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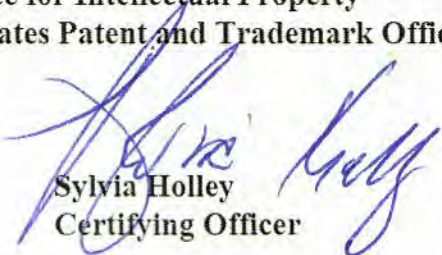
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(54) **CD19-SPECIFIC REDIRECTED IMMUNE CELLS**

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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.

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XbaI      (hGMSF signal peptide-)
-----
1 ATCTCTAGAG CCGCCACCAT GCTTCTCCTG GTGACAAGCC TTCTGCTCTG TGAGTTACCA
  TAGAGATCTC GCGCGTGGTA CGAAGAGGAC CACTGTTCCG AAGACGAGAC ACTCAATGTT

      (V1-)
51 H P A F L L E P D I Q M T Q T T S S L S
   CACCCAGCAT TCCTCCTGAT CCCAGACATC CAGATGACAC AGACTACATC CTCCTCTGCT
   GTGGGTCGTA 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 GTCACAGAGT CACCATCAGT TCCAGGGCAA GTCAGGACAT TAGTAAATAT
   CGGAGAGACC CTCTGTCTCA GTGGTAGTCA AGGTCCCGTT CAGTCTCTGA 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 ACTGTTAAAC TCCTGATCTP CCAATACATCA
   AATTAACCA TAGTCGTCTT TGGTCTACCT TGACAATTG AGGACTAGAT GGTATGTAGT

      R L H S G V P S R F S G S G S G T D Y S
241 AGATTACACT CAGGAGTCCC ATCAAGGTTT AGTGGCAGTG GGTCTGGAAC AGATTATTCT
   TCTAATGTGA GTCCTCAGGG TAGTTCCAAG TCACCGTCAC CCAGACCTTG TCTAATAAGA

      L T I S N L E Q E D I A T Y F C Q Q G N
301 CTACACATTA GCAACCTGGA GCAAGAAGAT ATTGCCACTT ACTTTTGCCA ACAGGGTAAAT
   GAGTGGTAAT CGTTGGACCT CGTTCTTCTA TAACGGTGAA TGAAAACGGT TGTCCCATTA

      (Whitlow linker-)
361 T L P Y T F G G G T K L E I T G S T S G
   ACGCTTCCGT ACACGTTCCG AGGGGGGACT AAGTTGGAAA TAACAGGCTC CACCTCTGGA
   TGCGAAGGCA TGTGCAAGCC TCCCCCTGA TCCAACCTTT ATTGTCCGAG GTGGAGACCT

      (V2-)
421 S S K F G S G E G S T K G E V K L Q E S
   TCCGGCAATC CCGGATCTGG CGAGGGATCC ACCAAGGGCG AGGTGAAACT GCAGGAGTCA
   AGGCCSTTCG GGCCTAGACC GCTCCCTAGG TGGTCCCGC 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 CATGCACCTGT CTCAGGGGTC
   CCTSGACCGG ACCACCGCGG GAGTGTCTCG GACAGGCAGT GTACGTGACA GAGTCCCCAG

      S L P D Y G V S W I R Q P P R K G L E W
541 TCATTA LCG ACTATGTTGT 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 TGAAACCACA TACTATAATT CAGCTCTCAA ATCCAGACTG
   GACCCCTATT ATACCCCATC ACTTTGGTGT ATGATATTAA GTCGAGAGTT TAGGTCTGAC

      T I I K D N S K S Q T F L K M N S L Q T
661 ACCATCATLA AGGACAACTC CAAGAGCTTT CTCTTCTTAA AAATGAACAG TCTGCAAACT
   TGGTAGTAGI TCCTGTTGAG 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 CATATTACTI ACGGTGGTAG CTATGCTATG
   CTA CTGTGTG GGTAAATGAT GACACGGTTT GTAATAATGA TGCCACCATC GATACGATAC
    
