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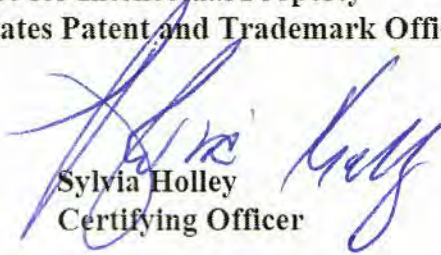
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(54) **CD19-SPECIFIC REDIRECTED IMMUNE CELLS**

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(57) **ABSTRACT**

(21) Appl. No.: **10/416,011**

Genetically engineered, CD19-specific redirected immune cells expressing a cell surface protein having an extracellular domain comprising a receptor which is specific for CD19, an intracellular signaling domain, and a transmembrane domain. Use of such cells for cellular immunotherapy of CD19<sup>+</sup> malignancies and for abrogating any untoward B cell function. In one embodiment, the immune cell is a T cell and the cell surface protein is a single chain scFvFc:ζ receptor where scFv designates the V<sub>H</sub> and V<sub>L</sub> chains of a single chain monoclonal antibody to CD19, Fc represents at least part of a constant region of an IgG<sub>1</sub>, and ζ represents the intracellular signaling domain of the zeta chain of human CD3. The extracellular domain scFvFc and the intracellular domain ζ are linked by a transmembrane domain such as the transmembrane domain of CD4. A method of making a redirected T cell expressing a chimeric T cell receptor by electroporation using naked DNA encoding the receptor.

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(86) PCT No.: **PCT/US01/42997**

**Related U.S. Application Data**

(60) Provisional application No. 60/246,117, filed on Nov. 7, 2000.

XbaI (hGMCSF signal peptide-)

M L L L V T S L L L C E L P

1 ATCTCTAGAG CGCCACCAT GCTTCTCCTG GTGACAAGCC TTCTGCTCTG TGAGTTACCA  
TAGAGATCTC GCGGGTGGTA CGAAGAGGAC CACTGTTCGG AAGACGAGAC ACTCAATGGT

(V<sub>1</sub>-)

H P A F L L I P D I Q M T Q T T S S L S

51 CACCCAGCAT TCCTCCTGAT CCCAGACATC CAGATGACAC AGACTACATC CTCCTGTCT  
GTSGGTCGTA AGGAGGACTA GGGTCTGTAG GTCTACTGTG TCTGATCTAG GAGGGACAGA

A S L G D R V T I S C R A S Q D I S K Y

121 GCCTCTCTGG GACACAGAGT CACCATCAGT TTAGGGCAA GTCAGGACAT TAGTAARTAT  
CGGAGAGACC CTCTGTCTCA GTGGTAGTCA ACGTCCCGTT CAGTCTGTG ATCATTTATA

L N W Y Q Q K P D G T V K L L I Y H T S

181 TTAATTGGT ATCAGCAGAA ACCAGATGGA ACTGTAAAC TCCTGATCTA CCTACATCA  
AATTAACCA TAGTCGTCTT TGGTCTACCT TGACAATTTG AGGACTAGAT GGTATGTAGT

R L H S G V P S R F S G S G S G T D Y S

241 AGATTACT CAGGAGTCCC ATCAAGGTTG AGIGGCAGTG GGTCTGGAAC AGATTATTCT  
TCTAATGGA GTCTCAGGG TAGTCCAAAG TCACCGTCAC CCAGACCTTG TCTAATAAGA

L T I S N L E Q E D I A T Y F C Q Q G N

301 CTCACCATTA GCAACCTGGA GCAAGAAGAT ATTGCCACTT ACTTTTGCCA ACAGGGTAAT  
GAGTGGTAAT CGTTGGACCT CGTTCTTCTA TAACGGTGAA TGAAAACGGT TGTCCCATTA

(Whitlow linker-)

T L P Y T F S G G T K L E I T G S T S G

361 ACGCTCCGT ACACGTTCGG AGGGGGGACT AAGTTGGAAA TAACAGGCTC CACCTCTGA  
TGCGAAGGCA TGTGCAAGCC TCCCCCTGA TCCAACTTT ATTGTCCGAG GTGGAGACCT

(V<sub>2</sub>-)

S S K F S S G E S S T K G E V K L Q E S

421 TCCGGCAATC CCGGATCTGG CGAGGGATCC ACCAAGGGCG AGGTGAAACT GCAGGAGTCA  
AGGCCSTTGG GGCCTAGACC GCTCCCTAGG TGSTTCCCGC TCCACTTTGA CGTCTCAGT

G P G L V A P S Q S L S V T C T V S G V

481 GGACCTGGCC TGGTGGCGCC CTCACAGAGC CTGTCCGTCA CATGCACTGT CTCAGGGGTC  
CCTGGACCGG ACCACCGCGG GAGTGTCTCG GACAGSCAGT GTACGTGACA GAGTCCCCAG

S L P D Y G V S W I R Q P P R K G L E W

541 TCATTA GCG ACTATGSGT AAGCTGGATT CGCCAGCCTC CACGAAAGGG TCTGGAGTGG  
AGTAATGGGC TGATACCACA TTCGACCTAA GCGGTGGGAG GTGCTTTCCC AGACCTCACC

L G V I W G S E T T Y Y N S A L K S R L

601 CTGGGAGTAA TATGGGGTAG TGAACCACA TACTATAATT CAGCTCTCAA ATCCAGACTG  
GACCCATCATT ATACCCCATC ACITTTGGTGT ATGATATTAA GTCGAGAGTT TAGGTCTGAC

T I I K D N S K S Q T F S K M N S L Q T

661 ACCATCATCA AGGACRACTC AAGAGCCCT TTTTCTTAA AAATGAACAG TCTGCAAACT  
TGGTAGTAGT TCCTGTGAG GTTCTCGGT TAAAAGAATT TTTACTTGTC AGACGTTTGA

D D T A I Y Y C A K H Y Y Y G G S Y A M

721 GATGACACAG CCATTTACTA CTGTGCCAAA CATTATTACT ACGGTGGTAG CTATGCTATG  
CTACTGTGTC GGTAATGAT SACACGGTTT GTAATAATGA TGCCACCATC GATACGATAC

FIGURE 1A

.hingeF<sub>1</sub>

781 D Y W G Q G T S V T V S S Y E P K S S D  
GACTACTGGG GTCAAGGAC CTCAGTCACC CTCCTCTCAG TAGAACCCAA ATCTTCTGAC  
CTSATGACCC CAGTTCTCTG GAGTCAGTGG CAGAGGAGTC ATCTTGGGTT TAGAAGACTG

841 K T H T C P F C P A P E L C G G P S Y F  
AAACTCACA GGTGCCACCC GTGCCAGCA CCTGAACCTC TGGGGGGACC CTCAGTCTTC  
TTTTGASTGT GCACGGGTGG CACGGGTGGT GGACTTGAGG ACCCCCTGG CAGTCAGAAG

901 L T F P K P K D T L M T S R T P E V I F  
CTCTTCCCGG CAARAACCAA GGACACCCCTC AGCATCTCCG TGACCCCTGA GGTCAATGG  
GAGAAGGGGG GTTTTGGGTT CCTGTGGGAG TACTAGAGGG CCTGGGGACT CCAGTGTAGG

961 V V V D V S H E D P E V K F N W Y V D G  
GTGGTGGTGG ACGTGAGCCA CGAAGACCCT GAGGTCAAGT TCAACTGGTA TGTGGACGGC  
CACCACCACC TGCCTCGGT GCTTCTGGGA CTCCAGTTCAGT AGTTGACCAT GCACCTGCCG

1021 V E V H N A K T K P R E E Q Y N S T Y R  
GTGGAGGTGC ATAATGCCAA GACAAAGCCG CGGGAGGAGC AGTACAACAG CACGTACCGT  
CACCTCCACG TATTACGGTT CTGTTTCGGC GCCCTCCTCG TCATGTTGTC GTGCATGGCA

1081 J V S V L T V L H Q D W L N G K E Y K C  
GTGGTCAGCG TCCTCACCCT CCTGCACCAG GACTGGCTGA ATGGCAAGGA GTACAAGTGC  
CACCAGTCGC AGGAGTGGCA GGACGTGGTC CTGACCGACT TACCGTTCCT CATGTTCCAG

1141 K V S N K A L P A P I E K T I S K A K G  
AAGGTCTCCA ACAAAGCCCT CCCAGCCCCC ATCGAGAAAA CCATCTCCAAGCCAAAGGG  
TTCCAGAGGT TGTTCGGGA GGGTGGGGG TAGCTCTTTT GGTAGAGGTT TCGGTTTCCC

1201 Q P R E P Q V Y T L P P S R D E L T K N  
CAGCCCGGAG AACCAAGGCT GTACACCCCTC CCACCATCAC GAGATGAGCT GACCAAGGAC  
CTCGGGGCTG TTGCTGTCCA CATGTGGGAC CTCTGTAGTG CCTTACTGCA CTGGTCTTTC

1241 Q V S L T I L V K G E Y P S D I A Y E W  
GAGTCTGAGT GAAAGGATGT GTTAAAGGCT TTTAAAGGCA GTTAAATGCT CCTTAAATGT  
GTCCAGTCGG ACTGGACCGA CCAGTTTCCG AAGATAGGGT CCTCTAGCG CCACCTCACG

1321 E S N G Q P E N N Y K T T P P V L D S D  
GAGAGCAATG GGCAGCCCGA GAACAACCTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC  
CTCTCGTTAC CCGTGGGCTT CTTGTTGATG TTCTGGTGGC GAGGGCACGA CCTGAGGCTG

1381 G S F F L V S K L T V D K S R W Q Q G N  
GGCTCCTCTC TCCTGTACAG CAAGCTCACG CTGGACAAGA GCAGGTGGCA GCAGGGGAC  
CCGAGGAAAG AGGAGATGTC GTTCGAGTGG CACCTGTTCT CGTCCACCCT CGTCCCTTG

1441 Y F S C S Y M H E A L H N H Y T Q K S L  
CTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCIC  
CAGAAGAGTA CGAGGCACTA CGTACTCCGA GAGTGTGGT TGATGTGCGT CTCTCTGGAG

1501 S L S F G K M A L I V L S G V A G L L L  
TCCCTGTCTC CCGGAAAAT GGCCCTGATT GTGCTGGGGG GCGTGGCCGG CCTCCTGCTT  
AGGGACAGAG GGCCCTTTTA CCGGGACTAA CAGGACCCCC CGCAGCCGGC GGAGGACGAA

1561 F I G L G I F F R V K F S R S A D A P A  
TTCATTGGGG TAGGCATCTT CTTCAGAGTG AAGTTCAGCA GGAGCGCAGR CCCCCCGCG  
AAGTAACCCG ATCCGTAGAA GAAGTCTCAC TTCAGTGGT CCTCGCGTCT CCGGGGGCGG

FIGURE 1B

Y Q Q G Q N Q L Y N E L N L G R R E E Y  
1621 TACCAGCAGG GCCAGAACCA GCTCTATAAC GAGCTCAATC TAGGACGAAG AGAGGAGTAC  
ATGGTTCGTCC CGGTCTTGGT CGAGATATTG CTCGAGTTAG ATCCTGCTTC TCTCCTCATG

D V L D K R R G R D P E M G G K P R R K  
1681 GATGTTTTGG ACAAGAGACG TGGCCGGGAC CCTGAGATGG GGGGAAAGCC GAGAAGGAAG  
CTACAAAACC TGTTCTCTGC ACCGGCCCTG GGACTCTACC CCCCTTTCGG CTCTTCCTTC

N P Q E G L Y N E L Q K D K M A E A Y D  
1741 AACCCCTCAGG AAGGCCTGTA CAATGAACTG CAGAAAGATA AGATGGCCGA GGCCTACAGT  
TTGGGAGTCC TCCGGACAT GTTACTTGAC GTCTTTCTAT TCTACCGCCT CCGGATGTCA

E I G M K G E R R R G K G H D G L Y Q G  
1801 GAGATTGGGA TGAAAGGCGA GCGCCGGAGG GGCAAGGGC ACGATGGCCT TTACCAGGT  
CTCTAACCCCT ACTTTCGCT CGCGGCCTCC CCGTTCOCCT TGCTACCGGA AATGGTCCCA

L S T A T K D T Y D A L H M Q A L P P R  
1861 CTCAGTACAG CCACCAAGGA CACCTACGAC GCCCTTACA TGCAGGCCCT GCCCCCTCGC  
GAGTCATGTC GGTGGTTCCT GTGGATGCTG CGGGAAGTGT ACGTCCGGGA CGGGGGAGCG

Not I  
-----  
1921 TAAGCGGCCG C  
ATTCGCCGGC G

FIGURE 1C

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