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(54) RECOMBINANT T-CELL RECEPTORS THAT
BIND THE NY-ESO-1 AND/OR LAGE-1A
CANCER ANTIGENS

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(52) U.S. Cl.

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40/4267 (2025.01); **A61K 40/4269** (2025.01);

A61P 35/00 (2018.01); **C12N 5/0636**

(2013.01); **C12N 2510/00** (2013.01)

ABSTRACT

The present invention relates to recombinant T-cell receptors that bind specifically, in a MHC restricted manner, to a particular epitope present in the shared cancer-testis antigen known as NY-ESO-1 and/or a particular epitope present in the closely related antigen LAGE-1. The invention provides T-cell receptor related polypeptides, fragments, and functional variants thereof, as well as nucleic acids encoding the T-cell receptor polypeptides of the invention, recombinant expression vectors, and genetically modified cells (for example, T-cells) expressing the T-cell receptors, and their use in methods for diagnosing, treating or preventing cancer in a subject.

Specification includes a Sequence Listing.

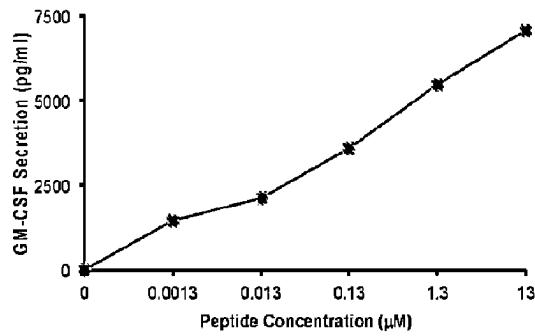
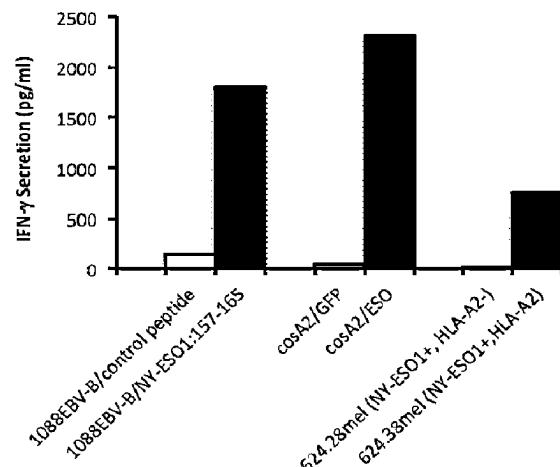


FIGURE 1A

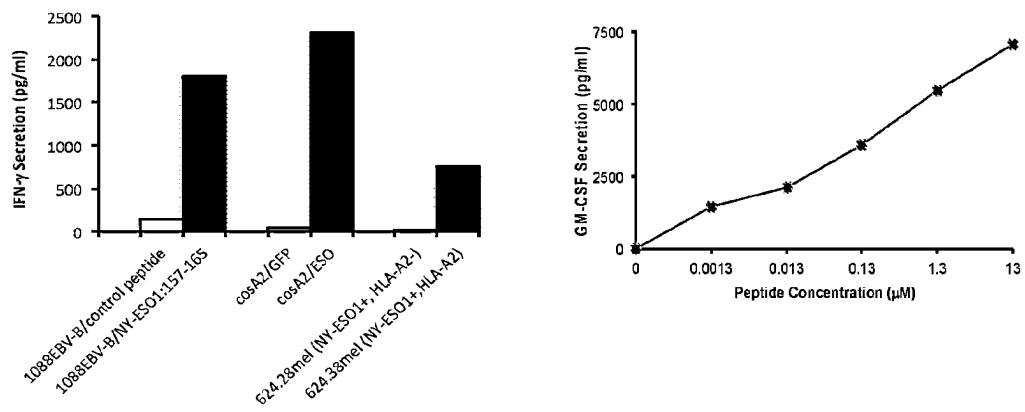


FIGURE 1B

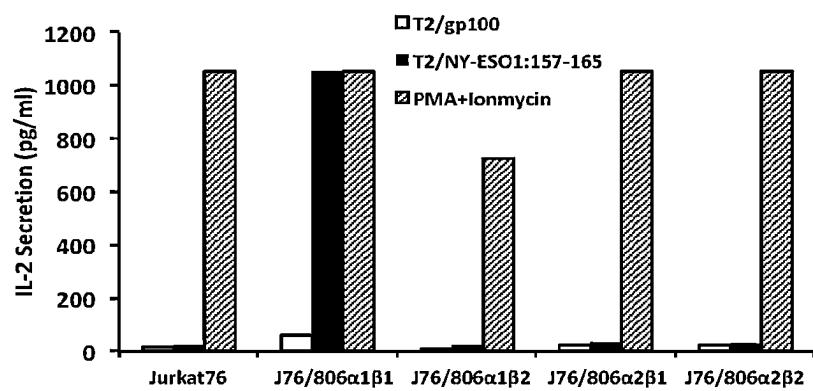


FIGURE 1C

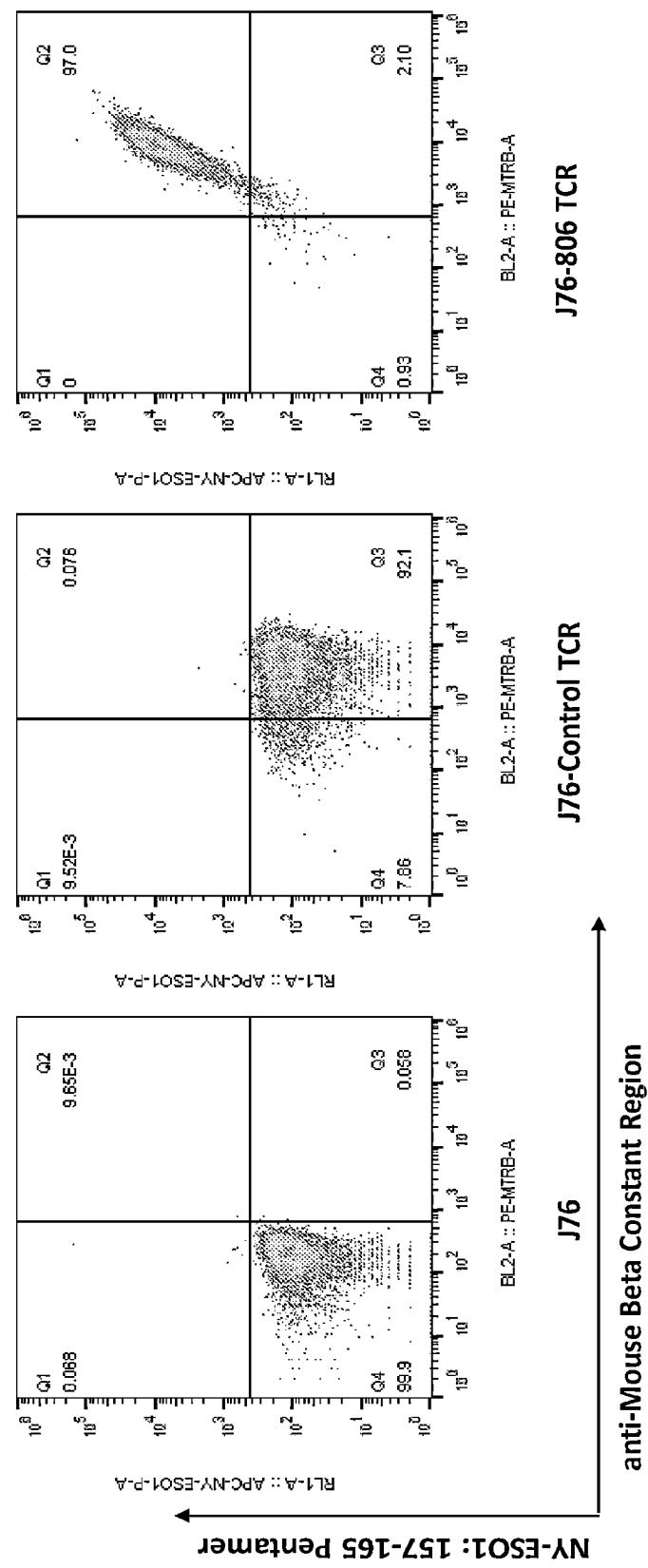


FIGURE 1D

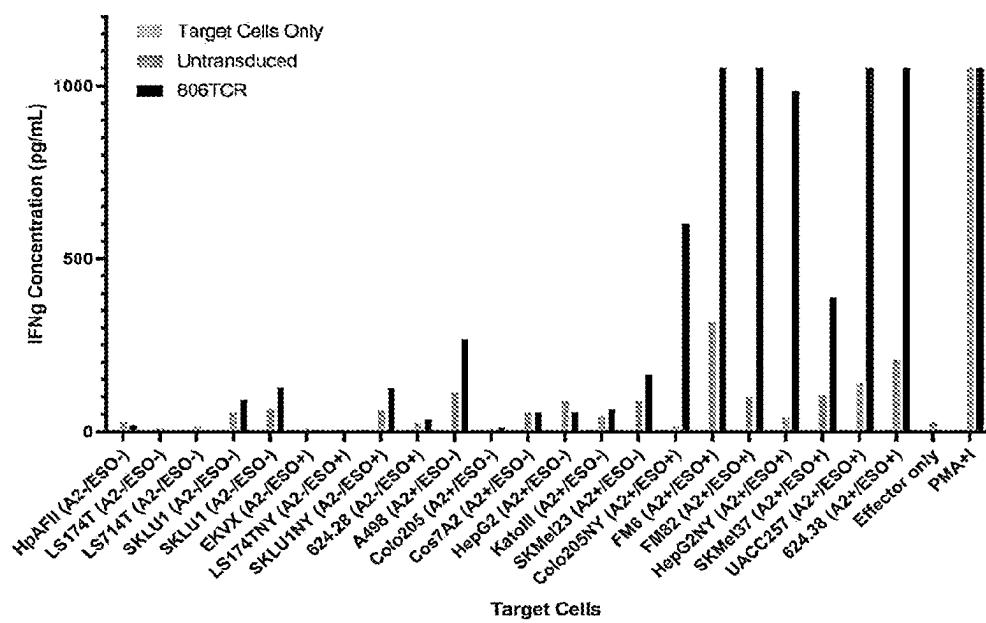


FIGURE 1E

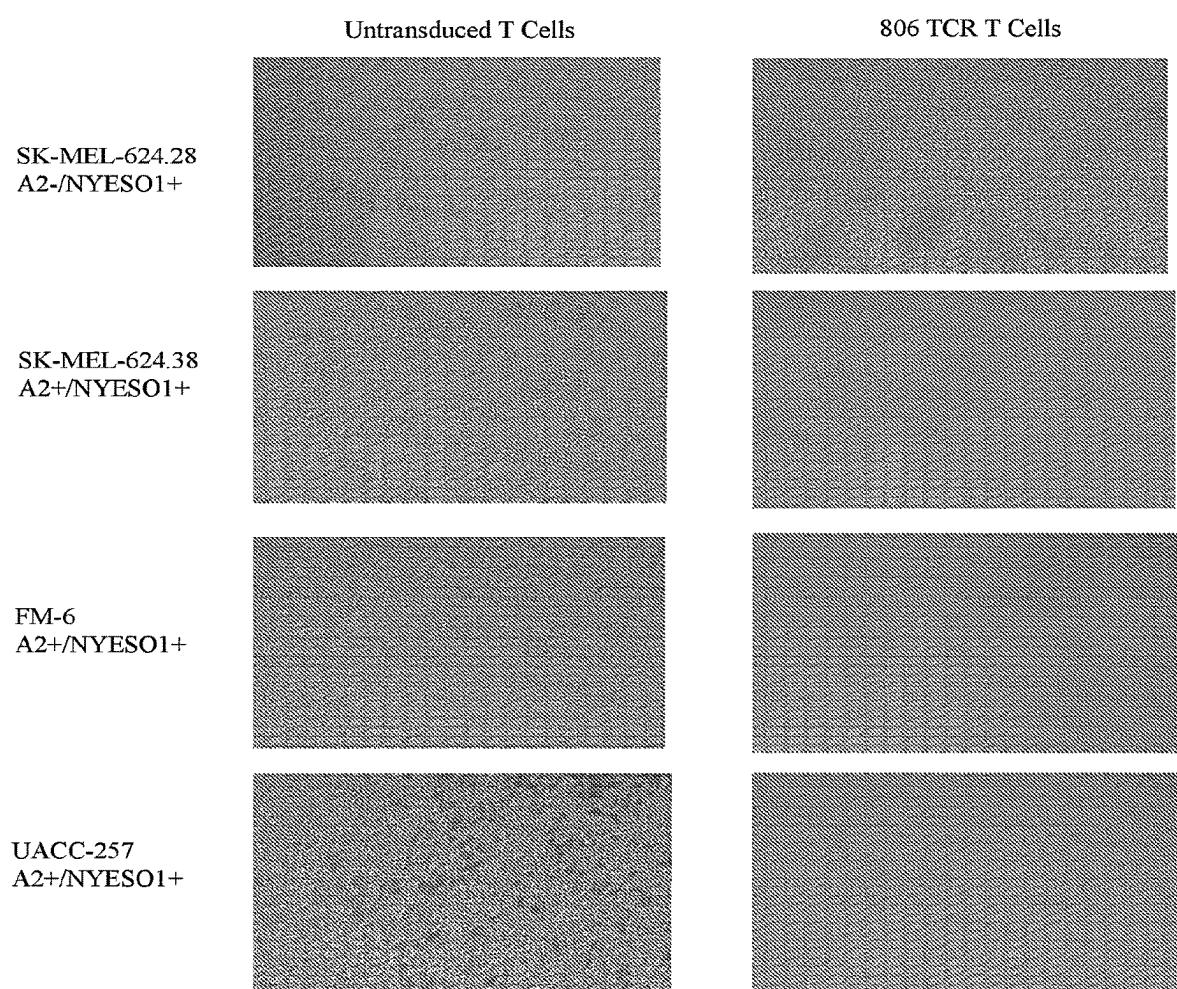


FIGURE 2A

METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFTDSALYNLQWFRQDPGKGLT
SLLLIQSSOREQTSGRLNASLDKSSGRSTLYIAASQLGDSATYLCAYLENTDKLIFGTGTRLQV
FPIQNPDPAVYQLRDSKSSDKSVCLTFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAV
AWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFTDTNLNFQNLNSVIGFRILLKV
AGFNLLMTLRLWSS

FIGURE 2B

ATGGAGACTCTGCTGGTCTCCTCATCCTGTGGCTACAGCTGCAGTGGTCTCGTCCAAGCAGG
AGGTGACCCAAATT CCTGCCGCGTGTCCGTGCCAGGGCGAGAACCTGGTGCTCAACTGCTC
CTTCACCGAGACGGCGCATCTACAACCTGCAGTGGTCCGCCAGGACCCCAGGAAGGGCCTGACC
AGCCTCTGCTTATCCAGAGCTCCAGCGGAAACAGACATCAGGCCGCTGAATGCAAGTTGG
ACAAATCTCTGCCGGTGCACCTGTATATTGCGGCTTCCCAGCTGGTGATTCTGCTACCTA
CCTGTGCCGCGTGTGCTAACACAGGAGAACAGCTGATCTTCGGCACCGGACTCGCCTGCAGGTT
TTTCCAATCCAGAACCCCTGACCCCTGCCGTGTACCAAGCTGAGAGACTCTAAATCCAGTGACAAGT
CTGCTGCCTATTCAACGATTGATTCTCAAACAAATGTGTACAAAGTAAGGATTCTGATGT
GTATATCACAGACAAAATGTGCTAGACATGAGGTCTATGGACTCAAGAGCAACAGTGCTGTG
GCCTGGAGCAACAAATCTGACTTGCATGTGAAACGCCCTCAACAAACAGCATTATCCAGAAC
ACACCTTCTTCCCCAGCCCAGAAAGTCTGTGATGTCAGCTGGTGAGAAAAGCTTGAAC
AGATACGAACCTAAACTTCAAAACCTGTCAAGTGTGATTGGGTTCCGAATCCTCCTGAAAGTG
GCCGGGTTAATCTGCTCATGACGCTGCGGCTGTGGTCCAGC

FIGURE 2C

MGTSLLCWMALCLLGADHADTGVSQNPRYKITKRGQNVTFRCDPISEHNRLYWYRQTLGQGPEF
LTYEONEAQLEKSRLLSDRFSAPERPKGSFSTLEIQRTEQGDSAMYLCASSSOSYEQYFGPGTRL
TVTEDLKNVFPKVAVFEPSEAEISHTQKATLVCLATGFYPDHVELSWWVNGKEVHSVGSTDPO
PLKEQPALNDSRYCLSSRLRVSATFWQNPRNHFRQCQVFYGLSENDEWTQDRAKPVTQIVSAEA
WGRADCGBTSESYQQGVLSATILYEILLGKATLYAVLVSALVLMAMVKRKDSRG

FIGURE 2D

ATGGGCACGAGCTTGCTTGCTGGATGCCCTGTGCCTGCTGGGGCGGACCATGCAGACACCG
GCGTCAGCCAGAATCCACGTTACAAGATTACCAAGCGCGGCCAGAACGTGACCTTCAGATGTGA
CCCCATCTCGGAGCAGAACCGGCTGTATTGGTACCGCCAGACTCTTGGACAGGGCCCTGAGTTC
CTGACCTACTTCCAGAACGAGGCTCAAGCTGGAGAAGTCCCGCCTGTTGAGTGACAGGTTTCAG
CCGAGCGGCCGAAAGGCTCCTCTGACCCCTAGAGATCCAGCGCACTGAACAAAGGTGATTCTGC
CATGTACCTGTGCCTCTCCCTCCAGAGCTACGAGCAGTACTTGGTCCCGGGACCCGTCTC
ACCGTACAGAGGACCTGAAAAACGTGTTCCACCCAAGGTGCGCTGTGTTGAGCCATCAGAAG
CAGAGATCTCCCACACCCAAAAGGCCACACTGGTGTGCCACAGGCTTCTACCCGACCA
CGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGTCAAGCACAGACCCGAG
CCCCCTCAAGGAGCAGCCCCGCCCTCAATGACTCCAGATACTGCCCTGAGCAGCCGCTGAGGGTCT
CGGCCACCTTCTGGCAGAACCCCCGCAACCACCTCCGCTGTCAAGTCCAGTTCTACGGGCTCTC
GGAGAATGACGAGTGGACCCAGGATAGGGCAAACCTGTCACCCAGATGTCAGCGCCGAGGCC
TGGGGTAGAGCAGACTGTGGCTTCACCTCCGAGTCTTACCAAGCAAGGGGTCTGTCTGCCACCA
TCCTCTATGAGATCTGCTAGGGAAGGCCACCTGTATGCCGTGCTGGTCAGTGCCCTCGTGC
GATGGCCATGGTCAAGAGAAAGGATTCCAGAGGC

FIGURE 3A

MGTSLLCWMALCLLGADHADTGVSQNPRYKITKRGQNVTFRCDPISEHNRLYWYRQTLGQQPEFLTYFQNEAQLEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYLCASSSQSYEQYFGPGTRLTVTEDLRNVTPPKVSIFPSKAEIANKQATLVCLARGFFPDHVELSWWVNGKEVHSGVCTDPQAYKESNYSYCLSSRLRVSATFWHNPBNHFRQCQVFHGLSEEDKWPEGSPKPVTQNI SAEAWGRA DCGITSASYQQGVLSATI LYI E ILLGKATLYAVLVSTL VVMAMVKRKNSRAKRSGSG **ATNFSLLK** **QAGDVEENPGPMETLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCST** DS A I YNL Q WFRQDPGKG L TS L L I QSS QRE QTSGR L N A S L D K S S G R S T L Y I A A S Q L G D S A T Y L C A V L F N T D K L I F GTGTRLQVFPIQNPEPAVYQLKDPRSQDSTLCLFTDFDSQINVPKTME GT FITDKCVLDM KAMDSKNSNGAIAWSNQTSFTCQDI FKETNATYPSSDVPCDATLTEKSFETDMNLFQNLLVIVL RILLLKVAGFNLLMTLRLWSS

FIGURE 3B

FIGURE 3C

METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVNCFTDSAIYNLQWFRQDPGKGLT
SLLLIQSSQREQTSGRLNASLDKSSGRSTLYIAASQLGDSATYLCAVLFNTDKLIFGTGTRLQV
FPIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQSKDSDVYITDKTVLDMRSMDFKSNSAV
AWSNKSDFACANAFNNSIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQNLSVIGFRILLKV
AGFNLLMTLRLWSRAKRSGSGATNFSLLKQAGDVEENPGPMGTSLLCWMALCLLGADHADTGV
SQNPRYKITKRGQNVTFRCDPISEHNRLYWYRQTLGQGPFEFLTYFQNEAQLEKSRLLSDRFSAE
RPKGSFSTLEIQRTEQGDSAMYLCASSSQSYEQFGPGTRLTVDLKNVFPPKVAVFEPSEAEI
SHTQKATLVCLATGFYPDHVELWWVNGKEVHSGVSTDQPQLKEQPALNDSYCLSSRLRVSAT
FWQNPRNHFRQCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWGRADCGFTSESYQQGVLSATILY
EILLGKATLYAVLVSALVIMAMVKRKDSRGEFGSGEGRGSLLTCGDVEENPGPprgwtalclls
11psgfms1dnngtatpelptqgtfsnvstnvsygetttpstlgsts1hpvsqhgneattnite
ttvkftstsvitsvygntnssvqsqtsvistvfttpanvstpettlkpslspgnvsdlsttsts
latstpkytssspilsdiakaeikcsgirevkltqgicleqnktsscaefkkdrgeglarvlcg
eeqadadagaqvcslllaqsevrpqcllvlanrteissklqlmkhqsdlkklgildfpeqdv
ashqsysqktliavtsgallavlgityflmnrrswsptgerlelep

FIGURE 3D

ATGGAGACTCTGCTGGTCTCCTCATCCTGTGGCTACAGCTGCAGTGGTCTCGTCCAAGCAGG
AGGTGACCAAATTCTGCCGCGTCCGTGCCCCAGGGCGAGAACCTGGTGCTCAACTGCTC
CTTCACCGACAGCGCCATCTACAACCTGCAGTGGTCCGCCAGGACCCCAGGAAGGGCCTGACC
AGCCTCTGTTATCCAGAGCTCCAGCGAACAGACATCAGGCCGCTGAATGCAAGTTGG
ACAAATCTCTGCCGGTCACCGCTGTATATTGCGGCTTCCCAGGCCGGTGATTCTGCTACCTA
CCTGTGCCGTGCTCAACACGGACAAGCTGATCTCGGCACCGGACTCGCCTGCAGGTT
TTTCAATCCAGAACCCCTGACCCCTGCCGTGACAGCTGAGAGACTCTAAATCCAGTGACAAGT
CTGTCTGCCTATTCAACGATTTGATTCTCAAACAAATGTGTCACAAAGTAAGGATTCTGATGT
GTATATCACAGACAAAATGTCAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTG
GCCTGGAGCAACAAATCTGACTTGCATGTGCAAACGCCCTCAACAAACAGCATTATTCCAGAAC
ACACCTCTCCCCAGCCCAGAAAGTCCCTGTGATGTCAGCTGGTCAGGAGAAAAGCTTGAAC
AGATAACGAACCTAAACTTCAAACCTGTCAGTGATTGGGTTCCGAATCCTCCTGAAAGTG
GCCGGGTTAATCTGCTCATGACGCTGCCGTGTTGAGCTGGTCAGGAGAAAAGCTTGAAC
GAGCCACCAACTCAGCCTGCTGAAGCAGGCCGGCACGTGGAGGAGAACCCGGCCCATGGG
CACGAGCTGCTGCTGGATGGCCCTGTGCTGCTGGGGCGGACATGCAGACACCGCGTC
AGCCAGAATCCACGTACAAGATTACCAAGCGCGGCCAGAACGTGACCTCAGATGTGACCCCA
TCTCGGAGCACAACCGCCTGTATTGGTACCGCCAGACTCTGGACAGGGCCCTGAGTTCTGAC
CTACTTCCAGAACGAGGCTCAGCTGGAGAAGTCCCGCCTGTTGAGTGACAGGTTTCAGCCGAG
CGGCCGAAAGGCTCCTCTGACCCCTAGAGATCCAGCGCACTGAACAAGGTGATTCTGCCATGT
ACCTGTGCGCCTCTTCCAGAGCTACGAGCAGTACTTGGTCCCAGGACCCGCTCACCCT
GACAGACCTGAAAAAGTGTGCTCCACCAAGGTGCTGTGTTGAGCCATCAGAACAGAGATC
TCCCACACCCAAAAGGCCACACTGGTGTGCCCTGCCACAGGCTTCTACCCGACCACGTGGAGC
TGAGCTGGTGGGTGAATGGGAAGGAGGTGCACAGTGGGTCAAGCACAGACCCGCAGCCCTCAA
GGAGCAGCCCGCCCTCAATGACTCCAGATACTGCCTGAGCAGCCGCTGAGGGTCTCGGCCACC
TTCTGGAGAACCCCGCAACCACCTCCGCTGTCAAGTCCAGTTCTACGGGCTCTCGGAGAATG
ACGAGTGGACCCAGGATAGGGCAAACCTGTCACCCAGATCGTCAGCGCCGAGGCCTGGGTAG
AGCAGACTGTGGCTTCACCTCCGAGTCTTACAGCAAGGGTCTGTCTGCCACCACCTCTAT
GAGATCTTGCTAGGGAAAGGCCACCTGTATGCCGTGGTCAGTGCCCTCGTGTGATGGCCA
TGGTCAGAGAAAGGATTCCAGAGGCGAATTGGCTCAGGCAGGGCAGAGGCAGTCTGCTAAC
ATGCGGTGATGTCGAAGAAAATCTGGCCCAccgcggggctggaccgcgttgcgtgagt
ttgctgcctctgggtcatgagttctgacaacaacggtaactgctacccagagttacctacc
agggAACATTTCAAATGTTCTACAAATGTATCCTACCAAGAAACTACAAACACCTAGTACCT
tggaaagtaccagcctgcaccctgtgtcaacatggcaatgaggccacaacaaacatcacagaa
acgacagtcaaattcacatctacacctgtgataacctcagttatggaaacacaaaactcttc
tccagtcacagacacctgttaatcagcacagtgtaactcaccaccccagccaacgttcaactcc
gacaacccctgaagcctagcctgtcacctggaaatgtttagacacccatcaccactagactag
cttgcacacatctccactaaaccctatacatcatcttcctatcctaagtgcacatcaaggcag
aaatcaaattgttcaggcatcagagaagtgaaattgactcagggcatctgcctggagcaaaataa
gacccctcagctgtcgaggatgttaagaaggacagggagagggcctggcccagtgctgtg
gaggagcaggctgtatgtatgtatgtatgtatgtatgtatgtatgtatgtatgtatgt
tgagacactcagttactgtgtttggccaaacagaacagaaattccagcaaaactccaact
tatgaaaaagcaccatctgacccatgtttactgtatgtatgtatgtatgtatgtatgt
gcaagccaccagagctattccaaaagaccctgattgcactggcacccctgctgg
ctgtctggcatcactggatattccatgtatgtatgtatgtatgtatgtatgtatgtatgt
gctggactagaaccatga

FIGURE 4A

		CDR
TRAV17-1a	METLLGVSLVILWLQLARVN SQQG-EEDPQALSIQEGERATMNC SYKT-SIINNLOWYRQN	58
1G4a	METLLG--LLI LWLQLQWVS SKQEV TQI PAALS VPEGENI VLNC SFTDSAT YNLQWFRQD	58
BC1a	METLLG--LLI LWLQLQWVS SKQEV TQI PAALS VPEGENI VLNC SFTDSAT YNLQWFRQD	58
1G4c113a	METLLG--LLI LWLQLQWVS SKQEV TQI PAALS VPEGENI VLNC SFTDSAT YNLQWFRQD	58
UC-1E4a	METLLG--LLI LWLQLQWVS SKQEV TQI PAALS VPEGENI VLNC SFTDSAT YNLQWFRQD	58
806TCRa	METLLG--LLI LWLQLQWVS SKQEV TQI PAALS VPEGENI VLNC SFTDSAT YNLQWFRQD	58
	***** *:***** *.*: * * *: **** .:****: . :* ****:***:	
	CDR	
TRAV17-1a	SGRGLVHLILIRENEKHSGRRLRVTLDTSKSSSLITASRAADTASYFCRT-----D	112
1G4a	PGKGLTSLLL IQSSQNSQEQTSGRLNASLDKSSGRSTLYIAASQFGDSATYLCAVNPQT---SG	116
BC1a	PGKGLTSLLL IQSSQNSQEQTSGRLNASLDKSSGRSTLYIAASQFGDSATYLCAVNPQT---TG	116
1G4c113a	PGKGLTSLLL IFWQNSQEQTSGRLNASLDKSSGRSTLYIAASQFGDSATYLCAVNPFL---LD	116
UC-1E4a	PGKGLTSLLL IQSSQNSQEQTSGRLNASLDKSSGRSTLYIAASQFGDSATYLCAVNSTAYSGG	118
806TCRa	PGKGLTSLLL IQSSQNSQEQTSGRLNASLDKSSGRSTLYIAASQFGDSATYLCAVNL-----	114
	:. *:*** :**; * * *..:***.*. *: * *:***: .:***:***.	
	CDR	
TRAV17-1a	GAGKSTYGDGTTLTVKPNIQKPDP AVYQLRDSKSSDKSVCLFTDFDSQTNVSQS KDS D VY	172
1G4a	GXYIPTFGRGTSLIVH PYI QNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQS KDS D VY	176
BC1a	GXYIPTFGRGTSLIVH PYI QNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQS KDS D VY	176
1G4c113a	GXYIPTFGRGTSLIVH PYI QNPDPAVYQLRDSKSSDKSVCLFTDFDSQTNVSQS KDS D VY	176
UC-1E4a	GRDGLITNGKGTHLIIQPYI QNPDPAVYQLKDPRSQ DSTLCLFTDFDSQINVPKTMESGTF	178
806TCRa	--TDKLIINGTGT RLQVFPIQNP E PAVYQLKDPRSQ DSTLCLFTDFDSQINVPKTMESGTF	172
	: * * * * : * *:***:*****: * :*. ,:*****: * * : : :*..:	
	CDR	
TRAV17-1a	ITDKTVLDMRSMDFKSNSAVAWSNKSD FACANAFNN SIIIPADTFFPSPESSCDVKLVEKS	232
1G4a	ITDKTVLDMRSMDFKSNSAVAWSNKSD FACANAFNN SIIIPADTFFPSPESSCDVKLVEKS	236
BC1a	ITDKTVLDMRSMDFKSNSAVAWSNKSD FACANAFNN SIIIPADTFFPSPESSCDVKLVEKS	236
1G4c113a	ITDKTVLDMRSMDFKSNSAVAWSNKSD FACANAFNN SIIIPADTFFPSPESSCDVKLVEKS	236
UC-1E4a	ITDKCVLDMKAMDSKSN GAI AWSNQ TSFTCQDIFKET----NATYPSSDVPCDATLTEKS	234
806TCRa	ITDKCVLDMKAMDSKSN GAI AWSNQ TSFTCQDIFKET----NATYPSSDVPCDATLTEKS	226
	***** *:***: *:***: .:***: * : *: : : :* * : * *..*.*:***	
	CDR	
TRAV17-1a	FETDTNLFQNL SVIGFRILLLK VAGFNLLMLT LRLWSS-	270
1G4a	FETDTNLFQNL SVIGFRILLLK VAGFNLLMLT LRLWSS-	274
BC1a	FETDTNLFQNL SVIGFRILLLK VAGFNLLMLT LRLWSS-	274
1G4c113a	FETDTNLFQNL SVIGFRILLLK VAGFNLLMLT LRLWSS-	274
UC-1E4a	FETDMNLFQNL LVIVLRLILLLK VAGFNLLMLT LRLWSS*	272
806TCRa	FETDMNLFQNL LVIVLRLILLLK VAGFNLLMLT LRLWSS*	266
	***** *:***** * * :*****:*****:*****	

FIGURE 4B

FIGURE 5A

METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLQCSFTDSAIYNLQWFRQDPGKGLT
SLLLIQSSQREQTSGRLQASLDKSSGRSTLYIAASQLGDSATYLCAVLFNTDKLIFGTGTRLQV
FPIQNPDPAVYQLRDSKSSDKSVCLFTDFDSQTQVSQSKDSDVYITDKTVLDMRSMDFKSNSAV
AWSQSKDFACANAFONSIIIPEDTFFPSPESSCDVKLVEKSFETDTNLNFQOLSVIGFRILLKV
AGFNLLMTLRLWSS

FIGURE 5B

ATGGAGACTCTGCTGGTCTCCTCATCCTGTGGCTACAGCTGCAGTGGTCTCGTCCAAGCAGG
AGGTGACCCAAATTCTGCCGCGTGTCCGTGCCGAGGGCGAGAACCTGGTGCTCCAGTGCTC
CTTCACCCACAGCGCCATCTACAACTTGCAGTGGTCCGCCAGGACCCCGGGAAGGGCCTGACC
AGCCTCTGTTATCCAGAGCTCCAGCGCGAACAGACATCAGGCCGCTGCCAGGCAAGTTGG
ACAAATCTCTGCCGGTGCACCTGTATATTGCGGCTTCCCAGCCGGTGATTCTGCTACCTA
CCTGTGCCGTGCTGTTAACACGGACAAGCTGATCTCGGCACCGGACTCGCCTGCAGGTT
TTTCCAATCCAGAACCCCTGACCCTGCCGTGTACCAGCTGAGAGACTCTAAATCCAGTGACAAGT
CTGTCTGCCTATTCAACGATTGATTCTCAAACACAGGTGTCACAAAGTAAGGATTCTGATGT
GTATATCACAGACAAAACTGTGCTAGACATGAGGTCTATGGACTTCAAGAGCAACAGTGCTGTG
GCCTGGAGCCAGAAATCTGACTTTGCATGTGCAAACGCCTTCCAGAACAGCATTATTCCAGAAG
ACACCTCTCCCCAGCCAGAAAGTCTGTGATGTCAAGCTGGTCGAGAAAAGCTTGAAAC
AGATACGAACCTAAACTTCAACAGCTGTCAGTGATTGGTTCCGAATCCTCCTGAAAGTG
GCCGGGTTAATCTGCTCATGACGCTGCCGTGTGGTCCAGC

FIGURE 5C

MGT SLLCWMALCLLGADHADTGVSQNPRYKITKRGQVTFRCDPISEHNRLYWYRQTLGQGPEF
LTYFQNEAQLEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYLCASSSQSYEQYFGPGTRL
TVTEDLKNVFPPKVAVFE PSEAE ISHTQKATLVCLATGFYPDHVELSWWVNGKEVHSVSTDPQP
LKEQPALQDSRYCLSSRLRVSATFWQNPRNHFCQVQFYGLSENDEWTQDRAKPVTQIVSAEAWG
RADCGFTSE SYQQGVLSATILYE ILLGKATLYAVLVSALVLMAMVKRKDSRG

FIGURE 5D

ATGGGCACGAGCTT GCTCTGCTGGATGGCCCTGTGCCTGCTGGGGCGGACCATGCAGACACCG
GCGTCAGCCAGAAATCCACGTACAAGATTACCAAGCGCGGCCAGCAGGTGACCTCAGATGTGA
CCCCATCTCGGAGCACAACCGCCTGTATTGGTACCGCCAGACTCTTGGACAGGGCCCTGAGTT
CTGACCTACTTCCAGAACGAGGCTCAGCTGGAGAAGTCCCCTGTTGAGTGACAGGTTTCAG
CCGAGCGGCCGAAAGGCTCCTCTCGACCCCTAGAGATCCAGCGCACTGAACAAGGTGATTCTGC
CATGTACCTGTGCGCCTCCTCTTCCAGAGCTACGAGCAGTACTTGGTCCCGGACCCGTCTC
ACCGTGACAGAGGACCTGAAAAACGTGTTCCCACCCAAGGTGCGCTGTGTTGAGCCATCAGAAG
CAGAGATCTCCACACCCAAAAGGCCACACTGGTGTGCCCTGGCACAGGCTTCTACCCCGACCA
CGTGGAGCTGAGCTGGTGGGTGAATGGGAAGGAGGTGCAAGTGGGTCAAGCACAGACCCGCAG
CCCCCTCAAGGAGCAGCCCCCCTCCAGGACTCCAGATACTGCCAGCAGCCGCTGAGGGTCT
CGGCCACCTTCTGGCAGAACCCCCGCAACCACCTCCGCTGTCAAGTCCAGTTCTACGGGCTCTC
GGAGAATGACGAGTGGACCCAGGATAGGGCAAACCTGTCACCCAGATCGTCAGCGCCGAGGCC
TGGGGTAGAGCAGACTGTGGCTTCACCTCCGAGTCTTACCAAGCAAGGGTCTGTCTGCCACCA
TCCTCTATGAGATCTTGCTAGGGAAAGGCCACCTTGTATGCCGTGGTCAGTGCCCTCGTGC
GATGCCATGGTCAAGAGAAAGGATTCCAGAGG

FIGURE 6A

METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLNCSFTDSAIYNLQWFQDPGKGLT
SLLLIQSSQREQTSGRLNASLDKSSGRSTLYIAASQLGDSATYLCAVLFNTDKLIFGTGTRLQV
FPIQNPEPAVYQLKDPRSQDSTLCLTFDSQINVPKTMESGTFITDKCVLDMKAMD SKSNGAI
AWSNQTSFTCQDIFKETNATYPSSDVPDCATLTEKSFE TDMNLNFQNLIVLIVLRIILLLKVAGFN
LLMTLRLWSS

FIGURE 6B

ATGGAGACTCTGCTGGTCTCCTCATCCTGTGGCTACAGCTGCAGTGGTCTCGTCCAAGCAGG
AGGTGACCCAAATTCTGCCGCGCTGTCCGTGCCGAGGGCGAGAACCTGGTGCTCAACTGCTC
CTTCACCGACAGCGCCATCTACAACCTGCACTGGTTCCGCCAGGACCCGGGAAGGGCCTGACC
AGCCTCTGCTTATCCAGAGCTCCAGCGAACAGACATCAGGCCGCTGAATGCAAGTTGG
ACAAATCTCTGCCGGTCGACCTGTATATTGCGGCTCCAGCCGGTGATTCTGCTACCTA
CCTGTGCCCGTGTGTTCAACACGACAAGCTGATCTCGGCACCGGACTCGCCTGCAGGTT
TTTCCAATCCAGAATCCCAGGCCTGCCGTGTACCAAGCTGAAGGACCCCCGCTCCCAGGATTCTA
CCCTGTGCCTGTTCACAGACTTGTGATTCCCAGATCAACGTGCCTAACACAATGGAGTCTGGCAC
CTTCATCACAGACAAGTGCCTGCTGGATATGAAGGCTATGGACTCCAAGTCTAACGGCGCCATC
GCCTGGTCTAACAGACCAAGCTTCACATGCCAGGATATCTTAAGGAGACCAACGCCACATACC
CTTCCTCTGACGTGCCATGTGATGCCACCTGACAGAGAAGAGCTCGAGACAGACATGAACCT
GAATTTCAAGAACCTGCTGGTCATCGTGCCTGCTGAAGGTGGCCGGTTAAC
CTGCTGATGACCTGAGACTGTGGAGCTCCTGA

FIGURE 6C

MGTSLLCWMALCLLGADHADTGVSQNPRYKITKRGQNVTFRCDPISEHNRLYWYRQTLGQGP
F
LTYFQNEAQLEKSRLLSDRFSAPERPKGSFSTLEIQRTEQGDSAMYLCAASSQS
YEQYFGPGTRL
TVTEDLRNVTPPKVSILFEPKAEIANKQKATLVLARFFPDHV
ELSWWVNGKEVHSGVCTDPQ
AYKESNSYCLSSRLRVSATFWHNPRNHFR
CQVFHGLSEEDKWPEGSPKPVTQNI
SAEAWGRA
DCGITSASYQQGVLSATILYEILLGKATLYAVLVSTL
VV
MAMVKRKNS

