CD3-EXPRESSING NATURAL KILLER CELLS WITH ENHANCED FUNCTION FOR ADOPTIVE IMMUNOTHERAPY

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 63/225,281, filed July 23, 2021, and also claims priority to U.S. Provisional Patent Application Serial No. 63/310,526, filed February 15, 2022, and also claims priority to U.S. Provisional Patent Application Serial No. 63/344,931, filed May 23, 2022, each of which are incorporated by reference herein in their entirety.

I. Technical Field

[0002] This disclosure relates at least to the fields of immunology, cell biology, molecular biology, and medicine, including at least cancer medicine.

II. Background

[0003] Natural killer (NK) cells have been studied as potential anti-tumor effectors, yet a number of barriers limit their therapeutic exploitation, mainly related to their lack of antigen specificity. One approach to overcome this is to transduce NK cells with a chimeric antigen receptor (CAR) or an engineered T-cell receptor (TCR) to target a desired antigen. In T cells, one can utilize a bispecific or multi-specific antibody, such as a bispecific T cell engager (BiTE) that binds CD3 on the surface of T cells and that also binds an antigen on the surface of cancer cells. CD3 is composed of four distinct chains, and in mammals, the complex contains a CD3γ chain, a CD3δ chain, and two CD3ε chains. These chains associate with the T-cell receptor (TCR) and the ζ-chain (zeta-chain) to generate an activation signal in T lymphocytes. However, NK cells do not naturally express the CD3 receptor complex or TCRs.

[0004] The present disclosure satisfies a long-felt need in the art to improve upon immunotherapies including those that utilize NK cells.

BRIEF SUMMARY

[0004a] In one aspect, provided herein is a composition, comprising NK cells modified to express all or part of a single chain or any combination of CD3ζ, CD3δ, CD3ε, or CD3γ.

[0004b] In another aspect, provided herein is a composition comprising a complex, comprising: (1) NK cells modified to express all or part of the CD3 receptor complex and optionally modified to express the T-cell receptor (TCR) αβ chains or the TCR γδ chains; and

(2) a bispecific or multi-specific antibody, wherein the bispecific or multi-specific antibody comprises an anti-CD3 antibody that is bound to CD3 on the NK cells.

[0004c] In another aspect, provided herein is use of the composition as described herein in the manufacture of a medicament for treating cancer in an individual.

[0004d] In another aspect, provided herein is use of the composition as described herein in the manufacture of medicament for redirecting the specificity of NK cells against a cancer antigen for treatment of an individual with a bispecific or multi-specific anti-CD3 antibody, wherein the antibody and NK cells optionally express all or part of a CD3 receptor complex and optionally express part or all of TCR $\alpha\beta$ chains or the TCR $\gamma\delta$ chains.

[0004e] In another aspect, provided herein is a polynucleotide or polypeptide comprising a sequence at least 85% identical to any one or more of SEQ ID NOs: 118-123.

[0004f] In another aspect, provided herein is the composition as described herein for use in therapy.

[0005] Embodiments of the disclosure include methods and compositions for treatment of an individual with cancer using adoptive cell therapy. In specific embodiments, the individual is provided a therapeutically effective amount of a bipartite therapy that includes both modified NK cells and antibodies that are capable of being able to bind the NK cells to initiate signaling, activation, and killing of target cells. The disclosure concerns NK cells that have been modified

