                  45

gga act gcc tct gtt gtg tgc ctg ctg aat aac ttc tat ccc aga gag      492
Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
            50                  55                  60

gcc aaa gta cag tgg aag gtg gat aac gcc ctc caa tcg ggt aac tcc      540
Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
        65                  70                  75
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cag gag agt gtc aca gag cag gac agc aag gac agc acc tac agc ctc      588
Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
    80                  85                  90

agc agc acc ctg acg ctg agc aaa gca gac tac gag aaa cac aaa gtc      636
Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
95                 100                 105                 110

tac gcc tgc gaa gtc acc cat cag ggc ctg agc tcg ccc gtc aca aag      684
Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
                115                 120                 125

agc ttc aac agg gga gag tgt taggggcccg tttaaacccg ctgatcagcc        735
Ser Phe Asn Arg Gly Glu Cys
130

tcgactgtgc cttctagttg ccagccatct gttgtttgcc cctcccccgt gccttccttg    795

accct                                                               800


<210> SEQ ID NO 76
<211> LENGTH: 800
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (307)..(384)
<220> FEATURE:
<221> NAME/KEY: CDS
<222> LOCATION: (386)..(712)

<400> SEQUENCE: 76

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

gccacc atg gcc tgg gct ctg ctg ctc ctc acc ctc ctc act cag ggc       348
       Met Ala Trp Ala Leu Leu Leu Leu Thr Leu Leu Thr Gln Gly
       1               5                   10

aca gga tcc tgg gct gat atc gtg atg cac gaa gtt a acc gtc cta ggt    397
Thr Gly Ser Trp Ala Asp Ile Val Met His Glu Val   Thr Val Leu Gly
15                  20                  25                  30

cag ccc aag gct gcc ccc tcg gtc act ctg ttc ccg ccc tcc tct gag      445
Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu
                35                  40                  45

gag ctt caa gcc aac aag gcc aca ctg gtg tgt ctc ata agt gac ttc      493
Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe
            50                  55                  60

tac ccg gga gcc gtg aca gtg gcc tgg aag gga gat agc agc ccc gtc      541
Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Gly Asp Ser Ser Pro Val
        65                  70                  75

aag gcg gga gtg gag acc acc aca ccc tcc aaa caa agc aac aac aag      589
Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys
    80                  85                  90

tac gcg gcc agc agc tat ctg agc ctg acg cct gag cag tgg aag tcc      637
Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser
95                 100                 105                 110