FIGURE 6D

ATGGGCACGAGCTTGCTCTGCTGGATGGCCCTGTGCCTGCTGGGGCGGACCATGCAGACACCG
GCGTCAGCCAGAACATCCACGTACAAGATTACCAAGCGCGGCCAGAACGTGACCTTCAGATGTGA
CCCCATCTCGGAGCACAACCGCCTGTATTGGTACCGCCAGACTCTTGGACAGGGCCCTGAGTTC
CTGACCTACTTCCAGAACGAGGCTCAGCTGGAGAAGTCCCGCCTGTTGAGTGACAGGTTTCAG
CCGAGCGGCCGAAAGGCTCTTCTCGACCCTAGAGATCCAGCGCACTGAACAAGGTGATTCTGC
CATGTACCTGTGCGCCTCCTCTCCAGAGCTACGAGCAGTACTTGGTCCCAGGGACCCGTCTC
ACCGTGACAGAGGATCTGCGCAATGTGACACCCCTAAGGTGTCCCTGTTGAGCCATCTAAGG
CCGAGATCGCCAACAAGCAGAACGGCCACCCCTGGTGTGCCCTGGCAAGGGGCTTCTTCCGATCA
CGTGGAGCTGAGCTGGTGGGTGAATGGCAAGGAGGTGCACTCCGGCGTGTGCACAGACCTCAAG
GCCTACAGGAGAGCAACTACTCCTATTGTCTGTCTAGCCGGCTGAGAGTGTCCGCCACCTTT
GGCACACCCCTAGGAATCACTCCGCTGCCAGGTGCAGTTCACGGCCTGAGCGAGGAGGATAA
GTGGCCAGAGGGATCCCCAAAGCCAGTGACCCAGAATATCTCTGCCAGGGCATGGGAAGGGCA
GAATGTGGAATCACATCCGCTCTTATCAGCAGGGCGTGTGAGCGCCACCATCCTGTACGAGA
TCCTGCTGGCAAGGCCACACTGTATGCCGTGCTGGTGTCTACCCCTGGTGGTATGGCTATGGT
GAAGAGAAAGAACAGC

FIGURE 7A

METLLGLLILWLQLQWVSSKQEVTQIPAALSVPEGENLVLQCSFTDSAIYNLQWFRQDPGKGLT
SLLLIQSSQREQTSGRQASLDKSSGRSTLYIAASQLGDSATYLCAVLFNTDKLIFGTGTRLQV
FPIQNPEPAVYQLKDPRSQDSTLCLFDFDSQINVPKTMESGTFITDKCVLDMKAMDSKSNGAI
AWSQTSFTCQDIFKETQATYPSSDVPCDATLTEKSFETDMNLNFQQNLIVLRILLKVAGFN
LLMTLRLWSS

FIGURE 7B

ATGGAGACTCTGCTGGTCTCCTCATCCTGTGGCTACAGCTGCAGTGGGTCTCGTCCAAGCAGG
AGGTGACCCAAATTCCCTGCCGCGTGTCCGTGCCGAGGGCGAGAACCTGGTGCTCCAGTGCTC
CTTCACCGACAGCGCCATCTACAACTTGCAGTGGTTCGCCAGGACCCGGGAAGGGCCTGACC
AGCCTCTGCTTATCCAGAGCTCCAGCGAACAGACATCAGGCCGCCTGCAGGCAAGTTGG
ACAAATCTCTGCCGGTCGACCCGTATATTGCGGCTCCCAGCCGGTGATTCTGCTACCTA
CCTGTGCCGTGCTGTTCAACACGGACAAGCTGATCTCGGCACCGGCACTCGCCTGCAGGTT
TTTCCAATCCAGAATCCCGAGCCTGCCGTGTACCAGCTGAAGGACCCCCGCTCCCAGGATTCTA
CCCTGTGCCCTGTTCACAGACTTGATTGATTCCCAGATCAACGTGCCTAACAGACAATGGAGCTGGCAC
CTTCATCACAGACAAGTGCGTGCTGGATATGAAGGCTATGGACTCCAAGTCTAACGGCGCCATC
GCCTGGTCTCAGCAGACCAGAGCTTCACATGCCAGGATATCTTTAAGGAGACCCCAGGCCACATACC
CTTCCTCTGACGTGCCATGTGATGCCACCCGTGCTGCGGATCTGCTGCTGAAGGTGGCCGGCTTTA
CTGCTGATGACCCCTGGAGACTGTGGAGCTCCTA

FIGURE 7C

MGTSLLCWMALCLLGADHADTGVSQNPRYKITKRGQQVTFRCDPISEHNRLYWYRQTLGQGPE
LTYFQNEAQLEKSRLLSDRFSAERPKGSFSTLEIQRTEQGDSAMYLCASSQSYEQYFGPGTRL
TVTEDLRQVTPPKVSLFEPSKAEIANKQKATLVCLARGFFPDHVELSWWVNGKEVHSGVCTDP
QAYKESQYSYCLSSRLRVSATFWHNPRNHFCQVFHGLSEEDKWPEGSPKPVTQQISAEAWGRA
DCGITSASYQQGVLSATILYEILLGKATLYAVLVSTLVVMAMVKRKNS

FIGURE 7D

ATGGGCACGAGCTTGCTCTGGATGGCCCTGTGCCTGCTGGGGCGGACCATGCAGACACCG
GCGTCAGCCAGAATCCACGTCACAAGATTACCAAGCGCGGCCAGCAGGTGACCTTCAGATGTGA
CCCCATCTCGGAGCACAACCGCCTGTATTGGTACCGCCAGACTCTTGGACAGGGCCCTGAGTTC
CTGACCTACTTCCAGAACGAGGCTCAGCTGGAGAAGTCCCGCCTGTTGAGTGACAGGTTTCAG
CCGAGCGGCCGAAAGGCTCCTCTCGACCCTAGAGATCCAGCGCACTGAACAAGGTGATTCTGC
CATGTACCTGTGCGCCTCCTCTCCCAGAGCTACGAGCAGTACTTGGTCCCAGGGACCCGTCTC
ACCGTGACAGAGGGATCTGCGCCAGGTGACACCCCTAAGGTGTCCTGTTGAGCCATCTAAGG
CCGAGATCGCCAACAAGCAGAAGGCCACCCCTGGTGTGCCCTGGCAAGGGGCTTCTTCCGATCA
CGTGGAGCTGAGCTGGTGGGTGAATGGCAAGGAGGTGCACTCCGGCGTGTGCACAGACCCCTCAG
GCCTACAGGAGAGCCAGTACTCCTATTGTCTGTCTAGCCGGCTGAGAGTGTCCGCCACCTTT
GGCACACCCCTAGGAATCATTCCGCTGCCAGGTGCAAGTTCACGGCCTGAGCGAGGAGGATAA
GTGGCCAGAGGGATCCCCAAAGCCAGTGACCCAGCAGATCTCTGCCAGGGATGGGAAGGGCA
GACTGTGGAATCACATCCGCTCTTATCAGCAGGGCGTGTGAGCGCCACCATCCTGTACGAGA
TCCTGCTGGCAAGGCCACACTGTATGCCGTGCTGGTGTCTACCCCTGGTGGTATGGCTATGGT
GAAGAGAAAGAACAGC

FIGURE 8

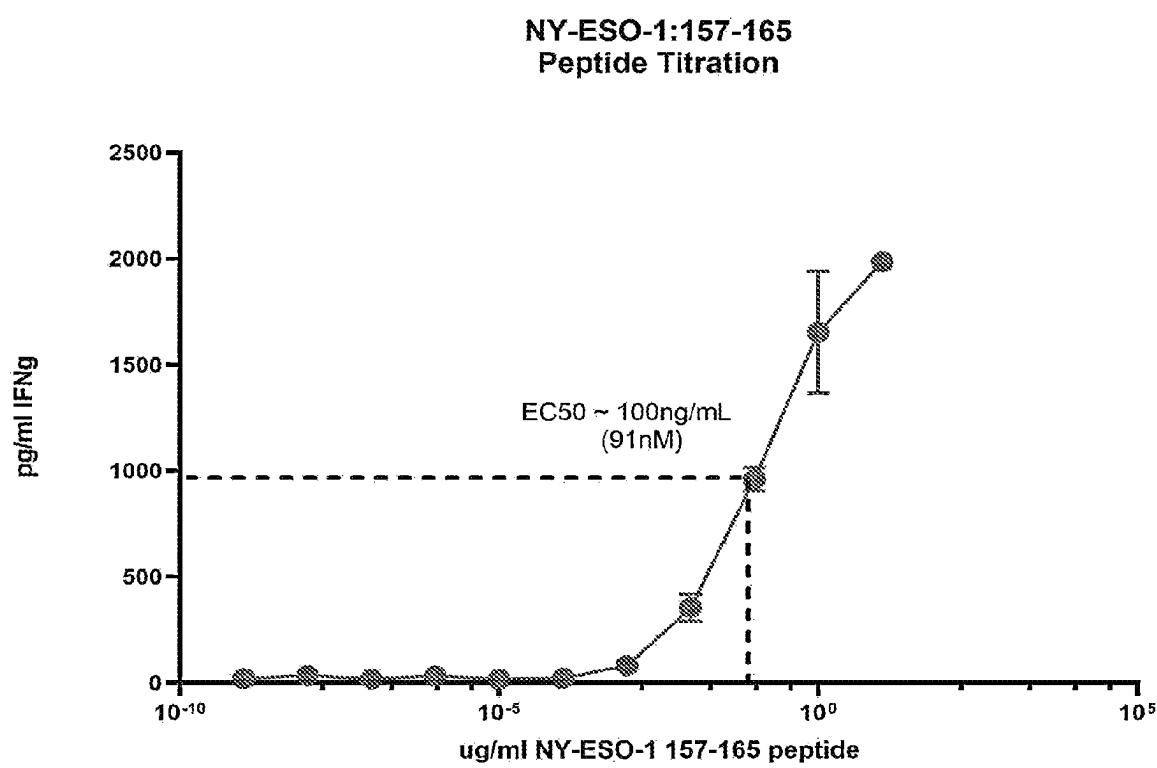
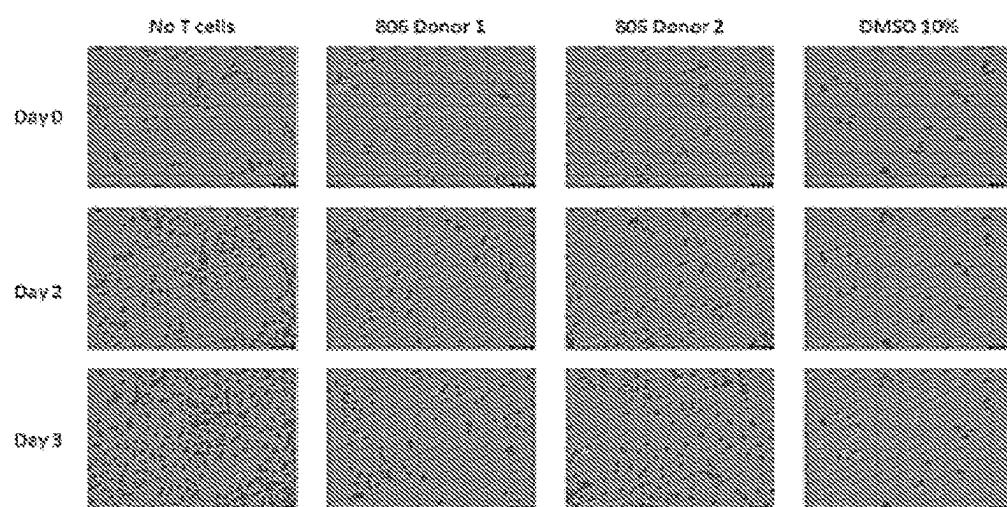


FIGURE 9



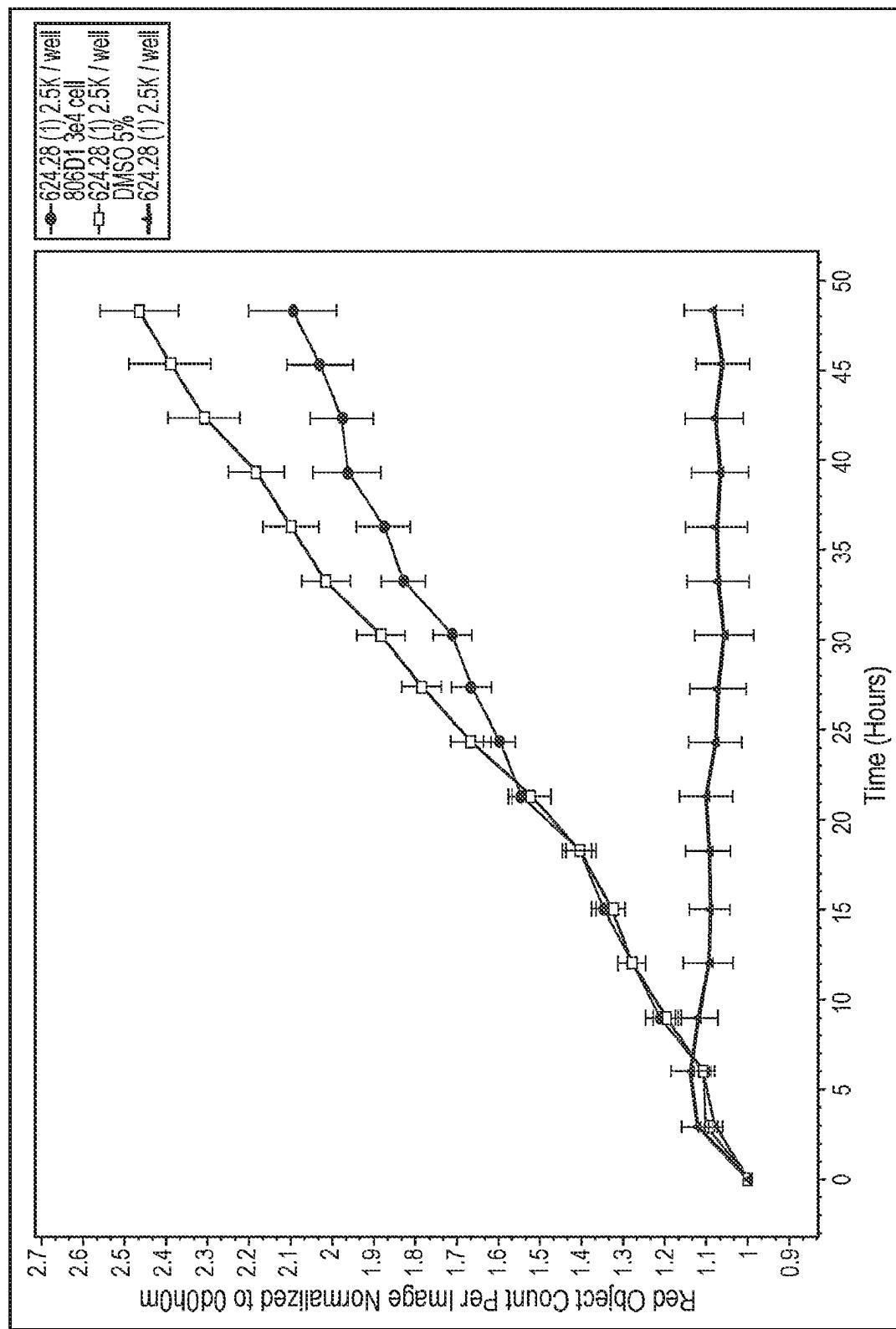


FIGURE 10A

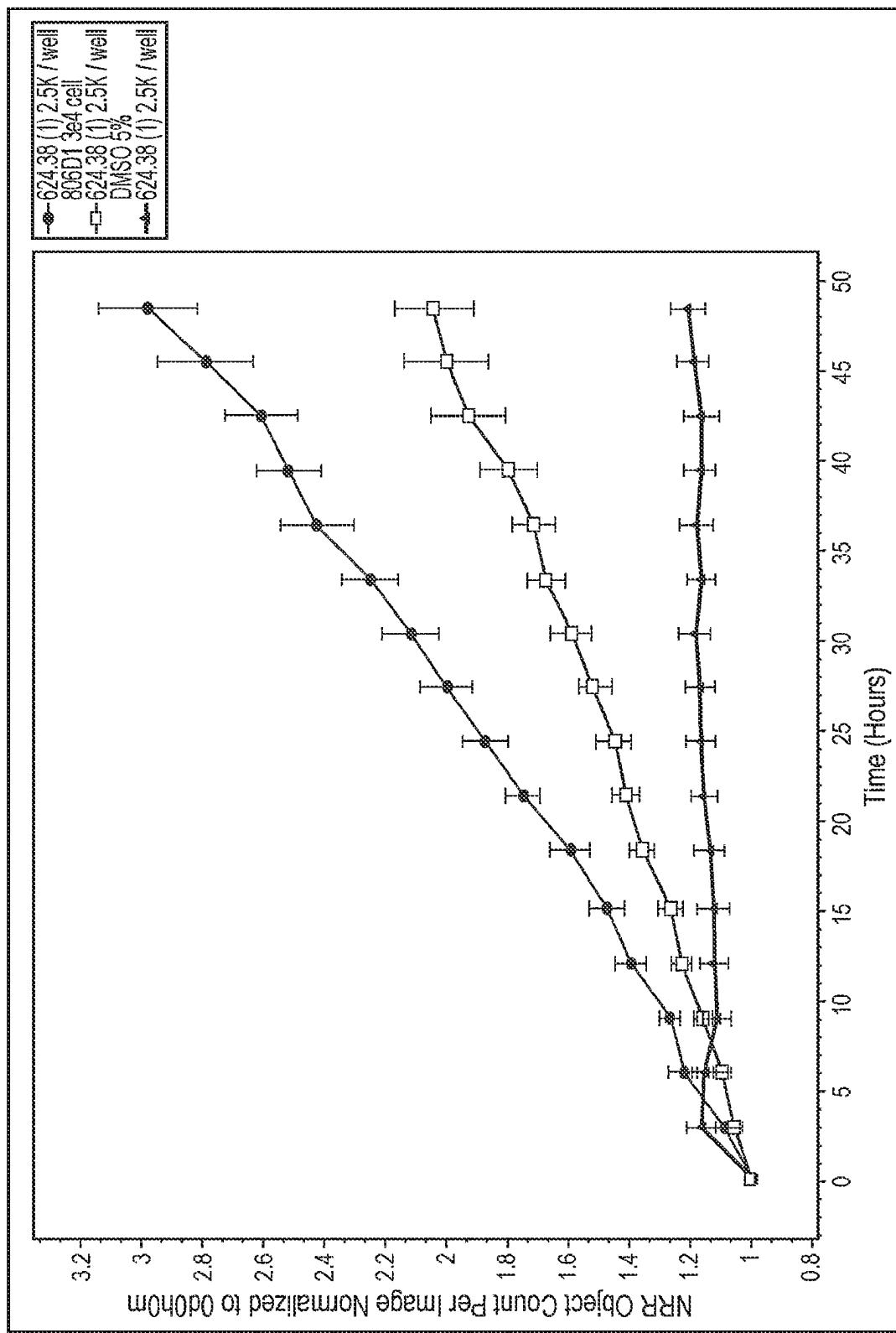
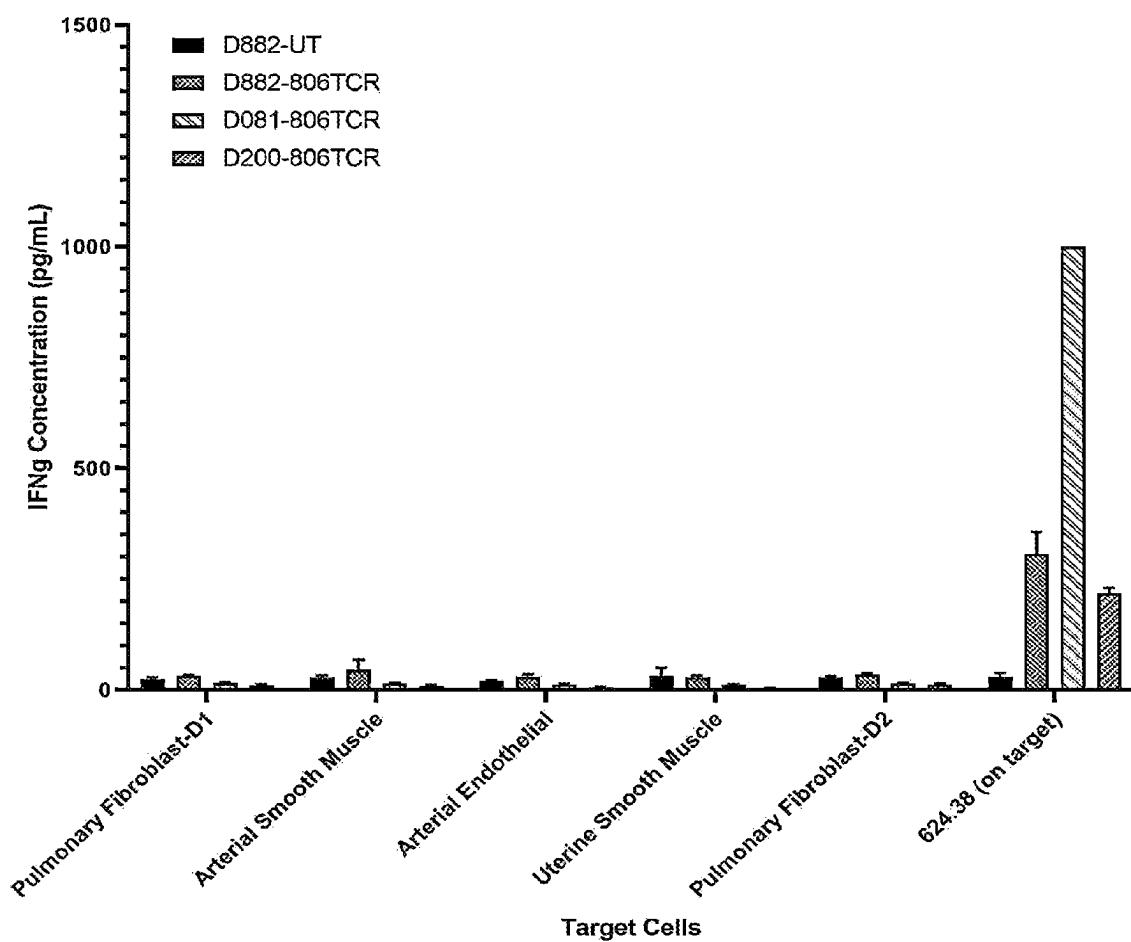


FIGURE 10B

FIGURE 11



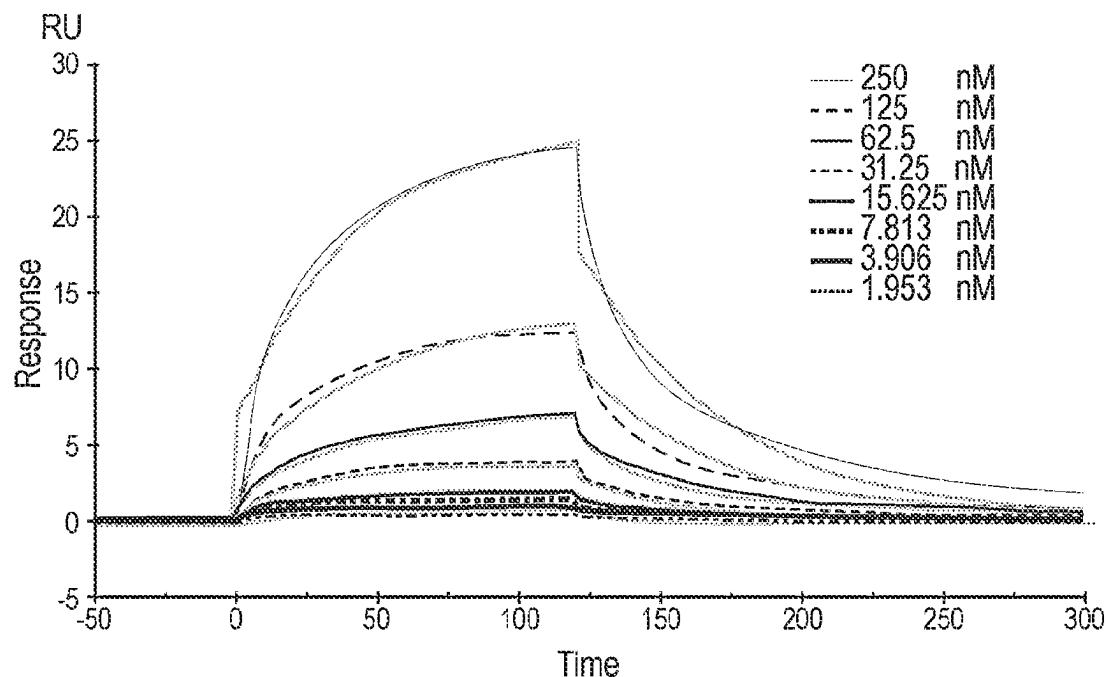


FIGURE 12A

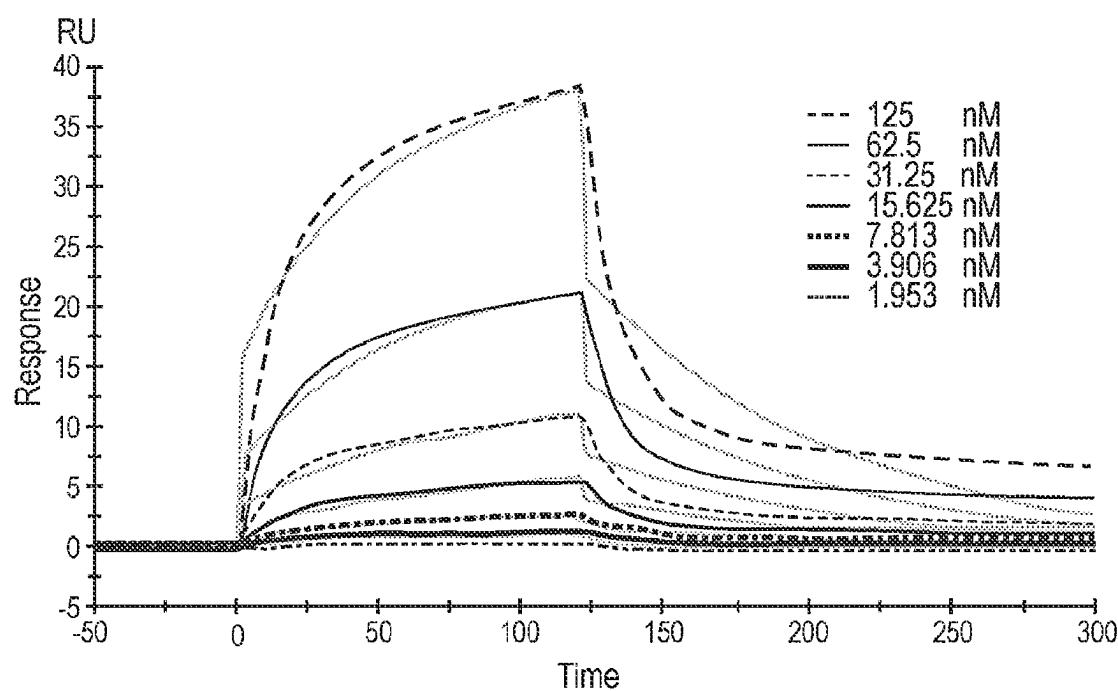


FIGURE 12B

**RECOMBINANT T-CELL RECEPTORS THAT
BIND THE NY-ESO-1 AND/OR LAGE-1A
CANCER ANTIGENS**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a U.S. national stage application, filed under 35 U.S.C. § 371, of International Application No. PCT/US2021/038086, filed on Jun. 18, 2021, which claims priority to and the benefit of U.S. Provisional Application No. 63/106,329, filed on Oct. 27, 2020, the entire disclosure of each of which is incorporated by reference herein in its entirety for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Sep. 25, 2023, is named TCB-002WOUS_SL.txt and is 197,232 bytes in size.

FIELD OF THE INVENTION

[0003] The invention relates generally to T-cell receptors and their use in therapy, and more specifically relates to T-cell receptors that bind, in an MHC restricted manner, to the shared cancer-testis antigen known as NY-ESO-1 and/or the closely related antigen known as LAGE-1a.

BACKGROUND OF THE INVENTION

[0004] T-cells have been found to play an important role in controlling the growth and proliferation of cancer cells and tumors. CD8⁺ T-cells appear to play a role in directly targeting cancer cells, whereas tumor antigen-specific CD4⁺ helper T-cells appear to play a critical role in the initiation, proliferation, maintenance, and co-ordination of overall anti-tumor immune responses, including CD8⁺ T-cell and antibody mediated immune responses. CD8⁺ T-cell-based immunotherapies in particular have shown encouraging results in clinical trials targeting various solid tumors (Robbins et al. (2011) J. CLIN. ONCOL. 29(7): 917; Robbins et al. (2015) CLIN. CANCER RES. 21(5): 1019-27; Rapoport et al. (2015) NAT. MED. 21(8): 914-21).

[0005] NY-ESO-1 is a cancer/testis antigen that has been detected in many tumor types, including melanoma, breast cancer, lung cancer, and others, but not in normal tissue except the immune privileged testis (Chen et al. (1997) PROC. NATL. ACAD. SCI. USA 94:1914-1918; Zeng et al. (2000) J. IMMUNOL. 165: 1153-1159). Reactivity of T-cells to the NY-ESO-1 antigen has been demonstrated, in some instances, to be restricted in an HLA-A2 restricted manner (Jager et al. (1998) J. EXP. MED. 187: 265; Wang et al. (1998) J. IMMUNOL. 161(7): 3596-3606). CD8⁺ T cells expressing TCRs recognizing HLA-A2-restricted NY-ESO-1 and/or LAGE-1a epitopes have led to clinical responses in subjects with melanoma, multiple myeloma and various sarcomas (Robbins et al. (2011) supra; Robbins et al. (2015) supra; Rapoport et al. (2015) supra). Given the limited availability of such immunoreagents, there is an ongoing and unmet need to provide additional new compositions and methods that can be used to for treatment of cancer subjects.

SUMMARY OF THE INVENTION

[0006] The present invention provides a T-cell receptor (TCR), as well as functional fragments or variants thereof, that binds to the core SLLMWITQC (SEQ ID NO: 1) epitope and/or the core SLLMWITQCFL (SEQ ID NO: 28) epitope present in the shared cancer-testis antigen NY-ESO-1 and/or the antigen LAGE-1a in an HLA-restricted manner. For example, the NY-ESO-1 and/or LAGE-1a antigens may be recognized by a T-cell receptor described herein in an HLA-A2 restricted manner. For example, the immunoreactivity to the NY-ESO-1 and/or LAGE-1a antigens can be HLA-A*0201 or HLA-A*0202 restricted.

[0007] T-cell receptors comprise two chains referred to as the α - and β -chains, that form a pair on the surface of a T-cell to form a heterodimeric receptor. The T-cell receptor is involved in recognition of MHC-restricted antigens. Each of α - and β -chain comprises two regions, a constant region and a variable region. Each variable region of the α - and β -chains defines three loops, referred to as complementary determining regions (CDRs) known as CDR₁, CDR₂, and CDR₃ that confer the T-cell receptor with antigen binding activity and binding specificity.

[0008] In one aspect, the invention provides an isolated, recombinant α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the core amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The α -chain comprises one or more of the following amino acid sequences: (i) an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87; (ii) an α -chain variable region amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; (iii) an α -chain CDR₃ amino acid sequence of SEQ ID NO: 7; (iv) an α -chain CDR₁ amino acid sequence of SEQ ID NO: 5; and (v) an α -chain CDR₂ amino acid sequence of SEQ ID NO: 6.

[0009] In another aspect, the invention provides an isolated recombinant β -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the core amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The β -chain comprises one or more of the following amino acid sequences: (i) an amino acid sequence of SEQ ID NO: 95 or SEQ ID NO: 99, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 95 or SEQ ID NO: 99; (ii) a β -chain variable region amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85; (iii) a β -chain CDR₃ amino acid sequence of SEQ ID NO: 13; (iv) a β -chain CDR₁ amino acid sequence of SEQ ID NO: 11; and (v) a β -chain CDR₂ amino acid sequence of SEQ ID NO: 12.

[0010] In another aspect, the invention provides a recombinant T-cell receptor immunoreactive with a SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) epitope comprising at least one of the foregoing α -chains and at least one of the foregoing β -chains.

[0011] In another aspect, the invention provides an isolated, recombinant T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising

the core amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The T-cell receptor comprises an α -chain and a β -chain, the α and β chains each comprising a CDR1, CDR2, and a CDR3, wherein the α -chain CDR3 comprises the amino acid sequence of SEQ ID NO: 7, and the β -chain CDR3 comprises the amino acid sequence of SEQ ID NO: 13. Optionally, or in addition, the T-cell receptor α -chain CDR1 comprises the amino acid sequence of SEQ ID NO: 5, and the β -chain CDR1 comprises the amino acid sequence of SEQ ID NO: 11. Optionally, or in addition, the T-cell receptor α -chain CDR2 comprises the amino acid sequence of SEQ ID NO: 6, and the β -chain CDR2 comprises the amino acid sequence of SEQ ID NO: 12.

[0012] In another aspect, the invention provides an isolated, recombinant T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the core amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The T-cell receptor comprises an α -chain variable region comprising an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; and a β -chain variable region comprising an amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85. Optionally, or in addition, the T-cell receptor α -chain comprises the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, and/or the β -chain comprises the amino acid sequence of SEQ ID NO: 95 or SEQ ID NO: 99, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 95 or SEQ ID NO: 99.

[0013] In each of the foregoing aspects, the T-cell receptor is optionally a single chain T-cell receptor, optionally where the α -chain is linked to the β -chain via an amino acid linker. For example, in certain embodiments, the isolated T-cell receptor can comprise the amino acid sequence of SEQ ID NO: 14, which can be encoded by the polynucleotide sequence of SEQ ID NO: 27 or the amino acid sequence of SEQ ID NO: 29, which can be encoded by the polynucleotide sequence of SEQ ID NO: 30.

[0014] In certain embodiments of each the foregoing aspects, the T-cell receptor is immunoreactive with the epitope SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) in an HLA-A2 restricted manner. For example, the immunoreactivity to the epitope SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) can be HLA-A*0201 or HLA-A*0202 restricted.

[0015] It is contemplated that, for each of the amino acid sequences provided herein, the sequences optionally include at least one amino acid not present at a given position in T-cell receptor cloned and sequenced in Examples 1 and 2.

[0016] It is understood that a T-cell receptor described herein may be conjugated with another binding moiety to produce a bispecific T-cell receptor protein. For example, a T-cell receptor described herein can be associated, for example, covalently or non-covalently associated, to an antibody or an antigen binding fragment thereof to provide a bispecific molecule where the T-cell receptor binds to the

SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) epitope and the other binding moiety binds to a different antigen. In certain embodiments, the antibody or the antigen binding fragment thereof is capable of modulating an immune response in a subject. In a specific embodiment, the antibody or the antigen binding fragment thereof may be anti-CD3 specific.

[0017] In certain embodiments, a T-cell receptor described herein, or a functional fragment thereof, further comprises a detectable label. As a result, the resulting conjugate can be used as a diagnostic or prognostic reagent. Furthermore, in certain embodiments, a T-cell receptor described herein may be associated with a therapeutic agent.

[0018] In certain embodiments, a T-cell receptor described herein binds to a SLLMWITQC (SEQ ID NO: 1) peptide/MHC complex with a K_D of 500 nM or lower, 400 nM or lower, 300 nM or lower, 200 nM or lower, 175 nM or lower, 150 nM or lower, 125 nM or lower, 100 nM or lower, 75 nM or lower, 50 nM or lower, 25 nM or lower, or 10 nM or lower, as measured by surface plasmon resonance.

[0019] In another aspect, the invention provides an isolated, recombinant nucleic acid encoding an α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The nucleic acid comprises one or more of the following nucleotide sequences: (i) a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87; (ii) a nucleotide sequence encoding an α -chain variable region amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; (iii) a nucleotide sequence of SEQ ID NO: 100; (iv) a nucleotide sequence encoding an α -chain CDR₃ amino acid sequence of SEQ ID NO: 7; (iv) a nucleotide sequence encoding an α -chain CDR₁ amino acid sequence of SEQ ID NO: 5; and (vi) a nucleotide sequence encoding an α -chain CDR₂ amino acid sequence of SEQ ID NO: 6.

[0020] In another aspect, the invention provides an isolated, recombinant nucleic acid encoding a T-cell receptor β -chain immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The nucleic acid comprises one or more of the following nucleotide sequences: (i) a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 95 or SEQ ID NO: 99, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 95 or SEQ ID NO: 99; (ii) a nucleotide sequence encoding a β -chain variable region amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85; (iii) a nucleotide sequence of SEQ ID NO: 102; (iv) a nucleotide sequence encoding a β -chain CDR₃ amino acid sequence of SEQ ID NO: 13; (v) a nucleotide sequence encoding a β -chain CDR₁ amino acid sequence of SEQ ID NO: 11; and (vi) a nucleotide sequence encoding a β -chain CDR₂ amino acid sequence of SEQ ID NO: 12.

[0021] In another aspect, the invention provides an isolated, recombinant nucleic acid encoding a T-cell receptor

immunoreactive with an epitope of an NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLL-MWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The T-cell receptor comprises an α -chain and a β -chain each comprising a CDR₁, CDR₂, and a CDR₃, wherein the α -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 7, and the β -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 13. Optionally, or in addition, the α -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 5, and the β -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 11. Optionally, or in addition, the α -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 6, and the β -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 12.

[0022] It is contemplated that, for each of the nucleic acids described herein, the nucleic acids may encode at least one amino acid not present at a given position in T-cell receptor cloned and sequenced in Examples 1 and 2, and/or the codon usage of the nucleic acids may be optimized to enhance the expression of the α -chain and/or the β -chain of the T-cell receptor in a given subject.

[0023] For each of the foregoing nucleic acids, the nucleic acid optionally encodes a single chain T-cell receptor, optionally where the α -chain is linked to the β -chain via an amino acid linker.

[0024] In an additional aspect, the invention provides an expression vector, for example, a viral expression vector, comprising one or more of the foregoing nucleic acid sequences. In certain embodiments, the viral vector is a lentivirus vector.

[0025] In an additional aspect, the invention provides a genetically modified cell that comprises one or more of the following: (i) an α -chain of a T-cell receptor protein described herein; (ii) a β -chain of a T-cell receptor protein described herein; (iii) a T-cell receptor described herein; (iv) a bispecific T-cell receptor described herein; (iv) a nucleic acid or recombinant expression vector described herein, wherein the cell expresses a T-cell receptor immunoreactive with an epitope comprising the amino acid sequence SLL-MWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28).

[0026] In certain embodiments of each of the foregoing cells, the cell is an immune-based cell, for example, a CD4⁺ helper T-cell or a CD8⁺ T-cell, or a progenitor cell, for example, a hematopoietic stem cell or a pluripotent stem cell. In certain embodiments, the cell is an autologous cell or a heterologous cell.

[0027] In another aspect, the invention provides a method for producing a T-cell immunoreactive with an epitope of an NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLL-MWITQCFL (SEQ ID NO: 28). The method comprises introducing one or more of the foregoing nucleic acids and/or expression vectors into the T-cell.

[0028] In certain embodiments of each of the foregoing methods, the T-cell may be a CD4⁺ helper T-cell or a CD8⁺ T-cell. The T-cell may be an autologous cell or a heterologous cell.

[0029] In another aspect, the invention provides a pharmaceutical composition comprising a genetically engineered cell produced by the methodologies described herein.

[0030] In another aspect, the invention provides a method of inhibiting the growth of cancer cells expressing a NY-

ESO-1 or LAGE-1a protein. The method comprises exposing the cancer cells to a genetically engineered cell described herein that is capable of inhibiting the growth of the cancer cells.

[0031] In another aspect, the invention provides a method of treating or preventing cancer in a subject. The method comprises administering to the subject autologous genetically modified T-cells (i) expressing an α -chain of a T-cell receptor described herein, (ii) expressing a β -chain of a T-cell receptor described herein, or (iii) expressing a T-cell receptor described herein, and/or (iv) transduced with one or more of the nucleic acids or the recombinant expression vectors described herein, in an amount effective to treat or prevent cancer in the subject.

