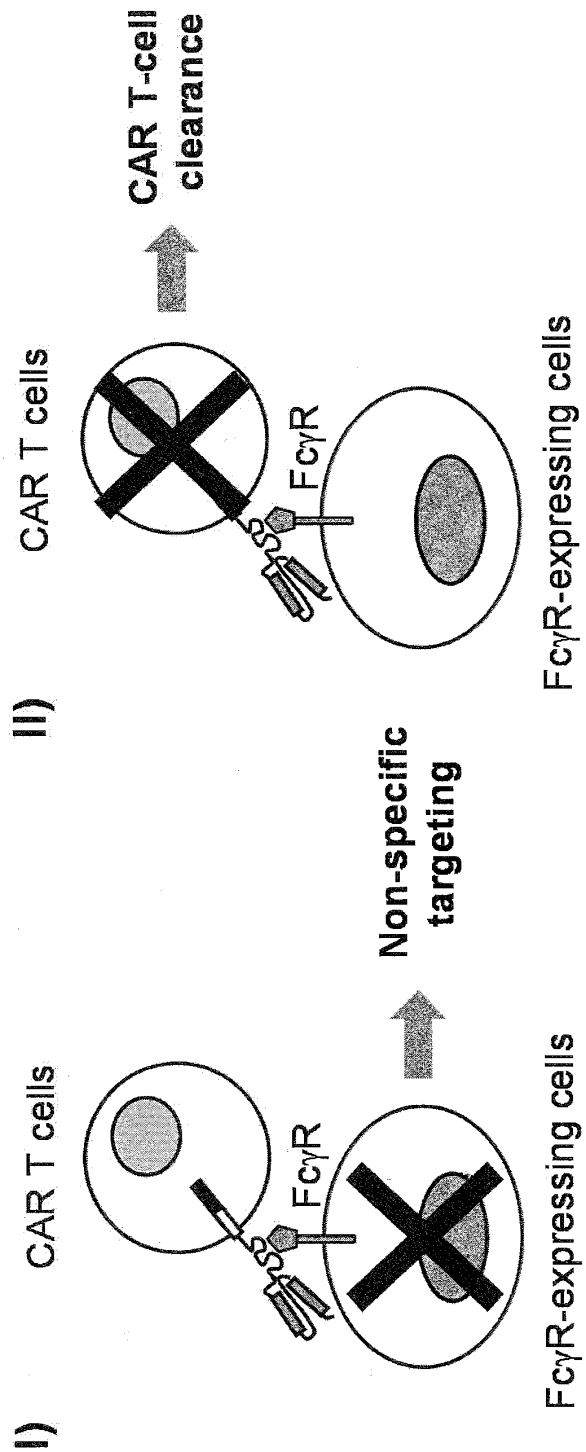

I)
CAR T cells
FcγR
FcγR-expressing cells
Non-specific targeting
II)
CAR T cells
FcγR
FcγR-expressing cells
CAR T-cell clearance

FIG. 1A

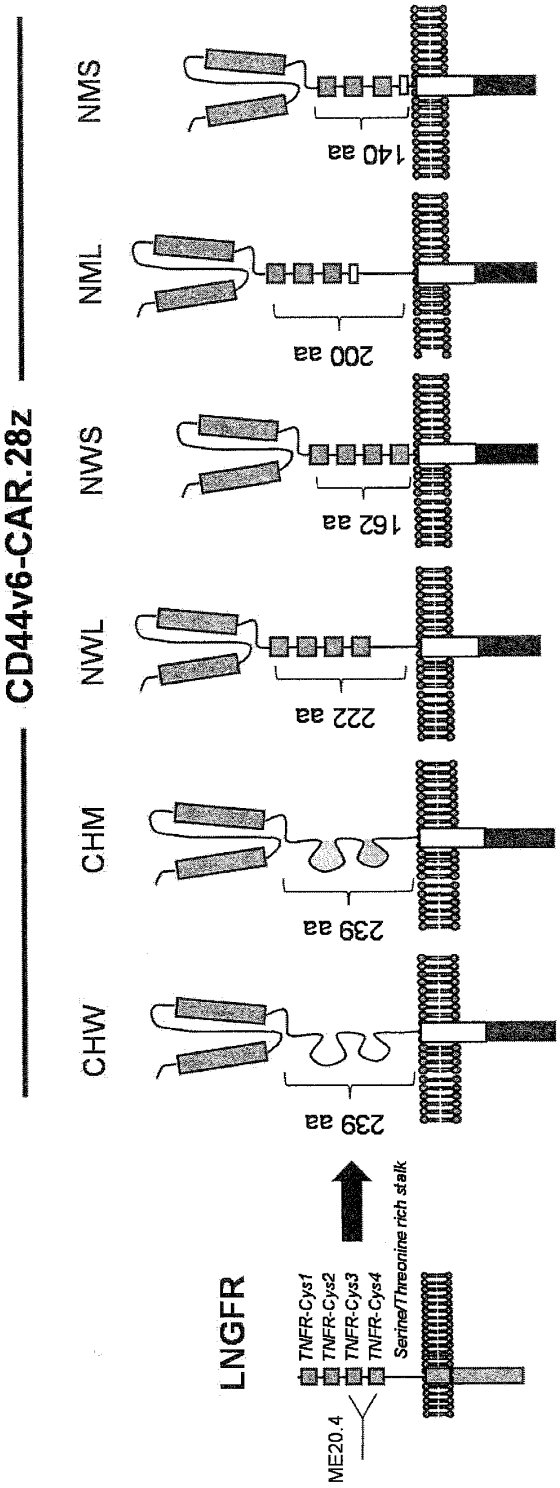

CD44v6-CAR.28z
CHW
CHM
NWL
NWS
NML
NMS
239 aa
239 aa
222 aa
162 aa
200 aa
140 aa
LNGFR
TNFR-Cys1
TNFR-Cys2
TNFR-Cys3
TNFR-Cys4
Serine/Threonine rich stalk
ME20.4