ATCGGCTTCCTAACTGAAGATAAAAAAAAATGGAATCTGGGAAGTAATGCCAAGGACCCTCG
TGGGATGTATCAGTGTAAAGGATCACAGAACAAGTCAAAACCACTCCAAGTGTATTACAGAA
TGTGTCAGAACTGCATTGAACTAAATGCAGCCACCATATCTGGCTTTCTCTTTGCTGAAATC
GTCAGCATTTTCGTCCTTGCTGTTGGGGTCTACTTCATTGCTGGACAGGATGGAGTTCGCCA
GTCGAGAGCTTCAGACAAGCAGACTCTGTTGCCCAATGACCAGCTCTACCAGCCCCTCAAGG
ATCGAGAAGATGACCAGTACAGCCACCTTCAAGGAAACCAGTTGAGGAGGAATGTGAAGCAG
ACCCTGAACTTCGACCTGCTGAAGCTGGCCGGCGACGTGGAGAGCAACCCCGGCCCCATGGA
GCACAGCACCTTCCTGAGCGGCCTGGTGCTGGCCACCCTGCTGAGCCAGGTGAGCCCCTTCA
AGATCCCCATCGAGGAGCTGGAGGACAGAGTGTTCGTGAACTGCAACACCAGCATCACCTGG
GTGGAGGGCACCGTGGGCACCCTGCTGAGCGACATCACCAGACTGGACCTGGGCAAGAGAAT
CCTGGACCCCAGAGGCATCTACAGATGCAACGGCACCGACATCTACAAGGACAAGGAGAGCA
CCGTGCAGGTGCACTACAGAATGTGCCAGAGCTGCGTGGAGCTGGACCCCGCCACCGTGGCC
GGCATCATCGTGACCGACGTGATCGCCACCCTGCTGCTGGCCCTGGGCGTGTTCTGCTTCGC
CGGCCACGAGACCGGCAGACTGAGCGGCGCCGCCGACACCCAGGCCCTGCTGAGAAACGACC
AGGTGTACCAGCCCCTGAGAGACAGAGACGACGCCCAGTACAGCCACCTGGGCGGCAACTGG
GCCAGAAACAAGGAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTGGAGGAGAACCCCGG
CCCCATGCAGAGCGGCACCCACTGGAGAGTGCTGGGCCTGTGCCTGCTGAGCGTGGGCGTGT
GGGGCCAGGACGGCAACGAGGAGATGGGCGGCATCACCCAGACCCCCTACAAGGTGAGCATC
AGCGGCACCACCGTGATCCTGACCTGCCCCCAGTACCCCGGCAGCGAGATCCTGTGGCAGCA
CAACGACAAGAACATCGGCGGCGACGAGGACGACAAGAACATCGGCAGCGACGAGGACCACC
TGAGCCTGAAGGAGTTCAGCGAGCTGGAGCAGAGCGGCTACTACGTGTGCTACCCCAGAGGC
AGCAAGCCCGAGGACGCCAACTTCTACCTGTACCTGAGAGCCAGAGTGTGCGAGAACTGCAT
GGAGATGGACGTGATGAGCGTGGCCACCATCGTGATCGTGGACATCTGCATCACCGGCGGCC
TGCTGCTGCTGGTGTACTACTGGAGCAAGAACAGAAAGGCCAAGGCCAAGCCCGTGACCAGA
GGCGCCGGCGCCGGCGGCAGACAGAGAGGCCAGAACAAGGAGAGACCCCCCCCCGTGCCCAA
CCCCGACTACGAGCCCATCAGAAAGGGCCAGAGAGACCTGTACAGCGGCCTGAACCAGAGAA
GAATCGGACCGCAGTGTACTAATTATGCTCTCTTGAAATTGGCTGGAGATGTTGAGAGCAAT
CCCGGGCCC (SEQ ID NO: 62)

[0131] SP CD8:

MRICLTSDRLAPAAGLAAPRRQAV (SEQ ID NO: 63)

atgcgcatttgcctgaccagcgatcgcctggcgccggcggcgggcctggcggcgccgcgccg
ccaggcggtg (SEQ ID NO: 64)

[0132] IL-21:

HKSSSQGQDRHMIRMRQLIDIVDQLKNYVNDLVPEFLPAPEDVETNCEWSAFSCFQKAQLKS
ANTGNNERIINVSIKKLKRKPPSTNAGRRQKHRLTCPSCDSYEKKPPKEFLERFKSLLQKMI
HQHLSSRTHGSEDS (SEQ ID NO: 65)

cataaatcttcctctcaaggtcaggaccgccatatgattcgaatgcggcagctgattgacat
agtcgatcaactgaagaactatgtgaatgatcttgtgcccgagttttgccagcccctgaag
acgtagaaactaattgtgagtggagtgccttttcctgctttcaaaaggcacagctgaaatcc
gccaacacgggcaataacgaacggataattaacgtatccattaagaagctgaagcggaagcc
gccctcaaccaatgcgggacggcggcaaaagcatcgcttgacctgtccgtcatgcgacagct
acgagaaaaagcccccgaaggagttcttggaacgcttcaagagtctccttcagaaaatgatt
caccagcacctgtcctcacggacgcacggaagcgaggacagt (SEQ ID NO: 66)

[0133] CD8 hinge:

TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 67)

GATCGAGAAGATGACCAGTACAGCCACCTTCAAGGAAACCAGTTGAGGAGGAATGTGAAGCA
GACCCTGAACTTCGACCTGCTGAAGCTGGCCGGCGACGTGGAGAGCAACCCCGGCCCCATGG
AGCACAGCACCTTCCTGAGCGGCCTGGTGCTGGCCACCCTGCTGAGCCAGGTGAGCCCCTTC
AAGATCCCCATCGAGGAGCTGGAGGACAGAGTGTTCGTGAACTGCAACACCAGCATCACCTG
GGTGGAGGGCACCGTGGGCACCCTGCTGAGCGACATCACCAGACTGGACCTGGGCAAGAGAA
TCCTGGACCCCAGAGGCATCTACAGATGCAACGGCACCGACATCTACAAGGACAAGGAGAGC
ACCGTGCAGGTGCACTACAGAATGTGCCAGAGCTGCGTGGAGCTGGACCCCGCCACCGTGGC
CGGCATCATCGTGACCGACGTGATCGCCACCCTGCTGCTGGCCCTGGGCGTGTTCTGCTTCG
CCGGCCACGAGACCGGCAGACTGAGCGGCGCCGCCGACACCCAGGCCCTGCTGAGAAACGAC
CAGGTGTACCAGCCCCTGAGAGACAGAGACGACGCCCAGTACAGCCACCTGGGCGGCAACTG
GGCCAGAAACAAGGAGGGCAGAGGCAGCCTGCTGACCTGCGGCGACGTGGAGGAGAACCCCG
GCCCCATGCAGAGCGGCACCCACTGGAGAGTGCTGGGCCTGTGCCTGCTGAGCGTGGGCGTG
TGGGGCCAGGACGGCAACGAGGAGATGGGCGGCATCACCCAGACCCCCTACAAGGTGAGCAT
CAGCGGCACCACCGTGATCCTGACCTGCCCCCAGTACCCCGGCAGCGAGATCCTGTGGCAGC
ACAACGACAAGAACATCGGCGGCGACGAGGACGACAAGAACATCGGCAGCGACGAGGACCAC
CTGAGCCTGAAGGAGTTCAGCGAGCTGGAGCAGAGCGGCTACTACGTGTGCTACCCCAGAGG
CAGCAAGCCCGAGGACGCCAACTTCTACCTGTACCTGAGAGCCAGAGTGTGCGAGAACTGCA
TGGAGATGGACGTGATGAGCGTGGCCACCATCGTGATCGTGGACATCTGCATCACCGGCGGC
CTGCTGCTGCTGGTGTACTACTGGAGCAAGAACAGAAAGGCCAAGGCCAAGCCCGTGACCAG
AGGCGCCGGCGCCGGCGGCAGACAGAGAGGCCAGAACAAGGAGAGACCCCCCCCCGTGCCCA
ACCCCGACTACGAGCCCATCAGAAAGGGCCAGAGAGACCTGTACAGCGGCCTGAACCAGAGA
AGAATCGGACCGCAGTGTACTAATTATGCTCTCTTGAAATTGGCTGGAGATGTTGAGAGCAA
TCCCGGGCCCATGCGCATTAGCAAGCCCCACCTGCGGAGCATCAGCATCCAGTGCTACCTGT
GCCTGCTGCTGAACAGCCACTTCCTGACCGAGGCCGGCATCCACGTGTTCATCCTGGGCTGC
TTCAGCGCCGGACTGCCCAAGACCGAGGCCAACTGGGTGAACGTGATCAGCGACCTGAAGAA
GATCGAGGACCTGATCCAGAGCATGCACATCGACGCCACCCTGTACACCGAGAGCGACGTGC
ACCCCAGCTGCAAGGTGACCGCCATGAAGTGCTTTCTGCTGGAACTGCAGGTGATCAGCCTG
GAAAGCGGCGACGCCAGCATCCACGACACCGTGGAGAACCTGATCATCCTGGCCAACAACAG
CCTGAGCAGCAACGGCAACGTGACCGAGAGCGGCTGCAAAGAGTGCGAGGAACTGGAAGAGA
AGAACATCAAAGAGTTTCTGCAGAGCTTCGTGCACATCGTGCAGATGTTCATCAACACCAGC
(SEQ ID NO: 118)