cac aga agc tac agc tgc cag gtc acg cat gaa ggg agc acc gtg gag      685
His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu
                115                 120                 125
```

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aag aca gtg gcc cct aca gaa tgt tca taggggcccg tttaaacccg 732
Lys Thr Val Ala Pro Thr Glu Cys Ser
130 135

ctgatcagcc tcgactgtgc cttctagttg ccagccatct gttgtttgcc cctcccccgt 792

gccttcct 800

<210> SEQ ID NO 77
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcggt attaatatgg agtctactcg tatttattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 78
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctcatg atggtaatgt taagtattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 79
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctatga atggtgatta tatttcttat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 80
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

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caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct attaatcttt ctggttctgc taagtattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 81
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttcttcta atggtgatat tacttattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 82
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctacta atggttggca gacttattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 83
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct attaatatga ttggtaatgt tactaattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 84
<211> LENGTH: 360

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagctat attaatccta atggtatgat gactaattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 85
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgtt atttctcctg gtggtgaggc taagtcttat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 86
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctggta atggtggtca tacttattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 87
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctatgg atggtgttta taagtattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

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<210> SEQ ID NO 88
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctaata atggtaatgt tacttattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 89
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttattata tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcgct atttctatgc atggtgatac tacttattat 180

gctgattctg ttaagggtcg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgatctt 300

cctcttgttt atactggttt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 90
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatgcta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagccat attcgtaaga agaatacttc ttatactact 180

gagtatgctg cttctgttaa gggtcgtttt accatttcac gtgataattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgcgtgcg gaagatacgg ccgtgtatta ttgcgcgcgt 300

gaggatggtt cttatatgac tgattatttt gcttattggg gccaaggcac cctggtgacg 360

gttagctca 369

<210> SEQ ID NO 91
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatgcta tgaattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat attcagcgtg ttggttctac ttattatgct 180

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gattctgtta agggtcgttt taccatttca cgtgataatt cgaaaaacac cctgtatctg 240

caaatgaaca gcctgcgtgc ggaagatacg gccgtgtatt attgcgcgcg tgaggatggt 300

tcttatatga ctgattattt tgcttattgg ggccaaggca ccctggtgac ggttagctca 360

<210> SEQ ID NO 92
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Gln 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

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

Ser Gly Ile Asn Met Glu Ser Thr Arg Ile 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 93
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

Gln 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

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

Ser Ala Ile Ser His Asp Gly Asn Val Lys 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 94
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 94

Gln 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

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

Ser Ala Ile Ser Met Asn Gly Asp Tyr Ile Ser 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 95
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Gln 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

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

Ser Ala Ile Asn Leu Ser Gly Ser Ala Lys 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 96
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Gln 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

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

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Ser Ala Ile Ser Ser Asn Gly Asp Ile 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 97
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Gln 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

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

Ser Ala Ile Ser Thr Asn Gly Trp Gln 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 98
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Gln 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

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

Ser Ala Ile Asn Met Ile Gly Asn Val Thr Asn 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110
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Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 99
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Gln 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

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

Ser Tyr Ile Asn Pro Asn Gly Met Met Thr Asn 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 100
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Gln 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

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

Ser Val Ile Ser Pro Gly Gly Glu Ala Lys Ser 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 101
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

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

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

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

Ser Ala Ile Ser Gly Asn Gly Gly His 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 102
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

Gln 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

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

Ser Ala Ile Ser Met Asp Gly Val Tyr Lys 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 103
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Gln 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

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

Ser Ala Ile Ser Asn Asn Gly Asn Val 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
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65                  70                  75                  80

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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 104
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Gln 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

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

Ser Ala Ile Ser Met His Gly Asp Thr 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

Ala Arg Asp Leu Pro Leu Val Tyr Thr Gly Phe Ala Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 105
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

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

Ser His Ile Arg Lys Lys Asn Thr Ser Tyr Thr Thr Glu Tyr Ala Ala
    50                  55                  60

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

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

Tyr Cys Ala Arg Glu Asp Gly Ser Tyr Met Thr Asp Tyr Phe Ala Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
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<210> SEQ ID NO 106
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

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

Ser Asn Ile Gln Arg Val Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

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

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

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

Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 107
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtcattat tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttattctgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtctgct gataattttc cttttgtgtt tggcggcggc 300

acgaagttaa ccgtcctagg tcag 324

<210> SEQ ID NO 108
<211> LENGTH: 330
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtcattat tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttcttgtgat ttattctgat tctaatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ccagtcttat actatgtctg atgttcttgt tgtgtttggc 300

ggcggcacga agttaaccgt cctaggtcag 330

<210> SEQ ID NO 109
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 109

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly His Tyr Tyr Val
            20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35 40 45

Ser Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Ala Asp Asn Phe Pro Phe Val
                85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100 105

<210> SEQ ID NO 110
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly His Tyr Tyr Val
            20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35 40 45

Ser Asp Ser Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

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

Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100 105 110

<210> SEQ ID NO 111
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

caggtgcaat tggttcagag cggcgcggaa 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

atttatttta ttcatggtat gcttgatttt tggggccaag gcaccctggt gacggttagc 360

tca 363

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<210> SEQ ID NO 112
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct aattatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atccgttctg atggtagctg gacctattat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtcgttat 300

tggtctaagt ctcatgcttc tgttactgat tattggggcc aaggcaccct ggtgacggtt 360

agctca 366

<210> SEQ ID NO 113