FIG. 1B

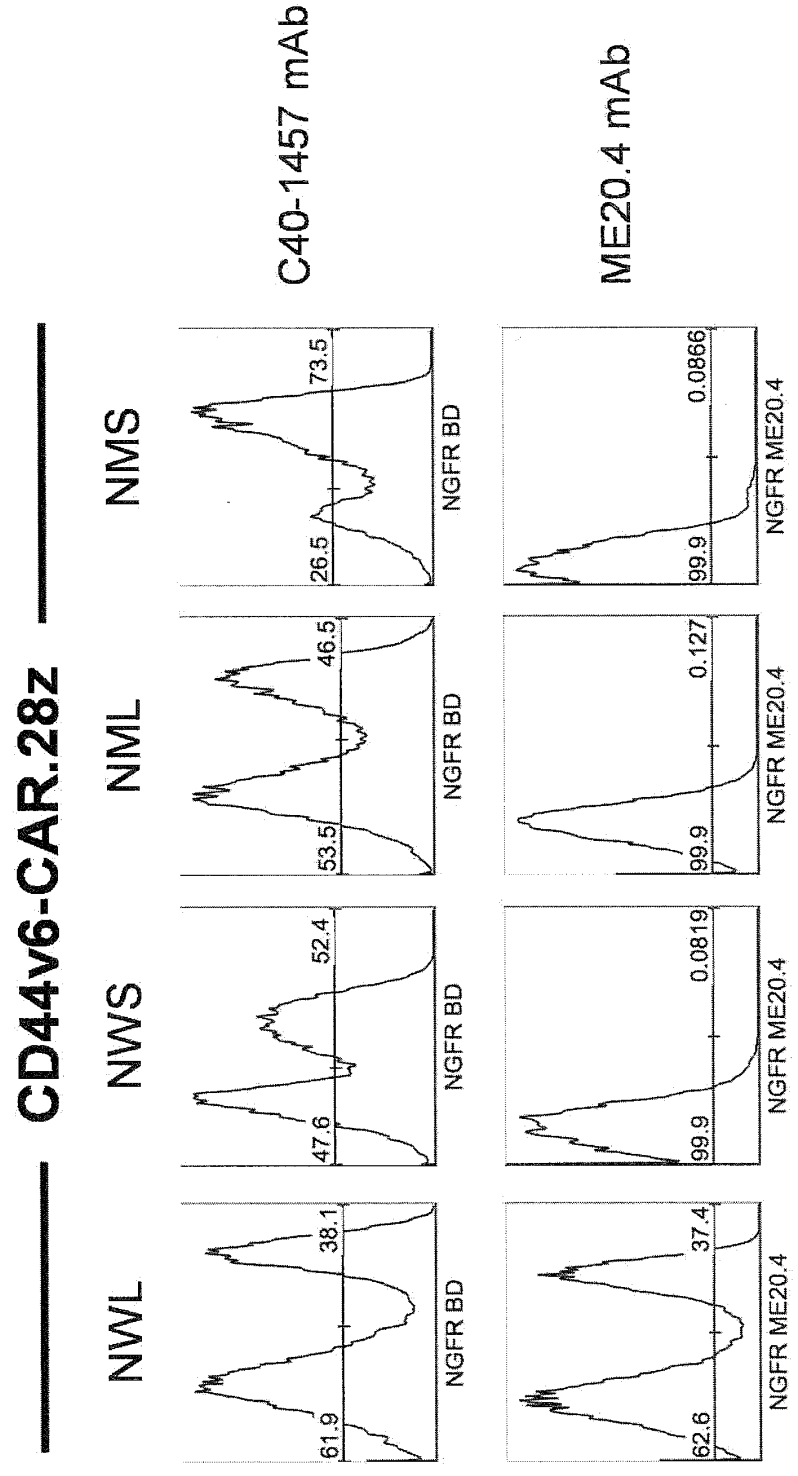

CD44v6-CAR.28z
NWL
NWS
NML
NMS
C40-1457 mAb
ME20.4 mAb
61.9
38.1
NGFR BD
47.6
52.4
NGFR BD
53.5
46.5
NGFR BD
26.5
73.5
NGFR BD
62.6
37.4
NGFR ME20.4
99.9
0.0819
NGFR ME20.4
99.9
0.127
NGFR ME20.4
99.9
0.0866
NGFR ME20.4

FIG. 2A

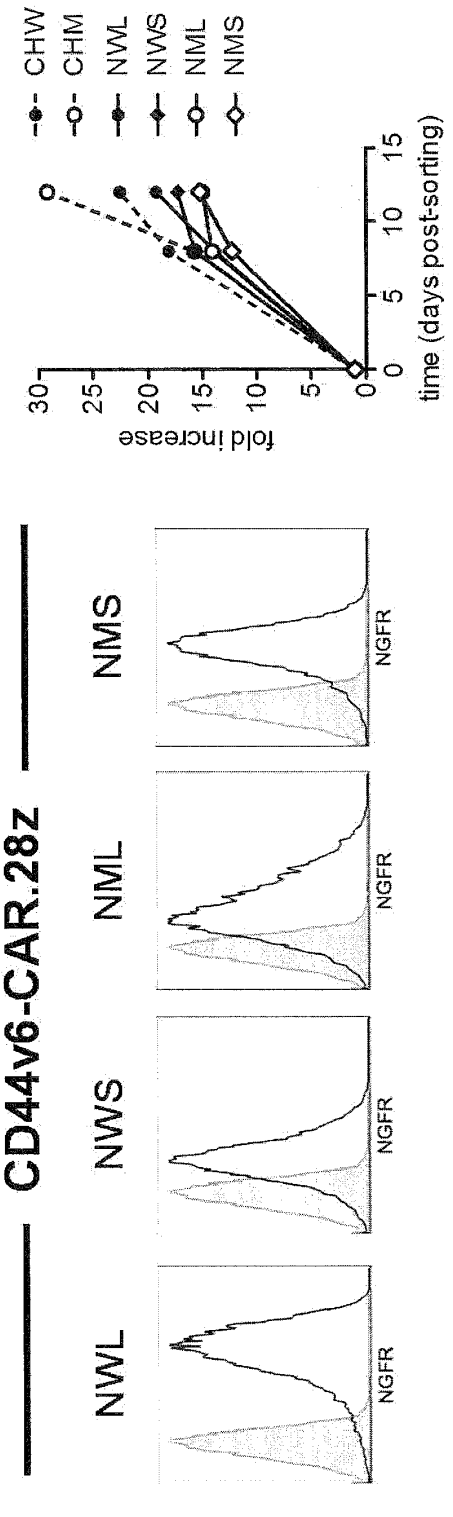

CD44v6-CAR.28z
NWL
NWS
NML
NMS
NGFR
NGFR
NGFR
NGFR
CHW
CHM
NWL
NWS
NML
NMS
fold increase
30
25
20
15
10
5
0
0
5
10
15
time (days post-sorting)

FIG. 2B

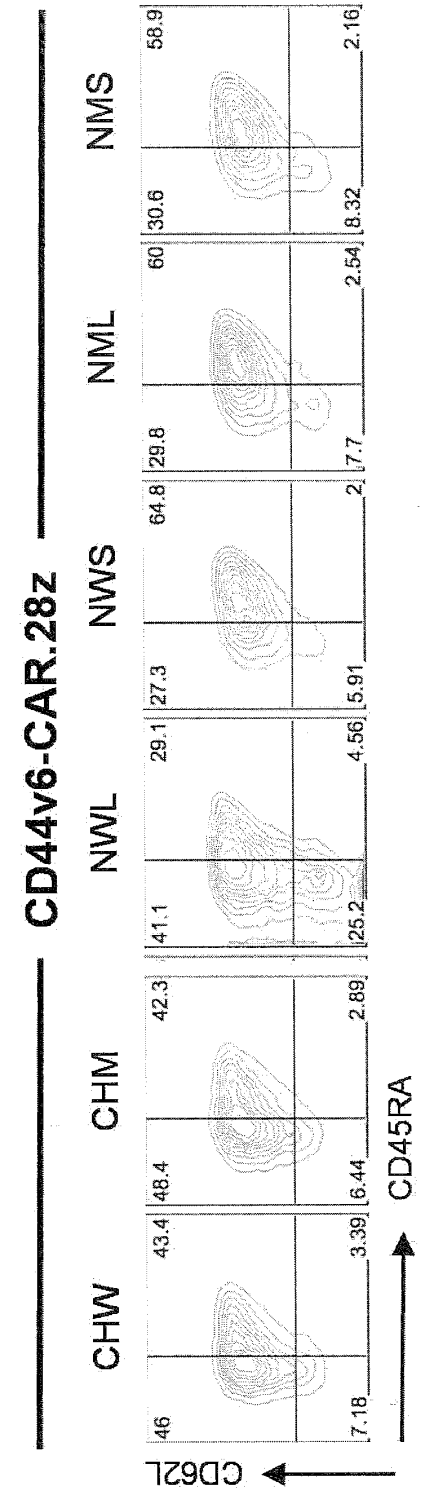

CD44v6-CAR.28z
CHW
CHM
NWL
NWS
NML
NMS
CD62L
CD45RA
46
43.4
48.4
42.3
41.1
29.1
27.3
64.8
29.8
60
30.6
58.9
7.18
3.39
6.44
2.89
25.2
4.56
5.91
2
7.7
2.54
8.32
2.16