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFLLCARPRRSPAQ
EDGKVYINMPGRGRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKP
QRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALP
PRQCTNYALLKLAGDVESNPGPMEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQEDG
SVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSNAKDPRGMYQCKGSQNKSKPLQVYYR
MCQNCIELNAATISGFLFAEIVSIFVLAVGVYFIAGQDGVRQSRASDKQTLLPNDQLYQPLK
DREDDQYSHLQGNQLRRNVKQTLNFDLLKLAGDVESNPGPMEHSTFLSGLVLATLLSQVSPF
KIPIEELEDRVFVNCNTSITWVEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDKES
TVQVHYRMCQSCVELDPATVAGIIVTDVIATLLLALGVFCFAGHETGRLSGAADTQALLRND
QVYQPLRDRDDAQYSHLGGNWARNKEGRGSLLTCGDVEENPGPMQSGTHWRVLGLCLLSVGV
WGQDGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDH
LSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITGG
LLLLVYYWSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLYSGLNQR
RIGPQCTNYALLKLAGDVESNPGPMRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGC
FSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISL
ESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS
(SEQ ID NO: 119)

GTGATGAGCGTGGCCACCATCGTGATCGTGGACATCTGCATCACCGGCGGCCTGCTGCTGCT
GGTGTACTACTGGAGCAAGAACAGAAAGGCCAAGGCCAAGCCCGTGACCAGAGGCGCCGGCG
CCGGCGGCAGACAGAGAGGCCAGAACAAGGAGAGACCCCCCCCCGTGCCCAACCCCGACTAC
GAGCCCATCAGAAAGGGCCAGAGAGACCTGTACAGCGGCCTGAACCAGAGAAGAATCGGACC
GCAGTGTACTAATTATGCTCTCTTGAAATTGGCTGGAGATGTTGAGAGCAATCCCGGGCCCA
TGCGCATTAGCAAGCCCCACCTGCGGAGCATCAGCATCCAGTGCTACCTGTGCCTGCTGCTG
AACAGCCACTTCCTGACCGAGGCCGGCATCCACGTGTTCATCCTGGGCTGCTTCAGCGCCGG
ACTGCCCAAGACCGAGGCCAACTGGGTGAACGTGATCAGCGACCTGAAGAAGATCGAGGACC
TGATCCAGAGCATGCACATCGACGCCACCCTGTACACCGAGAGCGACGTGCACCCCAGCTGC
AAGGTGACCGCCATGAAGTGCTTTCTGCTGGAACTGCAGGTGATCAGCCTGGAAAGCGGCGA
CGCCAGCATCCACGACACCGTGGAGAACCTGATCATCCTGGCCAACAACAGCCTGAGCAGCA
ACGGCAACGTGACCGAGAGCGGCTGCAAAGAGTGCGAGGAACTGGAAGAGAAGAACATCAAA
GAGTTTCTGCAGAGCTTCGTGCACATCGTGCAGATGTTCATCAACACCAGC(SEQ ID NO:
120)