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

caggtgcaat tggtggaaag cggcggcggc ctggtgcaac cgggcggcag cctgcgtctg 60

agctgcgcgg cctccggatt tacctttttct tcttatggta tgcattgggt gcgccaagcc 120

cctgggaagg gtctcgagtg ggtgagcaat atctattctg atggtagcaa tacctttttat 180

gcggatagcg tgaaaggccg ttttaccatt tcacgtgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtaatatg 300

tatcgttggc cttttcatta ttttttttgat tattggggcc aaggcaccct ggtgacggtt 360

agctca 366

<210> SEQ ID NO 114
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

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

Gly Tyr Ile Asp Pro Asn Arg Gly Asn Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Glu Tyr Ile Tyr Phe Ile His Gly Met Leu Asp Phe Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

-continued

<210> SEQ ID NO 115
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Gln 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 Asn Tyr
20 25 30

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

Ser Asn Ile Arg Ser Asp Gly Ser Trp 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

Ala Arg Arg Tyr Trp Ser Lys Ser His Ala Ser Val Thr Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 116
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

Gln 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

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
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

Ala Arg Asn Met Tyr Arg Trp Pro Phe His Tyr Phe Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 117
<211> LENGTH: 342
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

gatatcgtga tgacccagag cccactgagc ctgccagtga ctccgggcga gcctgcgagc 60

attagctgca gaagcagcca aagcctgctt tttattgatg gcaataatta tctgaattgg 120

taccttcaaa aaccaggtca aagcccgcag ctattaattt atcttggttc taatcgtgcc 180

-continued

agtggggtcc cggatcgttt tagcggctct ggatccggca ccgattttac cctgaaaatt 240

agccgtgtgg aagctgaaga cgtgggcgtg tattattgcc agcagtattc ttctaagtct 300

gctacctttg gccagggtac gaaagttgaa attaaacgta cg 342

<210> SEQ ID NO 118
<211> LENGTH: 327
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

gatatccaga tgacccagag cccgtctagc ctgagcgcga gcgtgggtga tcgtgtgacc 60

attacctgca gagcgagcca ggatatttct gcttttctga attggtacca gcagaaacca 120

ggtaaagcac cgaaactatt aatttataag gtttctaatt tgcaaagcgg ggtcccgtcc 180

cgttttagcg gctctggatc cggcactgat ttttaccctga ccattagcag cctgcaacct 240

gaagactttg cgacttatta ttgccagcag gcttattctg gttctattac ctttggccag 300

ggtacgaaag ttgaaattaa acgtacg 327

<210> SEQ ID NO 119
<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

gatatcgaac tgacccagcc gccttcagtg agcgttgcac caggtcagac cgcgcgtatc 60

tcgtgtagcg gcgataatat tggtaataag tatgtttctt ggtaccagca gaaacccggg 120

caggcgccag ttgttgtgat ttatggtgat aataatcgtc cctcaggcat cccggaacgc 180

tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240

gacgaagcgg attattattg ctcttcttat gattcttctt attttgtgtt tggcggcggc 300

acgaagttaa ccgttcttgg ccag 324

<210> SEQ ID NO 120
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

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 Phe Ile
20 25 30

Asp Gly Asn Asn Tyr Leu Asn 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 Tyr
85 90 95

Ser Ser Lys Ser Ala Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105 110

-continued

Arg Thr

<210> SEQ ID NO 121
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

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

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ala Phe
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Lys Val Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Tyr Ser Gly Ser Ile
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
100 105

<210> SEQ ID NO 122
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Lys Tyr Val
20 25 30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Val Val Ile Tyr
35 40 45

Gly Asp Asn Asn Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
50 55 60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65 70 75 80

Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Asp Ser Ser Tyr Phe Val
85 90 95

Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105

<210> SEQ ID NO 123
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 123

atggccaact gcgagttcag c 21

<210> SEQ ID NO 124
<211> LENGTH: 27

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 124

tcagatctca gatgtgcaag atgaatc 27

<210> SEQ ID NO 125
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 125

ttggtaccag gtggcgccag cagtg 25

<210> SEQ ID NO 126
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 126

ttggtaccat ggccaactgc gag 23

<210> SEQ ID NO 127
<211> LENGTH: 29
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 127

ccgatatcag atctcagatg tgcaagatg 29

<210> SEQ ID NO 128
<211> LENGTH: 28
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 128

ccgatatcga tctcagatgt gcaagatg 28

<210> SEQ ID NO 129
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 129

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
20 25

-continued

<210> SEQ ID NO 130
<211> LENGTH: 133
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 130

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 131
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 131

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
20 25

<210> SEQ ID NO 132
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 132

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

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Trp Gly Gly Asp Gly Phe Tyr Ala Met Asp Tyr Trp Gly Gln

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            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 133
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 133

Gln 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 Asn
            20                  25                  30

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

Ser Asn Ile Ser Tyr Leu Ser Ser 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

Ala Arg Phe Tyr Gly Tyr Phe Asn Tyr Ala Asp Val Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 134
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 134

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

Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly His Tyr Tyr Ala
            20                  25                  30

Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35                  40                  45

Arg Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser
    50                  55                  60

Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu
65                  70                  75                  80

Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Tyr Leu His Asp Phe
                85                  90                  95

Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105


<210> SEQ ID NO 135
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 135

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

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

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro Pro
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105


<210> SEQ ID NO 136
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 136

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 Thr


<210> SEQ ID NO 137
<211> LENGTH: 110
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (86)
<223> OTHER INFORMATION: Thr or Val

<400> SEQUENCE: 137

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

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

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Val Pro Ala Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu
65                  70                  75                  80
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Pro Glu Asp Phe Ala Xaa Tyr Tyr Cys Gln Gln His Tyr Thr Thr Pro
                85                  90                  95

Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr
            100                 105                 110


<210> SEQ ID NO 138
<211> LENGTH: 330
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 138

Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
1               5                   10                  15

Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30

Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45

Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80

Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95

Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110

Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125

Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140

Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160

Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175

Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190

His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205

Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220

Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240

Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255

Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270

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

Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300

Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320

Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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-continued

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                325                 330


<210> SEQ ID NO 139
<211> LENGTH: 109
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 139

Thr Val Leu Gly Gln Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro
1               5                   10                  15

Pro Ser Ser Glu Glu Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu
            20                  25                  30

Ile Ser Asp Phe Tyr Pro Gly Ala Val Thr Val Ala Trp Lys Gly Asp
        35                  40                  45

Ser Ser Pro Val Lys Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln
    50                  55                  60

Ser Asn Asn Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu
65                  70                  75                  80

Gln Trp Lys Ser His Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly
                85                  90                  95

Ser Thr Val Glu Lys Thr Val Ala Pro Thr Glu Cys Ser
            100                 105
```