FIG. 2C

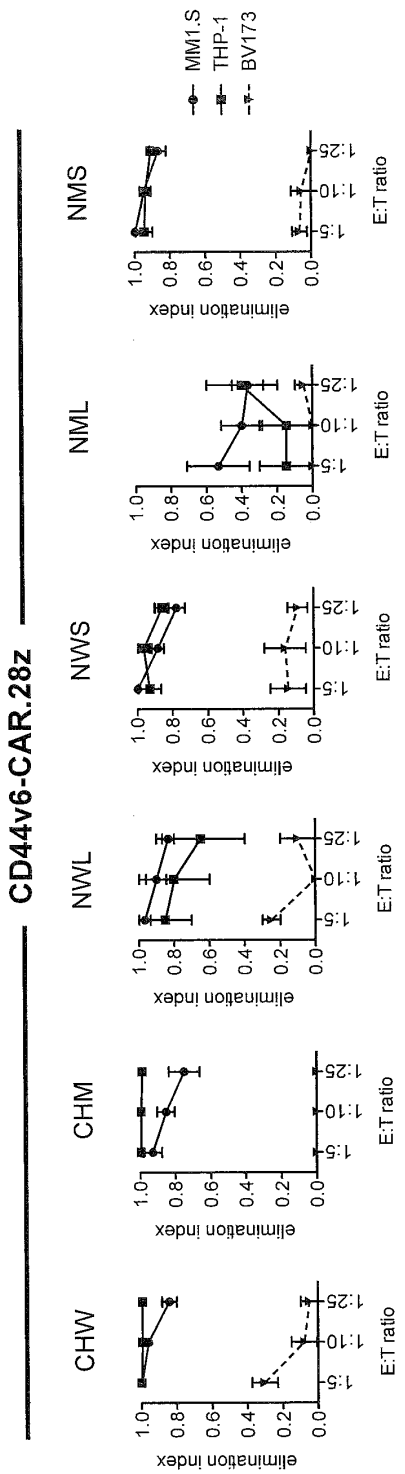

CD44v6-CAR.28z
CHW
CHM
NWL
NWS
NML
NMS
MM1.S
THP-1
BV173
elimination index
E:T ratio
1:5
1:10
1:25
0.0
0.2
0.4
0.6
0.8
1.0

FIG. 3A

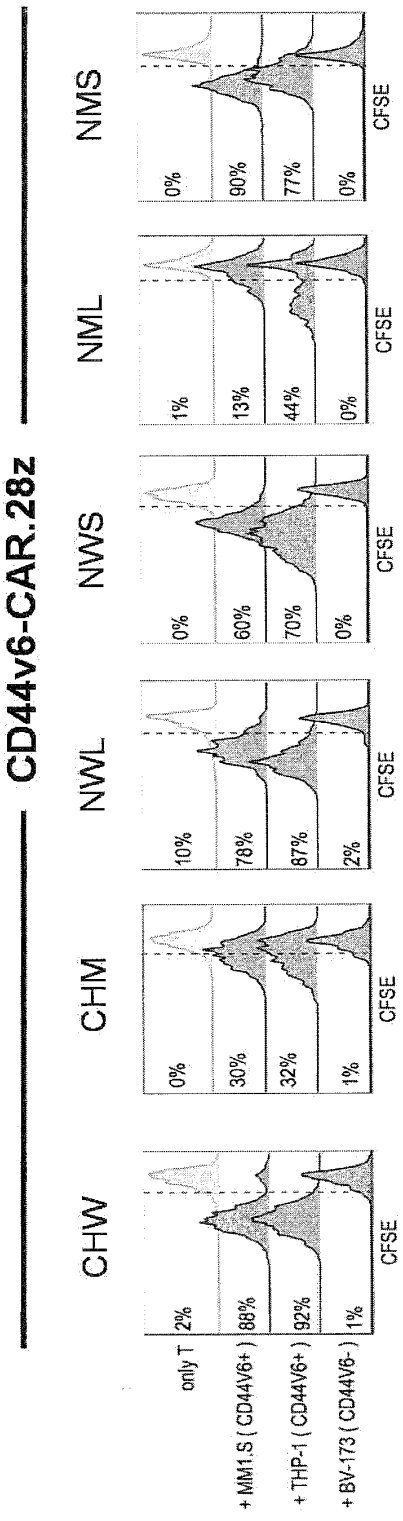

CD44v6-CAR.28z
CHW
CHM
NWL
NWS
NML
NMS
only T
+ MM1.S ( CD44V6+ )
+ THP-1 ( CD44V6+ )
+ BV-173 ( CD44V8- )
2%
88%
92%
1%
0%
30%
32%
1%
10%
78%
87%
2%
0%
60%
70%
0%
1%
13%
44%
0%
0%
90%
77%
0%
CFSE

FIG. 3B

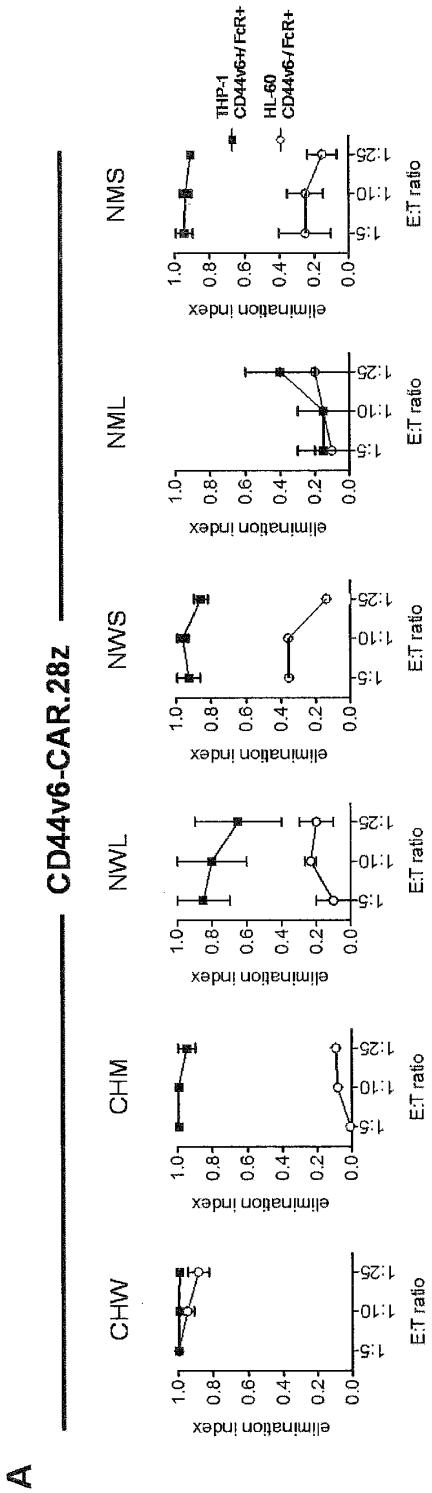

A
CD44v6-CAR.28z
CHW
CHM
NWL
NWS
NML
NMS
elimination index
E:T ratio
1:5
1:10
1:25
THP-1 CD44v6+/ FcR+
HL-60 CD44v6-/ FcR+
B
CD44v6-CAR.28z
+ THP-1 ( CD44V6+/ FcR+ )
+ HL-60 ( CD44V6-/ FcR+ )
+ BV-173 ( CD44V6-/ FcR- )
2%
92%
92%
32%
3%
1%
87%
8%
2%
70%
7%
0%
44%
0%
0%
77%
7%
0%
CFSE