MKWKALFTAAILQAQLPITEAQSFGLLDPKLCYLLDGILFIYGVILTALFLRSKRSRLLHSD
YMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEY
DVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGL
STATKDTYDALHMQALPPRQCTNYALLKLAGDVESNPGPMEQGKGLAVLILAIILLQGTLAQ
SIKGNHLVKVYDYQEDGSVLLTCDAEAKNITWFKDGKMIGFLTEDKKKWNLGSNAKDPRGMY
QCKGSQNKSKPLQVYYRMCQNCIELNAATISGFLFAEIVSIFVLAVGVYFIAGQDGVRQSRA
SDKQTLLPNDQLYQPLKDREDDQYSHLQGNQLRRNVKQTLNFDLLKLAGDVESNPGPMEHST
FLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSITWVEGTVGTLLSDITRLDLGKRILDP
RGIYRCNGTDIYKDKESTVQVHYRMCQSCVELDPATVAGIIVTDVIATLLLALGVFCFAGHE
TGRLSGAADTQALLRNDQVYQPLRDRDDAQYSHLGGNWARNKEGRGSLLTCGDVEENPGPMQ
SGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSISGTTVILTCPQYPGSEILWQHNDK
NIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENCMEMD
VMSVATIVIVDICITGGLLLLVYYWSKNRKAKAKPVTRGAGAGGRQRGQNKERPPPVPNPDY
EPIRKGQRDLYSGLNQRRIGPQCTNYALLKLAGDVESNPGPMRISKPHLRSISIQCYLCLLL
NSHFLTEAGIHVFILGCFSAGLPKTEANWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSC
KVTAMKCFLLELQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEKNIK
EFLQSFVHIVQMFINTS (SEQ ID NO: 121)

[0139] **UTNK15-28-DAP10**: refers to full length CD3zeta comprising a fusion with an intracellular co-stimulatory domain derived from DAP10 and an intracellular co-stimulatory domain derived from CD28, full length CD3 gamma, full length CD3 delta, and full length CD3 epsilon linked to IL15, it may be represented by a nucleotide sequence that is at least, or exactly, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 122. In certain embodiments, a UTNK15-28-DAP10 amino acid sequence may be represented by an amino acid sequence that is at least, or exactly, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 123.

ATGAAGTGGAAGGCGCTTTTCACCGCGGCCATCCTGCAGGCACAGTTGCCGATTACAGAGGC
ACAGAGCTTTGGCCTGCTGGATCCCAAACTCTGCTACCTGCTGGATGGAATCCTCTTCATCT
ATGGTGTCATTCTCACTGCCTTGTTCCTGAGGAGTAAGAGGAGCAGGCTCCTGCACAGTGAC

DAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAE
AYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPRQCTNYALLKLAGDVESNPG
PMEQGKGLAVLILAIILLQGTLAQSIKGNHLVKVYDYQEDGSVLLTCDAEAKNITWFKDGKM
IGFLTEDKKKWNLGSNAKDPRGMYQCKGSQNKSKPLQVYYRMCQNCIELNAATISGFLFAEI
VSIFVLAVGVYFIAGQDGVRQSRASDKQTLLPNDQLYQPLKDREDDQYSHLQGNQLRRNVKQ
TLNFDLLKLAGDVESNPGPMEHSTFLSGLVLATLLSQVSPFKIPIEELEDRVFVNCNTSITW
VEGTVGTLLSDITRLDLGKRILDPRGIYRCNGTDIYKDKESTVQVHYRMCQSCVELDPATVA
GIIVTDVIATLLLALGVFCFAGHETGRLSGAADTQALLRNDQVYQPLRDRDDAQYSHLGGNW
ARNKEGRGSLLTCGDVEENPGPMQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSI
SGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDHLSLKEFSELEQSGYYVCYPRG
SKPEDANFYLYLRARVCENCMEMDVMSVATIVIVDICITGGLLLLVYYWSKNRKAKAKPVTR
GAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLYSGLNQRRIGPQCTNYALLKLAGDVESN
PGPMRISKPHLRSISIQCYLCLLLNSHFLTEAGIHVFILGCFSAGLPKTEANWVNVISDLKK
IEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLELQVISLESGDASIHDTVENLIILANNS
LSSNGNVTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS (SEQ ID NO: 123)