1. An isolated antigen-binding region that is specific for CD38, which comprises (i) an H-CDR3 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) an H-CDR3 region that has at least a sixty percent identity to an H-CDR3 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

2. An isolated antigen-binding region according to claim **1**, further comprising (i) an H-CDR2 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) an H-CDR2 region that has at least a sixty percent identity to an H-CDR2 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

3. An isolated antigen-binding region according to claim **2**, further comprising (i) an H-CDR1 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) an H-CDR1 region that has at least a sixty percent identity to an H-CDR1 region depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

4. An isolated antibody or functional fragment thereof that is specific for CD38, which comprises (i) a variable heavy chain depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) a variable heavy chain that has at least a sixty percent identity to a variable heavy chain depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

5. An isolated antigen-binding region that is specific for CD38, which comprises (i) an L-CDR3 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) an L-CDR3 region that has at least a sixty percent identity to an L-CDR3 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

6. An isolated antigen-binding region according to claim **5**, further comprising (i) an L-CDR2 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) an L-CDR2 region that has at least a sixty percent identity to an L-CDR2 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

7. An isolated antigen-binding region according to claim **6**, further comprising (i) an L-CDR1 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) an L-CDR1 region that has at least a sixty percent identity to an L-CDR1 region depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

8. An isolated antibody or functional fragment thereof, which comprises (i) a variable light chain depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) a variable light chain that has at least a sixty percent identity to a variable light chain depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

9. An isolated immunoglobulin according to claim **4**, which is an IgG.

10. An isolated immunoglobulin according to claim **9**, which is an IgG1.

11. A variable heavy chain of an isolated antigen-binding region that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15,

77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91, wherein said antigen-binding region is specific for CD38.

12. A variable light chain of an isolated antigen-binding region that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108, wherein said antibody or functional fragment thereof is specific for CD38.

13. An isolated nucleic acid sequence that encodes an antigen-binding region of a human antibody or functional fragment thereof that is specific for CD38.