FIG. 4

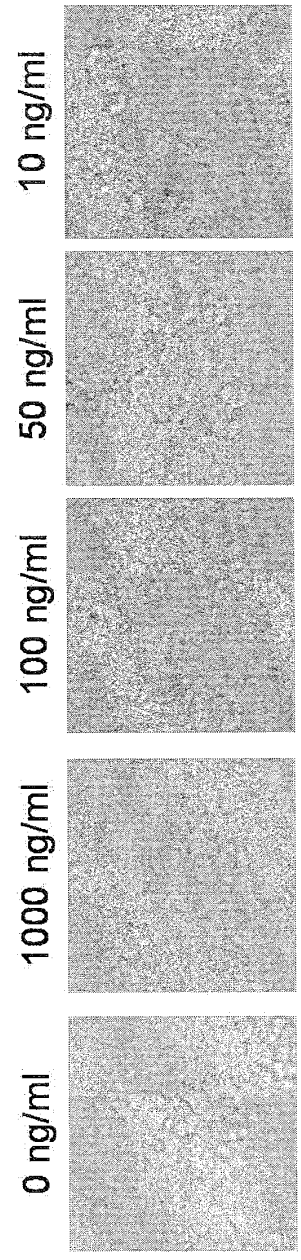



FIG. 5A

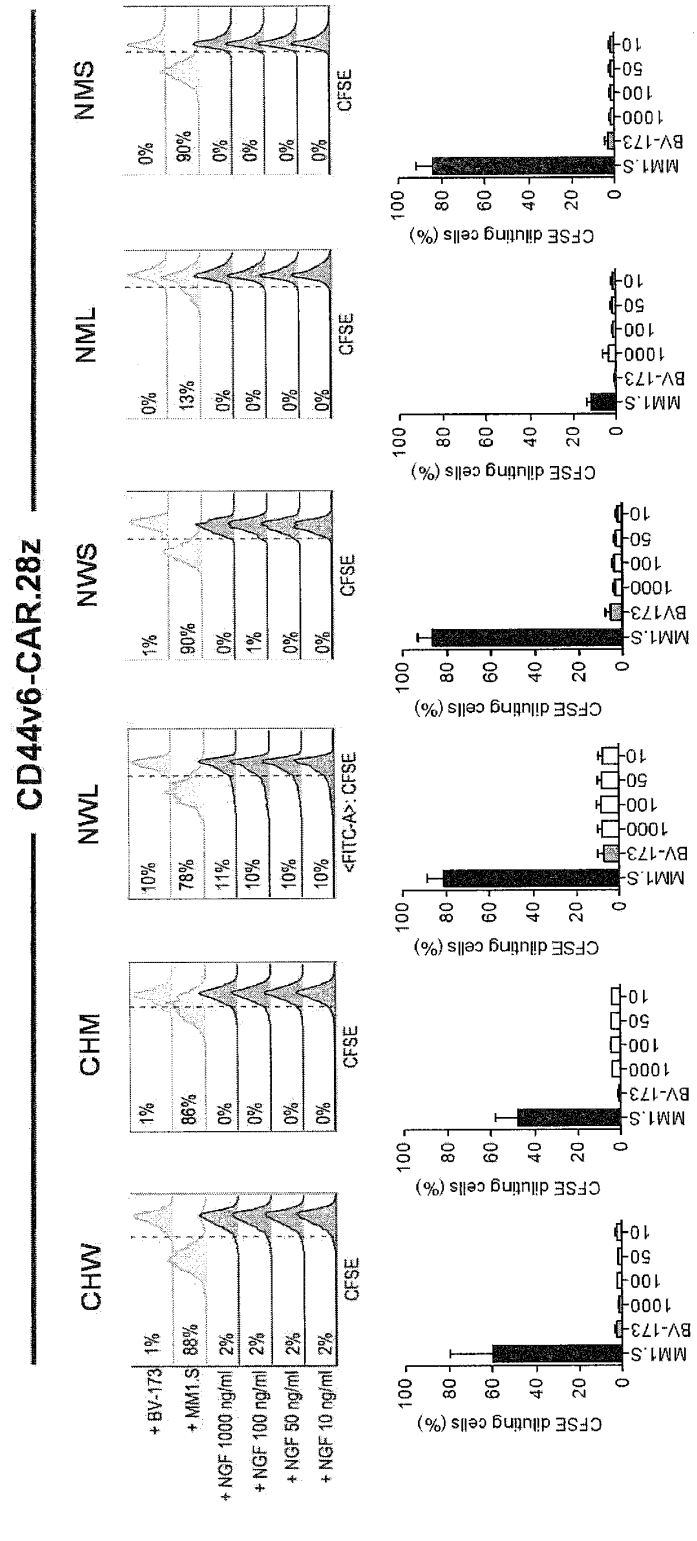

CD44v6-CAR.28z
CHW
CHM
NWL
NWS
NML
NMS
+ BV-173
+ MM1.S
+ NGF 1000 ng/ml
+ NGF 100 ng/ml
+ NGF 50 ng/ml
+ NGF 10 ng/ml
1%
88%
2%
2%
2%
2%
10%
78%
11%
10%
10%
10%
1%
90%
0%
1%
0%
0%
0%
13%
0%
0%
0%
0%
0%
90%
0%
0%
0%
0%
<FITC-A>: CFSE
CFSE
CFSE diluting cells (%)
MM1.S
BV-173
1000
100
50
10

FIG. 5B

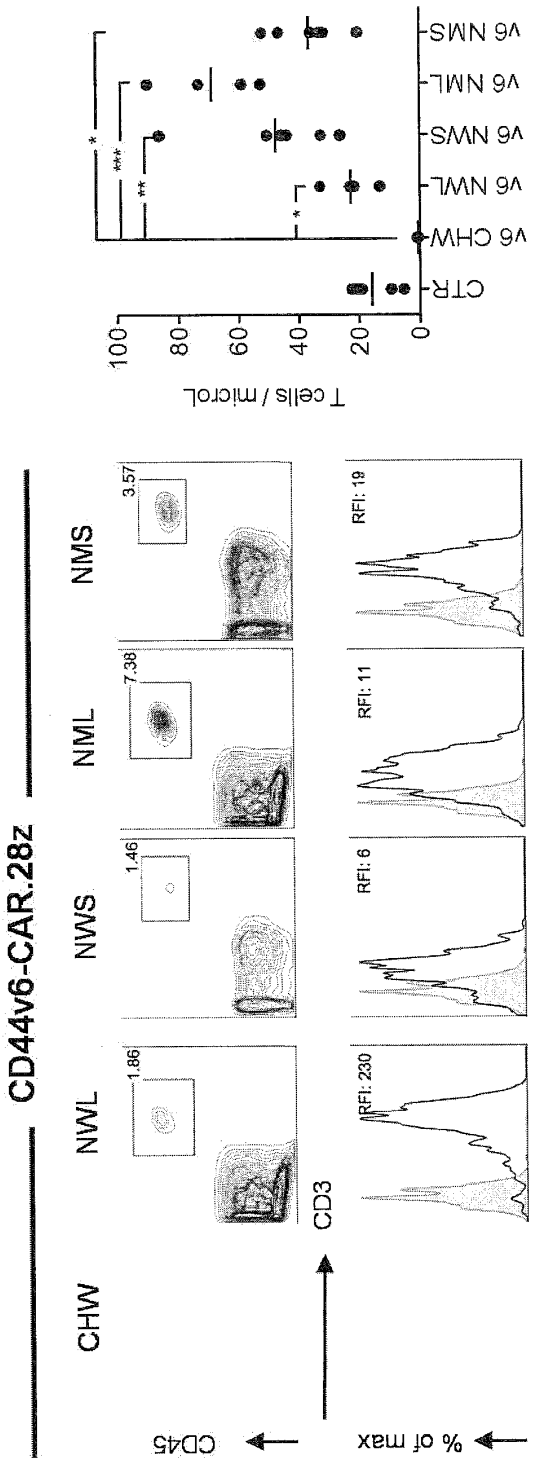
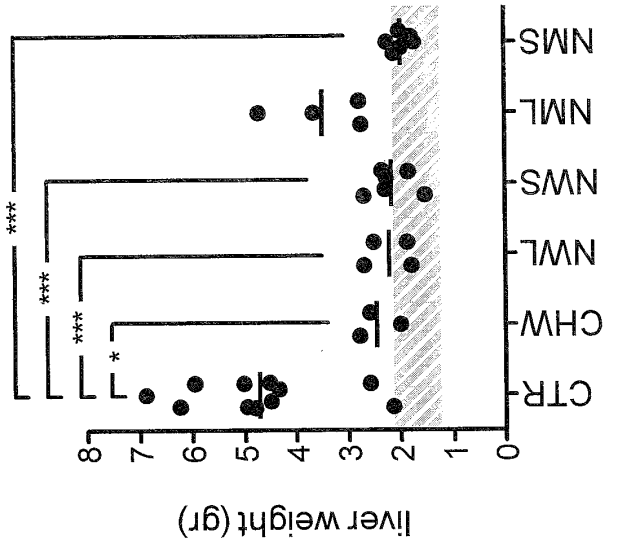