[0032] In another aspect, the invention provides a method for treating or preventing cancer in a subject. The method comprises the steps of (i) extracting T-cells from the subject; (ii) introducing into the T-cells one or more nucleic acids or one or more of the recombinant vectors described herein; and (iii) administering the T-cells produced by step (ii) to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] The foregoing and other objects, features and advantages of the invention will become apparent from the following description of preferred embodiments, as illustrated in the accompanying drawings, in which:

[0034] FIG. 1 shows the recognition of the HLA-A2 restricted NY-ESO-1:157-165 epitope ("ESOp157-165") of SEQ ID NO: 1 by CD8⁺ T-cell lines using IFN- γ and GM-CSF release as an indicator of target recognition. FIG. 1A depicts the identification of a T cell clone (806) recognizing HLA-A2/NY-ESO-1+ tumor cells. The 806 T-cells were shown to recognize the NY-ESO-1:157-165 peptide presented by HLA-A2+ 1088-B cells (FIG. 1A, left). The 806 T-cells were shown to recognize the NY-ESO-1 protein, but not GFP, when introduced into cosA2 presenting cells (FIG. 1A, left). The 806 T-cells were able to recognize the 624.38 melanoma line (HLA-A2+/NY-ESO-1+), but not the variant 624.28 melanoma cell line (HLA-A2-/NY-ESO-1+) (FIG. 1A, left). Titration studies measuring GM-CSF release at the indicated concentrations displayed a high avidity of the TCR for NY-ESO-1:157-165 (FIG. 1A, right). FIG. 1B depicts the discovery of a single TCR up pair recognizing NY-ESO-1:157-165. Jurkat76 (J76) cells were transduced with various α and β chain combinations obtained from the TCR sequencing results of the 806 T cell clone. Only the $\alpha\beta$ 1 combination demonstrated a specific response against NY-ESO-1:157-165-pulsed T2 cells. FIG. 1C depicts recognition of HLA-A2/NY-ESO-1:157-165 pentamers by 806 α 1 β 1. J76 cells transduced with either a control TCR or the 806 α 1 β 1 TCR construct were analyzed by flow cytometry for binding to a NY-ESO-1:157-165-pentamer. Only the 806 α 1 β 1 TCR demonstrated binding to the NY-ESO-1 pentamer. Antibodies against the mouse C terminal domain were used to assess the cell-surface expression of the TCR heterodimers. FIG. 1D depicts tumor cell recognition by the 806TCR. Transduced T cells (black), as opposed to untransduced cells (dark grey) or target cells alone (light grey), showed specific activation when exposed to a panel of A2+/NYESO1+ cells (Colo-205-NYESO1, FM-6, FM-82, HEPG2-NYESO, SK-MEL-37, UACC-257, and MEL-624, 38); while they showed no specific activity when exposed to A2-/NYESO1- cells (HpAF-II, LS174T, LS714T, and SK-

LU-1) or A2+/NYESO1- cells (SK-LU-1-NYESO, MEL-624.28, A549, Colo-205, Cos-7-A2, HepG-2, Kato-III, and SK-MEL-23). FIG. 1E depicts cell killing by the 806TCR. 806TCR transduced T cells showed the ability kill A2+/NY-ESO-1+ cells (MEL-624.38, FM-6, UACC-257) but not A2-/NY-ESO-1+ target cells (MEL-624.28) after culturing for 24 hours. Untransduced T cells demonstrated no killing activity.

[0035] FIG. 2 depicts the α -chain amino acid sequence (SEQ ID NO: 2; FIG. 2A), α -chain codon-optimized nucleotide sequence (SEQ ID NO: 100; FIG. 2B), β 1-chain amino acid sequence (SEQ ID NO: 95; FIG. 2C), and β 1-chain codon-optimized nucleotide sequence (SEQ ID NO: 102; FIG. 2D) of the 806 TCR including human α - and β -chain constant regions. The CDR regions are in red and are underlined.

[0036] FIGS. 3A and 3B depict the amino acid sequence of (SEQ ID NO: 14), and the polynucleotide sequence encoding (SEQ ID NO: 27), the 806 TCR α -P2A- β 1 fusion protein with the P2A sequence shown in bold. FIGS. 3C and 3D depict the amino acid sequence of (SEQ ID NO: 29), and the polynucleotide sequence encoding (SEQ ID NO: 30), the 806 TCR α -P2A- β 1-T2A-CD34t fusion protein with the P2A sequence bolded, the T2A sequence bolded and underlined, and the CD34t sequence in lower case.

[0037] FIG. 4 shows sequence alignments of amino acid sequences for the 806 T-cell receptor against sequences for other T-cell receptors that are able to recognize the NY-ESO-1:157-165 peptide. The 806 T-cell receptor α -chain amino acid sequence (FIG. 4A) and the 806 T-cell receptor β 1-chain amino acid sequence (FIG. 4B) were aligned with sequences from other TCR chains identified as 1G4 (as described in U.S. Patent Application Publication No. US2009/053184), BC1 (as described in International Patent Application Publication No. WO2020/188348), 1G4C113 (as described in International Patent Application Publication No. WO2005/113595), UC-1E4 (as described in International Patent Application Publication No. WO2020/086158), V17 and V12-4 (both as described in International Patent Application Publication No. WO2017/076308). For the T-cell receptor sequences, the CDR regions are bolded and in red and constant regions are underlined. FIG. 4A discloses SEQ ID Nos. 108-112 and SEQ ID NO: 37, respectively, in order of appearance. FIG. 4B discloses SEQ ID Nos. 113, 39, and 114-117, respectively, in order of appearance.

[0038] FIG. 5 depicts sequences of the 806 T-cell receptor (with human constant regions) with exemplary glycosylation sites mutated. The amino acid and polynucleotide sequences of the 806 T-cell receptor α -chain with exemplary mutations (SEQ ID NOS: 75 and 76, respectively; FIGS. 5A and 5B), and the 806 T-cell receptor β 1-chain with exemplary mutations (SEQ ID NOS: 97 and 98, respectively; FIGS. 5C and 5D) are depicted. The amino acid mutations and corresponding nucleotide sequence changes are shown as underlined. The constant regions are shown in bold.

[0039] FIG. 6 depicts the amino acid and polynucleotide sequences of 806 T-cell receptor α -chain (SEQ ID NOS: 37 and 38, respectively; FIGS. 6A-6B) and the β 1-chain (SEQ ID NOS: 39 and 40, respectively; FIGS. 6C-6D) with the constant regions replaced by those from a known murine TCR. The constant regions are shown in bold.

[0040] FIG. 7 depicts sequences of the 806 T-cell receptor (with murine constant regions) with exemplary glycosy-

lation sites mutated. The amino acid and polynucleotide sequences of the 806 T-cell receptor α -chain with exemplary mutations (SEQ ID NOS: 79 and 80, respectively; FIGS. 7A and 7B), and the 806 T-cell receptor β 1-chain with exemplary mutations (SEQ ID NOS: 81 and 82, respectively; FIGS. 7C and 7D) are depicted. The amino acid mutations and corresponding nucleotide sequence changes are shown as underlined. The constant regions are shown in bold.

[0041] FIG. 8 is a line graph showing 806TCR-T cell activity (as measured by interferon- γ release) as a function of NY-ESO-1157-165 peptide concentration. HLA-A*02:01+ antigen presenting cells were pulsed with NY-ESO-1:157-165 peptide at the indicated concentration, co-cultured with 806TCR-T cells, and interferon- γ release was measured by ELISA.

[0042] FIG. 9 depicts real-time fluorescent images of target MEL-624.38 cells incubated with the indicated 806TCR-T cells (or controls) at the indicated time points. Columns represent co-culture conditions: no T cells, donor 1 transduced 806TCR-T cells, donor 2 transduced 806TCR-T cells, and 10% DMSO (v/v) (dead cell control). Rows represent timepoints when images were taken: day 0 (0 hrs:12 min), day 2 (48 hrs:12 mins), and day 3 (72 hours:12 mins).

[0043] FIG. 10 depicts line graphs showing cell nuclei count over time (as measured by fluorescent microscopy) following incubation of non-target MEL-624.28 cells (FIG. 10A) or target MEL-624.38 cells (FIG. 10B) with 806TCR-T cells. Green lines represent target cells only (without T cells). Red lines depict dead cell control of 10% DMSO (v/v). Blue lines depict co-culture with 806TCR-T cells. Results are normalized to time 0 (0 hrs:12 mins).

[0044] FIG. 11 is a bar graphic depicting 806TCR-T cell activity (as measured by interferon- γ release) following co-culture with a panel of normal (non-cancerous) cells and one target cancerous cell line. UT indicates untransduced. D1 and D2 refer to different donors for pulmonary fibroblasts. D882, D081, and D200 refer to different donors for T cells.

[0045] FIG. 12 depicts binding of the 1G4LY TCR (FIG. 12A) and 806 TCR (FIG. 12B) to peptide/pMHC1 complex (biotin-HLA-A*02:01-SLLMWITQC (SEQ ID NO: 1)) as observed by surface plasmon resonance. Each trace corresponds to the indicated concentration of TCR. Results were used for the calculation of binding kinetics, as described in Example 7.

DETAILED DESCRIPTION OF THE INVENTION

[0046] The present invention provides T-cell receptors, as well as fragments and variants thereof, that bind to the NY-ESO-1 and/or the LAGE-1a antigens expressed on the surface of cancer cells in an HLA-restricted manner. An exemplary T-cell receptor of the invention is immunoreactive with the NY-ESO-1 and/or LAGE-1a epitope SLL-MWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). The binding can be in association with recognition of HLA-A2 restricted antigens. For example, the binding can be restricted to HLA-A*0201, HLA-A*0202 or potentially other HLA-A2 subtype-expressing cells. The expression of NY-ESO-1 and/or LAGE-1a on the surface of cancer cells provides a target for specific binding of the T-cell receptor, as well as fragments and variants thereof, to the surface of cancer cells. As used herein, the term "immu-

“noreactive” is understood to mean that a T-cell receptor, for example, a T-cell receptor of the invention, as well as fragments and variants thereof, can bind specifically to an epitope present in an antigen, for example, an NY-ESO-1 antigen or a LAGE-1a antigen, optionally in a MHC-restrictive manner.

I. T-Cell Receptors

[0047] The present invention provides an isolated recombinant T-cell receptor (for example, a non-naturally occurring T-cell receptor). In certain embodiments, the T-cell receptor comprises an α -chain and β -chain wherein the α -chain and β -chain variable regions define a binding site for binding to the NY-ESO-1 and/or LAGE-1a epitope SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) in an HLA-A2 restricted manner. In certain embodiments, the T-cell receptor comprises an α -chain and β -chain wherein the α -chain and β -chain variable regions define a binding site for binding to the NY-ESO-1 and/or LAGE-1a epitope SLLMWITQC (SEQ ID NO: 1) in an HLA-A2 restricted manner.

[0048] An exemplary TCR is characterized as follows. The full length α -chain and β -chain of the T-cell receptor comprise SEQ ID NOs: 2 and 95, respectively. The α -chain variable region comprises the amino acid of SEQ ID NO: 3, while the β -chain variable region comprises the amino acid sequence of SEQ ID NO: 9. The α -chain constant region comprises the amino acid sequence of SEQ ID NO: 4 and the β -chain constant region comprises the amino acid sequence of SEQ ID NO: 10. Each of the α -chain and β -chain variable regions comprises three CDR regions wherein the α -chain CDRs comprise the amino acid sequences of SEQ ID NO: 5 (CDR₁), SEQ ID NO: 6 (CDR₂) and SEQ ID NO: 7 (CDR₃) and the β -chain CDRs comprise the amino acid sequences of SEQ ID NO: 11 (CDR₁), SEQ ID NO: 12 (CDR₂) and SEQ ID NO: 13 (CDR₃).

[0049] An additional exemplary TCR is characterized as follows. The full length α -chain and β -chain of the T-cell receptor comprise SEQ ID NO: 87 and 99, respectively. The α -chain variable region comprises the amino acid of SEQ ID NO: 83, while the β -chain variable region comprises the amino acid sequence of SEQ ID NO: 85. The α -chain constant region comprises the amino acid sequence of SEQ ID NO: 4 and the β -chain constant region comprises the amino acid sequence of SEQ ID NO: 10. Each of the α -chain and β -chain variable regions comprises three CDR regions wherein the α -chain CDRs comprise the amino acid sequences of SEQ ID NO: 5 (CDR₁), SEQ ID NO: 6 (CDR₂) and SEQ ID NO: 7 (CDR₃) and the β -chain CDRs comprise the amino acid sequences of SEQ ID NO: 11 (CDR₁), SEQ ID NO: 12 (CDR₂) and SEQ ID NO: 13 (CDR₃).

[0050] For clarity, certain sequences are set forth in TABLE 1.

TABLE 1

SEQ ID	Type	Description
TCR Sequences		
2	Protein	α chain full length (human constant region)
87	Protein	α chain full length (human constant region)
3	Protein	α chain variable region

TABLE 1-continued

SEQ ID	Type	Description
83	Protein	α chain variable region
4	Protein	α chain constant region (human)
5	Protein	α chain CDR ₁
6	Protein	α chain CDR ₂
7	Protein	α chain CDR ₃
95	Protein	β chain full length (human constant region)
99	Protein	β chain full length (human constant region)
9	Protein	β chain variable region
85	Protein	β chain variable region
10	Protein	β chain constant region (human)
11	Protein	β chain CDR ₁
12	Protein	β chain CDR ₂
13	Protein	β chain CDR ₃
100	Nucleic Acid	α chain full length (human constant region)
15	Nucleic Acid	α chain full length (human constant region)
101	Nucleic Acid	α chain variable region
16	Nucleic Acid	α chain variable region
17	Nucleic Acid	α chain constant region (human)
18	Nucleic Acid	α chain CDR ₁
19	Nucleic Acid	α chain CDR ₂
20	Nucleic Acid	α chain CDR ₃
102	Nucleic Acid	β chain full length (human constant region)
96	Nucleic Acid	β chain full length (human constant region)
103	Nucleic Acid	β chain variable region
22	Nucleic Acid	β chain variable region
23	Nucleic Acid	β chain constant region (human)
24	Nucleic Acid	β chain CDR ₁
25	Nucleic Acid	β chain CDR ₂
26	Nucleic Acid	β chain CDR ₃
Binding Epitopes		
1	Protein	NY-ESO-1: 157-165
28	Protein	NY-ESO-1: 157-167
Single chain TCRs		
14	Protein	806 α P2A β 1 bi-cistron
27	Nucleic Acid	806 α P2A β 1 bi-cistron
29	Protein	806 α P2A β T2ACD34t tri-cistron
30	Nucleic Acid	806 α P2A β T2ACD34t tri-cistron
93	Protein	806 α P2A β T2ACD34t tri-cistron
94	Nucleic Acid	806 α P2A β T2ACD34t tri-cistron
TCR Variants/Engineered TCRs		
75	Protein	α chain full length (human constant region) N→Q
76	Nucleic Acid	α chain full length (human constant region) N→Q
97	Protein	β chain full length (human constant region) N→Q
98	Nucleic Acid	β chain full length (human constant region) N→Q
37	Protein	α chain full length (murine constant region)
84	Protein	α chain full length (murine constant region)
38	Nucleic Acid	α chain full length (murine constant region)
49	Protein	α chain constant region (murine)
50	Nucleic Acid	α chain constant region (murine)

TABLE 1-continued

SEQ ID	Type	Description
39	Protein	β chain full length (murine constant region)
86	Protein	β chain full length (murine constant region)
40	Nucleic Acid	β chain full length (murine constant region)
51	Protein	β chain constant region (murine)
52	Nucleic Acid	β chain constant region (murine)
79	Protein	α chain full length (murine constant region) N→Q
80	Nucleic Acid	α chain full length (murine constant region) N→Q
81	Protein	β chain full length (murine constant region) N→Q
82	Nucleic Acid	β chain full length (murine constant region) N→Q

[0051] An additional exemplary TCR is characterized as follows. The full length α -chain and β -chain of the T-cell receptor comprise SEQ ID NO: 87 and 99, respectively. The α -chain variable region comprises the amino acid of SEQ ID NO: 83, while the β -chain variable region comprises the amino acid sequence of SEQ ID NO: 85. The α -chain constant region comprises the amino acid sequence of SEQ ID NO: 4 and the β -chain constant region comprises the amino acid sequence of SEQ ID NO: 10. Each of the α -chain and β -chain variable regions comprises three CDR regions wherein the α -chain CDRs comprise the amino acid sequences of SEQ ID NO: 5 (CDR₁), SEQ ID NO: 6 (CDR₂) and SEQ ID NO: 7 (CDR₃) and the β -chain CDRs comprise the amino acid sequences of SEQ ID NO: 11 (CDR₁), SEQ ID NO: 12 (CDR₂) and SEQ ID NO: 13 (CDR₃).

[0052] An additional exemplary TCR is characterized as follows. The full length α -chain and β -chain of the T-cell receptor comprise SEQ ID NO: 53 and 56, respectively. The α -chain variable region comprises the amino acid of SEQ ID NO: 54, while the β -chain variable region comprises the amino acid sequence of SEQ ID NO: 57. The α -chain constant region comprises the amino acid sequence of SEQ ID NO: 55 and the β -chain constant region comprises the amino acid sequence of SEQ ID NO: 58. Each of the α -chain and β -chain variable regions comprises three CDR regions wherein the α -chain CDRs comprise the amino acid sequences of SEQ ID NO: 43 (CDR₁), SEQ ID NO: 44 (CDR₂) and SEQ ID NO: 45 (CDR₃) and the β -chain CDRs comprise the amino acid sequences of SEQ ID NO: 46 (CDR₁), SEQ ID NO: 47 (CDR₂) and SEQ ID NO: 48 (CDR₃).

[0053] In one aspect, the invention provides an isolated, recombinant α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). In another aspect, the invention provides an isolated, recombinant α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1). The α -chain comprises one or more of the following amino acid sequences: (i) an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87; (ii) an

α -chain variable region amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96%, 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; (iii) an α -chain CDR₃ amino acid sequence of SEQ ID NO: 7; (iv) an α -chain CDR₁ amino acid sequence of SEQ ID NO: 5; and (v) an α -chain CDR₂ amino acid sequence of SEQ ID NO: 6.

[0054] In another aspect, the invention provides an isolated recombinant β -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). In another aspect, the invention provides an isolated, recombinant β -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1). The β -chain comprises one or more of the following amino acid sequences: (i) an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99; (ii) a β -chain variable region amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85; (iii) a β -chain CDR₃ amino acid sequence of SEQ ID NO: 13; (iv) a β -chain CDR₁ amino acid sequence of SEQ ID NO: 11; and (v) a β -chain CDR₂ amino acid sequence of SEQ ID NO: 12.

[0055] In another aspect, the invention provides a recombinant T-cell receptor immunoreactive with a SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) epitope comprising at least one of the foregoing α -chains and at least one of the foregoing β -chains.

[0056] In another aspect, the invention provides an isolated, recombinant T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). In another aspect, the invention provides an isolated, recombinant T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1).

[0057] In certain embodiments, the T-cell receptor comprises an α -chain and a β -chain each comprising a CDR₁, CDR₂, and a CDR₃, wherein the α -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 7, and the β -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 13. Optionally, or in addition, the T-cell receptor α -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 5, and the β -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 11. Optionally, or in addition, the T-cell receptor α -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 6, and the β -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 12.

[0058] In certain embodiments, the T-cell receptor comprises an α -chain and a β -chain each comprising a CDR₁, CDR₂, and a CDR₃, wherein the α -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 45, and the β -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 48. Optionally, or in addition, the T-cell receptor α -chain CDR₁ comprises the amino acid sequence of SEQ ID NO:

43, and the β -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 46. Optionally, or in addition, the T-cell receptor α -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 44, and the β -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 47.

[0059] In certain embodiments, the T-cell receptor comprises an α -chain variable region comprising an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96%, 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; and a β -chain variable region comprising an amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85. Optionally, or in addition, the T-cell receptor α -chain comprises the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, and/or the β -chain comprises the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99.

[0060] In certain embodiments, the T-cell receptor comprises an α -chain variable region comprising an amino acid sequence of SEQ ID NO: 54 or an amino acid sequence having greater than 96%, 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 54; and/or a β -chain variable region comprising an amino acid sequence of SEQ ID NO: 57 or an amino acid an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 57. Optionally, or in addition, the T-cell receptor α -chain comprises the amino acid sequence of SEQ ID NO: 53 or an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 53, and/or the β -chain comprises the amino acid sequence of SEQ ID NO: 56 or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 56.

[0061] In each of the foregoing aspects, the T-cell receptor is optionally a single chain T-cell receptor, optionally where the α -chain is linked to the β -chain via an amino acid linker. For example, in one embodiment, the isolated T-cell receptor can comprise the amino acid sequence of SEQ ID NO: 14 or SEQ ID NO: 29, which can be encoded by the polynucleotide sequence of SEQ ID NO: 27 or SEQ ID NO: 30, respectively.

[0062] Furthermore, in certain embodiments of the foregoing aspects, the T-cell receptor is immunoreactive with the epitope SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) in an HLA-A2 restricted manner. For example, the immunoreactivity to the epitope SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) can be (i) HLA-A*0201 or (ii) HLA-A*0202 restricted. The T-cell receptor may potentially be restricted by other HLA-A2 subtypes, and other HLA class I molecules.

[0063] It is contemplated that, for each of the amino acid sequences provided herein, the sequences optionally include at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 amino acid substitutions not present at a given position. For example, contemplated herein are amino acid sequences having at

least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 amino acid substitutions not present in SEQ ID NOS: 2, 3, 4, 8, 9, 10, 83, 85, 87, 88, 95, or 99.

[0064] It is contemplated that included within the scope of the invention, are functional variants of a disclosed T-cell receptor. As used herein, the term "functional variant" is understood to mean a T-cell receptor α - and/or β -chain having substantial or significant sequence identity or similarity to the T-cell receptor α - and/or β -chain of the invention as described above, wherein said functional variants retain the ability to specifically bind (for example, avidity, affinity, association constant and/or dissociation constant) to an epitope (for example, an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28)), to a similar extent (for example, greater than 50%, 60%, 70%, 80%, 90% or 95%) of the T-cell receptor described herein. Such functional variants include polypeptides with partial sequence identity, peptides having one or more specific conservative and/or non-conservative amino acid substitutions.

[0065] Functional variants of the invention can, for example, comprise the amino acid sequence of the T-cell receptor as described above, as well as fragments thereof, but which have at least one conservative amino acid substitution. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same chemical or physical properties. Alternatively or additionally, the functional variants can comprise the amino acid sequence of the T-cell receptor of the invention with at least one non-conservative amino acid substitution wherein said non-conservative amino acid substitution does not interfere with or inhibit the biological activity of the functional variant.

[0066] The functional variants can be assayed in a number of different ways including the approaches set forth in the Examples. For example, target cells expressing NY-ESO-1 and/or LAGE-1a can be contacted with genetically engineered T-cells expressing the variant T-cell receptor. Release assays may then be conducted to detect the presence of IFN- γ or GM-CSF in culture media indicating recognition of NY-ESO-1 and/or LAGE-1a by the engineered T-cells and their subsequent activation.

[0067] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises an α -chain variable region that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to the α -chain variable region of SEQ ID NO: 3 or SEQ ID NO: 83. Optionally, or in addition, the T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises a β -chain variable region that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to the β -chain variable region of SEQ ID NO: 9 or SEQ ID NO: 85.

[0068] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises an α -chain variable region that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identity to the α -chain variable region of SEQ ID NO: 2 or SEQ ID NO: 87. Optionally, or in addition, the T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises a β -chain variable region that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%

identity to the β -chain variable region of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99.

[0069] Sequence identity may be determined in various ways that are within the skill of a person skilled in the art, e.g., using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. BLAST (Basic Local Alignment Search Tool) analysis using the algorithm employed by the programs blastp, blastn, blastx, tblastn and tblastx (Karlin et al., (1990) PROC. NATL. ACAD. SC. USA 87:2264-2268; Altschul, (1993) J. MOL. EVOL. 36:290-300; Altschul et al., (1997) NUCLEIC ACIDS RES. 25:3389-3402, incorporated by reference herein) are tailored for sequence similarity searching. For a discussion of basic issues in searching sequence databases see Altschul et al., (1994) NATURE GENETICS 6:119-129, which is fully incorporated by reference herein. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. The search parameters for histogram, descriptions, alignments, expect (i.e., the statistical significance threshold for reporting matches against database sequences), cutoff, matrix and filter are at the default settings. The default scoring matrix used by blastp, blastx, tblastn, and tblastx is the BLOSUM62 matrix (Henikoff et al., (1992) PROC. NATL. ACAD. SCI. USA 89:10915-10919, fully incorporated by reference herein). Four blastn parameters may be adjusted as follows: Q=10 (gap creation penalty); R=10 (gap extension penalty); wink=1 (generates word hits at every wink.sup.th position along the query); and gapw=16 (sets the window width within which gapped alignments are generated). The equivalent blastp parameter settings may be Q=9; R=2; wink=1; and gapw=32. Searches may also be conducted using the NCBI (National Center for Biotechnology Information) BLAST Advanced Option parameter (e.g.: -G, Cost to open gap [Integer]: default=5 for nucleotides/11 for proteins; -E, Cost to extend gap [Integer]: default=2 for nucleotides/1 for proteins; -q, Penalty for nucleotide mismatch [Integer]: default=-3; -r, reward for nucleotide match [Integer]: default=1; -e, expect value [Real]: default=10; —W, word-size [Integer]: default=11 for nucleotides/28 for megablast/3 for proteins; -y, Dropoff (X) for blast extensions in bits: default=20 for blastn/7 for others; —X, X dropoff value for gapped alignment (in bits): default=15 for all programs, not applicable to blastn; and —Z, final X dropoff value for gapped alignment (in bits): 50 for blastn, 25 for others). ClustalW for pairwise protein alignments may also be used (default parameters may include, e.g., Blosum62 matrix and Gap Opening Penalty=10 and Gap Extension Penalty=0.1). A Bestfit comparison between sequences, available in the GCG package version 10.0, uses DNA parameters GAP=50 (gap creation penalty) and LEN=3 (gap extension penalty). The equivalent settings in Bestfit protein comparisons are GAP=8 and LEN=2.

[0070] The invention further comprises proteins or polypeptides comprising one or more functional fragments of a T-cell receptor of the invention. With respect to such proteins or polypeptides, the functional fragment can be any fragment comprising amino acids of a T-cell receptor, including α - and β -chains, or functional variants thereof, of which it is a part, provided that the functional fragment specifically binds to NY-ESO-1 and/or LAGE-1a. The term "functional fragment" when used in reference to a T-cell

receptor, or functional variants thereof, refers to any part or fragment of the T-cell receptor, or functional variant thereof, which retains at least 50%, 60%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of one or more biological activities of the T-cell receptor of the invention. Functional fragments encompass, for example, those parts of a T-cell receptor, or functional variants thereof, that retain the ability to specifically bind to NY-ESO-1 and/or LAGE-1, or detect, treat, or prevent cancer, to a similar extent, the same extent, or to a higher extent, as a T-cell receptor of the invention, or functional variants thereof.

[0071] The functional fragment may comprise additional amino acids at the amino and/or carboxy termini of the fragment wherein the additional amino acids do not interfere with the biological function of the functional fragment, e.g., binding to the NY-ESO-1 and/or LAGE-1a antigen. In a preferred embodiment, the additional amino acids can be added to the functional fragment to provide a peptide tag to aid in the purification of a T-cell receptor or to enhance the biological activity of the T-cell receptor.

II. Engineered T-cell Receptors

[0072] The invention also provides engineered or modified T-cell receptors that retain the ability to bind to the NY-ESO-1 and/or LAGE-1a antigen. Such T-cell receptors include, for example, one or more point mutations, insertions, and/or deletions. Other engineered T-cell receptors include, for example, single chain fusions proteins, bispecific proteins, chimeric T-cell receptors and T-cell receptors associated with a detectable label or an effector therapeutic agent.

[0073] In one embodiment of the invention, the invention provides a modified T-cell receptor of the invention in the form of a single chain fusion protein comprising a linker peptide linking the α -chain of SEQ ID NO: 2 or SEQ ID NO: 87, and the β -chain of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99, as well as fragments and functional variants of said α - and β -chains.

[0074] The T-cell receptor α -chain may comprise one or more of the following amino acid sequences: (i) an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87; (ii) an α -chain variable region amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96%, 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; (iii) an α -chain CDR3 amino acid sequence of SEQ ID NO: 7; (iv) an α -chain CDR₁ amino acid sequence of SEQ ID NO: 5; and (v) an α -chain CDR2 amino acid sequence of SEQ ID NO: 6. The T-cell receptor β -chain may comprise one or more of the following amino acid sequences: (i) an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99; (ii) a β -chain variable region amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85; (iii) a β -chain CDR₃ amino acid sequence of SEQ ID NO: 13; (iv) a β -chain CDR₁ amino acid sequence of SEQ ID NO: 11; and (v) β -chain CDR₂ amino acid sequence of SEQ ID NO: 12.

[0075] Furthermore, the single chain T-cell receptor can comprise α - and β -chains each comprising a CDR₁, CDR₂, and a CDR₃, wherein the α -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 7, and the β -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 13. The T-cell receptor may further comprise the α -chain CDR₁ of SEQ ID NO: 5 and the β -chain CDR₁ of SEQ ID NO: 11 and/or the α -chain CDR₂ of SEQ ID NO: 6 and the β -chain CDR₂ of SEQ ID NO: 12.

[0076] In another embodiment, the single chain T-cell receptor comprises an α -chain variable region comprising an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96%, 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; and a β -chain variable region comprising an amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85.

[0077] A single chain T-cell receptor is also provided, wherein the α -chain comprises the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97%, 98%, or 99% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, and the β -chain comprises the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97%, 98%, 99% identity to the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99. In a specific embodiment, the invention provides a single chain T-cell receptor having the amino acid sequence of SEQ ID NO: 14. In a specific embodiment, the invention provides a single chain T-cell receptor having the amino acid sequence of SEQ ID NO: 29. In a specific embodiment, the invention provides a single chain T-cell receptor having the amino acid sequence of SEQ ID NO: 89. In a specific embodiment, the invention provides a single chain T-cell receptor having the amino acid sequence of SEQ ID NO: 91. In a specific embodiment, the invention provides a single chain T-cell receptor having the amino acid sequence of SEQ ID NO: 93.

[0078] It is contemplated that, for each of the amino acid sequences provided herein, the sequences optionally include at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 amino acid substitutions (mutations) not present at a given position. For example, contemplated herein are amino acid sequences having at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 amino acid substitutions not present in SEQ ID NOs: 2, 3, 4, 8, 9, 10, 83, 85, 87, 88, 95, or 99. Mutations can be carried out using any appropriate method including, but not limited to, those based on polymerase chain reaction (PCR), restriction enzyme-based cloning, or ligation independent cloning (LIC) procedures. These methods are detailed in many of the standard molecular biology texts. For further details regarding polymerase chain reaction (PCR) mutagenesis and restriction enzyme-based cloning see Sambrook & Russell, (2001) Molecular Cloning-A Laboratory Manual (3rd Ed.) CSHL Press. For further information on LIC procedures see Rashtchian (1995) CURR. OPIN. BIOTECHNOL. 6 (1): 30-6.

[0079] Mutagenesis of the T-cell receptors described herein may be performed to increase, for example, the affinity, specificity, membrane targeting, half-life and expression levels of a T-cell receptor, which can be benefi-

cial in clinical applications (Abate-Daga et al. (2014) PLoS ONE 9:e93321; Udyavar et al. (2009) J. IMMUNOL. 182:4439-4447; Kuball et al. (2009) J. EXP. MED. 206:463-475). Mutants of a T-cell receptor may comprise amino acid additions, deletions and/or insertions. The mutations may be concentrated in one or more regions such as constant regions, framework regions or variable regions, including the CDR variable regions of the α - and/or β -chains, or they may be spread throughout the molecule. The variants may be recombinantly or synthetically produced.

[0080] The present invention provides T-cell chimeric proteins where one or more regions of a human T-cell receptor of the invention are replaced with corresponding T-cell receptor regions derived from species other than human, such as a pig or rodent (for example, a rat or mouse). In one embodiment, the human constant regions of the α -and/or β -chains are replaced with known murine T-cell receptor constant regions. The pairing between murine TCR constant regions may reduce the mispairing of transduced T-cell receptors with endogenous T-cell receptors in a human subject.

[0081] Exemplary human α -chain constant regions are depicted in SEQ ID NOS: 4 and 55. Accordingly, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises SEQ ID NO: 4 or SEQ ID NO: 55, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 4 or SEQ ID NO: 55. An exemplary murine α -chain constant region is depicted in SEQ ID NO: 49. Accordingly, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises SEQ ID NO: 49, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 49. Exemplary human β -chain constant regions are depicted in SEQ ID NOS: 10 and 58. Accordingly, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises SEQ ID NO: 10 or SEQ ID NO: 58, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 10 or SEQ ID NO: 58. An exemplary murine β -chain constant region is depicted in SEQ ID NO: 51. Accordingly, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises SEQ ID NO: 51, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 51.

[0082] For example, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises (i) an α -chain that comprises the amino acid sequence of SEQ ID NO: 37 or SEQ ID NO: 84, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 37 or SEQ ID NO: 84, and/or (ii) a β -chain that comprises the amino acid sequence of SEQ ID NO: 39 or SEQ ID NO: 86, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 39 or SEQ ID NO: 86.

[0083] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises (i) an α -chain that comprises the amino acid sequence of SEQ ID NO: 71, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 71, and/or (ii) a β -chain that comprises the amino acid sequence of SEQ ID NO: 73, or an amino acid sequence that

has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 73.

[0084] T-cell receptors of the invention typically are glycosylated when expressed in transfected T-cells. In one aspect of the invention, the glycosylation pattern, for example, the N-glycosylation pattern of transfected T-cell receptors may be modified through mutagenesis wherein one or more of the N-glycosylation sites of a T-cell receptor, such as constant region glycosylation sites, are removed. Such mutations include, for example, a change in the key glycosylation site NXs/T to QXS/T in the constant region of the α - and/or β -chains. The T-cell receptor could possess the NXs/T to QXS/T mutation in one of the α - or β -chains or in both chains. Alternatively, in a chimeric protein, for example, a specific human/mouse chimera protein described herein, the key glycosylation site NQT in the murine constant region can be modified to QQT. In another aspect of the invention, cysteine residues may be engineered into the receptor protein enabling the formation of inter-chain disulfide bonds which can stabilize, for example, the resulting refolded soluble T-cell receptors. Furthermore, alanine residues in a T-cell receptor CDR3 region can be substituted with alternative amino acid residues to modulate the binding characteristics of the receptor. Mutagenesis can be carried out with a panel of primers carrying various mutations, followed by performance of functional assays as described above. Once a mutation is identified with the desired phenotype, the construct can be sequenced to identify the location of the mutation.

[0085] For example, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises (i) an α -chain that comprises the amino acid sequence of SEQ ID NO: 75, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 75, and/or (ii) a β -chain that comprises the amino acid sequence of SEQ ID NO: 77 or SEQ ID NO: 97, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 77 or SEQ ID NO: 97.

[0086] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises (i) an α -chain that comprises the amino acid sequence of SEQ ID NO: 79, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 79, and/or (ii) a β -chain that comprises the amino acid sequence of SEQ ID NO: 81, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 81.

[0087] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises (i) an α -chain that comprises the amino acid sequence of SEQ ID NO: 31 or SEQ ID NO: 33, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 31 or SEQ ID NO: 33, and/or (ii) a β -chain that comprises the amino acid sequence of SEQ ID NO: 35, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 35.

[0088] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises (i) an α -chain that comprises the amino acid sequence of SEQ ID NO: 41, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 41, and/or (ii) a β -chain that comprises the amino acid

sequence of SEQ ID NO: 73, or an amino acid sequence that has at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 73.

[0089] In certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises one or more mutations (e.g., NXs/T to QXS/T mutations) depicted in FIG. 5 or FIG. 7. For example, in certain embodiments, a T-cell receptor that binds to NY-ESO-1 and/or LAGE-1a comprises a substitution of an asparagine to glutamine at (i) a position corresponding to position 41, 82, 162, 196 and/or 243 of SEQ ID NO: 75, (ii) a position corresponding to position 37 and/or 200 of SEQ ID NO: 77, (iii) a position corresponding to position 37 and/or 201 of SEQ ID NO: 97, (iv) a position corresponding to position 41, 82, 196, and/or 210 of SEQ ID NO: 79, and/or (v) a position corresponding to position 37, 136, 198, and/or 247 of SEQ ID NO: 81.

[0090] In addition, the invention provides soluble versions of the T-cell receptors. Such soluble receptors may be engineered by removing of any portion of the intracellular or transmembrane domains of the TCR α -chain and/or β -chain. See, for example, U.S. Pat. No. 8,519,100, which describes the synthesis of soluble T-cell receptors. Soluble T-cell receptors may comprise the extracellular portion of the TCR as two individual soluble proteins, or as one single chain molecule linked by methods known in the art (Walseng et al. PLOS ONE (2015) 10:1371).

[0091] The binding characteristics of the T-cell receptors and T-cell receptor constructs herein can be determined using approaches known in the art. For example, binding affinity (inversely proportional to the equilibrium constant K_D) and binding half-life (expressed as $T_{1/2}$) can be determined by any appropriate method. It is contemplated that doubling the affinity of a T-cell receptor results in halving the K_D . $T_{1/2}$ is calculated as $\ln 2$ divided by the off-rate (k_{off}). As a result, doubling of $T_{1/2}$ results in a halving of k_{off} and K_D values. K_{off} values for T-cell receptors often are measured for soluble forms of the receptors, i.e. those forms which are truncated to remove hydrophobic transmembrane domain and the intracellular domain. It is to be understood that a given T-cell receptor satisfies the requirement it has a binding affinity for, and/or a binding half-life for, the SLL-MWITQC (SEQ ID NO: 1)-HLA-A2 and/or SLL-MWITQCFL (SEQ ID NO: 28)-HLA-A2 complex if a soluble form of that T-cell receptor analog lacking the transmembrane and intracellular domains meets that requirement. Preferably the binding affinity or binding half-life of a given T-cell receptor or T-cell receptor construct is measured several times, for example, 3 or more times, using the same assay protocol, and an average of the results is taken. In certain embodiments these measurements are made using Surface Plasmon Resonance (BIAcore).

[0092] For example, a T-cell receptor of the invention may have a K_D for the SLLMWITQC (SEQ ID NO: 1)-HLA-A2 and/or SLLMWITQCFL (SEQ ID NO: 28)-HLA-A2 complex of 8 μM or lower, 5 μM or lower, 1 μM or lower, 500 nM or lower, 400 nM or lower, 300 nM or lower, 200 nM or lower, 175 nM or lower, 150 nM or lower, 125 nM or lower, 100 nM or lower, 75 nM or lower, 50 nM or lower, 25 nM or lower, 10 nM or lower, 1 nM or lower, or 0.1 nM or lower.

[0093] In certain embodiments, a T-cell receptor of the invention may have a K_D for the SLLMWITQC (SEQ ID NO: 1)-HLA-A2 and/or SLLMWITQCFL (SEQ ID NO: 28)-HLA-A2 complex of from about 5 μM to about 0.1 nM,

from about 5 μM to about 1 nM, from about 5 μM to about 10 nM, from about 5 μM to about 100 nM, from about 5 μM to about 500 nM, from about 5 μM to about 1 μM or lower, from about 1 μM to about 0.1 nM, from about 1 μM to about 1 nM, from about 1 μM to about 10 nM, from about 1 μM to about 100 nM, from about 1 μM to about 500 nM, from about 500 nM to about 0.1 nM, from about 500 nM to about 1 nM, from about 500 nM to about 10 nM, from about 500 nM to about 100 nM, from about 100 nM to about 1 nM, from about 100 nM to about 10 nM, from about 10 nM to about 0.1 nM, from about 10 nM to about 1 nM, or from about 1 nM to about 0.1 nM.

[0094] In certain embodiments, a T-cell receptor of the invention, when expressed as a soluble form of the T-cell receptor lacking the transmembrane and intracellular domains, may have a K_D for the SLLMWITQC (SEQ ID NO: 1)-HLA-A2 and/or SLLMWITQCFL (SEQ ID NO: 28)-HLA-A2 complex of 8 μM or lower, 5 μM or lower, 1 μM or lower, 500 nM or lower, 400 nM or lower, 300 nM or lower, 200 nM or lower, 175 nM or lower, 150 nM or lower, 125 nM or lower, 100 nM or lower, 75 nM or lower, 50 nM or lower, 25 nM or lower, 10 nM or lower, 1 nM or lower, or 0.1 nM or lower.

[0095] In certain embodiments, a T-cell receptor of the invention may have a K_D for the SLLMWITQC (SEQ ID NO: 1)-HLA-A2 and/or SLLMWITQCFL (SEQ ID NO: 28)-HLA-A2 complex that is lower than the K_D of a reference T-cell receptor (e.g., 1G4LY TCR or 1G4 TCR as described in Example 7 herein) for the SLLMWITQC (SEQ ID NO: 1)-HLA-A2 and/or SLLMWITQCFL (SEQ ID NO: 28)-HLA-A2 complex. For example the T-cell receptor of the invention may have a K_D that is at least 1 μM , 500 nM, 400 nM, 300 nM, 200 nM, 175 nM, 150 nM, 125 nM, 100 nM, 75 nM, 50 nM, 25 nM, 10 nM, 1 nM, or 0.1 nM lower than the K_D of the reference T-cell receptor. K_D may be measured by any method known in the art, for example, surface plasmon resonance as described in Example 7 herein.

[0096] T-cell receptors of the invention may have a binding half-life ($T_{1/2}$) for the complex of ≥ 1.5 s, ≥ 3 s, ≥ 10 s, ≥ 20 s, ≥ 40 s, ≥ 60 s, ≥ 600 s, or ≥ 6000 s. The k_{on} may be $\geq 10^3 \text{ M}^{-1}\text{s}^{-1}$, $\geq 10^4 \text{ M}^{-1}\text{s}^{-1}$, $\geq 10^5 \text{ M}^{-1}\text{s}^{-1}$, $\geq 10^6 \text{ M}^{-1}\text{s}^{-1}$, or $\geq 10^7 \text{ M}^{-1}\text{s}^{-1}$ and/or the k_{off} may be $\leq 10^{-1}\text{s}^{-1}$, $\leq 10^{-2}\text{s}^{-1}$, $\leq 10^{-3}\text{s}^{-1}$, $\leq 10^{-4}\text{s}^{-1}$, $\leq 10^{-5}\text{s}^{-1}$, or $\leq 10^{-6}\text{s}^{-1}$.

[0097] The invention further provides bispecific T-cell receptor proteins comprising a T-cell receptor of the invention, as described above, including single chain T-cell receptors, in association with an additional binding moiety (for example, an antibody, or a different T-cell receptor, or an antigen binding fragment of any of the foregoing) that binds a second antigen other than the NY-ESO-1 and/or LAGE-1a antigen (Garber (1994) NAT. REV. DRUG DISCOV. 13:799-801). For example, the bispecific receptor protein may be a fusion protein comprising a T-cell receptor of the invention fused to an immune-modulating polypeptide such as an antibody or an antigen binding fragment thereof.

[0098] In one embodiment, the bispecific T-cell protein comprises a T-cell receptor of the invention, including single chain T-cell receptors, or fragments thereof, associated with an antibody or antigen binding fragment thereof, that binds the CD3 antigen. In an embodiment, the bispecific antibody may be a fusion protein comprising a linker sequence (for example, an amino acid linker sequence 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 amino acids in length) that links the T-cell

receptor polypeptide to the anti-CD3 binding moiety. In one embodiment, an anti-CD3 binding moiety, for example, a single-chain variable region (sFv) is fused, via an amino acid linker, to the N-terminus of a T-cell receptor β -chain. Under certain circumstances it can be desirable to remove the transmembrane domain and/or the intracellular domains from the constant region of the α -chain and/or the β -chain when creating the fusion constructs. For example, the invention also provides soluble versions of the T-cell receptors, including bispecific T-cell receptors proteins. Such soluble receptors may be engineered by the removal of any portion of the intracellular or transmembrane domains of the TCR α -chain and/or β -chain. Bispecific T-cell proteins that include anti-CD3 polypeptides and methods of making such proteins are described in U.S. Pat. No. 8,519,100, the disclosure of which is incorporated by reference herein. U.S. Pat. No. 8,519,100 describes methods for designing fusion constructs, making expression constructs, transfecting expression vectors into host cells, expressing fusion constructs, harvesting, purifying and refolding the fusion constructs. The expression of such a bispecific fusion T-cell receptor in engineered T-cells (as described in detail below) is designed to enhance the reactivity and cytotoxicity of the T-cells towards targeted cancer cells or tumor cells of a subject. Both bispecific T-cell receptors and soluble T-cell receptors allow the TCR or the peptide/MHC complex binding motif of the TCR to be utilized without the need of autologous and/or allogeneic cell transduction.

[0099] In another embodiment of the invention, chimeric T-cell receptors are provided wherein a T-cell receptor of the invention is expressed as a fusion with a second polypeptide. Such second polypeptides include for example, cytotoxic agents such as ricin, diphtheria toxin, bacterial exotoxin A, DNase and RNase. Such chimeric T-cell receptors may be useful in targeting such cytotoxic agents to cancer or tumor cells of a subject.

[0100] Also included in the invention is a T-cell receptor of the invention, as well as fragments and functional variants thereof, that are modified to comprise a detectable label. For example, soluble T-cell receptors of the invention maybe associated (covalently or non-covalently associated) with a detectable moiety such as a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), or a particle (e.g., a gold particle). Such molecules can be used in diagnostic screens to detect the presence of cancer cells within a subject.

[0101] Alternatively, an effector therapeutic agent may be associated with a T-cell receptor of the invention, as well as fragments and functional variants thereof. Such agents include for example, immune modulating antibody fragments such as anti-CD3 or anti-CD16 antibody fragments, toxins, radioisotopes, immuno-stimulants such as IL-2, IFN- γ , CCL21, or GM-CSF, chemotherapeutic agents or a drug. Such T-cell receptors can be used to target delivery of the effector molecule to cancer cells of a subject.

III. Nucleic Acids Encoding T-Cell Receptors and Engineered Variants Thereof

[0102] The invention further provides nucleic acids encoding the T-cell receptors of the invention (including non-naturally occurring T-cell receptors) as well as fragments and functional variants thereof.

[0103] The invention encompasses nucleic acids that encode the T-cell receptors of the invention, variants and fragments of T-cell receptors, fusion proteins such as single chain T-cell receptors, and bispecific receptor proteins. Nucleic acids include, but are not limited to, those sequences encoding full length α - and β -chains, α - and β -chain variable regions as well as α - and β -chain regions containing one or more of the CDR_{1,3} regions of SEQ ID NO: 5-7 (α -chain) and SEQ ID NO: 11-13 (β -chain). In an additional aspect, the invention provides an expression vector, for example, a viral expression vector, comprising one or more of a disclosed nucleic acid sequence. In certain embodiments, the viral vector is a lentivirus vector.

[0104] In one aspect, the invention provides an isolated, recombinant nucleic acid encoding an α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). In one aspect, the invention provides an isolated, recombinant nucleic acid encoding an α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1). The nucleic acid comprises one or more of the following nucleotide sequences: (i) a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87, or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 87; (ii) a nucleotide sequence encoding an α -chain variable region amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96%, 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83; (iii) a nucleotide sequence of SEQ ID NO: 15 or SEQ ID NO: 100; (iv) a nucleotide sequence encoding an α -chain CDR₃ amino acid sequence of SEQ ID NO: 7; (v) a nucleotide sequence encoding an α -chain CDR₁ amino acid sequence of SEQ ID NO: 5; and (vi) a nucleotide sequence encoding an α -chain CDR₂ amino acid sequence of SEQ ID NO: 6.

[0105] In another aspect, the invention provides an isolated, recombinant nucleic acid encoding a T-cell receptor β -chain immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). In one aspect, the invention provides an isolated, recombinant nucleic acid encoding a β -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1). The nucleic acid comprises one or more of the following nucleotide sequences: (i) a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 8, SEQ ID NO: 88, SEQ ID NO: 95, or SEQ ID NO: 99; (ii) a nucleotide sequence encoding a β -chain variable region amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97%, 98% or 99% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85; (iii) a nucleotide sequence of SEQ ID NO: 21, SEQ ID NO: 96, or SEQ ID NO: 102; (iv) a nucleotide sequence encoding a β -chain CDR₃ amino acid sequence of SEQ ID NO: 13; (v) a nucleotide sequence encoding a β -chain CDR₁

amino acid sequence of SEQ ID NO: 11; and (vi) a nucleotide sequence encoding a β -chain CDR₂ amino acid sequence of SEQ ID NO: 12.

[0106] In another aspect, the invention provides an isolated, recombinant nucleic acid encoding a T-cell receptor immunoreactive with an epitope of an NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28). In one aspect, the invention provides an isolated, recombinant nucleic acid encoding a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1). The T-cell receptor comprises an α -chain and a β -chain each comprising a CDR₁, CDR₂, and a CDR₃, wherein the α -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 7, and the β -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 13. Optionally, or in addition, the α -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 5, and the β -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 11. Optionally, or in addition, the α -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 6, and the β -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 12.

[0107] It is contemplated that, for each of the nucleic acids described herein, the nucleic acids may encode an amino acid sequence having at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 amino acid residues not present at a given position in T-cell receptor. For example, contemplated herein are nucleic acids encoding amino acid sequences having at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, or 20 amino acid substitutions not present in SEQ ID NOs: 2, 3, 4, 8, 9, 10, 83, 85, 87, 88, 95, or 99, and/or include codon optimization to enhance the expression of the α -chain and/or the β -chain of the T-cell receptor in a given cell type or subject.

[0108] For each of the foregoing aspects, the nucleic acid may encode a single chain T-cell receptor, optionally where the α -chain is linked to the β -chain via an amino acid linker. In an embodiment of the invention, the nucleic acids can encode a single chain T-cell receptor, or a bispecific T-cell receptor fusion protein. In a specific embodiment, the nucleic acid encodes an antibody that is an immune-modulating antibody.

[0109] In another aspect, the invention provides an isolated, recombinant nucleic acid encoding a fusion protein comprising a T-cell receptor immunoreactive with an epitope of an NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) and a CD34 protein or a truncated form of a CD34 protein. In certain embodiments, the truncated CD34 protein lacks an intracellular signaling domain. For example, in one embodiment, the invention provides an isolated, recombinant nucleic acid encoding the amino acid sequence of SEQ ID NO: 29 or comprising the nucleotide sequence of SEQ ID NO: 30.

[0110] The nucleic acids may be recombinant nucleic acids. The nucleic acids may be produced via chemical synthesis on a synthesizer and/or via enzymatic ligation reactions using procedures known in the art. See, for example, Sambrook et al., Molecular Cloning: A Laboratory Manual, 3.sup.rd ed., Cold Spring Harbor Press, Cold Spring Harbor, N.Y. 2001; and Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates and John

Wiley & Sons, NY, 1994). The nucleic acids encoding the T-cell receptors of the invention may be isolated using a variety of different methods known to those skilled in the art. For example, a cDNA library constructed using RNA from cells or tissue known to express a T-cell receptor, i.e., T-cells, can be screened using a labeled T-cell receptor nucleic acid probe. Alternatively, a genomic library may be screened to derive nucleic acid molecules encoding a T-cell receptor. Further, T-cell receptor nucleic acid sequences may be derived by performing PCR using oligonucleotide primers designed on the basis of the T-cell receptor nucleotide sequences disclosed herein. The template for the reaction may be cDNA obtained by reverse transcription of mRNA prepared from cell lines or tissue known to express the T-cell receptor.

[0111] The nucleic acid can comprise any nucleotide sequence which encodes any of the T-cell receptors of the invention, as well as fragments and functional variants thereof, described herein. The invention also provides a nucleic acid comprising a nucleotide sequence which is complementary to the nucleotide sequence of any of the nucleic acids described herein or a nucleotide sequence which hybridizes under stringent conditions to the nucleotide sequence of any of the nucleic acids described herein.

[0112] The nucleic acids of the invention include those nucleic acids (i) that hybridize to the nucleotide sequences encoding the T-cell receptors of the invention described herein under stringent conditions, e.g., hybridization to filter-bound DNA in 0.5 M NaHPO₄, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65° C., and washing in 0.1×SSC/0.1% SDS at 68° C. (Ausubel F. M. et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3); or (ii) that hybridize under less stringent conditions, such as moderately stringent conditions, e.g., washing in 0.2×SSC/0.1% SDS at 42° C. (Ausubel et al., 1989 *supra*).

[0113] The invention also provides a nucleic acid comprising a nucleotide sequence that is at least about 70% or more, e.g., about 80%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% identical to any of the nucleic acids described herein. Sequence identity can be determined as discussed above.

[0114] In certain embodiments, nucleic acids of the invention include those nucleic acids as described above, wherein the codon usage of the nucleic acid has been optimized to enhance the expression of the α-chain and/or the β-chain of a T-cell receptor in a particular cell type or subject. Nucleic acid sequences may be codon optimized to improve stability or heterologous expression in host cells without changing the encoded amino acid sequence. For example, codon optimization may be used to remove sequences that negatively impact gene expression, transcript stability, protein expression or protein stability, such as transcription splice sites, DNA instability motifs, polyadenylation sites, secondary structure, AU-rich RNA elements, secondary open reading frames (ORFs), codon tandem repeats, or long range repeats. Codon optimization may also be used to adjust the G/C content of a sequence of interest. Codon optimization replaces codons present in a DNA sequence with preferred codons encoding the same amino acid, for example, codons preferred for mammalian expression. Thus, the amino acid sequence is not altered during the process. Codon optimi-

zation can be performed using gene optimization software. The codon optimized nucleotide sequence is translated and aligned to the original protein sequence to ensure that no changes were made to the amino acid sequence. Methods of codon optimization are known in the art and are described, for example, in U.S. Application Publication No. 2008/0194511 and U.S. Pat. No. 6,114,148.

[0115] The invention also encompasses recombinant expression vectors that contain any of the nucleic acids described herein. Accordingly, the present invention encompasses a recombinant expression vector comprising a nucleic acid encoding a T-cell receptor described herein. The vector may comprise nucleic acids that encode the T-cell receptors described herein, variants and fragments of the T-cell receptors, fusion proteins such as single chain T-cell receptors, and bispecific receptor proteins. Nucleic acids include, but are not limited to, those sequences encoding the full length α- and β-chains, the α- and β-chain variable regions as well as α- and β-chain regions containing one or more of the CDR1-3 regions of SEQ ID NOS: 5-7 (α-chain) and SEQ ID NOS: 11-13 (β-chain).

[0116] For purposes herein, the term “recombinant expression vector” means a genetically-modified oligonucleotide or polynucleotide construct that permits the expression of an mRNA, protein, polypeptide, or peptide by a host cell, when the construct comprises a nucleotide sequence encoding the mRNA, protein, polypeptide, or peptide, and the vector is contacted with the cell under conditions sufficient to have the mRNA, protein, polypeptide, or peptide expressed within the cell. The recombinant expression vectors can comprise any type of nucleotides, including, but not limited to DNA and RNA, which can be single-stranded or double-stranded, synthesized or obtained in part from natural sources, and which can contain natural, non-natural or altered nucleotides.

[0117] It is contemplated that a variety of recombinant expression vectors can be used to express the T-cell receptors and T-cell receptor constructs described herein, and can be used to transform or transfect any suitable host cell. Suitable vectors include those designed for propagation and expansion or for expression or both, such as plasmids and viruses. The vector can be selected from the group consisting of the pUC series (Fermentas Life Sciences), the pBlue-script series (Stratagene, LaJolla, Calif.), the pET series (Novagen, Madison, Wis.), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, Calif.). Bacteriophage vectors, such as kGT10, kGT11, kZapII (Stratagene), KEMBL4, and kNM1149, also can be used. Examples of plant expression vectors include pBI01, pBI101.2, pBI101.3, pBI121 and pBIN19 (Clontech). Examples of animal expression vectors include pEUK-C1, pMAM and pMAMneo (Clontech). Preferably, the recombinant expression vector is a viral vector, e.g., a retroviral vector or a lentiviral vector.

[0118] The recombinant expression vectors of the invention can be prepared using standard recombinant DNA techniques. (Ausubel et al. (1989) *supra*; Sambrook et al. (2001) *supra*.) Constructs of expression vectors, which are circular or linear, can be prepared to contain a replication system functional in a prokaryotic or eukaryotic host cell. Replication systems can be derived, for example, from ColE1, 2μ plasmid, λ, SV40, bovine papilloma virus, and the like.

[0119] In one embodiment, the recombinant expression vector comprises regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host cell (e.g., bacterium, fungus, plant, or animal) into which the vector is to be introduced, as appropriate and taking into consideration whether the vector is DNA- or RNA-based.

[0120] The recombinant expression vector can include one or more marker genes, which allow for selection of transformed or transfected host cells. Marker genes include biocide resistance, e.g., resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host cell to provide prototrophy, and the like. Suitable marker genes for the inventive expression vectors include, for instance, neomycin/G418 resistance genes, hygromycin resistance genes, histidinol resistance genes, tetracycline resistance genes, and ampicillin resistance genes.

[0121] The recombinant expression vector can comprise a native or non-native promoter operably linked to the nucleotide sequence encoding a T-cell receptor, polypeptide, or protein (including functional variants thereof), or to the nucleotide sequence which is complementary to or which hybridizes to the nucleotide sequence encoding a T-cell receptor, polypeptide, or protein (including functional variants thereof). It is contemplated that the selection of appropriate promoters, for example, strong, weak, inducible, tissue-specific and developmental-specific, is within the ordinary skill of the artisan. Similarly, it is contemplated that the combination of a nucleotide sequence with a promoter is also within the skill of the artisan. The promoter can be a non-viral promoter or a viral promoter, e.g., murine stem cell virus (MSCV), a cytomegalovirus (CMV) promoter, an SV40 promoter, an RSV promoter, and a promoter found in the long-terminal repeat of the murine stem cell virus.

[0122] The recombinant expression vectors can be designed for transient expression, stable expression, or for both. Also, the recombinant expression vectors can be made for constitutive expression or for inducible expression. Further, the recombinant expression vectors can be made to include a suicide gene.

[0123] In one embodiment, viral based vector systems can be used to express the T-cell receptors and/or engineered T-cell receptor constructs. Such viral vector based systems include, but are not limited to, retroviral, lentivirus, adenoviral, adeno-associated, vaccinia and herpes simplex virus vectors for gene transfer. Integration in the host genome is possible with the retrovirus, lentivirus, and adeno-associated virus gene transfer methods, often resulting in long term expression of the inserted transgene.

IV. Genetically Engineered Host Cells

[0124] In addition, the invention provides genetically engineered host cells comprising any of the recombinant nucleic acids and/or expression vectors described hereinabove. The host cell can be a eukaryotic cell, e.g., animal (for example, human), fungi, or algae, or can be a prokaryotic cell, e.g., bacteria or protozoa. The host cell can be a cultured cell or a primary cell, i.e., isolated directly from an organism, e.g., a human. The host cell can be an adherent cell or a suspended cell, i.e., a cell that grows in suspension. Suitable host cells are known in the art and include, for instance, DH5 α *E. coli* cells, Chinese hamster ovarian cells, monkey VERO cells, COS cells, HEK293 cells, progenitor cells such as hematopoietic or progenitor stem cells and the

like. For purposes of amplifying or replicating the recombinant expression vector, the host cell can be a prokaryotic cell, e.g., a DH5 α cell.

[0125] For purposes of producing a recombinant T-cell receptor, polypeptide, or protein, the host cell preferably is a mammalian cell, for example, a human cell. While the host cell can be of any cell type, can originate from any type of tissue, and can be of any developmental stage, the host cell can be a peripheral blood lymphocyte (PBL) or a peripheral blood mononuclear cell (PBMC), or a Natural Killer (NK) cell. More preferably, the host cell is a T-cell. The T-cell can be any T-cell, such as a cultured T-cell, e.g., a primary T-cell, or a T-cell cell from a cultured T-cell line, e.g., Jurkat, SupTi, etc., or a T-cell obtained from a mammal. If obtained from a mammal, the T-cell can be obtained from numerous sources, including but not limited to blood, bone marrow, lymph node, the thymus, or other tissues or fluids. T-cells can also be enriched for or purified. Preferably, the T-cell is a human T-cell, which can be an autologous or heterologous cell. The T-cell can be any type of T-cell and can be of any developmental stage, including but not limited to, CD4 $^{+}$ /CD8 $^{+}$ double positive T-cells, CD4 $^{+}$ helper T-cells, e.g., Th₁ and Th₂ cells, CD4 $^{+}$ T-cells, CD8 $^{+}$ T-cells (e.g., cytotoxic T-cells), tumor infiltrating lymphocytes (TILs), memory T-cells (e.g., central memory T-cells and effector memory T-cells), naive T-cells, and the like. The T cells can also be previously engineered to knockdown or delete molecules that elicit immune rejections when otherwise transferred to an allogeneic host.

[0126] The cells can include autologous cells derived from a subject to be treated, or alternatively allogenic cells derived from a donor.

[0127] The population of cells can be a heterogeneous population comprising the host cell comprising any of the recombinant expression vectors described herein, in addition to at least one other cell, e.g., a host cell (e.g., a T-cell), which does not comprise any of the recombinant expression vectors, or a cell other than a T-cell, e.g., a B-cell, a macrophage, a neutrophil, an erythrocyte, a hepatocyte, an endothelial cell, an epithelial cells, a muscle cell, a brain cell, etc. Alternatively, the population of cells can be a substantially homogeneous population, in which the population comprises mainly of host cells (e.g., consisting essentially of) comprising the recombinant expression vector. The population also can be a clonal population of cells, in which all cells of the population are clones of a single host cell comprising a recombinant expression vector, such that all cells of the population comprise the recombinant expression vector. In one embodiment, the population of cells is a clonal population comprising host cells comprising a recombinant expression vector as described herein.

[0128] It is contemplated that standard transfection methods can be used to produce bacterial, mammalian, yeast or insect cell lines that express large quantities of protein, which are then purified using standard techniques (see, e.g., Colley et al. (1989) J. BIOL. CHEM. 264:17619-17622; Deutscher, ed. (1990) Guide to Protein Purification, METHODS IN ENZYMOLOGY, vol. 182).

[0129] Conventional gene transfer methods can be used to introduce nucleic acids encoding the T-cell receptors and T-cell receptor constructs described herein into host cells and target tissues. In certain embodiments, the nucleic acids encoding the T-cell receptors and T-cell receptor constructs are introduced into host cells for in vivo or ex vivo gene

therapy uses. Methods of nucleic acid delivery include electroporation, lipofection, microinjection, biolistics, virosomes, liposomes, immunoliposomes, polycation or lipid: nucleic acid conjugates, naked DNA, artificial virions, and agent-enhanced uptake of DNA. Sonoporation using, e.g., the Sonitron 2000 system (Rich-Mar) can also be used for delivery of nucleic acids.

[0130] Lipofection is described in e.g., U.S. Pat. Nos. 5,049,386; 4,946,787; and 4,897,355 and lipofection reagents are sold commercially (e.g., Transfectam and Lipofectin). The preparation of lipid:nucleic acid complexes, including targeted liposomes such as immunolipid complexes, is well known to one of skill in the art (see, e.g., Crystal (1995) SCIENCE 270:404-410; Blaese et al. (1995) CANCER GENE THER. 2:291-297; Behr et al. (1994) BIOCONJUGATE CHEM. 5:382-389; Remy et al. (1994) BIOCONJUGATE CHEM. 5:647-654; Gao et al. (1995) GENE THER. 2:710-722; Ahmad et al. (1992) CANCER RES. 52:4817-4820; U.S. Pat. Nos. 4,186,183; 4,217,344; 4,235,871; 4,261,975; 4,485,054; 4,501,728; 4,774,085; 4,837,028; and 4,946,787).

[0131] Viral vector delivery systems, such as of RNA or DNA viral based systems, may also be used to introduce nucleic acids encoding the T-cell receptors and T-cell receptor constructs into host cells. Viral vectors can be administered directly to patients (in vivo) or they can be used to treat cells *in vitro* (ex vivo) and the modified cells then are administered to a subject. Conventional viral based systems include, but are not limited to, retroviral, lentivirus, adenoviral, adeno-associated, vaccinia and herpes simplex virus vectors for gene transfer. Integration in the host genome is possible with the retrovirus, lentivirus, and adeno-associated virus gene transfer methods, often resulting in long term expression of the inserted transgene.

V. T-Cell Receptor Mediated Treatments

[0132] It is contemplated that pharmaceutical compositions (as described herein), comprising T-cell receptors, including fragments and functional variants thereof, nucleic acids, recombinant expression vectors, host cells, or populations of cells can be used in methods of treating or preventing cancer. The T-cell receptors, and functional variants thereof, are believed to bind specifically to the NY-ESO-1 and/or LAGE-1a antigen, such that the T-cell receptor, or related polypeptides or functional variants thereof, when expressed by a cell is able to mediate binding to a cell expressing NY-ESO-1 and/or LAGE-1a.

[0133] In this regard, the invention provides a method of treating or preventing cancer in a subject, comprising administering to the subject any of the pharmaceutical compositions, T-cell receptors (and functional variants thereof), polypeptides, or proteins described herein, any nucleic acid or recombinant expression vector comprising a nucleotide sequence encoding any of the T-cell receptors (and functional variants thereof), polypeptides, proteins described herein, or any host cell or population of cells comprising a recombinant vector which encodes any of the T-cell receptors (and functional variants thereof), polypeptides, or proteins described herein, in an amount effective to treat or prevent cancer in the subject.

[0134] The terms "treating", "treatment" or "prevention" of a disease (or a condition or a disorder) as used herein refers to preventing the disease from occurring in a subject that may be predisposed to the disease but does not yet

experience or exhibit symptoms of the disease (preventing), inhibiting the disease (slowing or arresting its development), providing relief from the symptoms or side-effects of the disease (including palliative treatment), and relieving the disease (causing regression of the disease). With regard to cancer, these terms also mean that the life expectancy of an individual affected with a cancer may be increased or that one or more of the symptoms of the disease is reduced. Compositions can be formulated by any of the means known in the art.

[0135] Representative cancers to be treated include, but are not limited to, bladder cancer, breast cancer, colorectal cancer, endometrial cancer, head and neck cancer, leukemia, lung cancer, lymphoma, melanoma, non-small-cell lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, cervical cancer, vulvar tumor, thyroid cancer, gastric cancer, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma, glioblastoma, ependymoma, Ewing's sarcoma family of tumors, germ cell tumor, extracranial cancer, liver cancer, medulloblastoma, neuroblastoma, brain tumors generally, osteosarcoma, malignant fibrous histiocytoma of bone, retinoblastoma, rhabdomyosarcoma, soft tissue sarcomas generally, supratentorial primitive neuroectodermal and pineal tumors, visual pathway and hypothalamic glioma, Wilms' tumor, esophageal cancer, hairy cell leukemia, kidney cancer, multiple myeloma, oral cancer, pancreatic cancer, primary central nervous system lymphoma, skin cancer, small-cell lung cancer, among others. Some of these cancers naturally express NY-ESO-1 and/or LAGE-1, while others can be induced to express NY-ESO-1 and/or LAGE-1a through the use of HDAC inhibitors.

[0136] As described herein, in certain embodiments, the T-cell receptors described herein recognize the NY-ESO-1 and/or LAGE-1a antigen in HLA A2 restrictive manner. Given the high percentage of HLA-A2 restricted subjects in North American (40%) and East Asian (30%) populations, the compositions and methods of the invention may be particularly well suited for treatment of cancer in this population subset.

[0137] In a specific embodiment, the T-cell receptors and T-cell receptor constructs may be used in adoptive T-cell immunotherapy for treatment of cancer. In such treatments, T-cells are genetically engineered to express a T-cell receptor or T-cell receptor constructs described herein followed by introduction of the engineered cells into the subject. Such engineered T-cells, by virtue of their T-cell receptor expression, are targeted to cancer cells expressing the NY-ESO-1 and/or LAGE-1a antigen. Preferably, such T-cells are cells into which a nucleic acid encoding the α -chain and/or β -chain, or fragments and functional variants thereof, of a T-cell receptor have been introduced. T-cells for use in the adoptive immunotherapy include autologous cells derived from a subject to be treated or allogenic cells derived from a donor who is an acceptable HLA-match.

[0138] When such a cancer therapy is performed, T-cell receptor encoding nucleic acids can be introduced into peripheral blood lymphocytes obtained from the cancer subject to be treated. Prior to reintroduction into the cancer subject, the lymphocytes into which T-cell receptor encoding nucleic acid has been introduced, as described above, may be cultured *ex vivo* to obtain a large amount of NY-ESO-1 and/or LAGE-1a specific lymphocytes. Further, specific subsets of the lymphocytes into which T-cell receptor encoding nucleic acid may be purified, or isolated using

methods known to those of skilled in the art. For example, subsets of CD8⁺ T-cells may be purified from the mixed population of peripheral blood lymphocytes, for example, using antibodies against a TCR or regions of a TCR (such as v007-09 or v005-01) expressed on cell surface. Subsets of CD8⁺ T-cells may be purified from the mixed population of peripheral blood lymphocytes also, for example, by coexpressing a TCR with a transgene, such as CD34 or a truncated form CD34, followed by identification of cells using anti-CD34 antibody based methods, for example, flow cytometry or immuno-magnetic methods.

[0139] In addition, the adoptive immunotherapy as described above may be combined with other cancer treatments including chemotherapy, radiotherapy and surgery. In a specific embodiment of the invention, the adoptive immunotherapy may be combined with the use of immunological checkpoint inhibitors. Such inhibitors include for example, anti-cytotoxic T-lymphocyte-associated antigen (CTLA-4) antibodies and anti-programmed cell death (PD)-1/PD-ligand-1 (PD-L1) antibodies.

[0140] In another embodiment, T-cell receptors, as well as fragments and functional variants thereof, associated an effector therapeutic agent may be used to treat cancer. Such agents include for example, immune modulating antibody fragments such as anti-CD3 or anti-CD16 antibody fragments, toxins, radioisotopes, immuno-stimulants such as IL-2 and IFN- γ , chemotherapeutic agents or a drug. Such T-cell receptors can be used to target delivery of the effector molecule to cancer cells of a subject thereby targeting destruction of the cancer cells.

VI. Pharmaceutical Compositions and Methods of Administration

[0141] For administration to patients, a T-cell receptor of the invention, including functional fragments and variants thereof, nucleic acids, recombinant expression vectors and host cells can be formulated into a pharmaceutical composition with a pharmaceutically acceptable carrier. Pharmaceutical compositions suitable for use in the present invention include compositions wherein the T-cell receptor related compositions are present in an amount effective to achieve the intended purpose. Determination of the effective amounts is within the level of those skilled in the art, especially in light of the detailed disclosure provided herein.

[0142] With respect to the pharmaceutical compositions, the carrier can be any of those conventionally used for the particular T-cell receptor related pharmaceutical composition to be administered. Such pharmaceutically acceptable carriers are well-known to those skilled in the art and are readily available. It is preferred that the pharmaceutically acceptable carrier be one which has no detrimental side effects or toxicity under the conditions of use.

[0143] The pharmaceutical composition may be in any suitable form, depending upon the desired mode of administration to a patient. The pharmaceutical composition may be adapted for administration by any appropriate route, preferably a parenteral (including subcutaneous, intramuscular, or preferably intravenous) route. The pharmaceutical compositions of the present disclosure may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes. Such compositions may be prepared by any

method known in the art of pharmacy, for example by mixing the active ingredient with the carrier(s) or excipient(s) under sterile conditions.

[0144] Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0145] Preferably, the pharmaceutical composition is administered by injection, e.g., intravenously. When the composition is a host cell expressing a T-cell receptor of the invention, or a fragment or functional variant thereof, the pharmaceutically acceptable carrier for the cells for injection may include any isotonic carrier such as, for example, normal saline (about 0.90% w/v of NaCl in water, about 300 mOsm/L NaCl in water, or about 9.0 g NaCl per liter of water), NORMOSOL R electrolyte solution (Abbott, Chicago, Ill.), PLASMA-LYTE A (Baxter, Deerfield, Ill.), about 5% dextrose in water, or Ringer's lactate. In an embodiment, the pharmaceutically acceptable carrier is supplemented with human serum albumen.

[0146] The amount or dose (e.g., numbers of cells when the composition is one or more cells, i.e., a population of cells) of the pharmaceutical composition administered should be sufficient to effect, e.g., a therapeutic or prophylactic response, in the subject or animal over a reasonable time frame. For example, the dose of a T-cell receptor related composition should be sufficient to bind to a cancer antigen, or detect, treat or prevent cancer in a subject. The dose will be determined by the efficacy of the particular pharmaceutical composition and the condition of the subject (e.g., human), as well as the body weight of the subject (e.g., human) to be treated. Assays for determining an administered dose are well known in the art. The cells can typically be prepared as injectables, especially for intravenous and intraperitoneal administration either as liquid solutions or suspensions.

[0147] The dose of the composition can also be determined by the existence, nature and extent of any adverse side effects that might accompany the administration of a particular composition. Typically, the attending physician will decide the dosage of the composition with which to treat each individual patient, taking into consideration a variety of factors, such as age, body weight, general health, diet, sex, route of administration, and the severity of the condition being treated. It is contemplated that the attending physician would know how to and when to terminate, interrupt, or adjust administration due to toxicity, or to organ dysfunctions. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response were not adequate (precluding toxicity). The magnitude of an administered dose in the management of the disorder of interest will vary with the severity of the condition to be treated and to the route of administration. The severity of the

condition may, for example, be evaluated, in part, by standard prognostic evaluation methods.

VII. Diagnostic Methods

[0148] Also provided by the present invention are diagnostic methods for use in detection of cancer in a mammal. The method comprises contacting a sample of cells or tissue derived from a subject suspected of having cancer with a T-cell receptor associated with a label, thereby forming a complex, and detecting the complex, wherein detection of the complex is indicative of the presence of cancer in the subject.

[0149] Samples for analysis in such methods can be any organ, tissue, cell, or cell extract isolated from a subject, such as a sample isolated from a mammal having cancer. For example, a sample can include, without limitation, cells or tissue (e.g., from a biopsy), blood, serum, tissue or fine needle biopsy samples, or any other specimen, or any extract thereof, obtained from a test subject. A sample may also include sections of tissues such as frozen sections taken for histological purposes.

[0150] For purposes of the diagnostic method, the contacting can take place in vitro or in vivo with respect to the subject. Detection of the complex can occur through any number of ways known in the art. For instance, a T-cell receptor can be labeled with a detectable label such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and particles (e.g., gold particles) as described above.

[0151] Finally, this invention provides kits for performing the instant diagnostic methods described herein. Each kit comprises a labeled T-cell receptor reagent, suitable solvents and instructions for using the kits. Such T-cell receptor based diagnostic kits and their methods of manufacture and use are well known.

[0152] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0153] In the application, where an element or component is said to be included in and/or selected from a list of recited elements or components, it should be understood that the element or component can be any one of the recited elements or components, or the element or component can be selected from a group consisting of two or more of the recited elements or components.

[0154] Further, it should be understood that elements and/or features of a composition or a method described herein can be combined in a variety of ways without departing from the spirit and scope of the present invention, whether explicit or implicit herein. For example, where reference is made to a particular compound, that compound can be used in various embodiments of compositions of the present invention and/or in methods of the present invention, unless otherwise understood from the context. In other words, within this application, embodiments have been described and depicted in a way that enables a clear and concise application to be written and drawn, but it is

intended and will be appreciated that embodiments may be variously combined or separated without parting from the present teachings and invention(s). For example, it will be appreciated that all features described and depicted herein can be applicable to all aspects of the invention(s) described and depicted herein.

[0155] It should be understood that the expression "at least one of" includes individually each of the recited objects after the expression and the various combinations of two or more of the recited objects unless otherwise understood from the context and use. The expression "and/or" in connection with three or more recited objects should be understood to have the same meaning unless otherwise understood from the context.

[0156] The use of the term "include," "includes," "including," "have," "has," "having," "contain," "contains," or "containing," including grammatical equivalents thereof, should be understood generally as open-ended and non-limiting, for example, not excluding additional unrecited elements or steps, unless otherwise specifically stated or understood from the context.

[0157] Where the use of the term "about" is before a quantitative value, the present invention also includes the specific quantitative value itself, unless specifically stated otherwise. As used herein, the term "about" refers to a $\pm 10\%$ variation from the nominal value unless otherwise indicated or inferred.

[0158] It should be understood that the order of steps or order for performing certain actions is immaterial so long as the present invention remain operable. Moreover, two or more steps or actions may be conducted simultaneously.

[0159] The use of any and all examples, or exemplary language herein, for example, "such as" or "including," is intended merely to illustrate better the present invention and does not pose a limitation on the scope of the invention unless claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the present invention.

EXAMPLES

[0160] Practice of the invention will be more fully understood from the foregoing examples, which are presented herein for illustrative purposes only, and should not be construed as limiting the invention in any way.

Example 1—Identification of 806 T-Cell Receptor

[0161] The following example describes the identification of newly created T-cells (e.g., new cells that contain new proteins and nucleic acids encoding such proteins that have not been identified as naturally occurring in nature) that recognize NY-ESO-1 and/or LAGE-1a epitopes in an HLA restricted manner.

[0162] Human T-cells that recognize tumor-associated antigens were isolated from peripheral blood lymphocytes using a "reverse immunology" approach (Zeng et al. (2000) J. IMMUNOL. 165:1153-1159; Zeng et al. (2001) PROC. NATL. ACAD. SCI. USA 98: 3964-3969). In this case, an in vitro sensitization procedure was carried out as described using the HLA-A2 restricted NY-ESO-1:157-165 epitope of SEQ ID NO: 1 (Zeng et al. (2000) supra). Briefly, lymphocytes from various donors were plated in a 96-well flat-bottom plate in the presence of 1 μ g/mL of the above mentioned peptide. On days 7 and 14, about 1×10^5 non-irradiated

lymphocytes were pulsed with 10 µg/mL peptide and washed twice. Subsequently, IL-2 at a final concentration of 120 units/mL was added to each well. On day 21, the cells were harvested and incubated with presenting cells overnight prior to collection of supernatants. Primary B cells activated with human IL-4 and CD40 ligands (“B cells”) and immortalized, Epstein-Barr virus infected B-cells (“EVB-B”) were used as presenting cells. Release assays were conducted to detect IFN-γ (BioLegend, San Diego, CA) or GM-CSF (eBioscience, San Diego, CA) as a means for determining the specific activity of T-cells and T-cell receptor-transduced target cells. T-cells from wells with high specific activities were pooled, enriched and then expanded using a rapid T-cell expansion method (Riddell et al. (1990) J. IMMUNOL. METHODS 128: 189-201). The HLA types of the donors and antigen presenting cells were determined using a molecular approach performed at LabCorp (West Hills, CA).

[0163] A few wells of cells showed significant growth with specific activities against presenting 1088 B cells pulsed with the NY-ESO-1:157-165 (ESO:157-165) peptide epitope, which has been previously shown to be restricted by HLA-A2 (Jager et al. (1997) J. EXP. MED.). FIG. 1A shows the recognition by the 806 CD8⁺ T-cell line of the ESO:157-165 peptide. The 806 CD8⁺ T-cell line bound the ESO:157-165 peptide when presented by HLA-A2+ 1088-B cells, as determined by an IFN-γ release assay. Similarly, 806 CD8⁺ T-cells recognized NY-ESO-1, but not GFP, presented by cosA2 cells. HLA specificity was confirmed as 806 T-cells recognized the 624.38 melanoma line (HLA-A2+/NY-ESO-1+) which expresses HLA-A2, but not the variant 624.28 melanoma line (HLA-A2-/NY-ESO-1+) which lacks HLA-A2 expression. The 806 CD8⁺ T-cell line was further tested for its ability to recognize the ESO:157-165 peptide epitope at various concentrations by a GM-CSF release assay. Results shown in FIG. 1B suggest a high avidity nature for the TCR peptide interaction. Cells transduced with the 806 α1β1 combination were further tested for binding to HLA-A2/NY-ESO-1:157-165 pentamers. Results, shown in FIG. 1C, demonstrated binding to the NY-ESO-1 pentamer. Additionally, cells transduced with the 806 TCR were assayed for activation upon exposure to a panel of tumor cells. Results, shown in FIG. 1D, demonstrated that transduced cells had specific activity when exposed to A2+/NYESO1+ cells (Colo-205-NYESO1, FM-6, FM-82, HEPG2-NYESO, SK-MEL-37, UACC-257, and MEL-624.38); while they had no specific activity when exposed to A2-/NYESO1- cells (HpAF-II, LS174T, LS714T, and SK-LU-1) or A2+/NYESO1- cells (SK-LU-1-NYESO, MEL-624.28, A549, Colo-205, Cos-7-A2, HepG-2, Kato-III, and SK-MEL-23).

Example 2—Cloning of 806 T-Cell Receptor

[0164] As described in Example 1, the 806 CD8⁺ T-cell line has immunoreactivity with the ESO:157-165 peptide epitope when the peptide is presented by HLA-A2 molecules. The following example describes the cloning and characterization of the T-cell receptor expressed by the 806 CD8⁺ T-cell line that mediates the recognition of ESO:157-165 and in the context of HLA-A2.

[0165] The 806 CD8⁺ T-cells identified in Example 1 were subjected to T-cell receptor (TCR) cloning. Total RNA from T-cell cultures (>1×10⁵ cells) was prepared using an RNeasy Mini Kit (Hawthorn, CA). A cDNA library was prepared

using a GeneRacer approach (Invitrogen, Carlsbad, CA) that generated a full-length cDNA library with oligo dT and a universal 5' rapid amplification of cDNA end (RACE) primer ligated to all the 5' capped mRNA ends. These cDNA libraries were used for subsequent experiments to generate specific TCR α and β chains.

[0166] TCR α and β chain variable region cDNAs were cloned by a 5'-RACE method (GeneRacer Kit, Invitrogen) as described (Zhao et al. (2006) J. IMMUNOL. 29: 398-406; Johnson et al. (2006) J. IMMUNOL. 177: 6548-6559; Morgan et al. (2006) SCIENCE 314: 126-129). Briefly, a 5' RACE primer (5'-CGACTGGAGCACGAGGACACTGA-3' (SEQ ID NO: 104)) was used together with a gene-specific 3' primer (5'-GTTAACTAGTTCAGCTGGAC-CACAGCCGCAGC-3' (SEQ ID NO: 105), 5'-CGGGTTAACTAGTTCAGAAATCCTTCTCTGACCATGGC-3' (SEQ ID NO: 106), or 5'-CTAGCCTCTGGAATCCTTCTCTG-3' (SEQ ID NO: 107)) to enrich cDNA for TCR α, TCR β1 or TCR β2 chains, respectively. A second round of PCR followed using a 5' nested PCR primer plus the original or a nested 3' primer. The TCR α and β chain variable regions were both expected to be approximately 500 bp in length. The PCR products were then purified using a PCR purification kit (Qiagen, Germantown, MD) and subcloned into pCR2.1 TOPO vector (Invitrogen), followed by DNA sequencing to identify the relative frequencies of individual T-cell receptor α- and β-chain genes.

[0167] The T cell receptor amino acid sequences are as follows: SEQ ID NOS: 83 and 85 represent the amino acid sequences of the variable regions of the 806 T-cell receptor α-chain and β-chains, respectively, SEQ ID NOS: 7, 5, and 6 represent the amino acid sequences of the CDR₃, CDR₁ and CDR₂ sequences of the 806 T-cell receptor α-chain, and SEQ ID NOS: 13, 11, and 12 represent the amino acid sequences of the CDR₃, CDR₁ and CDR₂ sequences of the 806 T-cell receptor β-chain.

[0168] The amino acid and nucleotide sequences of the 806 TCR α/β chains were compared with sequences from two groups of known TCR α/β chains in publicly available databases, as shown in FIG. 4.

Example 3—Mutagenesis of 806 T-Cell Receptor

[0169] As described above, mutagenesis of a TCR may increase the affinity, specificity, membrane targeting and expression levels of the TCR, which might be beneficial in clinical applications.

[0170] A particular engineered 806TCR included a P to L substitution at position 101 of the α-chain and an H to Y substitution at position 28 of the β-chain. The amino acid and nucleotide (codon optimized) sequences of this T-cell receptor are set forth in FIG. 2. SEQ ID NOS: 3 and 9 represent the amino acid sequences of the variable regions of the α-chain and β-chains, respectively, SEQ ID NOS: 7, 5, and 6 represent the amino acid sequences of the CDR₃, CDR₁ and CDR₂ sequences of the T-cell receptor α-chain, and SEQ ID NOS: 13, 11, and 12 represent the amino acid sequences of the CDR₃, CDR₁ and CDR₂ sequences of the T-cell receptor β-chain. SEQ ID NOS: 2 and 95 represent the amino acid sequences of a full-length receptor α-chain and β-chain, respectively, each including a human constant region. Certain foregoing amino acid sequences and the nucleotide sequences encoding such sequences are set forth in TABLE 1 above.

[0171] Additional potential mutations include, for example, a change in the key glycosylation site NXS/T to QXS/T (N→Q) in the constant region of the α- and/or β-chains. FIG. 5 depicts exemplary N→Q amino acid mutations in the 806 TCR α-chain and β-chain. An additional modification includes the use of murine constant regions, because pairing between murine TCR constant regions may reduce the mispairing of transduced T-cell receptors with endogenous T-cell receptors. FIG. 6 depicts amino acid and nucleotide sequences of 806 TCR α- and β-chains including an exemplary murine constant region. FIG. 7 depicts amino acid and nucleotide sequences of a 806 TCR α-chain that includes both a murine constant region and N→Q amino acid mutations.

Example 4—Further Characterization Of 806 T-Cell Receptor

[0172] HLA-A*02:01+ antigen presenting cells were pulsed with NY-ESO-1:157-165 peptide in 10-fold dilutions starting at 10 µg/mL (9.1 µM). Donor T cells were transduced with a lentiviral expression vector encoding the 806TCR (including an α-chain variable region amino acid sequence of SEQ ID NO: 3, a β-chain variable region amino acid sequence of SEQ ID NO: 9, and a murine constant region). The pulsed APCs were co-cultured with the transduced T cells for 16 hours. Interferon-γ release was measured by ELISA. Results are depicted in FIG. 8. The EC₅₀ was approximately 100 ng/mL (90.1 nM) for the 806TCR, with activity detectable at approximately 1 ng/mL (0.91 nM).

Example 5—Cancer Cell Killing Mediated By The 806 T-Cell Receptor

[0173] This Example describes killing of target cancer cells by T cells expressing the 806 TCR (“806TCR-T cells”).

[0174] MEL-624.38 cells (NY-ESO-1+, HLA-A*02:01+) were transduced with a red fluorescent protein (RFP) nuclear marker. 806TCR-T cells were generated by transducing donor T cells from two donors (Donor 1 and Donor 2) with a lentiviral expression vector encoding the 806TCR (including an α-chain variable region amino acid sequence of SEQ ID NO: 3, a β-chain variable region amino acid sequence of SEQ ID NO: 9, and a murine constant region).

[0175] MEL-624.38 cells were plated at equal concentration. After 24 hours, 806TCR-T cells were added and co-cultured with the MEL-624.38 cells. All wells contained equal concentrations of cells at time 0. Cells were monitored by fluorescence microscopy, and images are depicted in FIG. 9. As depicted, 806TCR-T cells reduced the number of cancer cells relative to controls.

[0176] Further images were collected over 48 hours, and analyzed to count cell nuclei from an integrated area of target cells over time. Results are shown in FIG. 10. As depicted, co-culture of target cells (MEL-624.38 cells; NY-ESO-1+, HLA-A*02:01+) with 806TCR-T cells resulted in cancer cell killing, as indicated by a reduction in the number of cell nuclei over time relative to control. However, co-culture of off-target cells (MEL-624.28 cells; NY-ESO-1+ and HLA-A*02:01-) with 806TCR-T cells did not result in cancer cell killing.

[0177] Together, these results show that T cells expressing the 806 TCR (“806TCR-T cells”) can specifically kill target cancer cells.

Example 6—Specificity Of 806 T-Cell Receptor Activity

[0178] This Example demonstrates a lack of off-target killing activity for T cells expressing the 806 TCR (“806TCR-T cells”).

[0179] 806TCR-T cells were generated by transducing donor T cells with a lentiviral expression vector encoding the 806TCR (including an α-chain variable region amino acid sequence of SEQ ID NO: 3, a β-chain variable region amino acid sequence of SEQ ID NO: 9, and a murine constant region). 806TCR-T cells were co-cultured with 4 non-cancerous cell types: pulmonary fibroblasts (2 donors), arterial smooth muscle, arterial endothelial cells, and uterine smooth muscle. Target cancer cells (MEL-624.38; NY-ESO-1+, HLA-A*02:01+) were also included as a positive control. Cells were co-cultured for 16 hours and interferon-gamma secretion was assayed by ELISA. Results are shown in FIG. 11. As depicted, no activity was observed following co-culture of 806TCR-expressing T cells with normal, non-cancerous cells. Activity was only observed following co-culture with the on-target cancer cells.

[0180] Together, these results show that T cells expressing the 806 TCR (“806TCR-T cells”) can specifically kill target cancer cells.

Example 7—806 T-Cell Receptor Binding Affinity

[0181] This Example demonstrates measurement of the binding affinity of the 806TCR for a peptide/MHC complex by surface plasmon resonance.

[0182] A soluble 806 TCR (including an α-chain variable region amino acid sequence of SEQ ID NO: 83, a β-chain variable region amino acid sequence of SEQ ID NO: 85) was generated by expressing the 806 TCR α-chain and β-chain variable regions linked together (and without constant region) in mammalian cells. For comparison, a soluble 1G4LY TCR was also generated. 1G4LY TCR (described in Robbins et al. (2008) J. IMMUNOL. 180:6116-6131 and Robbins et al. (2011) J. CLIN. ONCOL. 29(7):917-924) is an affinity enhanced version of the 1G4 TCR (described in US. Patent Application Publication No. US2009/053184).

[0183] Ligand (pMHC1 complex: Biotin-HLA-A*02:01-SLLMWITQC (SEQ ID NO: 1)) was immobilized onto a streptavidin (SA) sensor chip surface with an immobilization level of about 400 RU. Then, the analytes (soluble TCRs) at concentrations of 250, 125, 62.5, 31.25, 15.625, 7.813, 3.906, 1.953, and 0 nM were injected onto the sensor surface.

[0184] Results for 1G4LY TCR are depicted in FIG. 12A. A 1:1 binding model was used to measure the binding affinity and/or kinetics. For 1G4LY TCR the equilibrium dissociation constant (KD) was 7.61×10^{-7} M, the association rate constant (Ka) was 3.98×10^4 M⁻¹s⁻¹, and the dissociation rate constant (Kd) was 3.03×10^{-2} s⁻¹. These results are consistent with what has been previously reported (Robbins et al. (2008) J. IMMUNOL. 180:6116-6131). As expected, 1G4LY TCR had a higher binding affinity (lower KD) than wild-type 1G4 TCR (KD=32 µM).

[0185] Results for 806 TCR are depicted in FIG. 12B. A 1:1 binding model was used to measure the binding affinity and/or kinetics. For 806 TCR, the equilibrium dissociation constant (KD) was 1.34×10^{-7} M, the association rate constant (Ka) was 8.92×10^4 M⁻¹s⁻¹, and the dissociation rate constant (Kd) was 1.20×10^{-2} s⁻¹.

[0186] Together, these results show that 806 TCR has a higher binding affinity (lower KD) than the wild-type 1G4 TCR or the affinity-enhanced 1G4LY TCR, and that 806 TCR has a binding affinity that is in a range that is generally associated with high avidity (see, for example, Zhong et al. (2013) PNAS 110 (17):6973-6978, and Aleksic et al. (2012) EUR J IMMUNOL 42:3174-3179).

INCORPORATION BY REFERENCE

[0187] The entire disclosure of each of the patent and scientific documents referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0188] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

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Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys			
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Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn			
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Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val			
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20	25	30	
Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala			
35	40	45	
Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr			
50	55	60	
Ser Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg			
65	70	75	80
Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile			
85	90	95	
Ala Ala Ser Gln Leu Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu			
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20	25	30	
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35	40	45
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65	70	75
Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys Asp Val		
85	90	95
Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn Phe Gln		
100	105	110
Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val Ala Gly		
115	120	125
Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser		
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20          25          30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35          40          45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50          55          60

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
65          70          75          80

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85          90          95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100         105         110

Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
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Thr Val Thr Asp Leu Lys Asn Val Phe Pro Pro Lys Val Ala Val Phe
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Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser Trp Trp
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Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro
180         185         190

Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser
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Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe
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Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr
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Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp
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Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro Leu Lys Glu
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Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu Arg
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Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe  
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Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu  
65 70 75 80  
  
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100 105 110  
  
Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
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115	120	125
Thr Val Thr Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu		
130	135	140
Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu		
145	150	155
160		
Val Cys Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp		
165	170	175
Trp Val Asn Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln		
180	185	190
Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg		
195	200	205
Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln		
210	215	220
Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser		
225	230	235
240		
Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala		
245	250	255
Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala		
260	265	270
Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val		
275	280	285
Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser		
290	295	300
Arg Ala Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys		
305	310	315
320		
Gln Ala Gly Asp Val Glu Glu Asn Pro Gly Pro Met Glu Thr Leu Leu		
325	330	335
Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp Val Ser Ser Lys Gln		
340	345	350
Glu Val Thr Gln Ile Pro Ala Ala Leu Ser Val Pro Glu Gly Glu Asn		
355	360	365
Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile Tyr Asn Leu Gln		
370	375	380
Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser Leu Leu Leu Ile		
385	390	395
400		
Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu Asn Ala Ser Leu		
405	410	415
Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala Ala Ser Gln Leu		
420	425	430
Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe Asn Thr Asp Lys		
435	440	445
Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe Pro Ile Gln Asn		
450	455	460
Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg Ser Gln Asp Ser		
465	470	475
480		
Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile Asn Val Pro Lys		
485	490	495
Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Cys Val Leu Asp Met		
500	505	510
Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala Trp Ser Asn Gln		
515	520	525

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Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr Asn Ala Thr Tyr
530 535 540

Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu Thr Glu Lys Ser Phe
545 550 555 560

Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu
565 570 575

Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu
580 585 590

Arg Leu Trp Ser Ser
595

<210> SEQ ID NO 15

<211> LENGTH: 810

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 15

atggagactc tgctgggtct cctcatcctg tggctacagc tgcagtgggt ctgcgtccaaag	60
caggaggtga cccaaattcc tgccgcgtg tccgtgccc agggcgagaa cctggtgctc	120
aactgctct tcaccgacag cgccatctac aacttgcagt gttccgcca ggaccccccgg	180
aagggcctga ccagccttct gcttatccag agctcccagc gcgaacagac atcaggccgc	240
ctgaatgcaa gtttggacaa atcttctggc cggtcgaccc tgtatattgc ggcttccag	300
ccgggtgatt ctgctaccta cctgtgcgcgt gtgtgttca acacggacaa gctgatctc	360
ggcacccggca ctgcctgca ggttttcca atccagaacc ctgaccctgc cgtgtaccag	420
ctgagagact ctaaatccag tgacaagtct gtctgcctat tcaccgattt tgattctcaa	480
acaaatgtgt cacaaagtaa ggattctgat gtgtatatac cagacaaaac tgtgtagac	540
atgaggtcta tggacttcaa gagcaacagt gctgtggctt ggagcaacaa atctgacttt	600
gcatgtgcaa acgccttcaa caacagcatt attccagaag acaccttcc cccagccca	660
gaaaagttct gtgatgtcaa gctggtcgag aaaagcttg aaacagatac gaacctaaac	720
tttcaaaacc tgcgttgtat tgggttccga atcctcctcc tgaaagtggc cgggttaat	780
ctgctcatga cgctgcggct gtggccagc	810

<210> SEQ ID NO 16

<211> LENGTH: 390

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 16

atggagactc tgctgggtct cctcatcctg tggctacagc tgcagtgggt ctgcgtccaaag	60
caggaggtga cccaaattcc tgccgcgtg tccgtgccc agggcgagaa cctggtgctc	120
aactgctct tcaccgacag cgccatctac aacttgcagt gttccgcca ggaccccccgg	180
aagggcctga ccagccttct gcttatccag agctcccagc gcgaacagac atcaggccgc	240
ctgaatgcaa gtttggacaa atcttctggc cggtcgaccc tgtatattgc ggcttccag	300

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ccgggtgatt ctgctaccta cctgtgcgcc	gtgctgttca acacggacaa gctgatctc	360
ggcacccggca ctcgcctgca ggttttcca		390

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<210> SEQ ID NO 17
<211> LENGTH: 420
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

```

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<400> SEQUENCE: 17

atccagaacc ctgaccctgc cggttaccag ctgagagact ctaaatccag tgacaagtct    60
gtctgcctat tcaccgattt tgattctcaa acaaatgtgt cacaaagtaa ggattctgat    120
gtgtatatca cagacaaaac tggcttagac atgaggctca tggacttcaa gagcaacagt    180
gtgtgtggct ggagcaacaa atctgacttt gcatgtgcaa acgccttcaa caacagcatt    240
attccagaag acaccttctt ccccagccca gaaagttctt gtgatgtcaa gctggtcgag    300
aaaagcttg aaacagatac gaacctaaac tttcaaaaacc tggcgtgtat tgggtccga    360
atccctctcc tgaaaagtggc cgggttaat ctgctcatga cgctgcggct gtggtccagc    420

```

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<210> SEQ ID NO 18
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

```

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<400> SEQUENCE: 18

gacagcgcca tctacaac                                18

```

```

<210> SEQ ID NO 19
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

```

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<400> SEQUENCE: 19

atccagagct cccagcgca a                                21

```

```

<210> SEQ ID NO 20
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      oligonucleotide

```

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<400> SEQUENCE: 20

ggcgtgttgt tcaacacgga caaggtgatc                                30

```

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<210> SEQ ID NO 21
<211> LENGTH: 927
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

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-continued

<400> SEQUENCE: 21

atgggcacga	gcttgctctg	ctggatggcc	ctgtgcctgc	tggggcgaga	ccatgcagac	60
accggcgtca	gccagaatcc	acgtcacaag	attaccaagc	gcccgcagaa	cgtgacctc	120
agatgtgacc	ccatctcgga	gcacaaccgc	ctgtatttgt	accgcccagac	tcttggacag	180
ggccctgagt	tcctgaccta	cttccagaac	gaggctcagc	tggagaagtgc	ccgcctgttgc	240
agtgcacaggt	tttcagccga	gcccccgaaa	ggtccttctc	cgaccctaga	gatccagcgc	300
actgaacaag	gtgattctgc	catgtacctg	tgccgccttc	cttcccagag	ctacgagcag	360
tactttggtc	ccgggaccccg	tctcaccgtg	acagacctga	aaaacgttt	cccacccaag	420
gtcgctgtgt	ttgagccatc	agaagcagag	atctcccaca	cccaaaaggc	cacactggtg	480
tgccctggcca	caggcttcta	ccccgaccac	gtggagctga	gttgggtgggt	aatgggaag	540
gaggtgcaca	gtggggtcag	cacagaccccg	cagccctca	aggagcagcc	cgccctcaat	600
gactccagat	actgcctgag	cagccgcctg	agggtctcg	ccaccttc	gcagaacccc	660
cgcaaccact	tccgctgtca	agtccagttc	tacgggctct	cgagaaatga	cgagtggacc	720
caggataggg	ccaaacctgt	cacccagatc	gtcagcgccg	aggcctgggg	tagagcagac	780
tgtggcttca	cctccgagtc	ttaccagcaa	ggggctctgt	ctgccaccat	cctctatgag	840
atcttgtag	ggaaggccac	cttgtatgcc	gtgtgttca	gtgcctctgt	gtgtatggcc	900
atggtaaga	gaaaggattc	cagaggc				927

<210> SEQ ID NO 22

<211> LENGTH: 393

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 22

atgggcacga	gcttgctctg	ctggatggcc	ctgtgcctgc	tggggcgaga	ccatgcagac	60
accggcgtca	gccagaatcc	acgtcacaag	attaccaagc	gcccgcagaa	cgtgacctc	120
agatgtgacc	ccatctcgga	gcacaaccgc	ctgtatttgt	accgcccagac	tcttggacag	180
ggccctgagt	tcctgaccta	cttccagaac	gaggctcagc	tggagaagtgc	ccgcctgttgc	240
agtgcacaggt	tttcagccga	gcccccgaaa	ggtccttctc	cgaccctaga	gatccagcgc	300
actgaacaag	gtgattctgc	catgtacctg	tgccgccttc	cttcccagag	ctacgagcag	360
tactttggtc	ccgggaccccg	tctcaccgtg	aca			393

<210> SEQ ID NO 23

<211> LENGTH: 534

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 23

gacctgaaaa	acgtgttccc	acccaaggtc	gctgtgtttg	agccatcaga	agcagagatc	60
tcccacaccc	aaaaggccac	actggtgtgc	ctggccacag	gcttctaccc	cgaccacgtg	120
gagctgagct	ggtgggtgaa	tgggaaggag	gtgcacagtg	gggtcagcac	agacccgcag	180

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ccccctcaagg	agcagccgc	cctcaatgac	tccagatact	gcctgagcag	ccgcctgagg	240
gtctcgccca	ccttcggca	gaaccccccgc	aaccacttcc	gctgtcaagt	ccagttctac	300
gggctctcg	agaatgacga	gtggacccag	gatagggcca	aacctgtcac	ccagatcgct	360
agcggcagg	cctgggttag	agcagactgt	ggettcacct	ccgagtctta	ccagcaaggg	420
gtcctgtctg	ccaccatcct	ctatgagato	ttgcttaggaa	aggccacctt	gtatgccgtg	480
ctggtcagtg	ccctcgctgt	gatggccatg	gtcaagagaa	aggattccag	aggc	534

<210> SEQ ID NO 24	
<211> LENGTH: 15	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide	

<400> SEQUENCE: 24	
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tcggagcaca	accgc	15
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<210> SEQ ID NO 25	
<211> LENGTH: 18	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide	

<400> SEQUENCE: 25	
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ttccagaacg	aggctcag	18
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<210> SEQ ID NO 26	
<211> LENGTH: 30	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic oligonucleotide	

<400> SEQUENCE: 26	
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gcctcccttt	cccagagcta	cgagcagtag	30
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<210> SEQ ID NO 27	
<211> LENGTH: 1794	
<212> TYPE: DNA	
<213> ORGANISM: Artificial Sequence	
<220> FEATURE:	
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide	

<400> SEQUENCE: 27	
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atgggcacga	gcttgtctg	ctggatggcc	ctgtgcctgc	tggggggcgg	ccatgcagac	60
accggcgtca	gccagaatcc	acgttataag	attaccaagc	gcggccagaa	cgtgacccctc	120
agatgtgacc	ccatctcgga	gcacaaccgc	ctgtatttgg	accggccagac	tcttggacag	180
ggccctgagt	tcctgaccta	cttccagaac	gaggctcagc	tggagaagtc	ccgcctgttg	240
agtgcacgg	tttcagccga	gcggccgaaa	ggctcccttc	cgaccctaga	gatccagcgc	300
actgaacaag	gtgattctgc	catgtacctg	tgccgcctcc	cttcccagag	ctacgagcag	360
tactttggtc	ccgggaccccg	tctcaccgtg	acagaggatc	tgcgcaatgt	gacacccct	420

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aagggtgtccc	tgttcgagcc	atctaaggcc	gagatcgcca	acaaggcaga	aa	ggccaccctg	480
gtgtgcctgg	caaggggcctt	cttcccgat	cacgtggagc	tgagctggtg	gg	gtgaatggc	540
aaggaggtgc	actccggcgt	gtgcacagac	cctcaggect	acaaggagag	ca	actactcc	600
tattgtctgt	ctagccggct	gagagtgtcc	gccacccctt	ggcacaaccc	ta	ggaatcac	660
ttccgcgtcc	aggtgcagtt	tcacggcctg	agcgaggagg	ataagtggcc	ag	agggatcc	720
ccaaageccag	tgacccagaa	tatctctgc	gaggcatggg	gaagggcaga	ct	gtggaatc	780
acatccgcct	cttatcagca	gggcgtgctg	agcgccacca	tcctgtacga	ga	cctgctgctg	840
ggcaaggccca	cactgtatgc	cgtgtgggt	tctaccctgg	tggtcatggc	ta	tatggtaag	900
agaaaagaaca	gcagggcaaa	gagaagcgga	tccggagcca	caaattctc	cct	gctgaag	960
caggccggcg	atgtggagga	gaatcctggc	ccaatggaga	ctctgctggg	tct	cctcatc	1020
ctgtggctac	agctgcagtg	ggtctcgcc	aagcaggagg	tgacccaaat	tc	ctgcccgcg	1080
ctgtccgtgc	ccgagggcga	gaacctgggt	ctcaactgct	ccttcaccga	ca	gcccacatc	1140
tacaacttgc	agtgggtccg	ccaggacccc	gggaaggggcc	tgaccagcct	tct	gcttac	1200
cagagctccc	agcgcgaaca	gacatcaggc	cgcctgaatg	caagtttgg	ca	aatcttct	1260
ggccggctcg	ccctgtatat	tgccggttcc	cagctgggt	attctgctac	ct	acctgtgc	1320
gccgtgtgt	tcaacacgga	caagctgatc	ttccggcaccg	gcactcgct	gc	aggtttt	1380
ccaaatccaga	atcccggagcc	tgccgtgtac	cagctgaagg	accccccgtc	cc	aggattct	1440
accctgtgcc	tgttcacaga	ctttgattcc	cagatcaacg	tgcctaagac	aa	tggagtct	1500
ggcaccttca	tcacagacaa	gtgcgtgtct	gatatgaagg	ctatggactc	ca	gtcttaac	1560
ggcccatcg	cctggtctaa	tcagaccago	ttcacatgcc	aggatatctt	ta	aggagacc	1620
aacgccccat	acccttcctc	tgacgtgcca	tgtgtatgcca	ccctgacaga	ga	agagctc	1680
gagacagaca	tgaacctgaa	tttcagaac	ctgctggtca	tcgtgtgtcg	ga	cctgtct	1740
ctgaagggtgg	ccggctttaa	tctgtatgt	accctgagac	tgtggagctc	ct	ga	1794

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<210> SEQ ID NO 28
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      peptide
<220> FEATURE:
<223> OTHER INFORMATION: NY-ESO-1:157-167

<400> SEQUENCE: 28

Ser Leu Leu Met Trp Ile Thr Gln Cys Phe Leu
1           5           10

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<210> SEQ ID NO 29
<211> LENGTH: 944
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 29

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1           5           10           15

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Val Ser Ser Lys Gln Glu Val Thr Gln Ile Pro Ala Ala Leu Ser Val
 20 25 30
 Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala
 35 40 45
 Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr
 50 55 60
 Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
 65 70 75 80
 Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
 85 90 95
 Ala Ala Ser Gln Leu Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu
 100 105 110
 Phe Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val
 115 120 125
 Phe Pro Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
 130 135 140
 Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
 145 150 155 160
 Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
 165 170 175
 Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
 180 185 190
 Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
 195 200 205
 Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys
 210 215 220
 Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
 225 230 235 240
 Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val
 245 250 255
 Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser Arg Ala
 260 265 270
 Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala
 275 280 285
 Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Thr Ser Leu Leu Cys
 290 295 300
 Trp Met Ala Leu Cys Leu Leu Gly Ala Asp His Ala Asp Thr Gly Val
 305 310 315 320
 Ser Gln Asn Pro Arg Tyr Lys Ile Thr Lys Arg Gly Gln Asn Val Thr
 325 330 335
 Phe Arg Cys Asp Pro Ile Ser Glu His Asn Arg Leu Tyr Trp Tyr Arg
 340 345 350
 Gln Thr Leu Gly Gln Gly Pro Glu Phe Leu Thr Tyr Phe Gln Asn Glu
 355 360 365
 Ala Gln Leu Glu Lys Ser Arg Leu Leu Ser Asp Arg Phe Ser Ala Glu
 370 375 380
 Arg Pro Lys Gly Ser Phe Ser Thr Leu Glu Ile Gln Arg Thr Glu Gln
 385 390 395 400
 Gly Asp Ser Ala Met Tyr Leu Cys Ala Ser Ser Ser Gln Ser Tyr Glu
 405 410 415

-continued

Gln	Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu	Thr	Val	Thr	Asp	Leu	Lys	Asn
420															430
Val	Phe	Pro	Pro	Lys	Val	Ala	Val	Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile
435															445
Ser	His	Thr	Gln	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr
450															460
Pro	Asp	His	Val	Glu	Leu	Ser	Trp	Trp	Val	Asn	Gly	Lys	Glu	Val	His
465															480
Ser	Gly	Val	Ser	Thr	Asp	Pro	Gln	Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu
485															495
Asn	Asp	Ser	Arg	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg	Val	Ser	Ala	Thr
500															510
Phe	Trp	Gln	Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln	Val	Gln	Phe	Tyr
515															525
Gly	Leu	Ser	Glu	Asn	Asp	Glu	Trp	Thr	Gln	Asp	Arg	Ala	Lys	Pro	Val
530															540
Thr	Gln	Ile	Val	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala	Asp	Cys	Gly	Phe
545															560
Thr	Ser	Glu	Ser	Tyr	Gln	Gln	Gly	Val	Leu	Ser	Ala	Thr	Ile	Leu	Tyr
565															575
Glu	Ile	Leu	Gly	Lys	Ala	Thr	Leu	Tyr	Ala	Val	Leu	Val	Ser	Ala	
580															590
Leu	Val	Leu	Met	Ala	Met	Val	Lys	Arg	Lys	Asp	Ser	Arg	Gly	Glu	Phe
595															605
Gly	Ser	Gly	Glu	Gly	Arg	Gly	Ser	Leu	Leu	Thr	Cys	Gly	Asp	Val	Glu
610															620
Glu	Asn	Pro	Gly	Pro	Pro	Arg	Gly	Trp	Thr	Ala	Leu	Cys	Leu	Leu	Ser
625															640
Leu	Leu	Pro	Ser	Gly	Phe	Met	Ser	Leu	Asp	Asn	Asn	Gly	Thr	Ala	Thr
645															655
Pro	Glu	Leu	Pro	Thr	Gln	Gly	Thr	Phe	Ser	Asn	Val	Ser	Thr	Asn	Val
660															670
Ser	Tyr	Gln	Glu	Thr	Thr	Pro	Ser	Thr	Leu	Gly	Ser	Thr	Ser	Leu	
675															685
His	Pro	Val	Ser	Gln	His	Gly	Asn	Glu	Ala	Thr	Thr	Asn	Ile	Thr	Glu
690															700
Thr	Thr	Val	Lys	Phe	Thr	Ser	Thr	Ser	Val	Ile	Thr	Ser	Val	Tyr	Gly
705															720
Asn	Thr	Asn	Ser	Ser	Val	Gln	Ser	Gln	Thr	Ser	Val	Ile	Ser	Thr	Val
725															735
Phe	Thr	Thr	Pro	Ala	Asn	Val	Ser	Thr	Pro	Glu	Thr	Thr	Leu	Lys	Pro
740															750
Ser	Leu	Ser	Pro	Gly	Asn	Val	Ser	Asp	Leu	Ser	Thr	Thr	Ser	Thr	Ser
755															765
Leu	Ala	Thr	Ser	Pro	Thr	Lys	Pro	Tyr	Thr	Ser	Ser	Ser	Pro	Ile	Leu
770															780
Ser	Asp	Ile	Lys	Ala	Glu	Ile	Lys	Cys	Ser	Gly	Ile	Arg	Glu	Val	Lys
785															800
Leu	Thr	Gln	Gly	Ile	Cys	Leu	Glu	Gln	Asn	Lys	Thr	Ser	Ser	Cys	Ala
805															815
Glu	Phe	Lys	Lys	Asp	Arg	Gly	Glu	Gly	Leu	Ala	Arg	Val	Leu	Cys	Gly

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820	825	830
Glu Glu Gln Ala Asp Ala Asp Ala Gly Ala Gln Val Cys Ser Leu Leu		
835	840	845
Leu Ala Gln Ser Glu Val Arg Pro Gln Cys Leu Leu Val Leu Ala		
850	855	860
Asn Arg Thr Glu Ile Ser Ser Lys Leu Gln Leu Met Lys Lys His Gln		
865	870	875
Ser Asp Leu Lys Lys Leu Gly Ile Leu Asp Phe Thr Glu Gln Asp Val		
885	890	895
Ala Ser His Gln Ser Tyr Ser Gln Lys Thr Leu Ile Ala Leu Val Thr		
900	905	910
Ser Gly Ala Leu Leu Ala Val Leu Gly Ile Thr Gly Tyr Phe Leu Met		
915	920	925
Asn Arg Arg Ser Trp Ser Pro Thr Gly Glu Arg Leu Glu Leu Glu Pro		
930	935	940

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<210> SEQ ID NO 30
<211> LENGTH: 2835
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

```

<400> SEQUENCE: 30

atggagactc tgctgggtct cctcatcctg tggctacagc tgcagtgggt ctgtccaag	60
caggagggtga cccaaattcc tgccgcgctg tccgtccccg agggcgagaa cctggtgctc	120
aactgctct tcaccgacag cgccatctac aacttgcagt gttccgcga ggacccggg	180
aagggcctga ccagccttct gcttatccag agctcccagc gcaacagac atcaggccgc	240
ctgaatgcaa gtttggacaa atcttctggc cggtcgacc tggatattgc ggcttccag	300
ccgggtgatt ctgctaccta cctgtgcgcg gtgtgttca acacggacaa gctgatcttc	360
ggcacccggca ctcgcctgca gtttttcca atccagaacc ctgaccctgc cgttaccag	420
ctgagagact ctaaatccag tgacaagtct gtctgcctat tcaccgatt tgattctaa	480
acaatgtgt cacaaagtaa ggattctgtat gtgtatatac cagacaaaac tggtagac	540
atgaggctcta tggacttcaa gagcaacagt gctgtggccgt ggagcaacaa atctgacttt	600
gcatgtgcaa acgccttcaa caacagcatt attccagaag acaccttctt cccagccca	660
gaaaatgttct gtgatgtcaa gctggatcgag aaaagctttg aaacagatac gaacctaaac	720
tttcaaaacc tgcgttgtat tgggttccga atccctccctc tgaaagtggc cgggttaat	780
ctgctcatga cgctgcggct gtgttccagc cggcccaagc ggtccggatc cggagccacc	840
aacttcagcc tgctgaagca ggccggcgac gtggaggaga accccggccc catgggcacg	900
agcttgcctt gctggatggc cctgtgcctg ctggggcgcc accatgcaga caccggcg	960
agccagaatc cacgtcacaa gattaccaag cgccggccaga acgtgaccc tt cagatgtgac	1020
cccatctcggtt agcacaaccg cctgtattgg taccgcaga ctcttggaca gggccctgag	1080
ttcctgcaccc atttccagaa cgaggctcgat ctggagaagt cccgcctgtt gagtgacagg	1140
ttttcagccg agccggccaa aggctccctc tcgaccctag agatccagcg cactgaacaa	1200
ggtgattctg ccatgtaccc gtgcgcctcc tcttcccaga gctacgagca gtactttgg	1260

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ccggggaccc	gtctcaccgt	gacagacctg	aaaaacgtgt	tcccacccaa	ggtcgctgtg	1320
ttttagccat	cagaaggcaga	gatctccac	acccaaaagg	ccacactggt	gtgcctggcc	1380
acaggcctct	accccggacca	cgtggagctg	agctgggtggg	tgaatgggaa	ggaggtgcac	1440
agtggggtca	gcacagaccc	gcagccccctc	aaggagcage	ccgcctcaa	tgactccaga	1500
tactgcctga	cgagccgcct	gagggtctcg	gccaccttct	ggcagaaccc	ccgcaaccac	1560
ttccgcgtgc	aagtccagtt	ctacgggctc	tcggagaatg	acgagtggac	ccaggatagg	1620
gccaacacctg	tcacccagat	cgtcagcgcgc	gaggcctggg	gtagagcaga	ctgtggcttc	1680
acctccgagt	cttaccagca	aggggtcctg	tctgccacca	tcctctatga	gatcttgcta	1740
ggsaaggcoca	cottgtatgc	cgtgtggtc	agtgcctcgc	tgctgtatggc	catggtaaag	1800
agaaaggatt	ccagaggcga	attcggctca	ggcgagggca	gaggcagttc	gctaacaatgc	1860
gggtgatgtcg	aagaaaatcc	tggcccacccg	cggggctggg	ccgcgccttg	cttgcgtgagt	1920
ttgtgcctt	ctggggttcat	gagtottgac	aacaacggta	ctgctacccc	agagttacct	1980
acccaggaa	cattttcaaa	tgtttctaca	aatgtatcc	accaagaaac	tacaacacct	2040
agtacccttg	gaagtaccag	cctgcacccct	gtgtctcaac	atggcaatga	ggccacaaca	2100
aacatcacag	aaacgcacgt	caaattcaca	tctacctctg	tgataaccc	agtttatgga	2160
aacacaaaact	cttctgtcca	gtcacagacc	tctgtatca	gcacagtgtt	caccacccca	2220
gccaacgttt	caactccaga	gacaaccttg	aaggcttagcc	tgtcacctgg	aaatgttca	2280
gaccttcaa	caactagcac	tagccttgea	acatctccca	ctaaacccct	tacatcatct	2340
tcccttatcc	taagtgcacat	caaggcagaa	atcaaataatgtt	caggcatcag	agaagtgaaa	2400
ttgactcagg	gcatctgcct	ggagcaaaat	aagacctcca	gctgtgcggg	gtttaagaag	2460
gacagggggag	agggccctggc	ccgagtgctg	tgtggggagg	agcaggctga	tgctgtatgct	2520
ggggcccccagg	tatgctccct	gctccctgco	cagtctgagg	tgagacctca	gtgtctactg	2580
ctgggtctgg	ccaacagaac	agaaaattcc	agcaaaactcc	aacttatgaa	aaagcaccaa	2640
tctgacctga	aaaagctggg	catecttagat	ttcactgagc	aagatgttgc	aagccaccag	2700
agctattccc	aaaagaccct	gattgcactg	gtcacctcgg	gagccctgct	ggctgtcttg	2760
ggcatcactg	gttatttcct	gatgaatcgc	cgcagctgg	gccccacagg	agaaaggctg	2820
gaactagaac	catga					2835

```

<210> SEQ ID NO 31
<211> LENGTH: 270
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: 806 alpha

<400> SEQUENCE: 31

```

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val
 1 5 10 15

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile
 35 40 45

-continued

Tyr	Asn	Leu	Gln	Trp	Phe	Arg	Gln	Asp	Pro	Gly	Lys	Gly	Leu	Thr	Ser
50															
															60
Leu	Leu	Leu	Ile	Gln	Ser	Ser	Gln	Arg	Glu	Gln	Thr	Ser	Gly	Arg	Leu
65															80
Asn	Ala	Ser	Leu	Asp	Lys	Ser	Ser	Gly	Arg	Ser	Thr	Leu	Tyr	Ile	Ala
															95
Ala	Ser	Gln	Pro	Gly	Asp	Ser	Ala	Thr	Tyr	Leu	Cys	Ala	Val	Leu	Phe
															100
															105
Asn	Thr	Asp	Lys	Leu	Ile	Phe	Gly	Thr	Gly	Thr	Arg	Leu	Gln	Val	Phe
															110
Pro	Asn	Ile	Gln	Asn	Pro	Asp	Pro	Ala	Val	Tyr	Gln	Leu	Arg	Asp	Ser
															115
															120
															125
130															135
															140
Lys	Ser	Ser	Asp	Lys	Ser	Val	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln
															145
															150
															155
															160
Thr	Asn	Val	Ser	Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys
															165
															170
															175
Thr	Val	Leu	Asp	Met	Arg	Ser	Met	Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val
															180
															185
															190
Ala	Trp	Ser	Gln	Lys	Ser	Asp	Phe	Ala	Cys	Ala	Asn	Ala	Phe	Asn	Asn
															195
															200
															205
Ser	Ile	Ile	Pro	Glu	Asp	Thr	Phe	Phe	Pro	Ser	Pro	Glu	Ser	Ser	Cys
															210
															215
															220
Asp	Val	Lys	Leu	Val	Glu	Lys	Ser	Phe	Glu	Thr	Asp	Thr	Asn	Leu	Asn
															225
															230
															235
															240
Phe	Gln	Asn	Leu	Ser	Val	Ile	Gly	Phe	Arg	Ile	Leu	Leu	Lys	Val	
															245
															250
															255
Ala	Gly	Phe	Asn	Leu	Leu	Met	Thr	Leu	Arg	Leu	Trp	Ser	Ser		
															260
															265
															270

```

<210> SEQ ID NO 32
<211> LENGTH: 813
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
    polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: 806 alpha

<400> SEQUENCE: 32

atggaaaccc tgctgggct gctgattctg tggctgcagc tgcaggtgag cagcaaacag   60
gaagtgaccc agatccggc ggcgcgtgac gtgcggagaag gcgaaaacct ggtgtgaac   120
tgcagctta ccgatagcgc gatttataac ctgcagtggt ttgcgcaggaa tccggggcaaa   180
ggcctgacca gcctgtgtc gattcagcgc agccagcgcg aacagaccag cggccgcctg   240
aacgcgagcc tggataaaag cagcggccgc agcaccctgt atattgcggc gagccagccg   300
ggcgatagcg cgcacctatct gtgcgcgggt ctgtttaaca ccgataaaact gattttggc   360
accggcaccc gcctgcaggt gtttccgaac attcagaacc cggatccggc ggtgtatcag   420
ctgcgcgata gcaaaagcag cgataaaagc gtgtgcctgt ttaccgattt tgatagccag   480
accaacgtga gccagagcaa agatagcgat gtgtatatta ccgataaaac cgtgcaggat   540
atgcgcagca tggattttaa aagcaacago gcggtggcgt ggagccaaa aagcgatttt   600
gcgtgcgcga acgcgtttaa caacagcatt attccggaaag atacctttt tccgagccc   660

```

-continued

gaaagcagct gcgatgtgaa actggtgaa aaaagcttg aaaccgatac caacctgaaac	720
tttcagaacc tgagcgtat tggcttcgc attctgctgc tgaaaagtggc gggcttaac	780
ctgctgtatca ccctgcccgt gtggagcago taa	813

```

<210> SEQ ID NO 33
<211> LENGTH: 270
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: 806 alpha

<400> SEQUENCE: 33

```

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val			
1	5	10	15

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile		
35	40	45

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser		
50	55	60

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu			
65	70	75	80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala		
85	90	95

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe		
100	105	110

Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe		
115	120	125

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser		
130	135	140

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln			
145	150	155	160

Thr Gln Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys		
165	170	175

Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val		
180	185	190

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn		
195	200	205

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys		
210	215	220

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn			
225	230	235	240

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val		
245	250	255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser		
260	265	270

```

<210> SEQ ID NO 34
<211> LENGTH: 813
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

```

-continued

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

<220> FEATURE:
 <223> OTHER INFORMATION: 806 alpha

<400> SEQUENCE: 34

```

atggaaaccc tgctggcct gctgattctg tggctgcgc tcaggtgag cagcaaacag      60
gaagtgaccc agattccggc ggccgtgaga gtgcggaaag gcgaaaacct ggtgtgaac     120
tgcagctta ccgatagcgc gatttataac ctgcagtgt ttgcggcagga tccggggcaaa    180
ggcctgacca gcctgtgtct gattcagagc agccagcgcg aacagaccag cggccgcctg    240
aacgcgcgccc tggataaaaag cagggccgc agcaccctgt atattgcggc gagccagccg    300
ggcgatagcg cgacctatct gtgcgcgggt ctgtttaaca ccgataaaact gattttggc    360
acccggcaccgc gcctgcagggt gttccgaaac attcagaacc cggatccggc ggtgtatcag    420
ctgcgcgata gcaaaaggcag cgataaaaago gtgtgcctgt ttaccgattt tgatagccag    480
acccaaagtga gccagagcaa agatagcgat gtgtatattt ccgataaaac cgtgcaggat    540
atgcgcagca tggattttaa aagcaacago gcgggtggcgt ggagcaacaa aagcgattt    600
gcgtgcgcga acgcgtttaa caacgcatt attccggaaat atacctttt tccgagcccg    660
gaaaggcagct gcgatgtgaa actggtgaa aaaagcttt aaaccgatac caacctgaac    720
tttcagaacc tgagcgtgat tggcttcgc attctgtgc tgaaagtggc gggcttaac    780
ctgctgatga ccctgcgcct gtggagcago taa                                813

```

<210> SEQ ID NO 35
 <211> LENGTH: 309
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
 polypeptide

<220> FEATURE:
 <223> OTHER INFORMATION: 806 beta

<400> SEQUENCE: 35

```

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1           5          10          15

```

```

His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr Lys
20          25          30

```

```

Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His Asn
35          40          45

```

```

Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe Leu
50          55          60

```

```

Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu Ser
65          70          75          80

```

```

Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu Glu
85          90          95

```

```

Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala Ser
100         105         110

```

```

Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr
115         120         125

```

```

Val Thr Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe
130         135         140

```

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Glu	Pro	Ser	Glu	Ala	Glu	Ile	Ser	His	Thr	Gln	Lys	Ala	Thr	Leu	Val
145			150			155									160
Cys	Leu	Ala	Thr	Gly	Phe	Phe	Pro	Asp	His	Val	Glu	Leu	Ser	Trp	Trp
165					170										175
Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val	Ser	Thr	Asp	Pro	Gln	Pro
180					185										190
Leu	Lys	Glu	Gln	Pro	Ala	Leu	Gln	Asp	Ser	Arg	Tyr	Cys	Leu	Ser	Ser
195					200										205
Arg	Leu	Arg	Val	Ser	Ala	Thr	Phe	Trp	Gln	Asn	Pro	Arg	Asn	His	Phe
210					215										220
Arg	Cys	Gln	Val	Gln	Phe	Tyr	Gly	Leu	Ser	Glu	Asn	Asp	Glu	Trp	Thr
225					230										240
Gln	Asp	Arg	Ala	Lys	Pro	Val	Thr	Gln	Ile	Val	Ser	Ala	Glu	Ala	Trp
245					250										255
Gly	Arg	Ala	Asp	Cys	Gly	Phe	Thr	Ser	Val	Ser	Tyr	Gln	Gln	Gly	Val
260					265										270
Leu	Ser	Ala	Thr	Ile	Leu	Tyr	Glu	Ile	Leu	Leu	Gly	Lys	Ala	Thr	Leu
275					280										285
Tyr	Ala	Val	Leu	Val	Ser	Ala	Leu	Val	Leu	Met	Ala	Met	Val	Lys	Arg
290					295										300
Lys	Asp	Ser	Arg	Gly											
305															

```

<210> SEQ_ID NO 36
<211> LENGTH: 930
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER_INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<223> OTHER_INFORMATION: 806 beta

```

```

<400> SEQUENCE: 36

atgggcacca gctgtgtgt ctggatggcg ctgtgcctgc tggcgccgca tgccgatacc 60
ggcgtgagcc agaaccgcgc ccataaaatt accaaacgcgc gccagaacgt gacccctcgc 120
tgcgateccga ttagcgaaca taaccgcctg tattggatc gccagaccct gggccaggc 180
ccggatattc tgacctatcc tcagaacgaa gcgcagctgg aaaaaagccg cctgtgagc 240
gatcgcttta gcgcgaaacg cccgaaaggc agctttagca ccctggaaat tcagcgcacc 300
gaacagggcg atagcgcgat gatatgtgc gcgagcagca gccagagcta tgaacagtt 360
ttggccccc gcacccgcct gaccgtgacc gaagatctga aaaacgttt tccgcggaa 420
gtggcgatgt ttgaaccgag cgaagcggaa attagccata cccagaaacgc gaccctgg 480
tgcctggcga ccggcttttca tccggatcat gtggactgaa gctgggtgggt gaacggcaaa 540
gaagtgcata gcggcgtgag caccgatccg cagccgctga aagaacagcc ggcgctgcaa 600
gatagccgctt attcgcgtgag cagccgcctg cgccgtgagcc cgaccctttg gcagaacccg 660
cgcaaccatt ttcgcgtgcca ggtcagtt tatggctga gcaaaaacgc tgaatggacc 720
caggatcgcg cgaacccggt gacccagatt gtgagcgcgg aagcgtgggg ccgcgcggat 780
tgcggcttta ccagcgaaag ctatcagcag ggcgtgctga ggcgcgaccat tctgtatgaa 840
attctgtgg gcaaagcgac cctgttatgctgtgtgg ggcgcgtgg gctgtatggcg 900

```

-continued

atgggtgaaac gcaaagatag ccgcggctaa 930

<210> SEQ ID NO 37
<211> LENGTH: 266
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 37

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

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

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

Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

Ala Ala Ser Gln Leu Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu
100 105 110

Phe Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val
115 120 125

Phe Pro Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
130 135 140

Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
145 150 155 160

Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
165 170 175

Cys Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
180 185 190

Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
195 200 205

Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
210 215 220

Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
225 230 235 240

Leu Val Ile Val Leu Arg Ile Leu Leu Lys Val Ala Gly Phe Asn
245 250 255

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
260 265

<210> SEQ ID NO 38
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 38

atggagactc tgctgggtct cctcatcctg tggctacagc tgcagtgggt ctgcgtccaaag 60

-continued

caggaggtga	cccaaattcc	tgccgcgctg	tccgtgcccg	agggcgagaa	cctggtgctc	120
aactgctcct	tcacccgacag	cgccatctac	aacttgcagt	ggttccgcca	ggaccccccgg	180
aaggggcctga	ccagccttct	gcttatccag	agctcccaagc	gcgaacagac	atcaggccgc	240
ctgaatgc	atgtggacaa	atcttctggc	cggtcgacc	tgtatattgc	ggcttccag	300
ccgggtgatt	ctgctaccta	cctgtgcgc	gtgtgttca	acacggacaa	gctgatctc	360
ggcacccggca	ctcgccctgca	ggttttcca	atccagaatc	ccgagccctgc	cgtgtaccag	420
ctgaaggacc	cccgctccca	ggattctacc	ctgtgcctgt	tcacagactt	tgattccag	480
atcaaacgtgc	ctaagacaat	ggagtctggc	accttcatca	cagacaagtgc	cgtgtggat	540
atgaaggcta	tggactccaa	gtctaacggc	gccatgcct	ggtctaatac	gaccagctc	600
acatgccagg	atatcttaa	ggagaccaac	gccacatacc	cttcctctga	cgtgccatgt	660
gatgccacc	tgacagagaa	gagttcgag	acagacatga	acctgaattt	tcagaacctg	720
ctggtcatcg	tgctgcggat	cctgtgcgt	aagggtggccg	gctttaatct	gctgtatgacc	780
ctgagactgt	ggagctcctg	a				801

<210> SEQ ID NO 39
 <211> LENGTH: 304
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 39

Met	Gly	Thr	Ser	Leu	Leu	Cys	Trp	Met	Ala	Leu	Cys	Leu	Leu	Gly	Ala
1				5					10				15		

Asp	His	Ala	Asp	Thr	Gly	Val	Ser	Gln	Asn	Pro	Arg	Tyr	Lys	Ile	Thr
		20				25							30		

Lys	Arg	Gly	Gln	Asn	Val	Thr	Phe	Arg	Cys	Asp	Pro	Ile	Ser	Glu	His
					35		40					45			

Asn	Arg	Leu	Tyr	Trp	Tyr	Arg	Gln	Thr	Leu	Gly	Gln	Gly	Pro	Glu	Phe
		50			55			60							

Leu	Thr	Tyr	Phe	Gln	Asn	Glu	Ala	Gln	Leu	Glu	Lys	Ser	Arg	Leu	Leu
	65				70			75					80		

Ser	Asp	Arg	Phe	Ser	Ala	Glu	Arg	Pro	Lys	Gly	Ser	Phe	Ser	Thr	Leu
					85		90					95			

Glu	Ile	Gln	Arg	Thr	Glu	Gln	Gly	Asp	Ser	Ala	Met	Tyr	Leu	Cys	Ala
					100			105				110			

Ser	Ser	Ser	Gln	Ser	Tyr	Glu	Gln	Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu
	115				120			125							

Thr	Val	Thr	Glu	Asp	Leu	Arg	Asn	Val	Thr	Pro	Pro	Lys	Val	Ser	Leu
	130				135			140							

Phe	Glu	Pro	Ser	Lys	Ala	Glu	Ile	Ala	Asn	Lys	Gln	Lys	Ala	Thr	Leu
	145				150			155				160			

Val	Cys	Leu	Ala	Arg	Gly	Phe	Phe	Pro	Asp	His	Val	Glu	Leu	Ser	Trp
		165				170		175							

Trp	Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val	Cys	Thr	Asp	Pro	Gln
		180			185			190							

Ala	Tyr	Lys	Glu	Ser	Asn	Tyr	Ser	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg
		195			200			205							

-continued

Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln
210 215 220

Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser
225 230 235 240

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

Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala
260 265 270

Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val
275 280 285

Leu Val Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
290 295 300

<210> SEQ ID NO 40
<211> LENGTH: 912
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 40

atgggcacga	gcttgctctg	ctggatggcc	ctgtgcctgc	tgggggggga	ccatgcagac	60
accggcgtca	gccagaatcc	acgtcacaag	attaccaagc	gcggccagaa	cgtgacccctc	120
agatgtgacc	ccatctcgga	gcacaaccgc	ctgtattggt	accgcccagac	tcttggacag	180
ggccctgagt	tcctgaccta	cttccagaac	gaggctcagc	tggagaagtc	ccgccttttg	240
agtgacaggt	tttcagccga	gcggccgaaa	ggttccttct	cgaccctaga	gatccagcgc	300
actgaacaag	gtgattctgc	catgtacctg	tgegccttct	cttcccagag	ctacgagcag	360
tacttttgtc	ccgggaccctg	tctcacctgt	acagaggatc	tgcgcataatgt	gacacccct	420
aagggtgtccc	tgttcgagcc	atctaaggcc	gagatgcaca	acaaggcagaa	ggccaccttg	480
gtgtgcctgg	caaggggctt	cttcccgat	cacgtggagc	tgagctggtg	ggtgaatggc	540
aaggaggatgc	actccggcgt	gtgcacagac	cctcaggect	acaaggagag	caactactcc	600
tattgtctgt	ctagccggct	gagagtgtcc	gccacctttt	ggcacaaccc	taggaatcac	660
ttccgcgtcc	agggtcagtt	tcacggcct	agcgaggagg	ataagtggcc	agagggatcc	720
ccaaaggccag	tgacccagaa	tatctctgcc	gaggcatggg	gaagggcaga	ctgtggaatc	780
acatccgcct	cttacatcgca	gggcgtgctg	agcgccacca	tcctgtacga	gatcctgctg	840
ggcaaggccca	cactgtatgc	cgtgctggtg	tctaccctgg	tggcatggc	tatggtaag	900
agaaagaaca	gc					912

<210> SEQ ID NO 41
<211> LENGTH: 266
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide
<220> FEATURE:
<223> OTHER INFORMATION: 806 alpha

<400> SEQUENCE: 41

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val

-continued

1	5	10	15
Ser Ser Lys Gln Glu Val Thr Gln Ile Pro Ala Ala Leu Ser Val Pro			
20	25	30	
Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile			
35	40	45	
Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser			
50	55	60	
Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu			
65	70	75	80
Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala			
85	90	95	
Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe			
100	105	110	
Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe			
115	120	125	
Pro Asp Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro			
130	135	140	
Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln			
145	150	155	160
Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys			
165	170	175	
Thr Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile			
180	185	190	
Ala Trp Ser Gln Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu			
195	200	205	
Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu			
210	215	220	
Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu			
225	230	235	240
Ser Val Met Gly Leu Arg Ile Leu Leu Leu Lys Val Ala Gly Phe Asn			
245	250	255	
Leu Leu Met Thr Leu Arg Leu Trp Ser Ser			
260	265		

```

<210> SEQ ID NO 42
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
<220> FEATURE:
<223> OTHER INFORMATION: 806 alpha

<400> SEQUENCE: 42

```

atggaaaaccc tgctggccct gctgattctg tggctgcagc tgcaggtag cagcaaacag	60
gaagtgaccc agattccggc ggcgtgago gtgcggaa gcgaaaacct ggtgctgaac	120
tgcagcttta ccgatagcgc gatttataac ctgcagtgg ttcgcccagga tccggggaaa	180
ggcctgacca gcctgctgct gattcagago agccagcgcg aacagaccag cggccgcctg	240
aacgcgcgccc tggataaaag cagcggccgc agcaccctgt atattgoggc gagccagccg	300
ggcgatagcg cgaccttatct gtgcgcggtg ctgtttaaca ccgataaact gatttttggc	360
accggcaccc gcctgcaggt gtttccgcac atccagaacc cagaacctgc tgtgtaccag	420

-continued

ttaaaaagtc ctcggctca ggacagcacc ctctgcctgt tcaccgactt tgactccaa 480
atcaatgtgc cgaaaaccat ggaatctgga acgttcatca ctgacaaaac tgtgctggac 540
atgaaagcta tggattccaa gagcaatggg gccattgect ggagccaaca gacaagctc 600
acctgccaag atatctcaa agagaccaac gccacctacc ccagttcaga cgttccctgt 660
gatgccacgt tgaccgagaa aagcttgaa acagatatga acctaaacct tcaaaacctg 720
tcagttatgg gactccgaat cctctgctg aaagtagcgg gatttaacct gctcatgacg 780
ctgaggctgt ggtccagttg a 801

<210> SEQ ID NO 43
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CDR1
<400> SEQUENCE: 43

Asp Ser Ala Ile Tyr Asn
1 5

<210> SEQ ID NO 44
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CDR2
<400> SEQUENCE: 44

Ile Gln Ser Ser Gln
1 5

<210> SEQ ID NO 45
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CDR3
<400> SEQUENCE: 45

Cys Ala Val Leu Phe Asn Thr Asp Lys Leu Ile Phe
1 5 10

<210> SEQ ID NO 46
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CDR1
<400> SEQUENCE: 46

-continued

Ser Glu His Asn Arg
1 5

<210> SEQ ID NO 47
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CDR2

<400> SEQUENCE: 47

Gln Asn Glu Ala Gln Leu
1 5

<210> SEQ ID NO 48
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide
<220> FEATURE:
<223> OTHER INFORMATION: CDR3

<400> SEQUENCE: 48

Cys Ala Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe
1 5 10

<210> SEQ ID NO 49
<211> LENGTH: 136
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 49

Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro Arg Ser
1 5 10 15

Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln Ile Asn
20 25 30

Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys Cys Val
35 40 45

Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile Ala Trp
50 55 60

Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu Thr Asn
65 70 75 80

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

Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu Leu Val
100 105 110

Ile Val Leu Arg Ile Leu Leu Lys Val Ala Gly Phe Asn Leu Leu
115 120 125

Met Thr Leu Arg Leu Trp Ser Ser
130 135

<210> SEQ ID NO 50
<211> LENGTH: 411

-continued

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

```

<400> SEQUENCE: 50

```

atccagaatc ccgagcctgc cgtgtaccag ctgaaggacc cccgctccca ggattctacc      60
ctgtgcctgt tcacagactt tgattccag atcaacgtgc ctaagacaat ggagtctggc      120
accttcatca cagacaagtg cgtgtggat atgaaggcta tggactccaa gtctaacggc      180
gccatcgccc ggtctaatac gaccagcttc acatgccagg atatcttaa ggagaccaa      240
ggcacataacc cttectctga cgtgccatgt gatgccaccc tgacagagaa gagttcgag      300
acagacatga acctgaattt tcagaacctg ctggtcatcg tgctgeggat cctgctgctg      360
aagggtggccg gctttaatct gctgtatgacc ctgagactgt ggagctccctg a      411

```

```

<210> SEQ ID NO 51
<211> LENGTH: 173
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

```

<400> SEQUENCE: 51

```

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

```

```

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

```

```

Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp Val Asn
35          40          45

```

```

Gly Lys Glu Val His Ser Gly Val Cys Thr Asp Pro Gln Ala Tyr Lys
50          55          60

```

```

Glu Ser Asn Tyr Ser Tyr Cys Leu Ser Ser Arg Leu Arg Val Ser Ala
65          70          75          80

```

```

Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val Gln Phe
85          90          95

```

```

His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro Lys Pro
100         105         110

```

```

Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp Cys Gly
115         120         125

```

```

Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr Ile Leu
130         135         140

```

```

Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser
145         150         155         160

```

```

Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
165         170

```

```

<210> SEQ ID NO 52
<211> LENGTH: 519
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

```

<400> SEQUENCE: 52

-continued

gaggatctgc gcaatgtgac accccctaag gtgtccctgt tcgagccatc taaggccag	60
atcgccaaca agcagaaggc caccctggtg tgcctggcaa ggggcttctt tcccgtatcac	120
gtggagctga gtcggggta gaatggcaag gaggtgcact cggcggtgtg cacagacct	180
caggcctaca aggagagcaa ctactcctat tgtctgtcta gccggctgag agtgtccgc	240
acctttggc acaaccctag gaatcacttc cgctgccagg tgcagttca cggctgagc	300
gaggaggata agtggccaga gggatccccaa aagccagtga cccagaatat ctctgcccag	360
gcatggggaa gggcagactg tggaatcaca tccgccttattt atcagcaggc cgtgtgagc	420
gccaccatcc tgtacgagat cctgtgggc aaggccacac tggatgcccgt gctgggtct	480
accctgggtgg tcatggctat ggtgaagaga aagaacagc	519

<210> SEQ ID NO 53
<211> LENGTH: 270
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 53

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val			
1	5	10	15

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile			
35	40	45	

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser			
50	55	60	

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu			
65	70	75	80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala			
85	90	95	

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe			
100	105	110	

Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe			
115	120	125	

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser			
130	135	140	

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln			
145	150	155	160

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys			
165	170	175	

Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val			
180	185	190	

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn			
195	200	205	

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys			
210	215	220	

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn			
225	230	235	240

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val

-continued

245	250	255
-----	-----	-----

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser	260	265
---	-----	-----

270

```

<210> SEQ ID NO 54
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

```

<400> SEQUENCE: 54

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val	1	15
---	---	----

5	10	15
---	----	----

Ser Ser Lys Gln Glu Val Thr Gln Ile Pro Ala Ala Leu Ser Val Pro	20	25
---	----	----

25	30
----	----

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile	35	40
---	----	----

45

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser	50	55
---	----	----

60

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu	65	70
---	----	----

75

80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala	85	90
---	----	----

95

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe	100	105
---	-----	-----

110

Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe	115	120
---	-----	-----

125

```

<210> SEQ ID NO 55
<211> LENGTH: 142
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

```

<400> SEQUENCE: 55

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser	1	5
---	---	---

10

15

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln	20	25
---	----	----

30

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys	35	40
---	----	----

45

Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val	50	55
---	----	----

60

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn	65	70
---	----	----

75

80

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys	85	90
---	----	----

95

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn	100	105
---	-----	-----

110

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val	115	120
---	-----	-----

125

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser

-continued

130	135	140
-----	-----	-----

```

<210> SEQ ID NO 56
<211> LENGTH: 309
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 56

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1           5           10          15

His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr Lys
20          25          30

Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His Asn
35          40          45

Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe Leu
50          55          60

Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu Ser
65          70          75          80

Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu Glu
85          90          95

Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala Ser
100         105         110

Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr
115         120         125

Val Thr Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe
130         135         140

Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu Val
145         150         155         160

Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp
165         170         175

Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro
180         185         190

Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser
195         200         205

Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe
210         215         220

Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr
225         230         235         240

Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp
245         250         255

Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly Val
260         265         270

Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
275         280         285

Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg
290         295         300

Lys Asp Ser Arg Gly
305

```

<210> SEQ ID NO 57
<211> LENGTH: 130

-continued

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

<400> SEQUENCE: 57

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr Lys
20 25 30

Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His Asn
35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe Leu
50 55 60

Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu Ser
65 70 75 80

Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu Glu
85 90 95

Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala Ser
100 105 110

Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr
115 120 125

Val Thr
130

<210> SEQ ID NO 58
<211> LENGTH: 179
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 58

Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val Phe Glu Pro
1 5 10 15

Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu Val Cys Leu
20 25 30

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

Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro Leu Lys
50 55 60

Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser Arg Leu
65 70 75 80

Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe Arg Cys
85 90 95

Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr Gln Asp
100 105 110

Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp Gly Arg
115 120 125

Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly Val Leu Ser
130 135 140

Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala
145 150 155 160

-continued

Val	Leu	Val	Ser	Ala
Leu	Val	Leu	Met	Ala
165		170		175

Ser Arg Gly

```

<210> SEQ ID NO 59
<211> LENGTH: 813
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

```

<400> SEQUENCE: 59

atggaaaccc	tgctggcct	gctgattctg	tggctgcagc	tgcaaggtag	cagcaaacag	60
gaagtgaccc	agatccggc	ggcgctgago	gtgccggaag	gcgaaaacct	ggtgctgaac	120
tgcagctta	ccgatagcgc	gatttataac	ctgcagttgtt	tccggccagga	tccggggcaaa	180
ggcctgacca	gcctgtgtct	gattcagago	agccagcgcg	aacagaccag	cggccgcctg	240
aacgcgagcc	tggataaaag	cagcgccgc	agcacccctgt	atattgcggc	gagccagccg	300
ggcgatagcg	cgacctatct	gtgcgcgggt	ctgtttaaca	ccgataaaact	gatttttgtc	360
accggcaccc	gcctgcaggt	gttccgaaac	attcagaacc	cgatccggc	ggtgtatcag	420
ctgcgcgata	gcaaaagcag	cgataaaagc	gtgtgcctgt	ttaccgattt	tgatagccag	480
accaacgtga	gccagagca	agatagcgat	gtgtatatta	ccgataaaac	cgtgcaggat	540
atgcgcagca	tggattttaa	aagcaacago	gcggtggegt	ggagcaacaa	aagcgattt	600
gcgtgcgcga	acgcgtttaa	caacagcatt	attccggaaag	atacctttt	tccgagcccg	660
gaaagcagct	gcgatgtgaa	actggtgaa	aaaagcttg	aaaccgatac	caacctgaac	720
tttcagaacc	tgagcgtgat	tggcttcgc	attctgtgc	tgaaagtggc	gggctttaac	780
ctgctgatga	ccctgccc	gtggagcago	taa			813

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<210> SEQ ID NO 60
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide

```

<400> SEQUENCE: 60

atggaaaccc	tgctggcct	gctgattctg	tggctgcagc	tgcaaggtag	cagcaaacag	60
gaagtgaccc	agatccggc	ggcgctgago	gtgccggaag	gcgaaaacct	ggtgctgaac	120
tgcagctta	ccgatagcgc	gatttataac	ctgcagttgtt	tccggccagga	tccggggcaaa	180
ggcctgacca	gcctgtgtct	gattcagago	agccagcgcg	aacagaccag	cggccgcctg	240
aacgcgagcc	tggataaaag	cagcgccgc	agcacccctgt	atattgcggc	gagccagccg	300
ggcgatagcg	cgacctatct	gtgcgcgggt	ctgtttaaca	ccgataaaact	gatttttgtc	360
accggcaccc	gcctgcaggt	gttt				384

```

<210> SEQ ID NO 61
<211> LENGTH: 428
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic

```

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polynucleotide

<400> SEQUENCE: 61

```
ccgaacattc agaaccggta tccggcggtg tatcagctgc gcgatagcaa aagcagcgt 60
aaaagcgtgt gcctgtttac cgattttatgat agccagacca acgtgagccaa gagcaaaagat 120
agcgatgtgt atattaccga taaaaacgtg caggatatgc gcagcatgga ttttaaaagc 180
aacagcgccgg tggcggtggag caacaaaagg gatttgcgt ggcgaaacgc gtttacaac 240
agcattatttc cggaaagatac ctttttccg agccccggaaa gcagctgcgt tggaaactg 300
gtggaaaaaaa gctttgaaac cgataccaac ctgaacttgc agaacctgag cgtgattggc 360
tttcgcattc tgctgtgaa agtggcgccc tttaacctgc tggatgaccct ggcgcgtgtgg 420
agcagcta 428
```

<210> SEQ ID NO 62

```
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
```

<400> SEQUENCE: 62

```
gatagcgcga tttataac 18
```

<210> SEQ ID NO 63

```
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
<220> FEATURE:
<223> OTHER INFORMATION: 806 alpha cdr2
```

<400> SEQUENCE: 63

```
attcagagca gccag 15
```

<210> SEQ ID NO 64

```
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide
```

<400> SEQUENCE: 64

```
tgcgcgggtgc tgtttaacac cgataaaactg attttt 36
```

<210> SEQ ID NO 65

```
<211> LENGTH: 930
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide
```

<400> SEQUENCE: 65

```
atggggcacca gcctgtgtc ctggatggcg ctgtgcctgc tgggcgcgcg tgcggatacc 60
ggcgtgagcc agaaccggcg ccataaaatt accaaacgcg gccagaacgt gaccttcgc 120
```

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tgcgatccga ttagcgaaca taaccgcctg tattggtatac gccagaccct gggccaggc	180
ccggaatttc tgacctatcc tcagaacgaa gcgcagctgg aaaaaagccg cctgctgagc	240
gatcgcttta ggcggaaacg cccgaaaggc agctttagca ccctggaaat tcagcgcacc	300
gaacagggcg atagcgcgtat gtatctgtgc gcgcagcgcgca gccagagcta tgaacagtat	360
tttggcccccgcgcacccgcct gaccgtgacc gaagatctga aaaaactgtt tccgcggaa	420
gtggcgatgt ttgaaccgag cgaagcggaa attagccata cccagaaacg gaccctggtg	480
tgcctggcgcgcggctttatccggatcat gtggactga gctgggtgggt gaacggcaaa	540
gaagtgcata gccccgtgag caccgatccg cagccgtgaa aagaacagcc ggccgtgaa	600
gatagccgcgttattgcgtgag cagccgcctg cgcgtgagcg cgacccttttgcagaaccccg	660
cgcacccattttcgcgtgcca ggtgcagtttatggcctgaa gcgaaaacgaa tgaatggacc	720
caggatcgccgaaacccgggt gacccagattt gtgcgcggg aagcgtgggg ccgcgcggat	780
tgccggcttta ccagcgaag ctatcagcag ggccgtgctgaa ggcgcgaccat tctgtatgaa	840
attctgtcgccgaaacccgggt gacccagattt gtgcgtgggt ggcgcgaccat tctgtatgaa	900
atggtgaaac gcaaaagatag ccgcggctaa	930

<210> SEQ ID NO 66
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 66

atgggcacca gcctgctgtgttgcgtatggcg ctgtgcctgc tgggcgcgc tgcggataacc	60
ggcgtgagcc agaaccgcgc ccataaaattt accaaacgcgc gccagaacgtt gacccatcg	120
tgcgatccga ttagcgaaca taaccgcctg tattggtatac gccagaccct gggccaggc	180
ccggaatttc tgacctatcc tcagaacgaa gcgcagctgg aaaaaagccg cctgctgagc	240
gatcgcttta ggcggaaacg cccgaaaggc agctttagca ccctggaaat tcagcgcacc	300
gaacagggcg atagcgcgtat gtatctgtgc gcgcagcgcgca gccagagcta tgaacagtat	360
tttggcccccgcgcacccgcct gaccgtgacc	390

<210> SEQ ID NO 67
<211> LENGTH: 540
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 67

gaagatctga aaaaactgttttccgcggaa gtggcgatgt ttgaaccgag cgaagcggaa	60
attagccata cccagaaacg gaccctgggt tgcctggcgcgcggctttatccggatcat	120
gtggactga gctgggtgggtt gacccggaaa gaagtgcata gccccgtgag caccgatccg	180
cgcgcgtgaa aagaacagcc ggcgcgtgaaat gatagccgcgttattgcgtgag cagccgcctg	240
ccgcgtgagcc cgacccttttgcagaacccggcgcacccattttcgcgtgcca ggtgcagttt	300
tatggcctgaa gcgaaaacgaa tgaatggacc caggatcgccgaaacccgggt gacccagattt	360

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```

gtgagcgcgg aagcgctgggg ccgcgcggat tgcggctta ccagcgaag ctatcagcag      420
ggcggtgtga ggcgcaccat tctgtatgaa attctgtatgg gcaaaggcgc cctgtatgcg      480
gtgctggtga ggcgcgtggt gctgtatggcg atggtgaaac gcaaagatag ccgcggctaa      540

<210> SEQ ID NO 68
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 68
agcgaacata accgc                                         15

<210> SEQ ID NO 69
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 69
cagaacgaag cgcagctg                                         18

<210> SEQ ID NO 70
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
oligonucleotide

<400> SEQUENCE: 70
tgcgcgagca gcagccagag ctatgaacag tatttt                         36

<210> SEQ ID NO 71
<211> LENGTH: 266
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 71
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val
1          5           10          15

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile
35         40           45

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser
50         55           60

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu
65         70           75           80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala
85         90           95

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe
100        105          110

```

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Asn	Thr	Asp	Lys	Leu	Ile	Phe	Gly	Thr	Gly	Thr	Arg	Leu	Gln	Val	Phe
115															125
Pro	Asp	Ile	Gln	Asn	Pro	Glu	Pro	Ala	Val	Tyr	Gln	Leu	Lys	Asp	Pro
130															140
Arg	Ser	Gln	Asp	Ser	Thr	Leu	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln
145															160
Ile	Asn	Val	Pro	Lys	Thr	Met	Glu	Ser	Gly	Thr	Phe	Ile	Thr	Asp	Lys
165															175
Thr	Val	Leu	Asp	Met	Lys	Ala	Met	Asp	Ser	Lys	Ser	Asn	Gly	Ala	Ile
180															190
Ala	Trp	Ser	Asn	Gln	Thr	Ser	Phe	Thr	Cys	Gln	Asp	Ile	Phe	Lys	Glu
195															205
Thr	Asn	Ala	Thr	Tyr	Pro	Ser	Ser	Asp	Val	Pro	Cys	Asp	Ala	Thr	Leu
210															220
Thr	Glu	Lys	Ser	Phe	Glu	Thr	Asp	Met	Asn	Leu	Asn	Phe	Gln	Asn	Leu
225															240
Ser	Val	Met	Gly	Leu	Arg	Ile	Leu	Leu	Lys	Val	Ala	Gly	Phe	Asn	
245															255
Leu	Leu	Met	Thr	Leu	Arg	Leu	Trp	Ser	Ser						
260															265

```

<210> SEQ_ID NO 72
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

<400> SEQUENCE: 72

atggaaaacc tgcgtggccct gctgattctg tggctgcagc tgcagggttag cagcaaacag 60
gaagtgaccc agattccggc ggcgcgtgago gtgcggaaag gcgaaaaacct ggtgtgaac 120
tgcagcttta ccgatagcgc gatttataac ctgcagtggt ttgcgcagga tccggggcaaa 180
ggcctgacca gcctgtgtct gattcagago agecagecgcc aacagaccag cggccgcctg 240
aacgcgagcc tggataaaag cagcggccgc agcaccctgt atattgcggc gagccagccg 300
ggcgatagcg cgaccttatct gtgcgcgggt ctgtttaaaca ccgataaaact gattttggc 360
accggcaccc gcctgcaggt gttcccgac atccagaacc cagaacctgc tgtgtaccag 420
ttaaaagatc ctcggctcta ggacagcacc ctctgcctgt tcaccgactt tgactccaa 480
ataaatgtgc cgaaaaccat ggaatcttgc acgttcatca ctgacaaaac tgcgtggac 540
atgaaagcta tggattccaa gagcaatggg gccattgcct ggagcaacca gacaagctc 600
acctgccaag atatcttcaa agagaccaac gccacccattt ccagttcaga cgttccctgt 660
gatgccacgt tgaccgagaa aagcttgaa acagatatga acctaaacctt tcaaaacctg 720
tcagttatgg gactccgaat cctctgtgt aaagtagcgg gattnaacct gctcatgacg 780
ctgaggctgt ggtccagttt a 801

```

```

<210> SEQ_ID NO 73
<211> LENGTH: 302
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

```

-continued

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

<400> SEQUENCE: 73

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr Lys
20 25 30

Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His Asn
35 40 45

Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe Leu
50 55 60

Thr Tyr Phe Gln Asn Ala Gln Leu Glu Lys Ser Arg Leu Leu Ser
65 70 75 80

Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu Glu
85 90 95

Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala Ser
100 105 110

Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu Thr
115 120 125

Val Thr Glu Asp Leu Arg Asn Val Thr Pro Pro Lys Val Ser Leu Phe
130 135 140

Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys Gln Lys Ala Thr Leu Val
145 150 155 160

Cys Leu Ala Arg Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp Trp
165 170 175

Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Ala
180 185 190

Tyr Lys Glu Ser Asn Tyr Ser His Cys Leu Ser Ser Arg Leu Arg Val
195 200 205

Ser Ala Thr Phe Trp His Asn Pro Arg Asn His Phe Arg Cys Gln Val
210 215 220

Gln Phe His Gly Leu Ser Glu Glu Asp Lys Trp Pro Glu Gly Ser Pro
225 230 235 240

Lys Pro Val Thr Gln Asn Ile Ser Ala Glu Ala Trp Gly Arg Ala Asp
245 250 255

Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln Gly Val Leu Ser Ala Thr
260 265 270

Ile Leu Tyr Glu Ile Gln Leu Gly Lys Ala Thr Leu Tyr Ala Val Val
275 280 285

Ser Thr Leu Val Val Met Ala Met Val Lys Arg Lys Asn Ser
290 295 300

<210> SEQ ID NO 74

<211> LENGTH: 912

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 74

atgggcacca gcctgctgtc ctggatggcg ctgtgcctgc tggcgccgca tgccgatacc 60

ggcgtgagcc agaaccgcgc ccataaaatt accaaacgcg gccagaacgt gaccttcgc 120

-continued

tgcgatccga ttagcgaaca taaccgcctg tattggatc gccagacctt gggccaggc	180
cccgaaatttc tgacctatcc tcagaacgaa gcgcagctgg aaaaaagccg cctgtgagc	240
gatcgctta ggcggaaacg cccgaaaggc agctttagca ccctggaaat tcagcgacc	300
gaacaggggcg atagcgcat gtatctgtgc gcgagcagca gccagagcta tgaacagtat	360
tttggcccg gcacccgcct gaccegtgacc gaggatctga gaaatgtgac tccacccaag	420
gtctccttgt ttgagccatc aaaagcagag attgcaaaca aacaaaaggc taccctcg	480
tgcttggcca ggggcttctt ccctgaccac gtggagctga gctgggtggg gaatggcaag	540
gagggtccaca gtggggtcag cacggaccct caggcctaca aggagagcaa ttatagccac	600
tgccctgagca gcccgcctgag ggtctctgtc accttctggc acaatcctcg caaccactc	660
cgcgtgccaag tgcagttcca tgggcttca gaggaggaca agtggccaga gggctcaccc	720
aaacacctgtca cacagaacat cagtcagag gcctggggcc gaggcagactg tgggattacc	780
tcagcatcct atcaacaagg ggtcttgcgtc gccaccatcc tctatgagat ccagctaggg	840
aaaagccaccc tgttatgtgt gtctgtcagt acactgggtt gatggctat ggtcaaaaga	900
aagaattcct ga	912

<210> SEQ ID NO 75

<211> LENGTH: 270

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 75

Met	Glu	Thr	Leu	Leu	Gly	Leu	Leu	Ile	Leu	Trp	Leu	Gln	Leu	Gln	Trp
1															

5 10 15

Val	Ser	Ser	Lys	Gln	Glu	Val	Thr	Gln	Ile	Pro	Ala	Ala	Leu	Ser	Val
20															

25 30

Pro	Glu	Gly	Glu	Asn	Leu	Val	Leu	Gln	Cys	Ser	Phe	Thr	Asp	Ser	Ala
35															

35 40 45

Ile	Tyr	Asn	Leu	Gln	Trp	Phe	Arg	Gln	Asp	Pro	Gly	Lys	Gly	Leu	Thr
50															

55 60

Ser	Leu	Leu	Ile	Gln	Ser	Ser	Gln	Arg	Glu	Gln	Thr	Ser	Gly	Arg	
65															

70 75 80

Leu	Gln	Ala	Ser	Leu	Asp	Lys	Ser	Ser	Gly	Arg	Ser	Thr	Leu	Tyr	Ile
85															

90 95

Ala	Ala	Ser	Gln	Leu	Gly	Asp	Ser	Ala	Thr	Tyr	Leu	Cys	Ala	Val	Leu
100															

105 110

Phe	Asn	Thr	Asp	Lys	Leu	Ile	Phe	Gly	Thr	Gly	Thr	Arg	Leu	Gln	Val
115															

120 125

Phe	Pro	Ile	Gln	Asn	Pro	Asp	Pro	Ala	Val	Tyr	Gln	Leu	Arg	Asp	Ser
130															

135 140

Lys	Ser	Ser	Asp	Lys	Ser	Val	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln
145															

155 160

Thr	Gln	Val	Ser	Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys
165															

170 175

Thr	Val	Leu	Asp	Met	Arg	Ser	Met	Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val
180															

185 190

-continued

Ala Trp Ser Gln Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Gln Asn
195 200 205

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys
210 215 220

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
225 230 235 240

Phe Gln Gln Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val
245 250 255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
260 265 270

<210> SEQ ID NO 76

<211> LENGTH: 810

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 76

atggagactc tgctgggtct cctcatccctg tggctacagc tgcagtgggt ctgcgtccaag 60

caggagggtga cccaaattcc tgccgcgctg tccgtgcccc agggcgagaa cctggtgctc 120

cagtgcctct tcaccgacag cgccatctac aacttgcagt ggttccgcca ggaccccccgg 180

aaggggctga ccagccctct gcttatccag agtcccagc gcgaacagac atcaggccgc 240

ctgcaggcaa gtttggacaa atcttctggc cggtcgaccc tgtatattgc ggcttccag 300

ccgggtgatt ctgctacctta cctgtgcgcc gtgctgttca acacggacaa gctgatctc 360

ggcacccggca ctcgcctgca ggttttcca atccagaacc ctgaccctgc cgttaccag 420

ctgagagact ctaaatccag tgacaagtct gtctgcctat tcaccgattt tgattctcaa 480

acacaggtgt cacaaggtaa ggattctgat gtgtatatac cagacaaaac tgtgttagac 540

atgaggctcta tggacttcaa gagcaacagt gctgtggcgt ggagccagaa atctgacttt 600

gcatgtgcaa acgccttcca gaacagcatt attccagaag acaccttctt cccagccca 660

gaaaaggctct gtgatgtcaa gctggtcgag aaaagcttt aaacagatac gaaacctaaac 720

tttcaacagc tgtcagtgtat tgggttccga atcctctcc taaaaagtggc cgggttaat 780

ctgctcatga cgctgeggct gtggccagc 810

<210> SEQ ID NO 77

<211> LENGTH: 309

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 77

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg Tyr Lys Ile Thr
20 25 30

Lys Arg Gly Gln Gln Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

-continued

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
 65 70 75 80
 Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
 85 90 95
 Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
 100 105 110
 Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
 115 120 125
 Thr Val Thr Asp Leu Lys Asn Val Phe Pro Pro Lys Val Ala Val Phe
 130 135 140
 Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu Val
 145 150 155 160
 Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser Trp Trp
 165 170 175
 Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro
 180 185 190
 Leu Lys Glu Gln Pro Ala Leu Gln Asp Ser Arg Tyr Cys Leu Ser Ser
 195 200 205
 Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe
 210 215 220
 Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr
 225 230 235 240
 Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp
 245 250 255
 Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln Gly Val
 260 265 270
 Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu
 275 280 285
 Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg
 290 295 300
 Lys Asp Ser Arg Gly
 305

```

<210> SEQ ID NO 78
<211> LENGTH: 927
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
  
```

```

<400> SEQUENCE: 78
atgggcacga gttgtctcg ctggatggcc ctgtgcctgc tggggcgaga ccatgcagac 60
accggcgtca gccagaatcc acgtcacaag attaccaagc gcggccagca ggtgaccttc 120
agatgtgacc ccatctcgga gcacaaccgc ctgtattggt accgccagac tcttggacag 180
ggccctgagt tcctgaccta cttccagaac gaggctcagc tggagaagtc ccgcctgtt 240
agtgacaggt tttcagccga gcccccgaaa ggctccctct cgaccctaga gatccagcgc 300
actgaacaag gtgattctgc catgtacctg tgccgcctct cttcccagag ctacgagcag 360
tactttggtc cggggaccccg tctcaccgtg acagacctga aaaacgttgt cccacccaag 420
gtcgctgtgt ttgagccatc agaagcagag atctcccaca cccaaaaggc cacactggtg 480
  
```

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tgcctggcca caggcttcta ccccgaccac	gtggagctga gctgggtgggt	gaatggaaag	540
gaggtgcaca gtggggtcag cacagaccgc	cagcccctca aggagcagcc	cgccctccag	600
gactccagat actgcctgag cagccgcctg	agggtctcgg ccaccttctg	gcagaacccc	660
cgcaaccact tccgctgtca agtccagttc	tacgggctct cggagaatga	cgagtggacc	720
caggataggg ccaaaccctgt caccagatc	gtcagcgcgc aggctgggg	tagacagac	780
tgtggcttca cctccgagtc ttaccagca	ggggtctctgt ctgccaccat	cctctatgag	840
atcttgc tag ggaaggccac cttgtatgcc	gtgctggta gtgcctcgt	gctgtatgcc	900
atggtcaaga gaaaggattc cagaggc			927

```

<210> SEQ ID NO 79
<211> LENGTH: 266
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

```

<400> SEQUENCE: 79

Met	Glu	Thr	Leu	Leu	Gly	Leu	Leu	Ile	Leu	Trp	Leu	Gln	Leu	Gln	Trp
1															

Val	Ser	Ser	Lys	Gln	Glu	Val	Thr	Gln	Ile	Pro	Ala	Ala	Leu	Ser	Val
20															

Pro	Glu	Gly	Glu	Asn	Leu	Val	Leu	Gln	Cys	Ser	Phe	Thr	Asp	Ser	Ala
35															

Ile	Tyr	Asn	Leu	Gln	Trp	Phe	Arg	Gln	Asp	Pro	Gly	Lys	Gly	Leu	Thr
50															

Ser	Leu	Leu	Leu	Ile	Gln	Ser	Ser	Gln	Arg	Glu	Gln	Thr	Ser	Gly	Arg
65															

Leu	Gln	Ala	Ser	Leu	Asp	Lys	Ser	Ser	Gly	Arg	Ser	Thr	Leu	Tyr	Ile
85															

Ala	Ala	Ser	Gln	Leu	Gly	Asp	Ser	Ala	Thr	Tyr	Leu	Cys	Ala	Val	Leu
100															

Phe	Asn	Thr	Asp	Lys	Leu	Ile	Phe	Gly	Thr	Gly	Thr	Arg	Leu	Gln	Val
115															

Phe	Pro	Ile	Gln	Asn	Pro	Glu	Pro	Ala	Val	Tyr	Gln	Leu	Lys	Asp	Pro
130															

Arg	Ser	Gln	Asp	Ser	Thr	Leu	Cys	Leu	Phe	Thr	Asp	Phe	Asp	Ser	Gln
145															

Ile	Asn	Val	Pro	Lys	Thr	Met	Glu	Ser	Gly	Thr	Phe	Ile	Thr	Asp	Lys
165															

Cys	Val	Leu	Asp	Met	Lys	Ala	Met	Asp	Ser	Lys	Ser	Asn	Gly	Ala	Ile
180															

Ala	Trp	Ser	Gln	Gln	Thr	Ser	Phe	Thr	Cys	Gln	Asp	Ile	Phe	Lys	Glu
195															

Thr	Gln	Ala	Thr	Tyr	Pro	Ser	Ser	Asp	Val	Pro	Cys	Asp	Ala	Thr	Leu
210															

Thr	Glu	Lys	Ser	Phe	Glu	Thr	Asp	Met	Asn	Leu	Asn	Phe	Gln	Asn	Leu
225															

Leu	Val	Ile	Val	Leu	Arg	Ile	Leu	Leu	Lys	Val	Ala	Gly	Phe	Asn	
245															

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser

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260 265

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<210> SEQ ID NO 80
<211> LENGTH: 801
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polynucleotide
```

<400> SEQUENCE: 80

atggagactc tgctgggtct cctcatccctg tggcacccgc tcgcagggttc 60
caggaggtga cccaaattcc tgccgcgcgtc tccgtgccccg agggcgagaa cctggtgctc 120
cagtgcctctt tcaccgacag cggccatctac aacttgcagtt ggttcgcaca ggaccccgaa 180
aagggcctga ccagccttct gcttatccag agetcccagc gccaacacac atcaggccgc 240
ctgcaggcata gtttggacaa atcttctggc cggtcgaccc tggatattgc ggcttccca 300
ccgggtgatt ctgctaccta cctgtgcgcg gtgtgttca acacggacaa gctgtatctt 360
ggcacccggca ctgcgcgtca gggttttcca atccagaatc ccgagccgtc cgtgtaccag 420
ctgaaggacc cccgcgtccca ggattctacc ctgtgcctgt tcacagactt tgattccca 480
atcaagctgc ctaagacaat ggagtctggc accttcata cagacaatgt cgtgtggat 540
atgaaggcata tggactccaa gtctaaacggc gccatcgctt ggtctcggca gaccagttc 600
acatgccagg atatctttaa ggagaccccg gcccataacc ctccctctga cgtggccatgt 660
gtgccaccc tgacagagaa gagcttcgag acagacatga acctgaattt tcagaacctg 720
ctgggtcatcg tgctgcggat cctgtgtctt aagggtggccg gctttaatct gctgtatgacc 780
ctgagactgt ggagctccgt a 801

<210> SEQ ID NO 81
<211> LENGTH: 304
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 81

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg Tyr Lys Ile Thr
20 25 30

Lys Arg Gly Gln Gln Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
 35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
65 70 75 80

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala

Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu

115 120 125

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Thr	Val	Thr	Glu	Asp	Leu	Arg	Gln	Val	Thr	Pro	Pro	Lys	Val	Ser	Leu
130					135				140						
Phe	Glu	Pro	Ser	Lys	Ala	Glu	Ile	Ala	Asn	Lys	Gln	Lys	Ala	Thr	Leu
145					150			155							160
Val	Cys	Leu	Ala	Arg	Gly	Phe	Phe	Pro	Asp	His	Val	Glu	Leu	Ser	Trp
						165		170				175			
Trp	Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val	Cys	Thr	Asp	Pro	Gln
					180			185				190			
Ala	Tyr	Lys	Glu	Ser	Gln	Tyr	Ser	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg
					195		200			205					
Val	Ser	Ala	Thr	Phe	Trp	His	Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln
					210		215			220					
Val	Gln	Phe	His	Gly	Leu	Ser	Glu	Glu	Asp	Lys	Trp	Pro	Glu	Gly	Ser
					225		230		235			240			
Pro	Lys	Pro	Val	Thr	Gln	Gln	Ile	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala
					245			250			255				
Asp	Cys	Gly	Ile	Thr	Ser	Ala	Ser	Tyr	Gln	Gln	Gly	Val	Leu	Ser	Ala
					260			265			270				
Thr	Ile	Leu	Tyr	Glu	Ile	Leu	Leu	Gly	Lys	Ala	Thr	Leu	Tyr	Ala	Val
					275		280			285					
Leu	Val	Ser	Thr	Leu	Val	Val	Met	Ala	Met	Val	Lys	Arg	Lys	Asn	Ser
					290		295			300					

<210> SEQ ID NO 82
<211> LENGTH: 912
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 82

atgggcacga	gcttgcgtcg	ctggatggcc	ctgtgcctgc	tggggcgaga	ccatgcagac	60
accggcgtca	gccagaatcc	acgtcacaag	attaccaagc	gccccagca	ggtgacccctc	120
agatgtgacc	ccatctcgga	gcacaaccgc	ctgtattggt	accgcccagac	tcttggacag	180
ggccctgagt	tcctgaccta	cttccagaac	gaggctcagc	tggagaagtc	ccgcctgtt	240
agtgacaggt	tttcagccga	gcccccgaaa	ggctccttct	cgaccctaga	gatccagcgc	300
actgaacaag	gtgattctgc	catgtacctg	tgcgcctcct	cttcccagag	ctacgagcag	360
tactttggtc	ccgggaccccg	tctcaccgtg	acagaggatc	tgcgccaggt	gacacccct	420
aagggtgtccc	tgttgcagcc	atctaaggcc	gagatcgcca	acaaggcaga	ggccacctcg	480
gtgtgcctgg	caaggggctt	ctttcccgt	cacgtggagc	tgagctggtg	ggtgaatggc	540
aaggaggtgc	actccggcgt	gtgcacagac	cctcaggcct	acaaggagag	ccagtactcc	600
tattgtctgt	ctagccggct	gagagtgtcc	gccacctttt	ggcacaaccc	taggaatcac	660
ttcccgctgcc	aggtgcagtt	tcacggcctg	agcgaggagg	ataagtggcc	agaggatcc	720
ccaaaggccag	tgacccagca	gatctctgcc	gaggcatggg	gaagggcaga	ctgtggatc	780
acatccgcct	cttatcagca	ggcgctgctg	agcgcacca	tcctgtacga	gatcctgctg	840
ggcaaggcca	cactgtatgc	cgtgctggtg	tctaccctgg	tggtcatggc	tatggtaag	900
agaaagaaca	gc					912

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<210> SEQ ID NO 83
<211> LENGTH: 130
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 83

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

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

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

Ser Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

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

Phe Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val
115 120 125

Phe Pro
130

<210> SEQ ID NO 84
<211> LENGTH: 266
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 84

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

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

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

Ser Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

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

Phe Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val
115 120 125

Phe Pro Ile Gln Asn Pro Glu Pro Ala Val Tyr Gln Leu Lys Asp Pro
130 135 140

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Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe Thr Asp Phe Asp Ser Gln
145          150          155          160

Ile Asn Val Pro Lys Thr Met Glu Ser Gly Thr Phe Ile Thr Asp Lys
165          170          175

Cys Val Leu Asp Met Lys Ala Met Asp Ser Lys Ser Asn Gly Ala Ile
180          185          190

Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys Gln Asp Ile Phe Lys Glu
195          200          205

Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val Pro Cys Asp Ala Thr Leu
210          215          220

Thr Glu Lys Ser Phe Glu Thr Asp Met Asn Leu Asn Phe Gln Asn Leu
225          230          235          240

Leu Val Ile Val Leu Arg Ile Leu Leu Lys Val Ala Gly Phe Asn
245          250          255

Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
260          265

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<210> SEQ ID NO 85
<211> LENGTH: 131
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

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<400> SEQUENCE: 85
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Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1           5           10          15

Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr
20          25          30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35          40          45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50          55          60

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
65          70          75          80

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85          90          95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100         105         110

Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115         120         125

Thr Val Thr
130

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<210> SEQ ID NO 86
<211> LENGTH: 304
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

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<400> SEQUENCE: 86

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1           5           10          15
```

-continued

Asp	His	Ala	Asp	Thr	Gly	Val	Ser	Gln	Asn	Pro	Arg	His	Lys	Ile	Thr
20						25						30			
Lys	Arg	Gly	Gln	Asn	Val	Thr	Phe	Arg	Cys	Asp	Pro	Ile	Ser	Glu	His
35					40							45			
Asn	Arg	Leu	Tyr	Trp	Tyr	Arg	Gln	Thr	Leu	Gly	Gln	Gly	Pro	Glu	Phe
50					55				60						
Leu	Thr	Tyr	Phe	Gln	Asn	Glu	Ala	Gln	Leu	Glu	Lys	Ser	Arg	Leu	Leu
65					70				75					80	
Ser	Asp	Arg	Phe	Ser	Ala	Glu	Arg	Pro	Lys	Gly	Ser	Phe	Ser	Thr	Leu
85						90						95			
Glu	Ile	Gln	Arg	Thr	Glu	Gln	Gly	Asp	Ser	Ala	Met	Tyr	Leu	Cys	Ala
100					105				110						
Ser	Ser	Ser	Gln	Ser	Tyr	Glu	Gln	Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu
115					120				125						
Thr	Val	Thr	Glu	Asp	Leu	Arg	Asn	Val	Thr	Pro	Pro	Lys	Val	Ser	Leu
130					135				140						
Phe	Glu	Pro	Ser	Lys	Ala	Glu	Ile	Ala	Asn	Lys	Gln	Lys	Ala	Thr	Leu
145					150				155				160		
Val	Cys	Leu	Ala	Arg	Gly	Phe	Phe	Pro	Asp	His	Val	Glu	Leu	Ser	Trp
165					170				175						
Trp	Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val	Cys	Thr	Asp	Pro	Gln
180					185				190						
Ala	Tyr	Lys	Glu	Ser	Asn	Tyr	Ser	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg
195					200				205						
Val	Ser	Ala	Thr	Phe	Trp	His	Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln
210					215				220						
Val	Gln	Phe	His	Gly	Leu	Ser	Glu	Glu	Asp	Lys	Trp	Pro	Glu	Gly	Ser
225					230				235				240		
Pro	Lys	Pro	Val	Thr	Gln	Asn	Ile	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala
245					250				255						
Asp	Cys	Gly	Ile	Thr	Ser	Ala	Ser	Tyr	Gln	Gln	Gly	Val	Leu	Ser	Ala
260					265				270						
Thr	Ile	Leu	Tyr	Glu	Ile	Leu	Leu	Gly	Lys	Ala	Thr	Leu	Tyr	Ala	Val
275					280				285						
Leu	Val	Ser	Thr	Leu	Val	Val	Met	Ala	Met	Val	Lys	Arg	Lys	Asn	Ser
290					295				300						

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<210> SEQ ID NO 87
<211> LENGTH: 270
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 87

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

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

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

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Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg
65 70 75 80

Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile
85 90 95

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

Phe Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val
115 120 125

Phe Pro Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
130 135 140

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
145 150 155 160

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
165 170 175

Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
180 185 190

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
195 200 205

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys
210 215 220

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
225 230 235 240

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val
245 250 255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
260 265 270

<210> SEQ ID NO 88
<211> LENGTH: 309
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 88

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala
1 5 10 15

Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
65 70 75 80

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115 120 125

Thr Val Thr Asp Leu Lys Asn Val Phe Pro Pro Lys Val Ala Val Phe

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130	135	140
Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu Val		
145	150	155
		160
Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser Trp Trp		
	165	170
		175
Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln Pro		
	180	185
		190
Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser Ser		
	195	200
		205
Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His Phe		
	210	215
		220
Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp Thr		
	225	230
		235
		240
Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala Trp		
	245	250
		255
Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln Gly Val		
	260	265
		270
Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr Leu		
	275	280
		285
Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys Arg		
	290	295
		300
Lys Asp Ser Arg Gly		
305		

<210> SEQ ID NO 89
<211> LENGTH: 606
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 89

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile
35 40 45

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser
50 55 60

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu
65 70 75 80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala
85 90 95

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe
100 105 110

Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln

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Thr	Asn	Val	Ser	Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr	Ile	Thr	Asp	Lys
165							170								175
Thr	Val	Gln	Asp	Met	Arg	Ser	Met	Asp	Phe	Lys	Ser	Asn	Ser	Ala	Val
	180						185								190
Ala	Trp	Ser	Asn	Lys	Ser	Asp	Phe	Ala	Cys	Ala	Asn	Ala	Phe	Asn	Asn
	195						200								205
Ser	Ile	Ile	Pro	Glu	Asp	Thr	Phe	Phe	Pro	Ser	Pro	Glu	Ser	Ser	Cys
	210						215								220
Asp	Val	Lys	Leu	Val	Glu	Lys	Ser	Phe	Glu	Thr	Asp	Thr	Asn	Leu	Asn
	225						230								240
Phe	Gln	Asn	Leu	Ser	Val	Ile	Gly	Phe	Arg	Ile	Leu	Leu	Leu	Lys	Val
	245						250								255
Ala	Gly	Phe	Asn	Leu	Leu	Met	Thr	Leu	Arg	Leu	Trp	Ser	Ser	Arg	Ala
	260						265								270
Lys	Arg	Ser	Gly	Ser	Gly	Ala	Thr	Asn	Phe	Ser	Leu	Leu	Lys	Gln	Ala
	275						280								285
Gly	Asp	Val	Glu	Glu	Asn	Pro	Gly	Pro	Met	Gly	Thr	Ser	Leu	Leu	Cys
	290						295								300
Trp	Met	Ala	Leu	Cys	Leu	Leu	Gly	Ala	His	Ala	Asp	Thr	Gly	Val	Ser
	305						310								320
Gln	Asn	Pro	Arg	His	Lys	Ile	Thr	Lys	Arg	Gly	Gln	Asn	Val	Thr	Phe
	325						330								335
Arg	Cys	Asp	Pro	Ile	Ser	Glu	His	Asn	Arg	Leu	Tyr	Trp	Tyr	Arg	Gln
	340						345								350
Thr	Leu	Gly	Gln	Gly	Pro	Glu	Phe	Leu	Thr	Tyr	Phe	Gln	Asn	Glu	Ala
	355						360								365
Gln	Leu	Glu	Lys	Ser	Arg	Leu	Leu	Ser	Asp	Arg	Phe	Ser	Ala	Glu	Arg
	370						375								380
Pro	Lys	Gly	Ser	Phe	Ser	Thr	Leu	Glu	Ile	Gln	Arg	Thr	Glu	Gln	Gly
	385						390								400
Asp	Ser	Ala	Met	Tyr	Leu	Cys	Ala	Ser	Ser	Ser	Gln	Ser	Tyr	Glu	Gln
	405						410								415
Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu	Thr	Val	Thr	Glu	Asp	Leu	Lys	Asn
	420						425								430
Val	Phe	Pro	Pro	Glu	Val	Ala	Met	Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile
	435						440								445
Ser	His	Thr	Gln	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr
	450						455								460
Pro	Asp	His	Val	Glu	Leu	Ser	Trp	Trp	Val	Asn	Gly	Lys	Glu	Val	His
	465						470								480
Ser	Gly	Val	Ser	Thr	Asp	Pro	Gln	Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu
	485						490								495
Asn	Asp	Ser	Arg	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg	Val	Ser	Ala	Thr
	500						505								510
Phe	Trp	Gln	Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln	Val	Gln	Phe	Tyr
	515						520								525
Gly	Leu	Ser	Glu	Asn	Asp	Glu	Trp	Thr	Gln	Asp	Arg	Ala	Lys	Pro	Val
	530						535								540
Thr	Gln	Ile	Val	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala	Asp	Cys	Gly	Phe
	545						550								560
Thr	Ser	Glu	Ser	Tyr	Gln	Gln	Gly	Val	Leu	Ser	Ala	Thr	Ile	Leu	Tyr

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565	570	575
Glu Ile Leu Leu Gly Lys Ala Thr Leu Tyr Ala Val Leu Val Ser Ala		
580	585	590
Leu Val Leu Met Ala Met Val Lys Arg Lys Asp Ser Arg Gly		
595	600	605
<210> SEQ ID NO 90		
<211> LENGTH: 1821		
<212> TYPE: DNA		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide		
<400> SEQUENCE: 90		
atggaaaccc tgctggcct gctgattctg tggctgcagc tgcaggtgag cagcaaacag	60	
gaagtgacc agattccggc ggcgctgago gtgcggaaag gcgaaaacct ggtgctgaac	120	
tgcagcttta ccgatagcgc gatttataac ctgcagtggt ttgcgcaggaa tcggggcaaa	180	
ggcctgacca gcctgctgct gattcagago agccagcgcg aacagaccag cggccgcctg	240	
aacgcgagcc tggataaaag cagcgccgcg agcacccctgt atattgcggc gagccagccg	300	
ggcgatagcg cgacctatct gtgcgcgggt ctgtttaaca ccgataaaact gattttggc	360	
accggcaccc gcctgcaggt gttccgaaac attcagaacc cggatccggc ggtgtatcag	420	
ctgcgcgata gcaaaagcag cgataaaago gtgtgcctgt ttaccgattt tgatagccag	480	
accaacgtga gccagagcaa agatagcgat gtgtatatta ccgataaaac cgtgcaggat	540	
atgcgcgaca tggattttaa aagcaacago gcggtggcgt ggagcaacaa aagcgatttt	600	
gcgtgcgcga acgcgtttaa caacagcatt attccggaag atacctttt tccgagcccg	660	
gaaagcagct gcgatgtgaa actggtgaa aaaagcttg aaaccgatac caacctgaac	720	
tttcagaacc tgagcgtgat tggtttcgc attctgctgc taaaaagtggc gggcttaac	780	
ctgctgatga ccctgcgcct gtggagcago cgggccaagc ggtecgatc cggagccacc	840	
aacttcagcc tgctgaagca ggccggcgcgt gtggaggaga accccggccc catgggcacc	900	
agcctgtgt gctggatggc gctgtgcctg ctggcgccgc atgcggatac cggcgtgagc	960	
cagaacccgc gccataaaat taccaaacgc ggccagaacg tgaccttcg ctgcgatccg	1020	
attagcgaac ataaccgcct gtattggat cgccagaccc tggggccaggg cccgaaattt	1080	
ctgaccttatt ttcaaacga agcgcagctg gaaaaaagcc gctgtctgag cgatcgctt	1140	
agcgcggaaac gcccggaaagg cagtttagc accctggaaa ttcaagcgcac cgaacaggc	1200	
gatagcgcgaa tgtatctgtg cgccgagcago agccagagct atgaacagta ttttggcccg	1260	
ggcacccgcc tgaccgtgac cgaagatctg aaaaacgtgt ttccgcggaa agtggcgatg	1320	
tttgaaccga gcaagcggaa aattagccat acccagaaag cgacccttgt gtgcctggcg	1380	
accggctttt atccggatca tggaaactg agctggtggg tgaacggcaa agaagtgcac	1440	
agcggcgtga gcaccgatcc gcagccgcgt aaagaacagc cggcgtgaa cgatagccgc	1500	
tattgcctga gcagccgcct gcgcgtgago ggcacccctt ggcagaaccc ggcacccat	1560	
tttcgctgcc aggtgcagtt ttatggctgt agcggaaaacgc atgaatggac ccaggatcgc	1620	
gcgaaaccgg tgaccagat tggagcgcgg gaagcgtggg gccgcgcggaa ttgcggctt	1680	
accagcggaaa gctatcagca gggcgatctg agcgcgcacca ttctgtatga aattctgtc	1740	

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ggcaaagcga ccctgtatgc ggtgctggg agcgcgctgg tgctgatggc gatggtaaa 1800
cgcaaagata gccgcggcta a 1821

<210> SEQ ID NO 91
<211> LENGTH: 944
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 91

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val
1 5 10 15

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile
35 40 45

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser
50 55 60

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu
65 70 75 80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala
85 90 95

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe
100 105 110

Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe
115 120 125

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
130 135 140

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
145 150 155 160

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
165 170 175

Thr Val Gln Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
180 185 190

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
195 200 205

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys
210 215 220

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
225 230 235 240

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val
245 250 255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser Arg Ala
260 265 270

Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala
275 280 285

Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Thr Ser Leu Leu Cys
290 295 300

Trp Met Ala Leu Cys Leu Leu Gly Ala His Ala Asp Thr Gly Val Ser
305 310 315 320

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Gln	Asn	Pro	Arg	His	Lys	Ile	Thr	Lys	Arg	Gly	Gln	Asn	Val	Thr	Phe
325								330							335
Arg	Cys	Asp	Pro	Ile	Ser	Glu	His	Asn	Arg	Leu	Tyr	Trp	Tyr	Arg	Gln
340								345							350
Thr	Leu	Gly	Gln	Gly	Pro	Glu	Phe	Leu	Thr	Tyr	Phe	Gln	Asn	Glu	Ala
355								360							365
Gln	Leu	Glu	Lys	Ser	Arg	Leu	Leu	Ser	Asp	Arg	Phe	Ser	Ala	Glu	Arg
370								375							380
Pro	Lys	Gly	Ser	Phe	Ser	Thr	Leu	Glu	Ile	Gln	Arg	Thr	Glu	Gln	Gly
385								390							400
Asp	Ser	Ala	Met	Tyr	Leu	Cys	Ala	Ser	Ser	Ser	Gln	Ser	Tyr	Glu	Gln
405								410							415
Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu	Thr	Val	Thr	Glu	Asp	Leu	Lys	Asn
420								425							430
Val	Phe	Pro	Pro	Glu	Val	Ala	Met	Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile
435								440							445
Ser	His	Thr	Gln	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr
450								455							460
Pro	Asp	His	Val	Glu	Leu	Ser	Trp	Trp	Val	Asn	Gly	Lys	Glu	Val	His
465								470							480
Ser	Gly	Val	Ser	Thr	Asp	Pro	Gln	Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu
485								490							495
Asn	Asp	Ser	Arg	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg	Val	Ser	Ala	Thr
500								505							510
Phe	Trp	Gln	Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln	Val	Gln	Phe	Tyr
515								520							525
Gly	Leu	Ser	Glu	Asn	Asp	Glu	Trp	Thr	Gln	Asp	Arg	Ala	Lys	Pro	Val
530								535							540
Thr	Gln	Ile	Val	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala	Asp	Cys	Gly	Phe
545								550							560
Thr	Ser	Glu	Ser	Tyr	Gln	Gln	Gly	Val	Leu	Ser	Ala	Thr	Ile	Leu	Tyr
565								570							575
Glu	Ile	Leu	Leu	Gly	Lys	Ala	Thr	Leu	Tyr	Ala	Val	Leu	Val	Ser	Ala
580								585							590
Leu	Val	Leu	Met	Ala	Met	Val	Lys	Arg	Lys	Asp	Ser	Arg	Gly	Glu	Phe
595								600							605
Gly	Ser	Gly	Glu	Gly	Arg	Gly	Ser	Leu	Leu	Thr	Cys	Gly	Asp	Val	Glu
610								615							620
Glu	Asn	Pro	Gly	Pro	Pro	Arg	Gly	Trp	Thr	Ala	Leu	Cys	Leu	Leu	Ser
625								630							640
Leu	Leu	Pro	Ser	Gly	Phe	Met	Ser	Leu	Asp	Asn	Asn	Gly	Thr	Ala	Thr
645								650							655
Pro	Glu	Leu	Pro	Thr	Gln	Gly	Thr	Phe	Ser	Asn	Val	Ser	Thr	Asn	Val
660								665							670
Ser	Tyr	Gln	Glu	Thr	Thr	Pro	Ser	Thr	Leu	Gly	Ser	Thr	Ser	Leu	
675								680							685
His	Pro	Val	Ser	Gln	His	Gly	Asn	Glu	Ala	Thr	Thr	Asn	Ile	Thr	Glu
690								695							700
Thr	Thr	Val	Lys	Phe	Thr	Ser	Thr	Ser	Val	Ile	Thr	Ser	Val	Tyr	Gly
705								710							720
Asn	Thr	Asn	Ser	Ser	Val	Gln	Ser	Gln	Thr	Ser	Val	Ile	Ser	Thr	Val

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725	730	735
Phe Thr Thr Pro Ala Asn Val Ser Thr Pro Glu Thr Thr Leu Lys Pro		
740	745	750
Ser Leu Ser Pro Gly Asn Val Ser Asp Leu Ser Thr Thr Ser Thr Ser		
755	760	765
Leu Ala Thr Ser Pro Thr Lys Pro Tyr Thr Ser Ser Ser Pro Ile Leu		
770	775	780
Ser Asp Ile Lys Ala Glu Ile Lys Cys Ser Gly Ile Arg Glu Val Lys		
785	790	795
Leu Thr Gln Gly Ile Cys Leu Glu Gln Asn Lys Thr Ser Ser Cys Ala		
805	810	815
Glu Phe Lys Asp Arg Gly Glu Gly Leu Ala Arg Val Leu Cys Gly		
820	825	830
Glu Glu Gln Ala Asp Ala Asp Ala Gly Ala Gln Val Cys Ser Leu Leu		
835	840	845
Leu Ala Gln Ser Glu Val Arg Pro Gln Cys Leu Leu Leu Val Leu Ala		
850	855	860
Asn Arg Thr Glu Ile Ser Ser Lys Leu Gln Leu Met Lys Lys His Gln		
865	870	875
Ser Asp Leu Lys Leu Gly Ile Leu Asp Phe Thr Glu Gln Asp Val		
885	890	895
Ala Ser His Gln Ser Tyr Ser Gln Lys Thr Leu Ile Ala Leu Val Thr		
900	905	910
Ser Gly Ala Leu Leu Ala Val Leu Gly Ile Thr Gly Tyr Phe Leu Met		
915	920	925
Asn Arg Arg Ser Trp Ser Pro Thr Gly Glu Arg Leu Glu Leu Glu Pro		
930	935	940

<210> SEQ ID NO 92
 <211> LENGTH: 2835
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 92

atggaaaccc	tgctggccct	gctgattctg	tggctgcagc	tgcaggtag	cagcaaacag	60
gaagtgaccc	agattccggc	ggcgttgagc	gtgccggaa	gcgaaaacct	ggtgcgtaac	120
tgcagctta	ccgatagcgc	gatttataac	ctgcagtgg	ttcgccagga	tccggcaaa	180
ggcctgacca	gcctgtgt	gattcagago	agccagcgcg	aacagaccag	cggccgcctg	240
aacgcgagcc	tggataaaag	cagcggccgc	agcacccctg	atattgcggc	gagccagccg	300
ggcgatagcg	cgacctatct	gtgcgcggtg	ctgtttaaca	ccgataaaact	gattttggc	360
accggcaccc	gcctgcaggt	gtttccgaac	attcagaacc	cggatccggc	ggtgtatcatcg	420
ctgcgcgata	gaaaaagcag	cgataaaago	gtgtgcctgt	ttaccgattt	tgtatagccag	480
accaacgtga	gccagagcaa	agatagcgat	gtgtatatta	ccgataaaac	cgtcaggat	540
atgcgcgac	tggattttaa	aagcaacago	gcgggtggcg	ggagcaacaa	aagcgattt	600
gcgtgcgcga	acgcgtttaa	caacagcatt	attccggaa	atacctttt	tccgagcccg	660
gaaagcagct	gcgtgtgaa	actggtgaa	aaaagcttg	aaaccgatac	caacctgaac	720

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tttcagaacc tgagcgtgat tggcttcgc attctgtgc taaaaagtggc gggcttaac	780
ctgctgatga ccctgcgcct gtggagcago cgggccaage ggtecgatc cggagccacc	840
aacttcagcc tgctgaagca ggccggcgac gtggaggaga accccggccc catgggcacc	900
agcctgctgt gctggatggc gctgtgcctg ctggcgccgc atgcggatac cggcgtgagc	960
cagaacccgc gccataaaat taccaaacgc ggccagaacg tgaccttgc ctgcgatccg	1020
attagcgaac ataaccgcct gtattggat cgccagaccc tggggcaggc cccggaaattt	1080
ctgacctatt ttcagaacga agcgcagctg gaaaaaaagcc ggctgtgag cgatcgctt	1140
agcgcggAAC gcccggAAAGG cagcttagc accctggaaa ttcaegcAAC cgaacaggc	1200
gatagcgcgAA tggatctgtg cgcgcggcgc agccagagct atgaacagta ttttggcccg	1260
ggcacccggcc tgaccgtgac cgaagatctg aaaaacgtgt ttccgcggAA agtggcgatg	1320
tttgaacccgAA gcgaagcgAA aattagccat acccagaaAG cgaccctggt gtgcctggc	1380
accggctttt atccggatca tggaaactg agctggtggg tgaacggcaa agaagtgc	1440
agcggcgctgAA gcaccgcattc gcacgcgtgc aaagaacagc cggcgctgaa cgatagccgc	1500
tattgcgtgAA gcacgcgcct gcgcgtgago ggcacctttt ggcagaaccc ggcacccat	1560
tttcgcgtcc aggtgcagtt ttatggcctg agcggAAacg atgaatggac ccaggatcgc	1620
ggcaaaccgg tgacccagat tggagcggc gaagcgtggg ggcgcggAA ttgcggctt	1680
accagcggAA gctatcagca gggegtgcgt agcgcgaccc ttctgtatga aattctgt	1740
ggccaaacgAA ccctgtatgc ggtgtggcgt agcgcgtgg tgctgtggc gatggtggAA	1800
cccaaaagata ggcgcggcAA atccggctca ggccggggcA gaggcagtc gctaacatgc	1860
ggtgatgtcg aagaaaatcc tggcccacgg cggggctgga cgcgcgttgc ttgtgt	1920
ttgcgtgcctt ctgggttcat gagtcttgc aacaacggta ctgcgtaccc agatgtac	1980
acccaggAA cattttcaaa tggatctaca aatgtatccc accaagaaac tacaacac	2040
agtacccttgc agagtaccag cctgcaccct gtgtctcaac atggcaatga ggcacaaca	2100
aacatcacAG caacgacagt caaattcaca tctacccctg tgataaccc agtttatgg	2160
aacacaaact cttctgtcca gtcacagaccc tctgtatca gcacagtgtt caccaccc	2220
ggcaacgttt caactccaga gacaacccctg aagcctagcc tgcacccctgg aatgttca	2280
gacccttcaa ccactagcac tagccttgc acatctccca ctaaacccctt tacatcatct	2340
tctcctatcc taagtgcacat caaggcagaa atcaaattgtt caggcatcag agaagtggAA	2400
ttgactcagg gcatctgcct ggagcAAaat aagacccctca gctgtgcggAA gtttAAGAAG	2460
gacagggggAG agggccgtggc ccgagtgcgt tggtggggagg agcaggctgaa tgctgtgt	2520
ggggccccagg tatgtccctt gtccttgcct cagtctgagg tgagacccctca gtttactg	2580
ctgggtcttgg ccaacagaac agaaaattcc agcaaaactcc aacttatgaa aaagcaccaa	2640
tctgacccgtgAA aaaagctggg catccctagat ttcaactgagc aagatgttc aagccacc	2700
agctattccC aaaagccctt gattgcactg gtcacccctgg gagccctgtt ggctgtctt	2760
ggcatcactg gctatttccct gatgaatcgc cgcagctggA gccccacagg agaaaggctg	2820
gaactagaac catga	2835

<210> SEQ ID NO 93
<211> LENGTH: 944
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

<400> SEQUENCE: 93

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Val
1           5          10          15

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

Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala Ile
35          40          45

Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr Ser
50          55          60

Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg Leu
65          70          75          80

Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile Ala
85          90          95

Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Leu Phe
100         105         110

Asn Thr Asp Lys Leu Ile Phe Gly Thr Gly Thr Arg Leu Gln Val Phe
115         120         125

Pro Asn Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
130         135         140

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
145         150         155         160

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
165         170         175

Thr Val Gln Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
180         185         190

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
195         200         205

Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys
210         215         220

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
225         230         235         240

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Lys Val
245         250         255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser Arg Ala
260         265         270

Lys Arg Ser Gly Ser Gly Ala Thr Asn Phe Ser Leu Leu Lys Gln Ala
275         280         285

Gly Asp Val Glu Glu Asn Pro Gly Pro Met Gly Thr Ser Leu Leu Cys
290         295         300

Trp Met Ala Leu Cys Leu Leu Gly Ala His Ala Asp Thr Gly Val Ser
305         310         315         320

Gln Asn Pro Arg His Lys Ile Thr Lys Arg Gly Gln Asn Val Thr Phe
325         330         335

Arg Cys Asp Pro Ile Ser Glu His Asn Arg Leu Tyr Trp Tyr Arg Gln
340         345         350

Thr Leu Gly Gln Gly Pro Glu Phe Leu Thr Tyr Phe Gln Asn Glu Ala
355         360         365
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Gln	Leu	Glu	Lys	Ser	Arg	Leu	Leu	Ser	Asp	Arg	Phe	Ser	Ala	Glu	Arg
370						375					380				
Pro	Lys	Gly	Ser	Phe	Ser	Thr	Leu	Glu	Ile	Gln	Arg	Thr	Glu	Gln	Gly
385				390				395					400		
Asp	Ser	Ala	Met	Tyr	Leu	Cys	Ala	Ser	Ser	Ser	Gln	Ser	Tyr	Glu	Gln
								405		410			415		
Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu	Thr	Val	Thr	Glu	Asp	Leu	Lys	Asn
							420		425			430			
Val	Phe	Pro	Pro	Glu	Val	Ala	Met	Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile
							435		440			445			
Ser	His	Thr	Gln	Lys	Ala	Thr	Leu	Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr
							450		455			460			
Pro	Asp	His	Val	Glu	Leu	Ser	Trp	Trp	Val	Asn	Gly	Lys	Glu	Val	His
							465		470			475			480
Ser	Gly	Val	Ser	Thr	Asp	Pro	Gln	Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu
							485		490			495			
Asn	Asp	Ser	Arg	Tyr	Cys	Leu	Ser	Ser	Arg	Leu	Arg	Val	Ser	Ala	Thr
							500		505			510			
Phe	Trp	Gln	Asn	Pro	Arg	Asn	His	Phe	Arg	Cys	Gln	Val	Gln	Phe	Tyr
							515		520			525			
Gly	Leu	Ser	Glu	Asn	Asp	Glu	Trp	Thr	Gln	Asp	Arg	Ala	Lys	Pro	Val
							530		535			540			
Thr	Gln	Ile	Val	Ser	Ala	Glu	Ala	Trp	Gly	Arg	Ala	Asp	Cys	Gly	Phe
							545		550			555			560
Thr	Ser	Glu	Ser	Tyr	Gln	Gln	Gly	Val	Leu	Ser	Ala	Thr	Ile	Leu	Tyr
							565		570			575			
Glu	Ile	Leu	Leu	Gly	Lys	Ala	Thr	Leu	Tyr	Ala	Val	Leu	Val	Ser	Ala
							580		585			590			
Leu	Val	Leu	Met	Ala	Met	Val	Lys	Arg	Lys	Asp	Ser	Arg	Gly	Glu	Phe
							595		600			605			
Gly	Ser	Gly	Glu	Gly	Arg	Gly	Ser	Leu	Leu	Thr	Cys	Gly	Asp	Val	Glu
							610		615			620			
Glu	Asn	Pro	Gly	Pro	Pro	Arg	Gly	Trp	Thr	Ala	Leu	Cys	Leu	Leu	Ser
							625		630			635			640
Leu	Leu	Pro	Ser	Gly	Phe	Met	Ser	Leu	Asp	Asn	Asn	Gly	Thr	Ala	Thr
							645		650			655			
Pro	Glu	Leu	Pro	Thr	Gln	Gly	Thr	Phe	Ser	Asn	Val	Ser	Thr	Asn	Val
							660		665			670			
Ser	Tyr	Gln	Glu	Thr	Thr	Pro	Ser	Thr	Leu	Gly	Ser	Thr	Ser	Leu	
							675		680			685			
His	Pro	Val	Ser	Gln	His	Gly	Asn	Glu	Ala	Thr	Thr	Asn	Ile	Thr	Glu
							690		695			700			
Thr	Thr	Val	Lys	Phe	Thr	Ser	Thr	Ser	Val	Ile	Thr	Ser	Val	Tyr	Gly
							705		710			715			720
Asn	Thr	Asn	Ser	Ser	Val	Gln	Ser	Gln	Thr	Ser	Val	Ile	Ser	Thr	Val
							725		730			735			
Phe	Thr	Thr	Pro	Ala	Asn	Val	Ser	Thr	Pro	Glu	Thr	Thr	Leu	Lys	Pro
							740		745			750			
Ser	Leu	Ser	Pro	Gly	Asn	Val	Ser	Asp	Leu	Ser	Thr	Thr	Ser	Thr	Ser
							755		760			765			
Leu	Ala	Thr	Ser	Pro	Thr	Lys	Pro	Tyr	Thr	Ser	Ser	Ser	Pro	Ile	Leu

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770	775	780
Ser Asp Ile Lys Ala Glu Ile Lys Cys Ser Gly Ile Arg Glu Val Lys		
785	790	795
Leu Thr Gln Gly Ile Cys Leu Glu Gln Asn Lys Thr Ser Ser Cys Ala		
805	810	815
Glu Phe Lys Lys Asp Arg Gly Glu Gly Leu Ala Arg Val Leu Cys Gly		
820	825	830
Glu Glu Gln Ala Asp Ala Asp Ala Gly Ala Gln Val Cys Ser Leu Leu		
835	840	845
Leu Ala Gln Ser Glu Val Arg Pro Gln Cys Leu Leu Leu Val Leu Ala		
850	855	860
Asn Arg Thr Glu Ile Ser Ser Lys Leu Gln Leu Met Lys Lys His Gln		
865	870	875
Ser Asp Leu Lys Lys Leu Gly Ile Leu Asp Phe Thr Glu Gln Asp Val		
885	890	895
Ala Ser His Gln Ser Tyr Ser Gln Lys Thr Leu Ile Ala Leu Val Thr		
900	905	910
Ser Gly Ala Leu Leu Ala Val Leu Gly Ile Thr Gly Tyr Phe Leu Met		
915	920	925
Asn Arg Arg Ser Trp Ser Pro Thr Gly Glu Arg Leu Glu Leu Glu Pro		
930	935	940

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<210> SEQ ID NO 94
<211> LENGTH: 2835
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polynucleotide

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<400> SEQUENCE: 94
atggaaaccc tgctggcct gctgattctg tggctgcagc tgcaggtgag cagcaaacag 60
gaagtgaccc agattccggc ggcgcgtgac gtgcggaa gcgaaaacct ggtgtgaac 120
tgcagctta ccgatagcgc gatttataac ctgcagtggt ttgcgcagga tccggggaaa 180
ggcctgacca gcctgcgtct gattcagacg agccagcgcg aacagaccag cggccgcctg 240
aacgcgagcc tggataaaag cagcggccgc agcaccctgt atattgcggc gagccagccg 300
ggcgatagcg cgacctatct gtgcgcgggt ctgtttaaca ccgataaaact gattttggc 360
accggcaccc gcctgcaggt gtttccgaac attcagaacc cggatccggc ggtgtatcag 420
ctgcgcgata gaaaaagcag cgataaaagc gtgtgcctgt ttaccgattt tgatagccag 480
accaacgtga gccagagcaa agatagcgat gtgtatatta ccgataaaac cgtgcaggat 540
atgcgcgaca tggatttaa aagcaacago gcggtggcgt ggagcaacaa aagcgatttt 600
gcgtgcgca acgcgtttaa caacagcatt attccggaa atacctttt tccgagcccg 660
gaaaagcagct gcgtatgaa actgggtggaa aaaagctttg aaaccgatac caacctgaac 720
tttcagaacc tgagcgtgat tggcttcgc attctgctgc tgaaagtggc gggcttaac 780
ctgctgatga ccctgcgcct gtggagcagc cggggcaagc ggtccggatc cggagccacc 840
aacttcagcc tgctgaagca ggccggcgcac gtggaggaga accccggccc catgggcacc 900
agcctgctgt gctggatggc gctgtgcctg ctgggcgcgc atgcggatac cggcgtgagc 960
cagaacccgc gccataaaat taccaaacgc ggccagaacg tgaccttcg ctgcgatccg 1020

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attagcgaac ataaccgcct gtattggat cggccagaccc tggggcaggg cccggaaattt	1080
ctgacctatt ttcagaacga agcgcagctg gaaaaaaaggc gcctgtcgag cgatcgcttt	1140
agcgcgaaac gcccggaaagg cagctttago accctggaaa ttccagegcac cgaacaggc	1200
gatagcgcga tgttatctgtc cgcgagcago agecagagct atgaacagta ttttggcccg	1260
ggcacccgccc tgaccgtgac cgaagatctg aaaaacgtgt ttccggcggg agtggcgatg	1320
tttgaaccga gcgaagcggg aattagccat acccagaaaag cgaccctgggt gtgcctggcg	1380
accggctttt atccggatca tgtggaactg agctgggtgg tgaacggcaa agaagtgcatt	1440
agcggcgatcgc acaccgatcc gcacccggctg aaagaacacgc cggcgctgaa cgatagccgc	1500
tattgcctga gcagccgcct gcgcgtgago ggcacccctt ggcagaacccc ggcacccat	1560
tttcgctgcc aggtgcagtt ttatggcctg agcggaaaacg atgaatggac ccaggatcgc	1620
gcgaaaacccgg tgacccagat tgtgagcgtgg gaagcgtggg gcccggcggg ttgcggcttt	1680
accagcgaaa gctatcagca gggcgctgctg agcgcgcacca ttctgtatga aattctgctg	1740
ggcaaaggcga ccctgtatgc ggtgtgggtg agcgcgcgtgg tgctgtatggc gatggtgaaa	1800
cgcggcggcga attcggctca ggcgaggcga gaggcagtct gctaacatgc	1860
ggtgatgtcg aagaaaatcc tggcccaccc cgccggctggg ccgcgccttg cttgtgatgt	1920
ttgctgcctt ctgggttcat gagttttgc aacaacggta ctgttacccc agagttaccc	1980
acccaggaa cattttcaaa tgtttctaca aatgtatcct accaagaaac tacaacacct	2040
agtacccttg gaagtaccag cctgcaccct gtgtctcaac atggcaatga ggccacaaca	2100
aacatcacag aaacgcacgt caaatcaca tctacacctg tgataaccc tcgttatggaa	2160
aacacaaaact cttctgtcca gtcacagaccc tctgtatca gcacagtgtt caccacccca	2220
gccaacgttt caactccaga gacaacacctt aagccttagcc tgcacactgg aaatgtttca	2280
gaccttcaa ccactagcac tagccttgc acatctccca ctaaacccta tacatcatct	2340
tctcctatcc taagtgcacat caaggcggaa atcaaattgtt caggcatcag agaagtggaaa	2400
ttgactcagg gcatctgcct ggagcggaaat aagaccttca gctgtgggg gttttaagaag	2460
gacagggggag agggccctggc ccgagctgtg tggggggagg agcaggctga tgctgtatgt	2520
ggggccccagg tatgtccct gtccttgc cagtctgagg tgagacctca gtgtctactg	2580
ctgggtcttgg ccaacagaac agaaaattcc agcaaaactcc aacttatgaa aaagcaccaa	2640
tctgacccatgaaa aaaaagctggg catccttagat ttcaactgagc aagatgttgc aagccaccag	2700
agctattcccc aaaagaccctt gattgcactg gtcacccctgg gaggccctgtt ggctgtcttg	2760
ggcatcaactg gctattccct gatgaatcgc cgcagctggg gccccacagg agaaaggctg	2820
gaactagaac catga	2835

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<210> SEQ ID NO 95
<211> LENGTH: 310
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

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<400> SEQUENCE: 95

Met	Gly	Thr	Ser	Leu	Leu	Cys	Trp	Met	Ala	Leu	Cys	Leu	Leu	Gly	Ala
1				5				10				15			

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Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg Tyr Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
65 70 75 80

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115 120 125

Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Lys Val Ala Val
130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

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

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Ser Arg Gly
305 310

<210> SEQ ID NO 96
<211> LENGTH: 930
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 96

atggggcacga	gcttgctctg	ctggatggcc	ctgtgcctgc	tggggggcggaa	ccatgcagac	60
accggcgta	gccagaatcc	acgtcacaag	attaccaaggc	ggggccagaa	cgtgaccc	120
agatgtgacc	ccatctcgga	gcacaaccgc	ctgtattggt	accgccagac	tcttggacag	180
ggccctgagt	tcctgaccta	cttccagaac	gaggctcagc	tggagaagtc	ccgcctttg	240

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agtgcacaggt	tttcagccga	gcccccgaaa	ggtccttct	cgaccctaga	gatccagcgc	300
actgaacaag	gtgattctgc	catgtacctg	tgegcctct	cttcccagag	ctacgagcag	360
tactttggtc	cggggaccccg	tctcacccgt	acagaggacc	tgaaaaacgt	gttcccaccc	420
aagggtcgctg	tgtttgagcc	atcagaagca	gagatctccc	acacccaaaa	ggccacactg	480
gtgtgcctgg	ccacaggctt	ctaccccgac	cacgtggagc	tgagctggtg	ggtgaatggg	540
aaggagggtgc	acagtggggt	cagcacagac	ccgcagcccc	tcaaggagca	gccccccctc	600
aatgactcca	gatactgcct	gagcagccgc	ctgagggtct	cggccacctt	ctggcagaac	660
ccccgcaccc	acttccgctg	tcaagtccag	ttctacgggc	tctcggagaa	tgacqagtgg	720
acccaggata	ggccaaacc	tgtcacccag	atcgtcagcg	ccgaggcctg	ggtagagca	780
gactgtggct	tcaccccgta	gtcttaccag	caaggggtcc	tgtctgccac	catcctctat	840
gagatcttgc	taggaaaggc	cacccgttat	gccgtgctgg	tcagtgccct	cgtgctgatg	900
gcatggtca	agagaaagga	ttccagaggc				930

<210> SEQ_ID NO 97
<211> LENGTH: 310
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 97

Met	Gly	Thr	Ser	Leu	Leu	Cys	Trp	Met	Ala	Leu	Cys	Leu	Leu	Gly	Ala
1				5				10				15			

Asp	His	Ala	Asp	Thr	Gly	Val	Ser	Gln	Asn	Pro	Arg	Tyr	Lys	Ile	Thr
20						25						30			

Lys	Arg	Gly	Gln	Gln	Val	Thr	Phe	Arg	Cys	Asp	Pro	Ile	Ser	Glu	His
35					40						45				

Asn	Arg	Leu	Tyr	Trp	Tyr	Arg	Gln	Thr	Leu	Gly	Gln	Gly	Pro	Glu	Phe
50						55			60						

Leu	Thr	Tyr	Phe	Gln	Asn	Glu	Ala	Gln	Leu	Glu	Lys	Ser	Arg	Leu	Leu
65					70				75			80			

Ser	Asp	Arg	Phe	Ser	Ala	Glu	Arg	Pro	Lys	Gly	Ser	Phe	Ser	Thr	Leu
85					90				95						

Glu	Ile	Gln	Arg	Thr	Glu	Gln	Gly	Asp	Ser	Ala	Met	Tyr	Ley	Cys	Ala
100					105				110						

Ser	Ser	Ser	Gln	Ser	Tyr	Glu	Gln	Tyr	Phe	Gly	Pro	Gly	Thr	Arg	Leu
115					120				125						

Thr	Val	Thr	Glu	Asp	Leu	Lys	Asn	Val	Phe	Pro	Pro	Lys	Val	Ala	Val
130					135			140							

Phe	Glu	Pro	Ser	Glu	Ala	Glu	Ile	Ser	His	Thr	Gln	Lys	Ala	Thr	Leu
145					150			155			160				

Val	Cys	Leu	Ala	Thr	Gly	Phe	Tyr	Pro	Asp	His	Val	Glu	Leu	Ser	Trp
165					170			175							

Trp	Val	Asn	Gly	Lys	Glu	Val	His	Ser	Gly	Val	Ser	Thr	Asp	Pro	Gln
180					185			190							

Pro	Leu	Lys	Glu	Gln	Pro	Ala	Leu	Gln	Asp	Ser	Arg	Tyr	Cys	Leu	Ser
195					200			205							

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His

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210	215	220
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Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp	225	230	235	240
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Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu Ala	245	250	255
---	-----	-----	-----

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln Gly	260	265	270
---	-----	-----	-----

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr	275	280	285
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Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys	290	295	300
---	-----	-----	-----

Arg Lys Asp Ser Arg Gly	305	310
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<210> SEQ ID NO 98

<211> LENGTH: 930

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 98

atgggcacga gcttgctctg ctggatggcc ctgtgcctgc tggggcgaga ccatgcagac	60
accggcgtca gccagaatcc acgtcacaag attaccaagc gcggccagca ggtgaccc	120
agatgtgacc ccatctcgga gcacaaccgc ctgtattggt accggccagac tcttggacag	180
ggccctgagt tcctgaccta cttccagaac gaggctcagc tggagaagtc ccgccttg	240
agtgacaggt ttccagccga gcggccgaaa ggctccttct cgaccctaga gatccagcgc	300
actgaacaag gtgattctgc catgtacctg tgccgcctct cttcccagag ctacgagcag	360
tactttggtc cggggacccg tctcacccgtg acagaggacc taaaaaacgt gttcccaccc	420
aaggtcgtg tgtttgagcc atcagaagca gagatctccc acacccaaaa ggccacactg	480
gtgtgcctgg ccacaggctt ctacccgcac cacgtggagc tgagctggc ggtgaatgg	540
aaggaggtgc acagtggggt cagcacagac ccgcagcccc tcaaggagca gcccgcctc	600
caggactcca gatactgcct gagcagccgc ctgagggtct cggccaccc ttggcagaac	660
ccccgcaccc acttccgctg tcaagtccag ttctacgggg tctcggagaa tgacgagtgg	720
acccaggata gggccaaacc tgtcacccag atcgtcagcg ccgaggccctg gggtagagca	780
gactgtggct tcacctccga gtcttaccag caaggggtcc tgcgtccac catcctctat	840
gagatcttgc taggaaaggc caccttgtat gccgtgctgg tcagtgccct cgtgtgtat	900
gccatggta agagaaagga ttccagaggc	930

<210> SEQ ID NO 99

<211> LENGTH: 310

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 99

Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala	1	5
	10	15

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Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr
20 25 30

Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His
35 40 45

Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe
50 55 60

Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu
65 70 75 80

Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu
85 90 95

Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala
100 105 110

Ser Ser Ser Gln Ser Tyr Glu Gln Tyr Phe Gly Pro Gly Thr Arg Leu
115 120 125

Thr Val Thr Glu Asp Leu Lys Asn Val Phe Pro Pro Lys Val Ala Val
130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

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

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Lys Asp Ser Arg Gly
305 310

<210> SEQ ID NO 100
<211> LENGTH: 810
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 100

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atggagactc tgctgggtct cctcatcctg tggctacagc tgcagtgggt ctgcgtccaag 60
caggaggtga cccaaattcc tgccgcgtcg tccgtccccg agggcgagaa cctggtgctc 120
aactgctcct tcaccgacag cgccatctac aacttgcagt ggttccgcga ggaccccgaa 180
aagggcctga ccagccttct gcttatccag agctcccagc gcgaacagac atcaggccgc 240
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ctgaatgcaa gtttggacaa atcttctggc cggtcgaccc tgtatattgc ggcttccag	300
ctgggtgatt ctgctaccta cctgtgcgcc gtgctgttca acacggacaa gctgatctc	360
ggcacccggca ctcgcctgca ggttttcca atccagaacc ctgaccctgc cgtgtacca	420
ctgagagact ctaaatccag tgacaagtct gtctgcctat tcaccgatt tgattctaa	480
acaaatgtgt cacaaagtaa ggattctgat gtgtatatac cagacaaaac tgtgttagac	540
atgaggctca tggactcaa gagcaacagt gctgtggcgt ggagcaacaa atctgacttt	600
gcatgtgcaa acgccttcaa caacagcatt attccagaag acaccttctt ccccagccaa	660
gaaaagttct gtgatgtcaa gctggtcgag aaaagcttt aaacagatac gaacctaaac	720
tttcaaaacc tgtcagtgat tgggttccga atccctctcc taaaaagtggc cgggttaat	780
ctgctcatga cgctgcggct gtggtccagc	810

<210> SEQ ID NO 101
<211> LENGTH: 390
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 101	
atggagactc tgctgggtct cctcatcctg tggctacagc tgcagtgggt ctgcgtccaa	60
caggagggtga cccaaattcc tgccgcgcgtc tccgtgcccc agggcgagaa cctggtgctc	120
aactgctcct tcacccgacag cgccatctac aacttgcagt gttccgcga ggaccccccgg	180
aagggcctga ccagccttct gcttatccag agtcccagc gcaacagac atcaggccgc	240
ctgaatgcaa gtttggacaa atcttctggc cggtcgaccc tgtatattgc ggcttccag	300
ctgggtgatt ctgctaccta cctgtgcgcc gtgctgttca acacggacaa gctgatctc	360
ggcacccggca ctcgcctgca ggttttcca	390

<210> SEQ ID NO 102
<211> LENGTH: 930
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 102	
atgggcacga gcttgctctg ctggatggcc ctgtgcctgc tgggggggcca ccatgcagac	60
acccggcgtca gccagaatcc acgttacaag attaccaagc gggccagaa cgtgacccctc	120
agatgtgacc ccatctcgga gcacaaccgc ctgtattggt accggccagac tcttggacag	180
ggccctgagt tcctgaccta cttccagaac gaggctcagc tggagaagtc ccgcctgttg	240
agtgcacagggt ttccagccga gcccggaaa ggctccttc cgaccctaga gatccagcgc	300
actgaacaag gtgattctgc catgtacctg tgccgcctct cttccagag ctacgagcag	360
tactttggtc cggggacccg tctcaccgtc acagaggacc taaaaacgt gttccacacc	420
aagggtcgctg tgtttgcgtc atcagaagca gagatctccc acacccaaaa ggccacactg	480
gtgtgcctgg ccacaggctt ctacccgcac cacgtggagc tgagctgggt ggtgaatggg	540
aaggagggtgc acagtgggtt cagcacagac ccgcagcccc tcaaggagca gcccgcctc	600

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aatgactcca gatactgcct gagcagccgc ctgagggtct cggccaccc ttggcagaac	660
ccccgcacc accttccgctg tcaagtccag ttctacgggc tctcgagaa tgacgagtgg	720
acccaggata gggccaaacc tgtcacccag atcgtaacgc ccgaggccctg gggtagagca	780
gactgtggct tcacacctcgat gtcttaccag caaggggtcc tgtctgccac catcctctat	840
gagatcttgc taggaaaggc caccttgtat gccgtgtgg tcaagtgcct cgtgtgtatg	900
gcatggtca agagaaaaggc ttccagaggc	930

<210> SEQ ID NO 103
<211> LENGTH: 393
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide

<400> SEQUENCE: 103	
atgggcacga gttgtctg ctggatggcc ctgtgcctgc tgggggggcca ccatgcacac	60
acggcgatca gccaatcc acgttacaag attaccaagc gggccagaa cgtgacccatc	120
agatgtgacc ccatctcgat gcacaaccgc ctgtattggt accggccagac tcttggacag	180
ggccctgagt tcttgaccta ctccagaac gaggctcagc tggagaagtc ccgcctgttgc	240
agtgcacgggt tttcagccga gcccggaaa gggtcccttc cgaccctaga gatccagcgc	300
actgaacaag gtgattctgc catgtacctg tgegcctctt ctcccagag ctacgaggcag	360
tactttggtc cggggaccgc tctcaccgtg aca	393

<210> SEQ ID NO 104
<211> LENGTH: 23
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 104	
cgactggagc acgaggacac tga	23

<210> SEQ ID NO 105
<211> LENGTH: 32
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 105	
gttaactagt tcagctggac cacagccgca gc	32

<210> SEQ ID NO 106
<211> LENGTH: 40
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 106	
cgggttaact agttcagaaa tccttctct tgaccatggc	40

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<210> SEQ ID NO 107
<211> LENGTH: 25
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic primer

<400> SEQUENCE: 107

ctagcctctg gaatcccttc tcttg 25

<210> SEQ ID NO 108
<211> LENGTH: 270
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 108

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

Ala Arg Val Asn Ser Gln Gln Gly Glu Glu Asp Pro Gln Ala Leu Ser
20 25 30

Ile Gln Glu Gly Glu Asn Ala Thr Met Asn Cys Ser Tyr Lys Thr Ser
35 40 45

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

His Leu Ile Leu Ile Arg Ser Asn Glu Arg Glu Lys His Ser Gly Arg
65 70 75 80

Leu Arg Val Thr Leu Asp Thr Ser Lys Lys Ser Ser Ser Leu Leu Ile
85 90 95

Thr Ala Ser Arg Ala Ala Asp Thr Ala Ser Tyr Phe Cys Ala Thr Asp
100 105 110

Gly Ala Gly Lys Ser Thr Phe Gly Asp Gly Thr Thr Leu Thr Val Lys
115 120 125

Pro Asn Ile Gln Lys Pro Asp Pro Ala Val Tyr Gln Leu Arg Asp Ser
130 135 140

Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp Phe Asp Ser Gln
145 150 155 160

Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr Ile Thr Asp Lys
165 170 175

Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser Asn Ser Ala Val
180 185 190

Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn Ala Phe Asn Asn
195 200 205

Ser Ile Ile Pro Ala Asp Thr Phe Phe Pro Ser Pro Glu Ser Ser Cys
210 215 220

Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp Thr Asn Leu Asn
225 230 235 240

Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu Leu Leu Lys Val
245 250 255

Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser
260 265 270

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<210> SEQ ID NO 109
<211> LENGTH: 274
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

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<400> SEQUENCE: 109

Met	Glu	Thr	Leu	Leu	Gly	Leu	Leu	Ile	Leu	Trp	Leu	Gln	Leu	Gln	Trp
1						5			10			15			

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

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

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

Ser	Leu	Leu	Leu	Ile	Gln	Ser	Ser	Gln	Arg	Glu	Gln	Thr	Ser	Gly	Arg
65						70			75			80			

Leu	Asn	Ala	Ser	Leu	Asp	Lys	Ser	Ser	Gly	Arg	Ser	Thr	Leu	Tyr	Ile
						85			90			95			

Ala	Ala	Ser	Gln	Pro	Gly	Asp	Ser	Ala	Thr	Tyr	Leu	Cys	Ala	Val	Arg
						100			105			110			

Pro	Thr	Ser	Gly	Gly	Ser	Tyr	Ile	Pro	Thr	Phe	Gly	Arg	Gly	Thr	Ser
						115			120			125			

Leu	Ile	Val	His	Pro	Tyr	Ile	Gln	Asn	Pro	Asp	Pro	Ala	Val	Tyr	Gln
						130			135			140			

Leu	Arg	Asp	Ser	Lys	Ser	Ser	Asp	Lys	Ser	Val	Cys	Leu	Phe	Thr	Asp
145							150			155			160		

Phe	Asp	Ser	Gln	Thr	Asn	Val	Ser	Gln	Ser	Lys	Asp	Ser	Asp	Val	Tyr
						165			170			175			

Ile	Thr	Asp	Lys	Thr	Val	Leu	Asp	Met	Arg	Ser	Met	Asp	Phe	Lys	Ser
						180			185			190			

Asn	Ser	Ala	Val	Ala	Trp	Ser	Asn	Lys	Ser	Asp	Phe	Ala	Cys	Ala	Asn
						195			200			205			

Ala	Phe	Asn	Asn	Ser	Ile	Ile	Pro	Glu	Asp	Thr	Phe	Phe	Pro	Ser	Pro
						210			215			220			

Glu	Ser	Ser	Cys	Asp	Val	Lys	Leu	Val	Glu	Lys	Ser	Phe	Glu	Thr	Asp
225						230			235			240			

Thr	Asn	Leu	Asn	Phe	Gln	Asn	Leu	Ser	Val	Ile	Gly	Phe	Arg	Ile	Leu
						245			250			255			

Leu	Leu	Lys	Val	Ala	Gly	Phe	Asn	Leu	Leu	Met	Thr	Leu	Arg	Leu	Trp
						260			265			270			

Ser Ser

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<210> SEQ ID NO 110
<211> LENGTH: 274
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

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<400> SEQUENCE: 110

Met	Glu	Thr	Leu	Leu	Gly	Leu	Leu	Ile	Leu	Trp	Leu	Gln	Leu	Gln	Trp
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

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1	5	10	15
Val Ser Ser Lys Gln Glu Val Thr Gln Ile Pro Ala Ala Leu Ser Val			
20	25	30	
Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala			
35	40	45	
Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr			
50	55	60	
Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg			
65	70	75	80
Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile			
85	90	95	
Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg			
100	105	110	
Pro Gln Thr Gly Gly Ser Tyr Ile Pro Thr Phe Gly Arg Gly Thr Ser			
115	120	125	
Leu Ile Val His Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln			
130	135	140	
Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp			
145	150	155	160
Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr			
165	170	175	
Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser			
180	185	190	
Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn			
195	200	205	
Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro			
210	215	220	
Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp			
225	230	235	240
Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu			
245	250	255	
Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp			
260	265	270	
Ser Ser			

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<210> SEQ_ID NO 111
<211> LENGTH: 274
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

<400> SEQUENCE: 111

Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp
1 5 10 15

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

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

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

Ser Leu Leu Leu Ile Thr Pro Trp Gln Arg Glu Gln Thr Ser Gly Arg

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65	70	75	80
Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile			
85	90	95	
Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Arg			
100	105	110	
Pro Leu Leu Asp Gly Thr Tyr Ile Pro Thr Phe Gly Arg Gly Thr Ser			
115	120	125	
Leu Ile Val His Pro Tyr Ile Gln Asn Pro Asp Pro Ala Val Tyr Gln			
130	135	140	
Leu Arg Asp Ser Lys Ser Ser Asp Lys Ser Val Cys Leu Phe Thr Asp			
145	150	155	160
Phe Asp Ser Gln Thr Asn Val Ser Gln Ser Lys Asp Ser Asp Val Tyr			
165	170	175	
Ile Thr Asp Lys Thr Val Leu Asp Met Arg Ser Met Asp Phe Lys Ser			
180	185	190	
Asn Ser Ala Val Ala Trp Ser Asn Lys Ser Asp Phe Ala Cys Ala Asn			
195	200	205	
Ala Phe Asn Asn Ser Ile Ile Pro Glu Asp Thr Phe Phe Pro Ser Pro			
210	215	220	
Glu Ser Ser Cys Asp Val Lys Leu Val Glu Lys Ser Phe Glu Thr Asp			
225	230	235	240
Thr Asn Leu Asn Phe Gln Asn Leu Ser Val Ile Gly Phe Arg Ile Leu			
245	250	255	
Leu Leu Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp			
260	265	270	
Ser Ser			

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<210> SEQ ID NO 112
<211> LENGTH: 272
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
      polypeptide

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<400> SEQUENCE: 112

1	5	10	15
Met Glu Thr Leu Leu Gly Leu Leu Ile Leu Trp Leu Gln Leu Gln Trp			
Val Ser Ser Lys Gln Glu Val Thr Gln Ile Pro Ala Ala Leu Ser Val			
20	25	30	
Pro Glu Gly Glu Asn Leu Val Leu Asn Cys Ser Phe Thr Asp Ser Ala			
35	40	45	
Ile Tyr Asn Leu Gln Trp Phe Arg Gln Asp Pro Gly Lys Gly Leu Thr			
50	55	60	
Ser Leu Leu Leu Ile Gln Ser Ser Gln Arg Glu Gln Thr Ser Gly Arg			
65	70	75	80
Leu Asn Ala Ser Leu Asp Lys Ser Ser Gly Arg Ser Thr Leu Tyr Ile			
85	90	95	
Ala Ala Ser Gln Pro Gly Asp Ser Ala Thr Tyr Leu Cys Ala Val Ser			
100	105	110	
Thr Ala Tyr Ser Gly Gly Ala Asp Gly Leu Thr Phe Gly Lys Gly			
115	120	125	
Thr His Leu Ile Ile Gln Pro Tyr Ile Gln Asn Pro Glu Pro Ala Val			

-continued

130	135	140	
Tyr Gln Leu Lys Asp Pro Arg Ser Gln Asp Ser Thr Leu Cys Leu Phe			
145	150	155	160
Thr Asp Phe Asp Ser Gln Ile Asn Val Pro Lys Thr Met Glu Ser Gly			
165	170	175	
Thr Phe Ile Thr Asp Lys Cys Val Leu Asp Met Lys Ala Met Asp Ser			
180	185	190	
Lys Ser Asn Gly Ala Ile Ala Trp Ser Asn Gln Thr Ser Phe Thr Cys			
195	200	205	
Gln Asp Ile Phe Lys Glu Thr Asn Ala Thr Tyr Pro Ser Ser Asp Val			
210	215	220	
Pro Cys Asp Ala Thr Leu Thr Glu Lys Ser Phe Glu Thr Asp Met Asn			
225	230	235	240
Leu Asn Phe Gln Asn Leu Leu Val Ile Val Leu Arg Ile Leu Leu Leu			
245	250	255	
Lys Val Ala Gly Phe Asn Leu Leu Met Thr Leu Arg Leu Trp Ser Ser			
260	265	270	

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<210> SEQ ID NO 113
<211> LENGTH: 309
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide

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1	5	10	15	
Met Gly Thr Ser Leu Leu Cys Trp Met Ala Leu Cys Leu Leu Gly Ala				
Asp His Ala Asp Thr Gly Val Ser Gln Asn Pro Arg His Lys Ile Thr				
20	25	30		
Lys Arg Gly Gln Asn Val Thr Phe Arg Cys Asp Pro Ile Ser Glu His				
35	40	45		
Asn Arg Leu Tyr Trp Tyr Arg Gln Thr Leu Gly Gln Gly Pro Glu Phe				
50	55	60		
Leu Thr Tyr Phe Gln Asn Glu Ala Gln Leu Glu Lys Ser Arg Leu Leu				
65	70	75	80	
Ser Asp Arg Phe Ser Ala Glu Arg Pro Lys Gly Ser Phe Ser Thr Leu				
85	90	95		
Glu Ile Gln Arg Thr Glu Gln Gly Asp Ser Ala Met Tyr Leu Cys Ala				
100	105	110		
Ser Ser Pro Pro Thr Val Arg Val Tyr Gly Tyr Thr Phe Gly Ser Gly				
115	120	125		
Thr Arg Leu Thr Val Val Glu Asp Glu Asp Leu Arg Asn Val Thr Pro				
130	135	140		
Pro Lys Val Ser Leu Phe Glu Pro Ser Lys Ala Glu Ile Ala Asn Lys				
145	150	155	160	
Gln Lys Ala Thr Leu Val Cys Leu Ala Arg Gly Phe Phe Pro Asp His				
165	170	175		
Val Glu Leu Ser Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val				
180	185	190		
Cys Thr Asp Pro Gln Ala Tyr Lys Glu Ser Asn Tyr Ser Tyr Cys Leu				
195	200	205		

-continued

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp His Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe His Gly Leu Ser Glu Glu Asp Lys
225 230 235 240

Trp Pro Glu Gly Ser Pro Lys Pro Val Thr Gln Asn Ile Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Ile Thr Ser Ala Ser Tyr Gln Gln
260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Thr Leu Val Val Met Ala Met Val
290 295 300

Lys Arg Lys Asn Ser
305

<210> SEQ ID NO 114

<211> LENGTH: 308

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 114

Met Asp Ser Trp Thr Leu Cys Cys Val Ser Leu Cys Ile Leu Val Ala
1 5 10 15

Lys His Thr Asp Ala Gly Val Ile Gln Ser Pro Arg His Glu Val Thr
20 25 30

Glu Met Gly Gln Glu Val Thr Leu Arg Cys Lys Pro Ile Ser Gly His
35 40 45

Asp Tyr Leu Phe Trp Tyr Arg Gln Thr Met Met Arg Gly Leu Glu Leu
50 55 60

Leu Ile Tyr Phe Asn Asn Asn Val Pro Ile Asn Asp Ser Gly Met Pro
65 70 75 80

Glu Asp Arg Phe Ser Ala Lys Met Pro Asn Ala Ser Phe Ser Thr Leu
85 90 95

Lys Ile Gln Pro Ser Glu Pro Arg Asp Ser Ala Val Tyr Phe Cys Ala
100 105 110

Ser Thr Ile Gly Ala Gln Pro Gln His Phe Gly Asp Gly Thr Arg Leu
115 120 125

Ser Ile Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala Val
130 135 140

Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr Leu
145 150 155 160

Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser Trp
165 170 175

Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro Gln
180 185 190

Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu Ser
195 200 205

Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn His
210 215 220

Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu Trp
225 230 235 240

-continued

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

Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln Gly
260 265 270

Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala Thr
275 280 285

Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val Lys
290 295 300

Arg Leu Asp Phe
305

<210> SEQ ID NO 115

<211> LENGTH: 311

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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

<400> SEQUENCE: 115

Met Ala Pro Arg Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

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

Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg
85 90 95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
100 105 110

Ser Tyr Val Gly Ala Ala Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
115 120 125

Leu Thr Val Leu Glu Asp Leu Asn Lys Val Phe Pro Pro Glu Val Ala
130 135 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Phe Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225 230 235 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Val Ser Tyr Gln Gln

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260	265	270	
Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala			
275	280	285	
Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val			
290	295	300	
Lys Arg Lys Asp Ser Arg Gly			
305	310		
 <210> SEQ ID NO 116			
<211> LENGTH: 311			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide			
 <400> SEQUENCE: 116			
Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala			
1	5	10	15
Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu			
20	25	30	
Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His			
35	40	45	
Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu			
50	55	60	
Ile His Tyr Ser Val Gly Ala Gly Ile Thr Asp Gln Gly Glu Val Pro			
65	70	75	80
Asn Gly Tyr Asn Val Ser Arg Ser Thr Thr Glu Asp Phe Pro Leu Arg			
85	90	95	
Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser			
100	105	110	
Ser Tyr Val Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg			
115	120	125	
Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala			
130	135	140	
Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr			
145	150	155	160
Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser			
165	170	175	
Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro			
180	185	190	
Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu			
195	200	205	
Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn			
210	215	220	
His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu			
225	230	235	240
Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu			
245	250	255	
Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln			
260	265	270	
Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala			
275	280	285	

-continued

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Ser Arg Gly
305 310

<210> SEQ ID NO 117
<211> LENGTH: 311
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide

<400> SEQUENCE: 117

Met Ser Ile Gly Leu Leu Cys Cys Ala Ala Leu Ser Leu Leu Trp Ala
1 5 10 15

Gly Pro Val Asn Ala Gly Val Thr Gln Thr Pro Lys Phe Gln Val Leu
20 25 30

Lys Thr Gly Gln Ser Met Thr Leu Gln Cys Ala Gln Asp Met Asn His
35 40 45

Glu Tyr Met Ser Trp Tyr Arg Gln Asp Pro Gly Met Gly Leu Arg Leu
50 55 60

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

Asn Gly Tyr Asn Val Ser Arg Ser Thr Ile Glu Asp Phe Pro Leu Arg
85 90 95

Leu Leu Ser Ala Ala Pro Ser Gln Thr Ser Val Tyr Phe Cys Ala Ser
100 105 110

Ser Tyr Leu Gly Asn Thr Gly Glu Leu Phe Phe Gly Glu Gly Ser Arg
115 120 125

Leu Thr Val Leu Glu Asp Leu Lys Asn Val Phe Pro Pro Glu Val Ala
130 135 140

Val Phe Glu Pro Ser Glu Ala Glu Ile Ser His Thr Gln Lys Ala Thr
145 150 155 160

Leu Val Cys Leu Ala Thr Gly Phe Tyr Pro Asp His Val Glu Leu Ser
165 170 175

Trp Trp Val Asn Gly Lys Glu Val His Ser Gly Val Ser Thr Asp Pro
180 185 190

Gln Pro Leu Lys Glu Gln Pro Ala Leu Asn Asp Ser Arg Tyr Cys Leu
195 200 205

Ser Ser Arg Leu Arg Val Ser Ala Thr Phe Trp Gln Asn Pro Arg Asn
210 215 220

His Phe Arg Cys Gln Val Gln Phe Tyr Gly Leu Ser Glu Asn Asp Glu
225 230 235 240

Trp Thr Gln Asp Arg Ala Lys Pro Val Thr Gln Ile Val Ser Ala Glu
245 250 255

Ala Trp Gly Arg Ala Asp Cys Gly Phe Thr Ser Glu Ser Tyr Gln Gln
260 265 270

Gly Val Leu Ser Ala Thr Ile Leu Tyr Glu Ile Leu Leu Gly Lys Ala
275 280 285

Thr Leu Tyr Ala Val Leu Val Ser Ala Leu Val Leu Met Ala Met Val
290 295 300

Lys Arg Lys Asp Ser Arg Gly
305 310

- continued

1. An isolated recombinant α -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLL-MWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28), wherein the α -chain comprises one or more of the following amino acid sequences:
 - (i) an amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 2, or SEQ ID NO: 87, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 2, or SEQ ID NO: 87;
 - (ii) an α -chain variable region amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83;
 - (iii) an α -chain CDR₃ amino acid sequence of SEQ ID NO: 7;
 - (iv) an α -chain CDR₁ amino acid sequence of SEQ ID NO: 5; and
 - (v) an α -chain CDR₂ amino acid sequence of SEQ ID NO: 6.
 2. An isolated recombinant β -chain of a T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLL-MWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28), wherein the β -chain comprises one or more of the following amino acid sequences:
 - (i) an amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 95, or SEQ ID NO: 99;
 - (ii) a β -chain variable region amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85;
 - (iii) a β -chain CDR₃ amino acid sequence of SEQ ID NO: 13;
 - (iv) a β -chain CDR₁ amino acid sequence of SEQ ID NO: 11; and
 - (v) a β -chain CDR₂ amino acid sequence of SEQ ID NO: 12.
 3. (canceled)
 4. An isolated, recombinant T-cell receptor immunoreactive with an epitope of a NY-ESO-1 and/or LAGE-1a protein comprising the amino acid sequence SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28), the T-cell receptor comprising an α -chain and a β -chain, the α and β chains each comprising a CDR₁, CDR₂, and a CDR₃, wherein the α -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 7, and the β -chain CDR₃ comprises the amino acid sequence of SEQ ID NO: 13.
 5. The T-cell receptor of claim 4, wherein:
 - (i) the α -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 5, and the β -chain CDR₁ comprises the amino acid sequence of SEQ ID NO: 11;
 - (ii) the α -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 6, and the β -chain CDR₂ comprises the amino acid sequence of SEQ ID NO: 12;
 - (iii) the T-cell receptor comprises an α -chain variable region comprising an amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83, or an amino acid sequence having greater than 96% identity to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 83;
 - (iv) the T-cell receptor comprises a β -chain variable region comprising an amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 85;
 - (v) the α -chain comprises the amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 2, or SEQ ID NO: 87, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 37, SEQ ID NO: 2, or SEQ ID NO: 87; and/or
 - (vi) the β -chain comprises the amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 95, or SEQ ID NO: 99, or an amino acid sequence having greater than 97% identity to the amino acid sequence of SEQ ID NO: 39, SEQ ID NO: 95, or SEQ ID NO: 99.
- 6-8. (canceled)**
- 9.** The T-cell receptor of claim 5, wherein the immunoreactivity to the epitope SLLMWITQC (SEQ ID NO: 1) and/or SLLMWITQCFL (SEQ ID NO: 28) is:
- (a) HLA-A2 restricted; and/or
 - (b) HLA-A*0201 or HLA-A*0202 restricted.
- 10. (canceled)**
- 11.** The T-cell receptor of claim 9, wherein the T-cell receptor is a single chain T-cell receptor, optionally where the α -chain is linked to the β -chain via an amino acid linker.
- 12.** The T-cell receptor of claim 11, further comprising a detectable label.
- 13.** The T-cell receptor of claim 12, associated with a therapeutic agent.
- 14.** A bispecific T-cell receptor protein comprising an antibody or an antigen binding fragment thereof associated with, optionally fused to, the T-cell receptor of claim 4.
- 15. (canceled)**
- 16.** An isolated recombinant nucleic acid encoding the T-cell receptor α -chain of claim 1.
- 17.** An isolated recombinant nucleic acid encoding the T-cell receptor β -chain of claim 2.
- 18.** An isolated recombinant nucleic acid encoding the T-cell receptor of claim 4.
- 19-22. (canceled)**
- 23.** The the T-cell receptor of claim 4, wherein the α -chain, the β -chain, or both the α - and β -chains comprise a mutation not present in the naturally occurring T-cell receptor, optionally including a point mutation to remove at least one glycosylation site in the α -chain, the β -chain, or both the α - and β -chains.
- 24.** A recombinant expression vector comprising one or more of the nucleic acids of claim 18.
- 25-26. (canceled)**
- 27.** A genetically modified cell that comprises the T-cell receptor of claim 4.
- 28-33. (canceled)**
- 34.** A method for producing a T-cell immunoreactive with an epitope of an NY-ESO-1 and/or LAGE-1a protein and/or

with an epitope of a LAGE-1a protein, the method comprising introducing one or more of the nucleic acids of claim 18 into the T-cell.

35-37. (canceled)

38. A pharmaceutical composition comprising the cell of claim 27.

39. A method of inhibiting the growth of cancer cells expressing an NY-ESO-1 and/or LAGE-1a protein, the method comprising exposing the cancer cells to a cell of claim 27 capable of inhibiting the growth of the cancer cells.

40. A method for treating or preventing cancer in a subject, the method comprising administering to the subject autologous genetically modified T-cells expressing the T-cell receptor of claim 4 in an amount effective to treat or prevent cancer in the subject.

41. A method for treating or preventing cancer in a subject, said method comprising the steps of

(i) extracting T-cells from the subject;

(ii) introducing into the T-cells one or more nucleic acids of claim 18; and

(iii) administering the T-cells produced by step (ii) to the subject.

42-43. (canceled)

44. The T-cell receptor of claim 4, wherein the α -chain comprises the amino acid sequence of SEQ ID NO: 37 and the β -chain comprises the amino acid sequence of SEQ ID NO: 39.

45. The T-cell receptor of claim 4, wherein the α -chain comprises the amino acid sequence of SEQ ID NO: 2 and the β -chain comprises the amino acid sequence of SEQ ID NO: 95.

46. The T-cell receptor of claim 4, wherein the α -chain comprises the amino acid sequence of SEQ ID NO: 87 and the β -chain comprises the amino acid sequence of SEQ ID NO: 99.

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