14. A nucleic acid sequence encoding a variable heavy chain of an isolated antigen-binding region, which comprises (i) a sequence selected from the group consisting of SEQ ID NOS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 and 91 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91, wherein said antigen-binding region is specific for CD38.

15. A nucleic acid sequence encoding a variable light chain of an isolated antigen-binding region, which comprises (i) a sequence selected from the group consisting of SEQ ID NOS: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 and 108 or (ii) a nucleic acid sequence that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 wherein said antigen-binding region is specific for CD38.

16. A vector comprising a nucleic acid sequence according to claim **13**.

17. An isolated cell comprising a vector according to claim **16**.

18. An isolated cell according to claim **17**, wherein said cell is bacterial.

19. An isolated cell according to claim **17**, wherein said cell is mammalian.

20. A pharmaceutical composition comprising an antibody or function fragment thereof according to claim **4** and a pharmaceutically acceptable carrier or excipient therefor.

21. A method for treating a disorder or condition associated with the undesired presence of CD38+ cells, comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition according to claim **20**.

22. A method according to claim **21**, wherein said disorder or condition is a haematological disease.

23. A method according to claim **22**, wherein said haematological disease is taken from the list of multiple myeloma, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia and acute lymphocytic leukemia.

24. A method according to claim **21**, wherein said disorder or condition is an inflammatory disease.

25. A method according to claim **24**, wherein said inflammatory disease is taken from the list of rheumatoid arthritis and systemic lupus erythematosus.

26. An isolated antigen-binding region according to claim **1**, wherein said sequence identity is at least 80%.

27. A method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody comprises (i) a nucleic acid sequence encoding a heavy chain depicted in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91, wherein said antibody or a functional fragment thereof is specific for CD38.

28. A method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody comprises (i) a nucleic acid sequence encoding a light chain depicted in SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to the complementary strand of SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108, wherein said antibody or a functional fragment thereof is specific for CD38.

29. A method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody or said functional fragment thereof comprises (i) a heavy chain amino acid sequence depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 or (ii) a variable heavy chain that has at least a sixty percent identity to a variable heavy chain depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106.

30. A method of inducing specific killing of tumor cells that express CD38, wherein said specific killing occurs by CD38 cross-linking, comprising the step of incubating said cells in the presence of a sufficient amount of an isolated human or humanized anti-CD38 antibody or a functional fragment thereof, wherein said human or humanized anti-CD38 antibody comprises (i) and/or a light chain amino acid sequence depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110 or (ii) a variable light chain that has at least a sixty percent identity to a variable light chain depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

31. A method of detecting specific killing of tumor cells that express CD38, by CD38 cross-linking, comprising the steps of:

(i) administering to a subject in need thereof an effective amount of a human or humanized anti-CD38 antibody or a functional fragment thereof, and

(ii) detecting the specific killing activity of said human or humanized anti-CD38 antibody or said functional fragment thereof.

32. A method according to claim **31**, wherein said tumor cells are of human, minipig or rabbit origin.

33. A method of detecting the presence of CD38 in a tissue or a cell of minipig origin, comprising the steps of:

(i) allowing a human or humanized anti-CD38 antibody or a functional fragment thereof to come into contact with said CD38, and

(ii) detecting the specific binding of said human or humanized anti-CD38 antibody or functional fragment thereof to said CD38 minipig cells, wherein said antibody or functional fragment thereof is also able to specifically bind to CD38 of human origin.

34. A method according to claim **33**, wherein said CD38 of minipig origin is comprised within an isolated cell type selected from the group consisting of peripheral blood monocyte, erythrocyte, lymphocyte, thymocyte, muscle cell, cerebellum cell, pancreas cell, lymph-node cell, tonsil cell, spleen cell, prostate cell, skin cell and a cell of the retina.

35. A method according to claim **34**, wherein said human or humanized anti-CD38 antibody or functional fragment thereof comprises (i) a nucleic acid sequence encoding a heavy chain depicted in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 and/or a nucleic acid sequence encoding a light chain depicted in SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108 or (ii) a sequence having at least 60 percent identity in the heavy chain regions depicted in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 and/or a sequence having at least 60 percent identity in the light chain regions depicted in SEQ ID NO 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108.

36. A method of detecting CD38 in a CD38-expressing erythrocyte, comprising the steps of:

(i) allowing a human or humanized anti-CD38 antibody or a functional fragment thereof to come into contact with said CD38-expressing erythrocyte, and

(ii) detecting the specific binding of said human or humanized anti-CD38 antibody or functional fragment thereof to said CD38-expressing erythrocytes, wherein said antibody or functional fragment thereof is also able to specifically bind to human CD38 from a cell or tissue other than human erythrocytes.

37. A method according to claim **36**, wherein said antibody or functional fragment thereof is also able to specifically bind to human CD38 from a cell that is a human lymphocyte.

38. A method according to claim **36**, wherein said human or humanized anti-CD38 antibody or functional fragment thereof comprises (i) a nucleic acid sequence encoding a heavy chain depicted in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 and/or a nucleic acid sequence encoding a light chain depicted in SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44 or 45, 107 or 108 or (ii) a sequence having at least 60 percent identity in the heavy chain regions depicted in SEQ ID NO 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90 or 91 and a sequence having at least 60 percent identity in the light chain regions depicted in SEQ ID NO: 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 107 or 108.

39. A method according to claim **36**, wherein said human or humanized anti-CD38 antibody or functional fragment thereof comprises (i) a heavy chain amino acid sequence depicted in SEQ ID NO: 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 and/or a light chain amino acid sequence depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110; or (ii) a sequence having at least 60 percent identity in the heavy chain regions depicted in SEQ ID NO 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105 or 106 and a sequence having at least 60 percent identity in the light chain regions depicted in SEQ ID NO: 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 109 or 110.

40. A diagnostic composition comprising an antibody or functional fragment thereof according to claim **4**; and an acceptable carrier or excipient.

41. An isolated antibody or functional fragment thereof according to claim **1**, which comprises (i) an H-CDR3 region depicted in SEQ ID NO: 21 or 22 or (ii) an H-CDR3 region at least a sixty percent identity thereto, and that is specific for human CD38 and marmoset CD38.

42. An isolated antibody or functional fragment thereof according to claim **5**, which comprises (i) an L-CDR3 region depicted in SEQ ID NO: 51 or 52 or (ii) an L-CDR3 region at least a sixty percent identity thereto, that is specific for human CD38 and marmoset CD38.

43. A variable heavy chain of an isolated antigen-binding region according to claim **11**, that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 6 or 7 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to a complementary strand thereof, which antigen-binding region is specific for human CD38 and marmoset CD38.

44. A variable light chain of an isolated antigen-binding region according to claim **12**, that is encoded by (i) a nucleic acid sequence comprising SEQ ID NO: 36 or 37 or (ii) a nucleic acid sequences that hybridizes under high stringency conditions to a complementary strand thereof, which antigen-binding region is specific for human CD38 and marmoset CD38.

* * * * *

专利名称(译)	人CD38特异性全人源金源治疗性抗体的产生和分析		
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[标]申请(专利权)人(译)	莫佛塞斯公司		
申请(专利权)人(译)	MorphoSys公司AG		
当前申请(专利权)人(译)	MorphoSys公司AG		
[标]发明人	TESAR MICHAEL		
发明人	TESAR, MICHAEL		
IPC分类号	A61K39/395 C07K16/28 C07K16/30 C12N1/21 C12N5/10 C12N15/13 G01N33/574 G01N33/53 C12N15/63 C12N15/85 C12N5/00 A61P35/00 A61P35/02 A61P37/00		
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摘要(译)

本发明提供了新的抗体和使用重组抗原结合区和抗体的方法以及含有对CD38特异的抗原结合区的功能片段，其在各种病症或病症中起着不可或缺的作用。这些方法利用了新发现的抗体和这些抗体的令人惊讶的特性，例如结合小型猪来源的CD38的能力和通过交联诱导表达CD38的细胞的特异性杀伤的能力。这些抗体以及使用这些抗体的新方法可用于治疗例如血液恶性肿瘤，例如多发性骨髓瘤。