CD44v6-CAR.28z
CHW
NWL
NWS
NML
NMS
CD45
CD3
% of max
LNGFR
1.86
1.46
7.38
3.57
RFI: 230
RFI: 6
RFI: 11
RFI: 19
T cells / microL
100
80
60
40
20
0
CTR
v6 CHW
v6 NWL
v6 NWS
v6 NML
v6 NMS
*
**
***
*

FIG. 6A


C
liver weight (gr)
0
1
2
3
4
5
6
7
8
CTR
CHW
NWL
NWS
NML
NMS
*
***
***
***

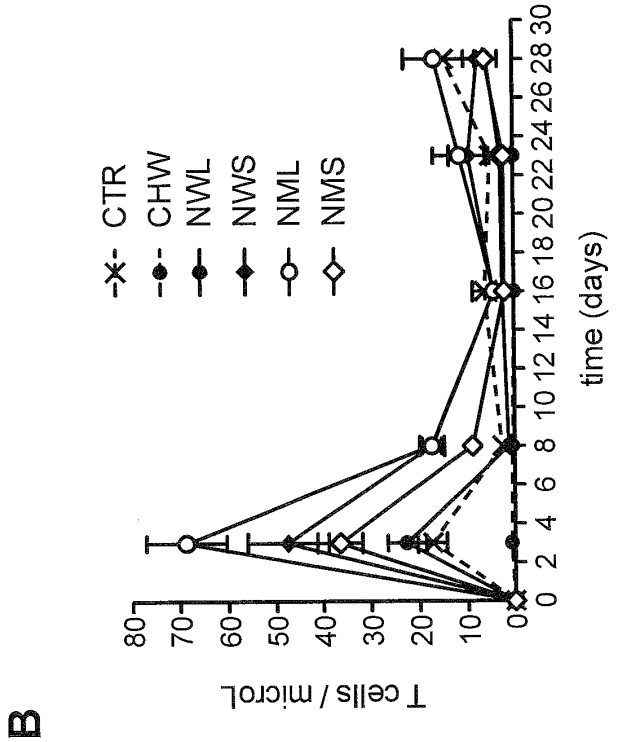

B
T cells / microL
0
10
20
30
40
50
60
70
80
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
time (days)
CTR
CHW
NWL
NWS
NML
NMS

FIG. 6B-C

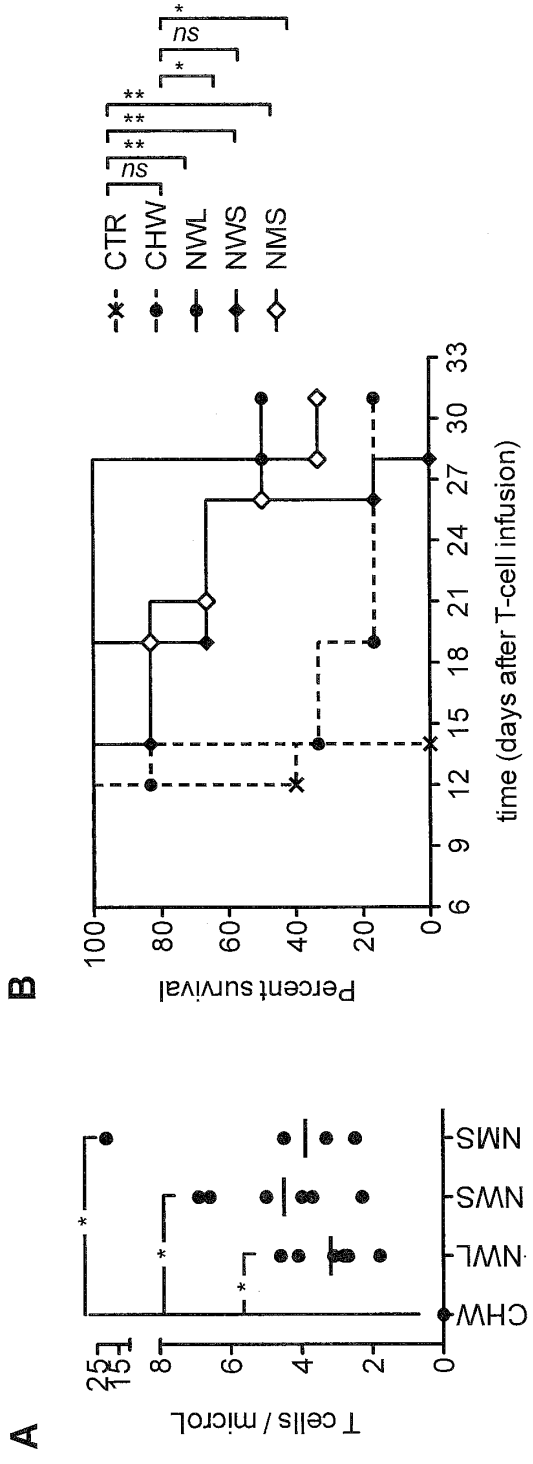

A
T cells / microL
0
2
4
6
8
15
25
CHW
NWL
NWS
NMS
*
B
Percent survival
0
20
40
60
80
100
6
9
12
15
18
21
24
27
30
33
time (days after T-cell infusion)
CTR
CHW
NWL
NWS
NMS
ns
**
**
**
*
ns
*

FIG. 7

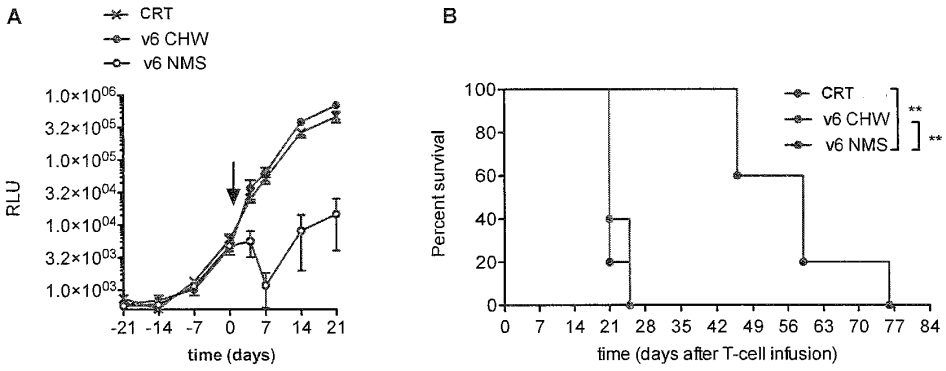

A
CRT
v6 CHW
v6 NMS
RLU
1.0×10^06
3.2×10^05
1.0×10^05
3.2×10^04
1.0×10^04
3.2×10^03
1.0×10^03
-21 -14 -7 0 7 14 21
time (days)
B
Percent survival
100
80
60
40
20
0
CRT
v6 CHW
v6 NMS
**
**
0 7 14 21 28 35 42 49 56 63 70 77 84
time (days after T-cell infusion)

Figure 7BIS

```
        10         20         30         40         50         60
MGAGATGRAM DGPRLLLLLL LGVSLGGAKE ACPTGLYTHS GECCKACNLG EGVAQPCGAN

        70         80         90        100        110        120
QTVCEPCLDS VTFSDVVSAT EPCKPCTECV GLQSMSAPCV EADDAVCRCA YGYYQDETTG

       130        140        150        160        170        180
RCEACRVCEA GSGLVFSCQD KQNTVCEECP DGTYSDEANH VDPCLPCTVC EDTERQLREC

       190        200        210        220        230        240
TRWADAECEE IPGRWITRST PPEGSDSTAP STQEPEAPPE QDLIASTVAG VVTTVMGSSQ

       250        260        270        280        290        300
PVVTRGTTDN LIPVYCSILA AVVVGLVAYI AFKRWNSCKQ NKQGANSRPV NQTPPPEGEK

       310        320        330        340        350        360
LHSDSGISVD SQSLHDQQPH TQTASGQALK GDGGLYSSLP PAKREEVEKL LNGSAGDTWR

       370        380        390        400        410        420
HLAGELGYQP EHIDSFTHEA CPVRALLASW ATQDSATLDA LLAALRRIQR ADLVESLCSE


STATSPV
```