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FIGURE 1A

...hingeF<sub>1</sub>-1

781 D Y W G Q G T S V I V S S Y E P K S S D  
 GACTACTGGG GTC AAGGAAC CTCAGTCACC GTCTCCTCAG TAGAACCCAA ATCTTCTGAC  
 CTGATGACCC CAGTTCCCTG GAGTCAGTGG CAGAGGAGTC ATCTTGGGTT TAGAAGACTG

841 K T H T C P P C P A P E L L G G P S V F  
 AAAACTCACA CGTGCCCAAC GTGCCACGCA CCTGAACCTC TGJGGGGACC CTCAGTCTTC  
 TTTTGASTGT GCACGGGTGG CACGGGTGCT GGACTTGAGG ACCCCCTCTGG CAGTCAGAA G

901 L T P P K P K D T L N I S R T P E V T I  
 CTCTTCCCGG CAAAACCCAA GCACACCCCTC ATGATCTCCG GCACCCCTGA GTCACATGG  
 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 CTGGGACGGC  
 CACCACCACC TGCACCTCGGT GCTTCTGGGA CTCCAGTTCA 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 CACGTACCCT  
 CACCTCCACG TATTACGGTT CTGTTTCCGC 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 TCCTCACCGT 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 CCATCTCCA AGCCAAGGG  
 TTCCAGAGST TGTTCGGGA GGGTCGGGGG TAGCTCTTTT GGTAGAGSTT TCGTITTCCT

1201 Q P R E P R V Y T L P P S R D E L T K N  
 CAGCCCGGAG AACCAAGGCT GTACACCCCTC CCACCATCAC GAGATGAGCT GACCAAGGAC  
 GTGGGGGCTC TTGCTCTCCA CATGTGGGAG GCTGTAGCTG CCTACTGCA TTGCTCTCTG

1241 Q V S L T D L V K G E Y P S D I A V E W  
 TACTCTAGGG CCAATCTGAT GTGAGAGGCT TCTCATGCGA GTACTACTCT CTTTCTCTTT  
 GTCCAGTCGG ACTGGACCGA CCAGTTTCCG AAGATAGGGT CCCTGTAGCG GCACCTCAGC

1321 E S N G Q P E N N Y K T T P P V L D S D  
 GAGAGCAATG GGCAGCCGGA GAACAACCTAC AAGACCAGCG CTCCCGTGCT GGACTCCGAC  
 CTCTCGTTAC CCGTCCGGCT CTTGTTGATG TTCTGGTGCG GAGGGCACGA CCTGAGGCTG

1381 G S F F L Y S K L T Y D K S R W Q Q G N  
 GGCTCCTTCT TCCTCTACAG CAAGCTCACG GTGGACAAGA GCAGGTGGCA GCAGGGGAC  
 CCGAGGAAGA AGGAGATGTC GTTCGAGTGG CACCTGTTCT CGTCCACCCT CGTCCCCTTG

1441 Y F S C S V M H E A L H N H Y T Q K S L  
 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC  
 CAGAAGAGTA CGAGGCACTA CGTACTCCGA GACGTGTTGG TGATGTGCGT CTTCTCCGAG

1501 S L S P G K M A L I V L S G V A G L L L  
 TCCCTGTCTC CCGGAAAAT GGCCCTGATT GTGCTGGGGG GCGTCCCGCG CCTCCTGCTT  
 AGGGACAGAG GGCCTTTTA CCGGGACTAA CACGACCCCC CGCAGCGGCC GGAGGAGGAA

1561 F I G L G I F F R V K F S R S A D A P A  
 TTCATTGGGC TAGGCATCTT CTTCAGAGTG AAGTTCAGCA GGAGCGCAGA CCCCCCGCG  
 AAGTAACCCG ATCCGTAGAA GAAGTCTCAC TTCRAGTGGT CCTGCGCTCT GCGGGGGCGC

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
      ATGGTCGTCC 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 TCCCGGACAT 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 ACTTTCCGCT CGCGGCCTCC CCGTTCCCG 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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