[0140] As depicted in FIG. 3 and described above, the term "linked" refers to being present on the same polynucleotide vector and does not necessarily mean that the two polypeptides are expressed as one polypeptide. For example, a cytokine produced from a vector of the disclosure may ultimately be produced as a separate molecule from any one or more TCR/CD3 receptor complex components. Whereas, the term "fused" or "fusion" refers to two polypeptides that comprise a peptide bond conjoining the two molecules, i.e. that the two polypeptides are covalently bound by an amide bond and are not separated by a splitting element, such as a 2A element.

[0141] One specific example of a TCR that may be utilized in the cells is NY-ESO TCR, and specific examples of sequences include at least the following:

[0142] TCRα:

XQEVTQIPAALSVPEGENLVLNCSFTDSAIYNLQWFRQDPGKGLTSLLLIQSSQREQTSGRL
NASLDKSSGRSTLYIAASQPGDSATYLCAVRPLYGGSYIPTFGRGTSLIVHPYIQNPDPAVY
QLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAVAWSNKSDFA
CANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLLKVAGFNLLM
TLRLWSS (SEQ ID NO: 25)

[0143] TCRβ:

GVTQTPKFQVLKTGQSMTLQCAQDMNHEYMSWYRQDPGMGLRLIHYSVGAGITDQGEVPNGY
NVSRSTTEDFPLRLLSAAPSQTSVYFCASSYVGNTGELFFGEGSRLTVLEDLKNVFPPKVAV
FEPSEAEISHTQKATLVCLATGFYPDHVELSWWVNGKEVHSGVSTDPQPLKEQPALNDSRYC
LSSRLRVSATFWQNPRNHFRCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSES
YQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRG (SEQ ID NO: 26)

[0144] In certain embodiments, a TCR may comprise a TCR alpha chain variable region encoded by a nucleotide sequence that is at least, or exactly, 80%, 81%, 82%, 83%, 84%, 85%,

AGACCAGCGTGTACTTCTGCGCCATCAGCGACTACGAGGGCACCGAGGCCTTTTTTGGCCAA
GGCACAAGACTGACCGTGGTGGAAGATCTCCGGAACGTGACCCCCCCTAAAGTGACCCTGTT
CGAACCCAGCAAGGCCGAGATCGCCAACAAGCAGAAAGCCACCCTCGTGTGCCTGGCCAGAG
GCTTCTTCCCCGACCATGTGGAACTGTCTTGGTGGGTCAACGGCAAAGAGGTGCACAGCGGA
GTGTCCACCGACCCTCAGGCCTACAAAGAGAGCAACTACAGCTACTGCCTGAGCAGCAGACT
GCGGGTGTCCGCCACCTTCTGGCACAACCCCCGGAACCACTTCAGATGCCAGGTGCAGTTTC
ACGGCCTGAGCGAAGAGGACAAGTGGCCCGAAGGCTCCCCCAAGCCCGTGACCCAGAATATC
TCTGCCGAGGCCTGGGGCAGAGCCGACTGTGGAATTACCAGCGCCAGCTACCACCAGGGCGT
GCTGTCTGCCACCATCCTGTACGAGATCCTGCTGGGCAAGGCCACCCTGTACGCCGTGCTGG
TGTCTGGCCTGGTGCTGATGGCCATGGTCAAGAAGAAGAACAGC (SEQ ID NO: 151)