**FIG. 8** (SEQ ID NO:14)

**FIG. 9** - CD44v6CAR.28z (SEQ ID NO: 15)

**Nucleotides**

**ATGGAAGCCCCTGCCCAGCTGCTGTTCCTGCTGCTGCTGTGGCTGCCCGACAC**
**CACCGGCGAGATCGTGCTGACACAGAGCCCCGCCACCCTGTCTCTGAGCCCTG**
**GCGAGAGAGCCACCCTGAGCTGTAGCGCCAGCAGCAGCATCAACTACATCTAC**
**TGGCTGCAGCAGAAGCCCGGCCAGGCCCCCAGAATCCTGATCTACCTGACCAG**
**CAACCTGGCCAGCGGCGTGCCCGCCAGATTTTCTGGCAGCGGCAGCGGCACCG**
**ACTTCACCCTGACCATCAGCAGCCTGGAACCCGAGGACTTCGCCGTGTACTAC**
**TGCCTGCAGTGGTCCAGCAACCCCCTGACCTTCGGCGGAGGCACCAAGGTGGA**
**AATCAAGCGGGGTGGTGGTGGTTCTGGTGGTGGTGGTTCTGGCGGCGGCGGCT**
**CCGGTGGTGGTGGATCTGAGGTGCAGCTGGTGGAAAGCGGCGGAGGCCTGGTC**
**AAGCCTGGCGGCAGCCTGAGACTGAGCTGTGCCGCCAGCGGCTTCACCTTCAG**
**CAGCTACGACATGAGCTGGGTCCGACAGGCTCCAGGCAAGGGACTGGAATGGG**
**TGTCCACCATCAGCAGCGGCGGCAGCTACACCTACTACCTGGACAGCATCAAG**
**GGCCGGTTCACCATCAGCCGGGACAACGCCAAGAACAGCCTGTACCTGCAGAT**
**GAACAGCCTGCGGGCCGAGGACACCGCCGTCTACTACTGTGCCCGGCAGGGCC**
**TCGACTACTGGGGCAGAGGCACCCTGGTCACCGTGTC***CAGCGGGGATCCCGCC*
*GAGCCCAAATCTCCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGA*
*ACTCCTGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCC*
*TCATGATCTCCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCAC*
*GAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAA*
*TGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTCA*
*GCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC*
*AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGC*
*CAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATG*
*AGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCC*
*AGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAACCGGAGAACAACTACAA*
*GACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGC*
*TCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTG*
*ATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTC*C
GGGTAAAAAAG**ATCCCAAATTTTGGGTGCTGGTGGTGGTTGGTGGAGTCCTGG**
**CTTGCTATAGCTTGCTAGTAACAGTGGCCTTTATTATTTTCTGGGTGAGGAGT**
**AAGAGGAGCAGGCTCCTGCACAGTGACTACATGAACATGACTCCCCGCCGCCC**
**CGGGCCCACCCGCAAGCATTACCAGCCCTATGCCCCACCACGCGACTTCGCAG**
**CCT***ATCGCTCCAGAGTGAAGTTCAGCAGGAGCGCAGACGCCCCCGCGTACCAG*
*CAGGGCCAGAACCAGCTCTATAACGAGCTCAATCTAGGACGAAGAGAGGAGTA*
*CGATGTTTTGGACAAGAGACGTGGCCGGGACCCTGAGATGGGGGGAAAGCCGA*
*GAAGGAAGAACCCTCAGGAAGGCCTGTACAATGAACTGCAGAAAGATAAGATG*
*GCGGAGGCCTACAGTGAGATTGGGATGAAAGGCGAGCGCCGGAGGGGCAAGGG*
*GCACGATGGCCTTTACCAGGGTCTCAGTACAGCCACCAAGGACACCTACGACG*
*CCCTTCACATGCAGGCCCTGCCCCCTCGCTAA*

**Protein** (SEQ ID NO: 16)

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSSINYIY**
**WLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSLEPEDFAVYY**
**CLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGSGGGGSEVQLVESGGGLV**
**KPGGSLRLSCAASGFTFSSYDMSWVRQAPGKGLEWVSTISSGGSYTYYLDSIK**

**GRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQGLDYWGRGTLVTVSS**GDP*A*
*EPKSPDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH*
*EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC*
*KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYP*
*SDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV*
*MHEALHNHYTQKSLSLSPGKKD*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVRS**
**KRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQ*
*QGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKM*
*AEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR*

Features :
**SCFV**
*CH2CH3*
**CD28**
*zeta chain*

FIG. 10 - CD44v6-CAR28z with spacer LNGFR wild-type long (NWL)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWA*
*DAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVV*
*TTVMGSSQPVVTRGTTDN*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVR**
**SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSR*
*SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQR*
*RKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTA*
*TKDTYDALHMQALPPR*

**Legend**

**CD44v6-specific single-chain fragment**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-250)

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143)

FIG. 11 - CD44v6-CAR28z with spacer LNGFR wild-type short (NWS)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWA*
*DAECEE*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY**
**MNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQQG*
*QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNE*
*LQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQ*
*ALPPR*

**Legend**

**CD44v6-specific single-chain fragment**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-190).

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143)

FIG. 12 - CD44v6-CAR28z with spacer LNGFR mutated long (NML)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEA**ARA**ADAECEEIPGRWITRSTPPEGSDS*
*TAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDN*PK**FW**
**VLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP**
**TRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQQGQNQLYNELNLG*
*RREEYDVLDKRRGRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYS*
*EIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR*

## Legend

### CD44v6-specific single-chain fragment

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-250). **Bold**: amminoacids that, in the mutated version, has been substituted to the original residues (deleted aa: NHVDPCLPCTVCEDTERQLRECTRW))

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143)

FIG. 13 - CD44v6-CAR28z with spacer LNGFR mutated short (NMS)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GD*PKEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEA**ARA**ADAECEE*PK**FWVLVVVGGVLACY**
**SLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPR**
**DFAAYRS***RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRR*
*GRDPEMGGKPQRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRG*
*KGHDGLYQGLSTATKDTYDALHMQALPPR*

## Legend

### CD44v6-specific single-chain fragment

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-190). **Bold**: amminoacids that, in the mutated version, has been substituted to the original residues (deleted aa: NHVDPCLPCTVCEDTERQLRECTRW)).

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220)).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-14)

FIG. 14 - CD44v6-CAR28z with spacer LNGFR wild-type long (NWL)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWA*
*DAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVV*
*TTVMGSSQPVVTRGTTDN*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVR**
**SKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSR*
*SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRK*
*NPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK*
*DTYDALHMQALPPR*

**Legend**

**CD44v6-specific single-chain fragment**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-250)

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80))

FIG. 15 - CD44v6-CAR28z with spacer LNGFR wild-type short (NWS)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEANHVDPCLPCTVCEDTERQLRECTRWA*
*DAECEE*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDY**
**MNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQQG*
*QNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNEL*
*QKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQA*
*LPPR*

**Legend**

**CD44v6-specific single-chain fragment**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-190).

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80))

FIG. 16 - CD44v6-CAR28z with spacer LNGFR mutated long (NML)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEA**ARA**ADAECEEIPGRWITRSTPPEGSDS*
*TAPSTQEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDN*PK**FW**
**VLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGP**
**TRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQQGQNQLYNELNLG*
*RREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSE*
*IGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR*

## Legend

### CD44v6-specific single-chain fragment

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-250). **Bold**: amminoacids that, in the mutated version, has been substituted to the original residues (deleted aa: NHVDPCLPCTVCEDTERQLRECTRW))

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80))

FIG. 17 - CD44v6-CAR28z with spacer LNGFR mutated short (NMS)

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSS**
**INYIYWLQQKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSL**
**EPEDFAVYYCLQWSSNPLTFGGGTKVEIKRGGGGSGGGGSGGGGS**
**GGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTFSSYDMSWVRQA**
**PGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMNSLRA**
**EDTAVYYCARQGLDYWGRGTLVTVSS**GD*PKEACPTGLYTHSGECCK*
*ACNLGEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGL*
*QSMSAPCVEADDAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSC*
*QDKQNTVCEECPDGTYSDEA**ARA**ADAECEE*PK**FWVLVVVGGVLACY**
**SLLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPR**
**DFAAYRS***RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRR*
*GRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGK*
*GHDGLYQGLSTATKDTYDALHMQALPPR*

## Legend

### CD44v6-specific single-chain fragment

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-190). **Bold**: amminoacids that, in the mutated version, has been substituted to the original residues (deleted aa: NHVDPCLPCTVCEDTERQLRECTRW)).

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220)).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80))

**Figure 18 - CD44v6-4GS2-CAR28z with spacer LNGFR wild-type long (NWL)**

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSSINYIYWLQ**
**QKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCLQWSS**
**NPLTFGGGTKVEIKRGGGGSGGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTF**
**SSYDMSWVRQAPGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMN**
**SLRAEDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCKACNL*
*GEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEAD*
*DAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE*
*ANHVDPCLPCTVCEDTERQLRECTRWADAECEEIPGRWITRSTPPEGSDSTAPST*
*QEPEAPPEQDLIASTVAGVVTTVMGSSQPVVTRGTTDN*PK**FWVLVVVGGVLACYS**
**LLVTVAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RV*
*KFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQ*
*EGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQAL*
*PPR*

**Legend**

**CD44v6-4GS2: a CD44v6-specific single-chain fragment (SEQ. ID NO 31)**

*LNGFR (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-250)*

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220)

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80)

**Figure 19 - CD44v6-4GS2-CAR28z with spacer LNGFR wild-type short (NWS)**

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSSINYIYWLQ**
**QKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCLQWSS**
**NPLTFGGGTKVEIKRGGGGSGGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTF**
**SSYDMSWVRQAPGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMN**
**SLRAEDTAVYYCARQGLDYWGRGTLVTVSS**GDPKEACPTGLYTHSGECCKACNL
GEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEAD
DAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE
ANHVDPCLPCTVCEDTERQLRECTRWADAECEEPK**FWVLVVVGGVLACYSLLVT**
**VAFIIFWVRSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSR*
*SADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLY*
*NELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR*

**Legend**

**CD44v6-4GS2: a CD44v6-specific single-chain fragment (SEQ ID NO 31)**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-190).

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220)

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80)

**Figure 20 - CD44v6-4GS2-CAR28z with spacer LNGFR mutated long (NML)**

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSSINYIYWLQ**
**QKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCLQWSS**
**NPLTFGGGTKVEIKRGGGGSGGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTF**
**SSYDMSWVRQAPGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMN**
**SLRAEDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCKACNL*
*GEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEAD*
*DAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE*
*A**ARA**ADAECEEIPGRWITRSTPPEGSDSTAPSTQEPEAPPEQDLIASTVAGVVTTV*
*MGSSQPVVTRGTTDN*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSD**
**YMNMTPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQQGQNQLYNE*
*LNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGM*
*KGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR*

**Legend**

**CD44v6-4GS2: a CD44v6-specific single-chain fragment (SEQ ID NO 31)**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-250). **Bold**: amminoacids that, in the mutated version, has been substituted to the original residues (deleted aa: NHVDPCLPCTVCEDTERQLRECTRW))

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80))

**Figure 21 - CD44v6-4GS2-CAR28z with spacer LNGFR mutated short (NMS)**

Protein sequence

**MEAPAQLLFLLLLWLPDTTGEIVLTQSPATLSLSPGERATLSCSASSSINYIYWLQ**
**QKPGQAPRILIYLTSNLASGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCLQWSS**
**NPLTFGGGTKVEIKRGGGGSGGGGSEVQLVESGGGLVKPGGSLRLSCAASGFTF**
**SSYDMSWVRQAPGKGLEWVSTISSGGSYTYYLDSIKGRFTISRDNAKNSLYLQMN**
**SLRAEDTAVYYCARQGLDYWGRGTLVTVSS**GDP*KEACPTGLYTHSGECCKACNL*
*GEGVAQPCGANQTVCEPCLDSVTFSDVVSATEPCKPCTECVGLQSMSAPCVEAD*
*DAVCRCAYGYYQDETTGRCEACRVCEAGSGLVFSCQDKQNTVCEECPDGTYSDE*
*A**ARA**ADAECEE*PK**FWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSDYMNM**
**TPRRPGPTRKHYQPYAPPRDFAAYRS***RVKFSRSADAPAYQQGQNQLYNELNLGR*
*REEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERI*
*GKGHDGLYQGLSTATKDTYDALHMQALPPR*

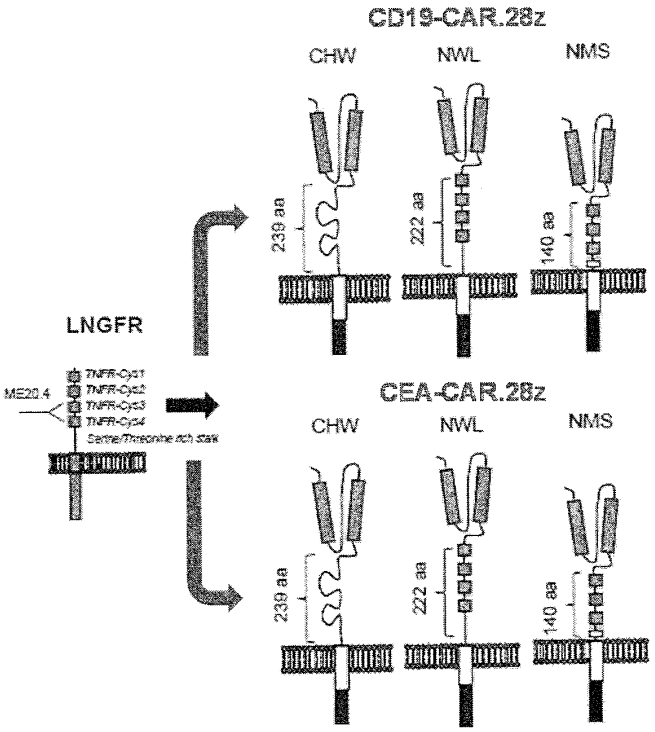
**Legend**

**CD44v6-4GS2: a CD44v6-specific single-chain fragment (SEQ ID NO 31)**

*LNGFR* (sequence taken from the UNIPROT database (P08138, TNR16_HUMAN, position 29-190). **Bold**: amminoacids that, in the mutated version, has been substituted to the original residues (deleted aa: NHVDPCLPCTVCEDTERQLRECTRW).

**CD28** (sequence taken from the UNIPROT database (P10747, CD28_HUMAN, position 153-220).

*CD3 zeta-chain* (sequence taken from the UNIPROT database (P20963, CD3Z_HUMAN, position 31-143, without Q at position 80)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CHW
NWL
NMS
239 aa
222 aa
140 aa
LNGFR
ME20.4
TNFR-Cys1
TNFR-Cys2
TNFR-Cys3
TNFR-Cys4
Serine/Threonine rich stalk
CEA-CAR.28z
CHW
NWL
NMS
239 aa
222 aa
140 aa

Figure 22

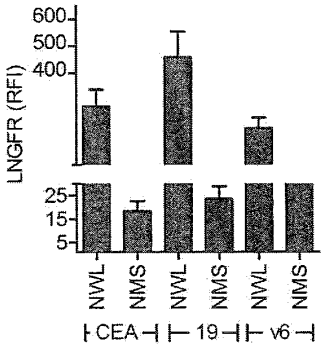
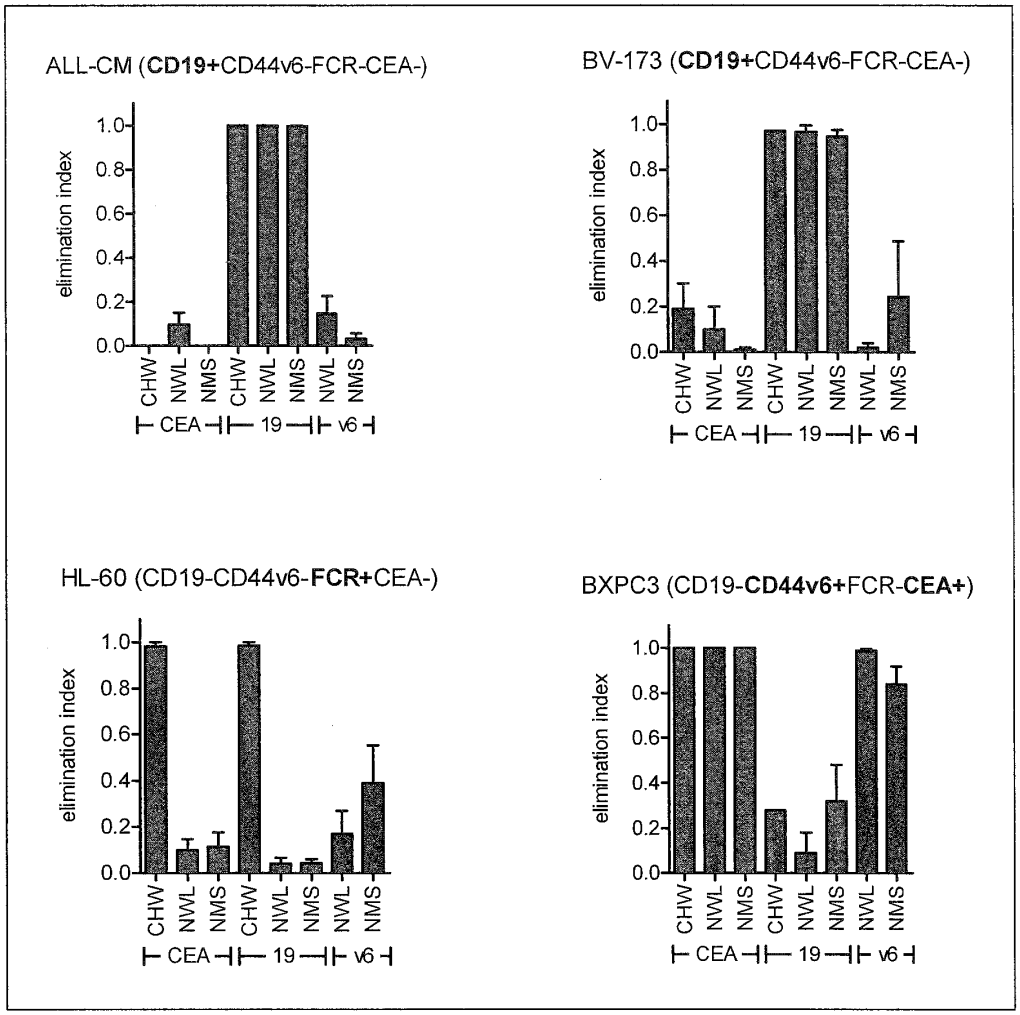



Figure 23

A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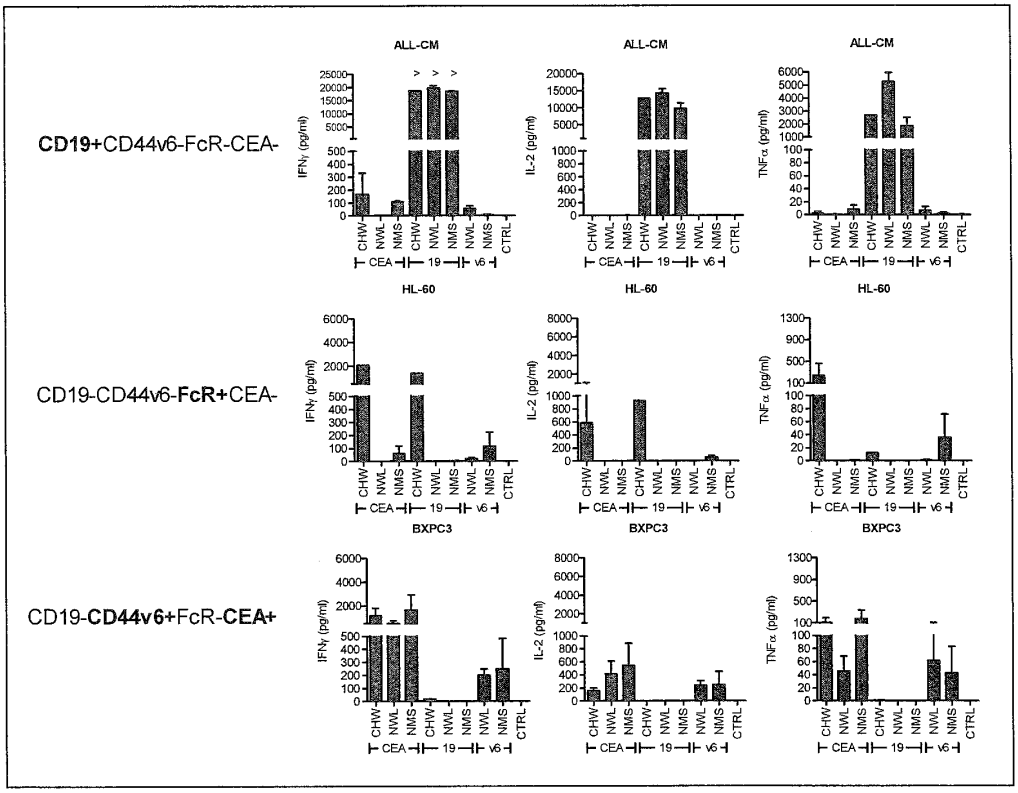
BV-173 (CD19+CD44v6-FCR-CEA-)
HL-60 (CD19-CD44v6-FCR+CEA-)
BXPC3 (CD19-CD44v6+FCR-CEA+)
elimination index
1.0
0.8
0.6
0.4
0.2
0.0
CHW
NWL
NMS
CEA
19
v6

Figure 24

B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CD19-CD44v6-FcR+CEA-
CD19-CD44v6+FcR-CEA+
ALL-CM
HL-60
BXPC3
IFNγ (pg/ml)
IL-2 (pg/ml)
TNFα (pg/ml)
CHW
NWL
NMS
CTRL
CEA
19
v6

Figure 24

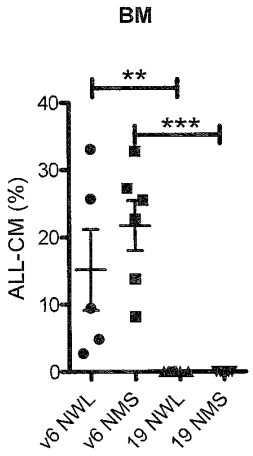


Figure 25

Figure 26

CD44v6-4GS2-CAR.28Z NGFR WILD TYPE LONG (V6 NWL) dna.gb

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Figure 27

CD44V6-4GS2-CAR.28Z NGFR WILD TYPE SHORT (V6 NWS) dna.gb

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Figure 28

CD44v6-4GS2-CAR.28Z NGFR MUTATED LONG (V6 NML) dna.gbb

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Figure 29

CD44v6-4GS2-CAR.28Z NGFR MUTATED SHORT (V6 NMS) dna.gb

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