ATGCTGTGTTCTCTGCTGGCTCTGCTGCTGGGCACCTTTTTTGGCGTCAGAAGCCAGACCAT
CCACCAGTGGCCTGCTACACTGGTGCAGCCTGTTGGAAGCCCTCTGAGCCTGGAATGTACCG
TGGAAGGCACCAGCAATCCCAACCTGTACTGGTACAGACAGGCCGCTGGAAGAGGACTGCAG
CTGCTGTTTTACAGCGTCGGCATCGGCCAGATCAGCAGCGAGGTTCCACAGAATCTGAGCGC
CAGCAGACCCCAGGACAGACAGTTTATCCTGAGCAGCAAGAAGCTGCTGCTGAGCGACAGCG
GCTTCTACCTGTGTGCTTGGAGCCTCGGAGCCGGCTACACCGACACACAGTATTTTGGCCCT
GGCACCAGACTGACCGTGCTGGAAGATCTCCGGAACGTGACCCCCCCTAAAGTGACCCTGTT
CGAACCCAGCAAGGCCGAGATCGCCAACAAGCAGAAAGCCACCCTCGTGTGCCTGGCCAGAG
GCTTCTTCCCCGACCATGTGGAACTGTCTTGGTGGGTCAACGGCAAAGAGGTGCACAGCGGA
GTGTCCACCGACCCTCAGGCCTACAAAGAGAGCAACTACAGCTACTGCCTGAGCAGCAGACT
GCGGGTGTCCGCCACCTTCTGGCACAACCCCCGGAACCACTTCAGATGCCAGGTGCAGTTTC
ACGGCCTGAGCGAAGAGGACAAGTGGCCCGAAGGCTCCCCCAAGCCCGTGACCCAGAATATC
TCTGCCGAGGCCTGGGGCAGAGCCGACTGTGGAATTACCAGCGCCAGCTACCACCAGGGCGT
GCTGTCTGCCACCATCCTGTACGAGATCCTGCTGGGCAAGGCCACCCTGTACGCCGTGCTGG
TGTCTGGCCTGGTGCTGATGGCCATGGTCAAGAAGAAGAACAGC (SEQ ID NO: 152)

METLLKVLSGTLLWQLTWVRSQQPVQSPQAVILREGEDAVINCSSSKALYSVHWYRQKHGEA
PVFLMILLKGGEQKGHEKISASFNEKKQQSSLYLTASQLSYSGTYFCGTANSGGSNYKLTFG
KGTLLTVNPN (SEQ ID NO: 153)

MLLITSMLVLWMQLSQVNGQQVMQIPQYQHVQEGEDFTTYCNSSTTLSNIQWYKQRPGGHPV
FLIQLVKSGEVKKQKRLTFQFGEAKKNSSLHITATQTTDVGTYFCAGALPRAGSYQLTFGKG
TKLSVIPN (SEQ ID NO: 154)

IQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKTVLDMKAMDSKSNGAI
AWSNQTSFTCQDIFKETNATYPSSDVPCDATLTEKSFETDMNLNFQNLSVMGLRILLLKVAG
FNLLMTLRLWSS (SEQ ID NO: 155)

IQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAV
AWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLL
KVAGFNLLMTLRLWSS (SEQ ID NO: 156)

IQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAV
AWSNKSDFACANAFNNSIIPEDTFFPSSDVPCDVKLVEKSFETDTNLNFQNLSVIGFRILLL
KVAGFNLLMTLRLWSS (SEQ ID NO: 157)

METLLKVLSGTLLWQLTWVRSQQPVQSPQAVILREGEDAVINCSSSKALYSVHWYRQKHGEA
PVFLMILLKGGEQKGHEKISASFNEKKQQSSLYLTASQLSYSGTYFCGTANSGGSNYKLTFG
KGTLLTVNPNIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTMESGTFITDKTVLDMK