

FIGURE 1

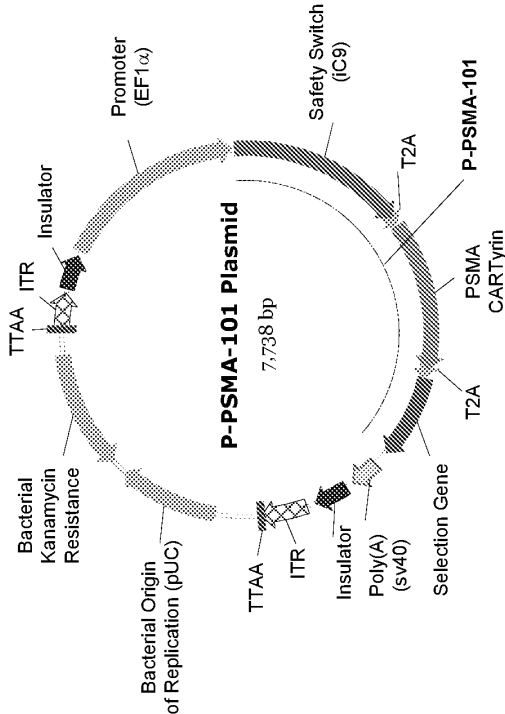


FIGURE 2

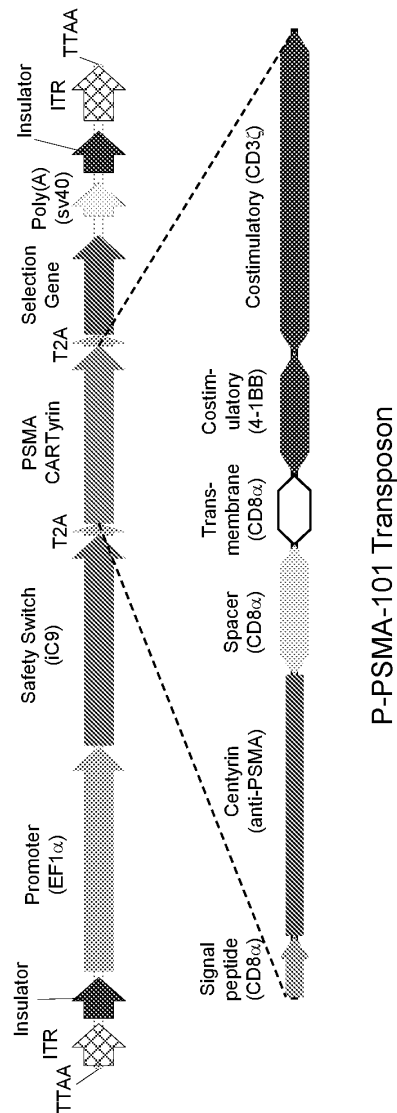


FIGURE 3A

**PSMA5 CARTYRIN:**  
SIGNAL PEPTIDE: MALPVTALLPLALLHAARP (SEQ ID NO: 18004)  
CENTYRIN (PSMA5):  
MLPAPKNLVVSRVTEDSARLSWDIDEQRDWFESFLIQYQSEKVGAEIVLTPGSESYDLTGLKPGTEYTVSYGV  
YHVYRSNPLSAFTT (SEQ ID NO: 18000)  
HINGE (CD8<sub>α</sub>): TTTAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 18014)  
TRANSMEMBRANE (CD8<sub>α</sub>): IYWAPLAGTCGVLLSLVITLYC (SEQ ID NO: 18006)  
COSTIMULATORY DOMAIN #1 (4-1BB): KRGRKKLLYIFKQPFMRPVQTTQEEEDGCSRCRFEEEEGGCEL (SEQ  
ID NO: 18012)  
COSTIMULATORY DOMAIN #2 (CD3<sub>ζ</sub>):  
RVKFSRSADAPAYKQGQNLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEI  
GMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 18008)

**P-PSMA5-101 CONSTRUCT:**  
MALPVTALLPLALLHAARPMLPAPKNLVVSRVTEDSARLSWDIDEQRDWFESFLIQYQSEKVGAEIVLTPGSE  
RSYDLTGLKPGTEYTVSYGVYHVYRSNPLSAFTTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD  
FACDIYWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEEDGCSRCRFEEEEGGCELRVKFSRS  
ADAPAYKQGQNLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGER  
RRKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 18063)

FIGURE 3B

**PSMA5 CARTYRIN:**  
**SIGNAL PEPTIDE:**  
ATGGCACTGCCTGTGACAGCCCTGCTGCTGCCTCTGGCCCTGCTGCTGCACGCACACGGGCC  
(SEQ ID NO: 18064)  
**CENTYRIN (PSMA5):**  
ATGCTGCTGCACCAAGAAACCTGGTGGTGTCTCGGGTGACCGAGGACTCTGCCAGACTGAGCTGGGACATC  
GATGAGCAGAGGATTGGTTGAGAGCTTTCTGATCCAGTATCAGGAGTCCGAGAAATGGCGAGGCCATC  
GTGCTGACAGTGCTGGCAGCGCGGTCTATGACCTGACCGGCTGAAGCCAGGCACAGATACACCGT  
GTCCATCTACGGGTGTATCACGTGTACAGGTCCAACTCTCTGTCTGCCATCTTACCACA  
(SEQ ID NO: 18001)  
**HINGE (CD8<sub>α</sub>):**  
ACCACAACCCCTGCCCCCGAGACCTCCACACCCGCCCTACCATCGGAGCCAGCCACTGTCCCTGCGGCCT  
GAGCCCTGCCGCCGCCGCCGCGGAGCAGTGCAACACGGGGCTGGACTTTGCCTGTGAC  
(SEQ ID NO: 18065)  
**TRANSMEMBRANE (CD8<sub>α</sub>):**  
ATCTACATATGGGCACCAC TGGCAGGAACCTGCGGCGTGCTGCTGCTGAGCCTGGTCATCACCCCTGTACTGT  
(SEQ ID NO: 18066)  
**COSTIMULATORY DOMAIN #1 (4-1BB):**  
AAGAGAGCGCAGGAAGAGCTGCTGTATATCTTCAAGCAGCCCTTCATGAGACCCGTGCAGACCACACAGGAG  
GAGGACGGCTGCTCTGTAGGTTCCACAGAGGAGGAGGGAGGATGCCGAGCTG (SEQ ID NO: 18067)  
**COSTIMULATORY DOMAIN #2 (CD3<sub>ε</sub>):**  
CGCGTGAAGTTTAGCCGGTCCGCGATGCACCTGCATACAAAGCAGGGACAGAACAGCTGTATAACGAGCTG  
AATCTGGGCCGGAGAGAGGAGTACGACGTGCTGGATAAGAGGCGGGGCCCGGACCCCGAGATGGAGGCA  
AGCCTCGGAGAAAGAACCCACAGGAGGCGCTGTACAATGAGCTGCAAAAGGACAAAGATGCCCGAGGCCATT  
CTGAGATCGGATGAAGGAGAGAGGCGCCGGGCAAGGGACAGCATGGCCTGTACCGGCGCTGAGCAC  
CGCCACAAAGGACACCTATGATGCCCTGCACATGCAGGCCCTGCCCCCTAGA (SEQ ID NO: 18068)



FIGURE 4A

**PSMA8 CARTYRIN:**  
SIGNAL PEPTIDE: MALPVTALLPLALLHAARP (SEQ ID NO: 18004)  
CENTYRIN (PSMA8):  
MLPAPKNLVVSRVTEDSARLSWAIDEQRDWFEFLIQYQSEKVGAEIVLTPGSESYDLTGLKPGTEYTVSYGV  
YHVYRSNPLSAFTT (SEQ ID NO: 18002)  
HINGE (CD8<sub>α</sub>): TTTAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD (SEQ ID NO: 18014)  
TRANSMEMBRANE (CD8<sub>α</sub>): IYWAPLAGTCGVLLSLVITLYC (SEQ ID NO: 18006)  
COSTIMULATORY DOMAIN #1 (4-1BB): KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL (SEQ  
ID NO: 18012)  
COSTIMULATORY DOMAIN #2 (CD3<sub>ζ</sub>):  
RVKFSRSADAPAYKQGQNLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEI  
GMKGERRRGKGDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 18008)

**P-PSMA8-101 CONSTRUCT:**  
LALPVTALLPLALLHAARPMILPAPKNLVVSRVTEDSARLSWAIDEQRDWFEFLIQYQSEKVGAEIVLTPGSE  
RSYDLTGLKPGTEYTVSYGVYHVYRSNPLSAFTTTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLD  
FACDIYWAPLAGTCGVLLSLVITLYCKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRS  
ADAPAYKQGQNLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQDKMAEAYSEIGMKGER  
RRGKGHDGLYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 18070)

FIGURE 4B

**PSMA8 CARTYRIN:**  
**SIGNAL PEPTIDE:**  
ATGGCACTGCCTGTGCACAGCCCTGCTGCTGCCCTCTGGCCCTGCTGCTGCACGACAGCGGCCCC  
(SEQ ID NO: 18064)  
**CENTYRIN (PSMA8):**  
ATGCTGCCTGCACCAAGAACCTGGTGGTGTCTCGGGTGACCGAGGACTCTGCCAGACTGAGCTGGGCCATC  
GACGAGCAGAGGGATTGGTTTCGAGAGCTTTCTGATCCAGTATCAGGAGTCCGAGAAAGTGGCGAGGCCATC  
GTGCTGACAGTGCCTGGCAGCGAGCGGTCTATGATCTGACCGGCTGAAGCCAGGCACAGAGTACACCGT  
GTCCATCTACGGCGTGTATCACGTGTACAGGTCCAAATCCTCTGTCTGCCATCTTCACCACA  
(SEQ ID NO: 18003)  
**HINGE (CD8<sub>α</sub>):**  
ACCAACACCCCTGCCCCAGACCTCCACACCCGCCCTACCATCGCGAGCCAGCCCACTGTCCCTGCGGCCT  
GAGGCCTGCCGGCGCCCGCGCGGAGCAGTGCAACACGCGGCGCTGGACTTTGCCCTGTGAC  
(SEQ ID NO: 18065)  
**TRANSMEMBRANE (CD8<sub>α</sub>):**  
ATCTACATATGGGCACCACTGGCAGGAACCTGCGCGGTGCTGCTGCTGAGCCCTGGTCAATCACCCTGTACTGT  
(SEQ ID NO: 18066)  
**COSTIMULATORY DOMAIN #1 (4-1BB):**  
AAGAGAGGCAGGAAGAGCTGCTGTATATCTTCAAGCAGCCCTTCAAGACCCGTGCAGACACACAGGAG  
GAGGACGGCTGCTCTGTAGGTTCCAGAGGAGGAGGAGGAGGATGCGAGCTG (SEQ ID NO: 18067)  
**COSTIMULATORY DOMAIN #2 (CD3ζ):**  
CGCGTGAAGTTTACCGGTCCCGCATGCACCTGCATACAAGCAGGGAGACAGACCAGCTGTATAACGAGCTG  
AATCTGGGCGCGAGAGAGGAGTACGACGTGCTGGATAAGAGCGGGGCGCGGACCCCGAGATGGAGGCA  
AGCCTCGAGAAAGAACCCACAGAGGGCTGTACAAATGAGCTGCAAAAGGACAAGATGGCCGAGGCTATT  
CTGAGATCGGCATGAAGGAGAGAGGCGCCGGGCAAGGGACACGATGGCCTGTACCAGGCTGAGCAC  
CGCCACAAAGGACCACTATGATGCCCCTGACATGCGAGGCCCTGCCCCCTAGA (SEQ ID NO: 18068)

FIGURE 4C

**P-PSMA8-101 CONSTRUCT:**  
CTGGCACTGCCTGTGACAGCCCTGCTGCCTCTGGCCCTGCTGTGCACGGACACGGCCCATGCTGCCT  
GCACCAAGAACTGGTGTCTCGGTGACCGAGACTCTGCCAGACTGAGCTGGGCCATCGACGAGCA  
GAGGGATTGGTTCGAGAGCTTCTGATCCAGTATCAGGAGTCCGAGAAAGTGGCGAGGCCATCGTGTGAC  
AGTGCCCTGGCAGCGAGCGGTCTATGATCTGACCCGGCTGAAGCCAGGCACAGATACACCGTGTCCATCTA  
CGGCGTGTATCAGGTGTACAGGTCCAATCCTCTGTGTCATCTTACCCAAACCCACCCCTGCCCCGAG  
CCTCCACACCCGCCCTACCATCGGAGCGGCCACTGTCCCTGCGGCTGAGGCTGCCGCGCCGCGC  
CGGCGGAGCAGTGACACACGGGCCCTGGACTTTGCCTGTGACATCTACATATGGGCACCACTGGCAGGAA  
CCTGCGGCTGCTGCTGAGCCCTGGTCTACCCCTGACTGTAAAGAGGCGGAGGAGCTGCTGTATA  
TCTTCAAGCAGCCCTTCAAGACCCGTGCAGACACACAGGAGGAGGAGCGGCTGCTCTTGTAGGTTCCAG  
AGGAGGAGGAGGAGGATGCGAGCTGCGCGTGAAGTTAGCCGGTCCGCCGATGCACCTGCATACAAGCAG  
GGACAGAACCCAGCTGTATAACGAGCTGAACTCTGGCCGGAAGAGGAGTACGACGTGCTGGATAAGAGCG  
GGCCCGGACCCCGAGATGGAGCAAGCTCGGAGAAAGAACCCACAGGAGGCGCTGTACAAATGAGCTG  
CAAAGGACAAAGATGCCGAGGCCTATTCTGAGATCGGCATGAAGGAGAGAGGCGCCGGGCAAGGGACA  
CGATGGCTGTACCGAGGCTGAGCACCCGCCACAAAGGACACCTATGATGCCCTGCACATGCAGGCCCTGC  
CCCCTAGA (SEQ ID NO: 18071)

FIGURE 5

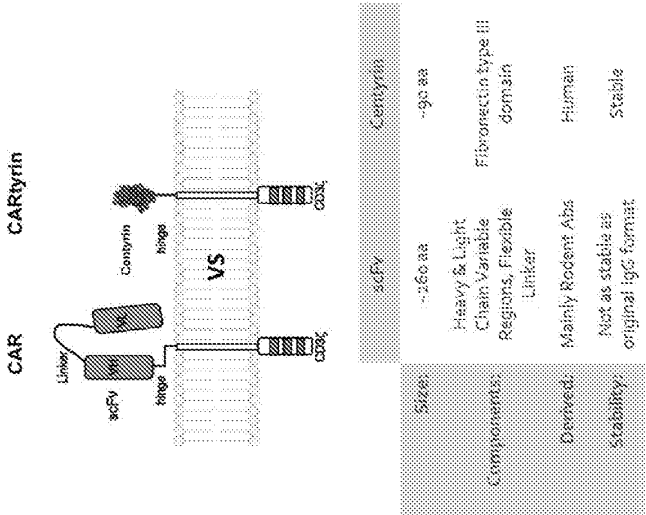
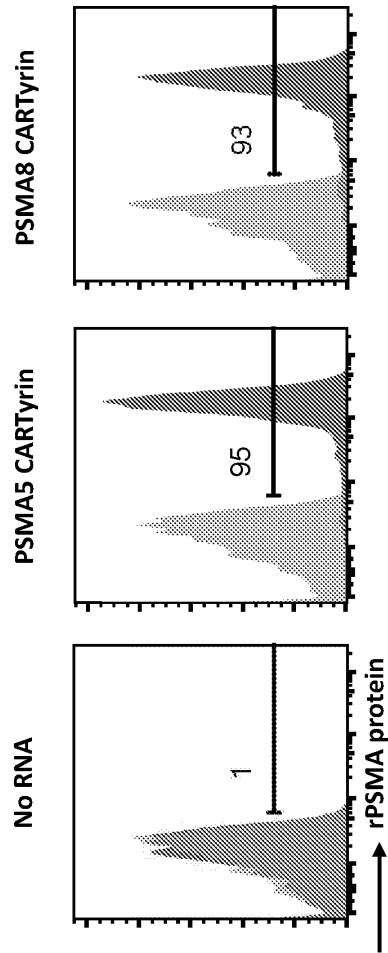
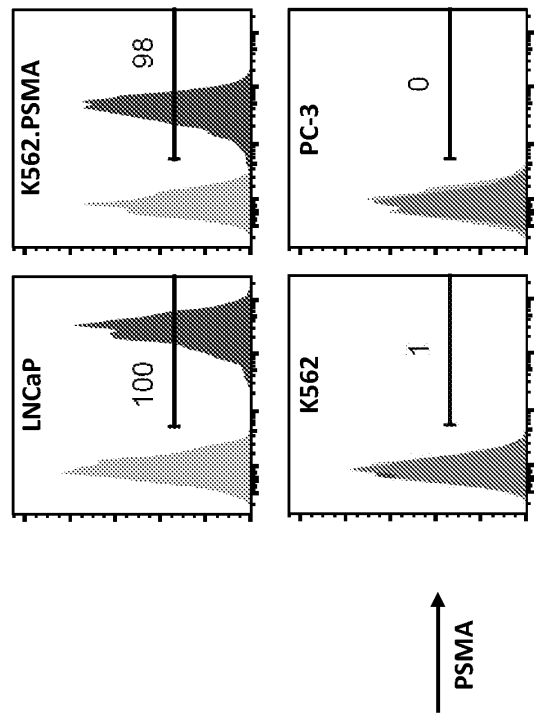


FIGURE 6A



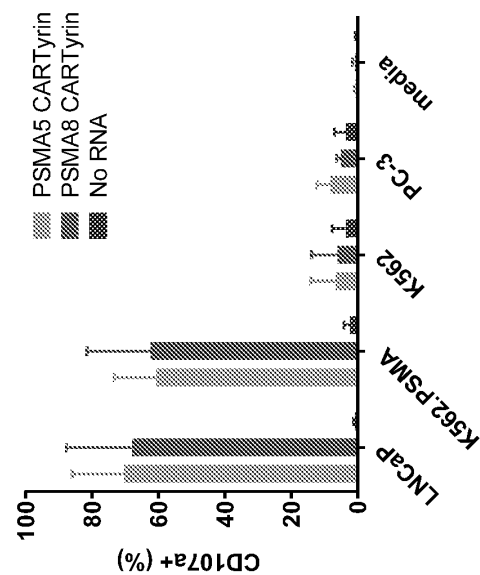
A) PSMA CARTyirin surface expression 24 hours post mRNA transfection of human pan T cells

FIGURE 6B



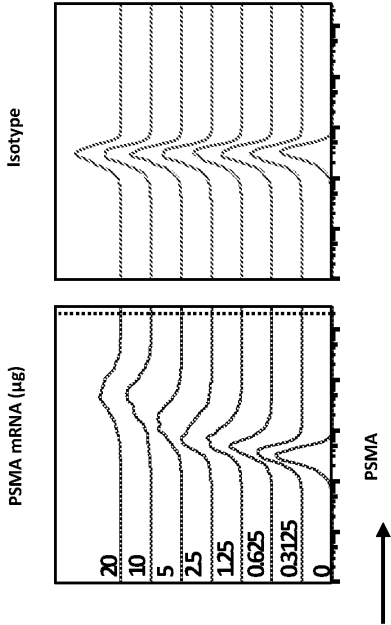
B) Expression of PSMA protein on tumor cell lines. Gray histogram represents the isotype control

FIGURE 6C



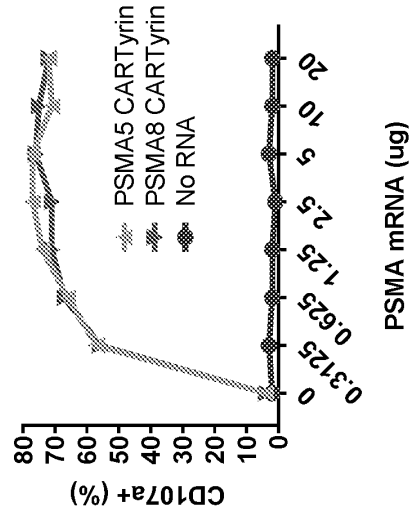
C) Degranulation of RNA-electroporated PSMA CARTyrin T cells against PSMA+ tumor cell lines

FIGURE 6D



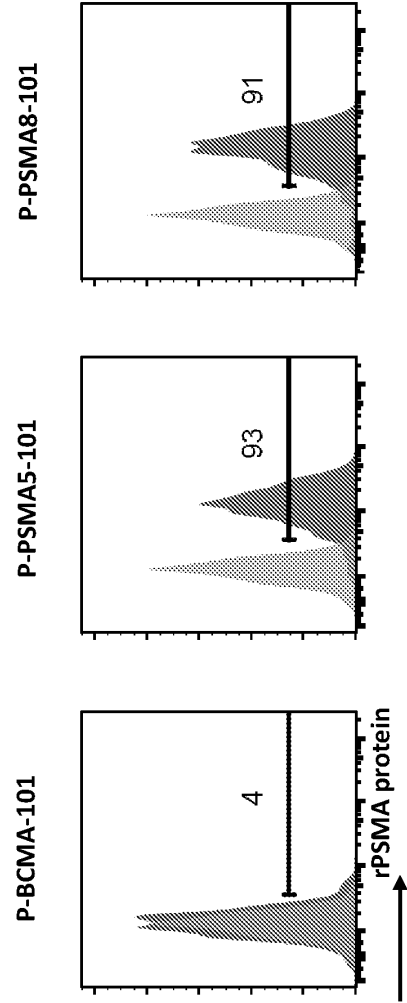
D) PSMA surface expression following transfection of K562 using various amounts of PSMA mRNA

FIGURE 6E



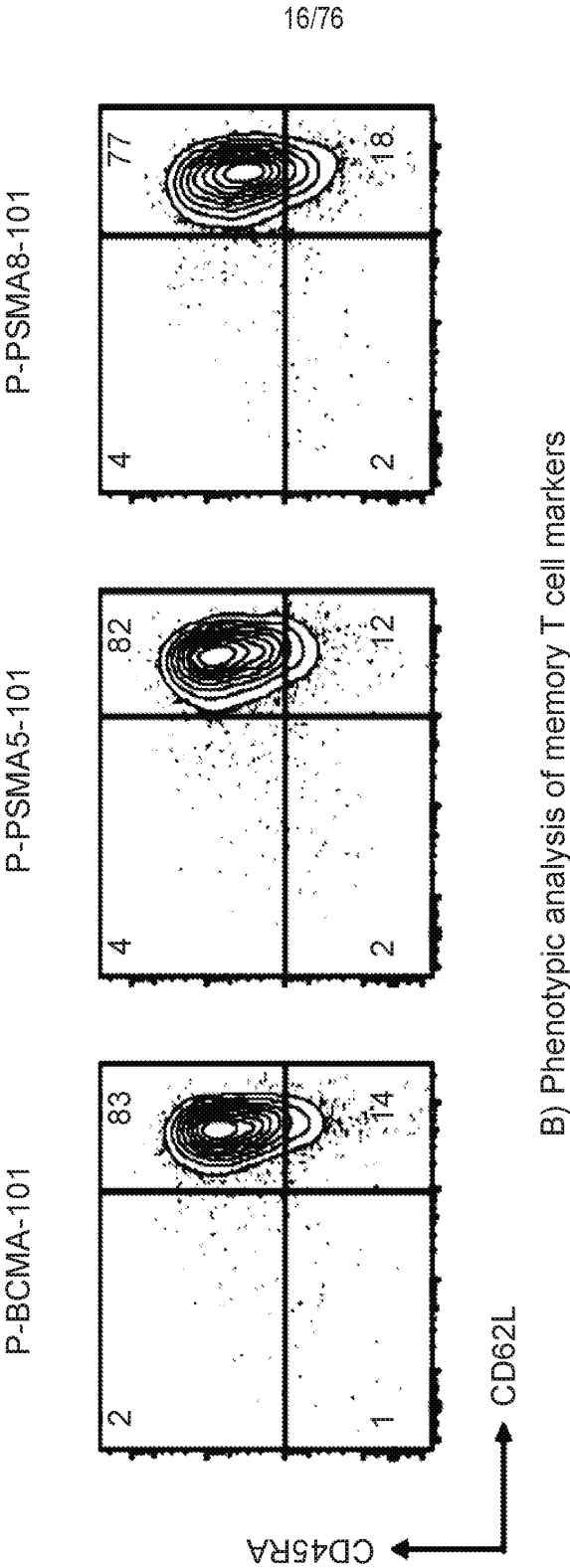
E) Degranulation of RNA-electroporated PSMA CARTyrin T cells against K562 expressing various amounts of PSMA protein

FIGURE 7A



A) P-PSMA-101 T cells bind cognate recombinant soluble PSMA antigen

FIGURE 7B



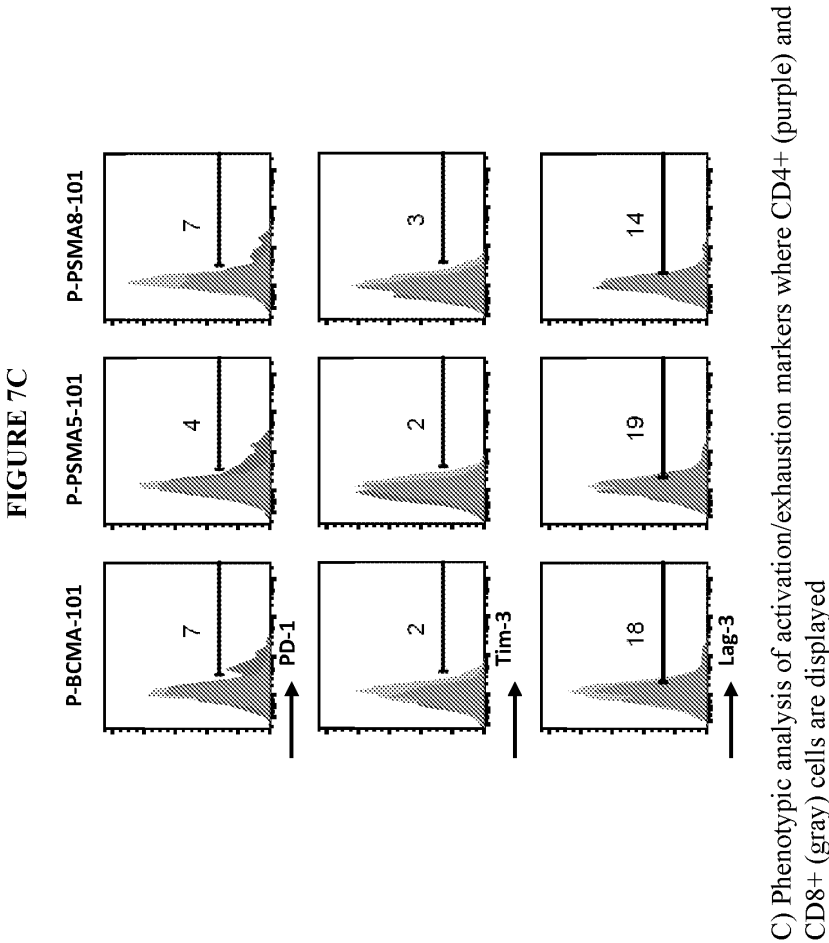
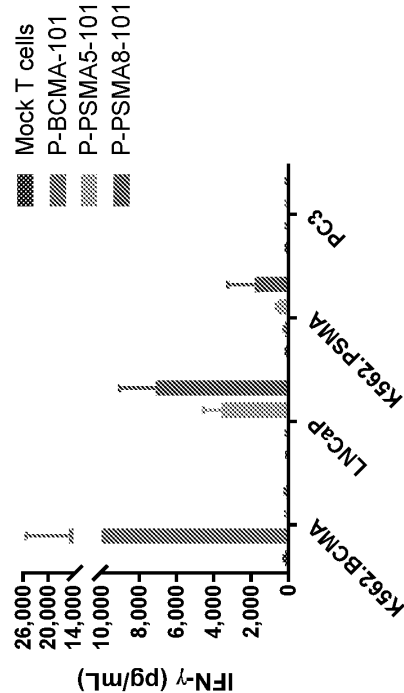
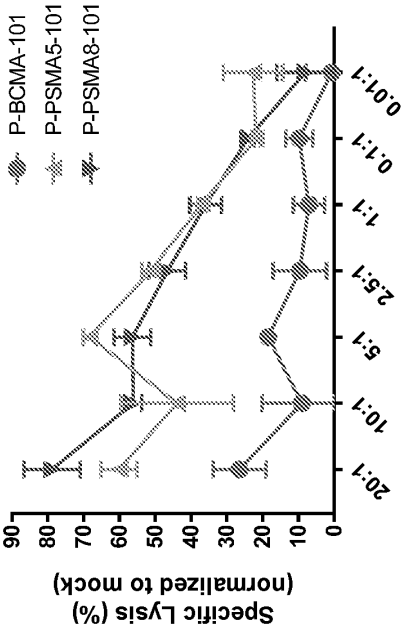


FIGURE 7D



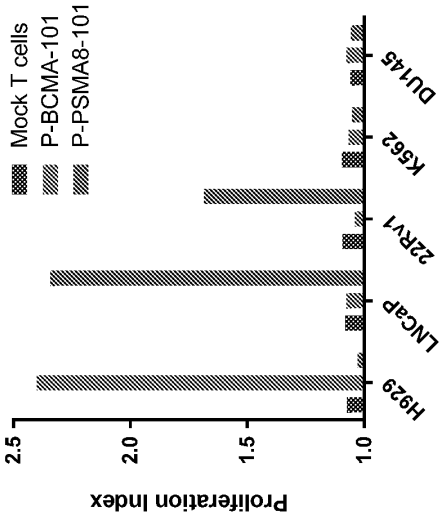
D) IFN- $\gamma$  secretion of P-PSMA-101 against PSMA<sup>+</sup> cell lines  
K562.PSMA and LNCaP

FIGURE 7E



E) Killing of PSMA<sup>+</sup> LNCaP by P-PSMA-101 or control P-BCMA-101 at the indicated effector to target ratios

FIGURE 7F



F) Proliferation of P-PSMA-101 against cell lines H929 (PSMA<sup>+</sup>/BCMA<sup>+</sup>), LNCaP (PSMA<sup>+</sup>/BCMA<sup>-</sup>), 22Rv1 (PSMA<sup>+</sup>/BCMA<sup>-</sup>), K562 (PSMA<sup>-</sup>/BCMA<sup>-</sup>), and DU145 (PSMA<sup>-</sup>/BCMA<sup>-</sup>)

FIGURE 8A

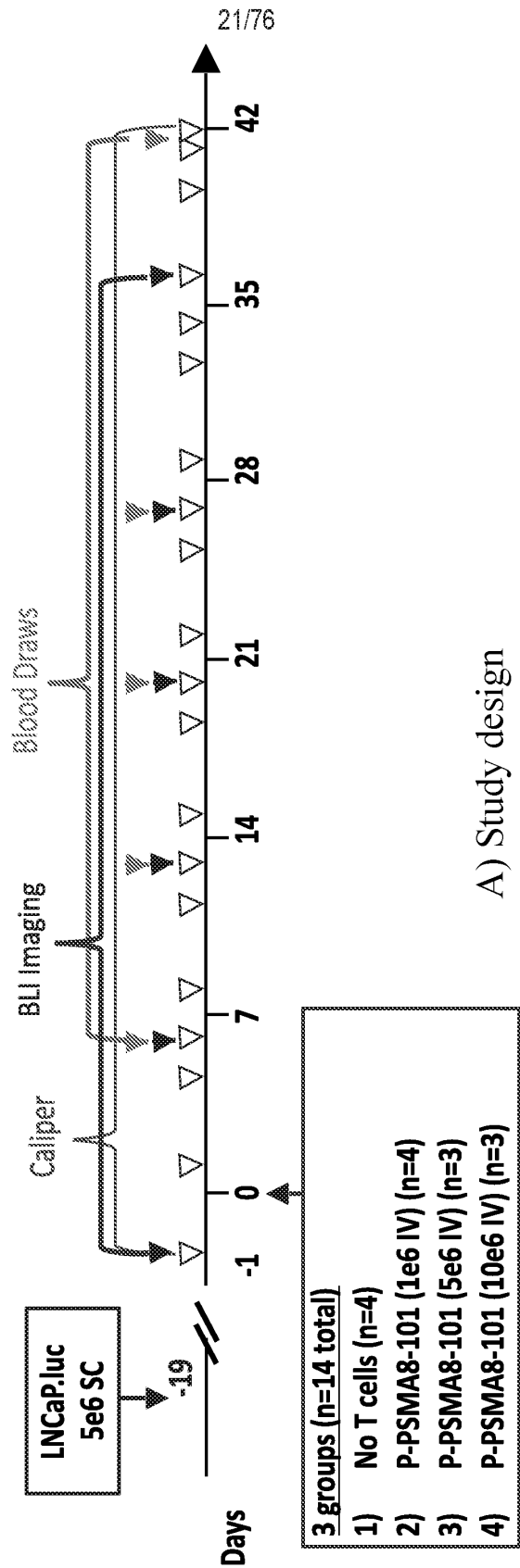
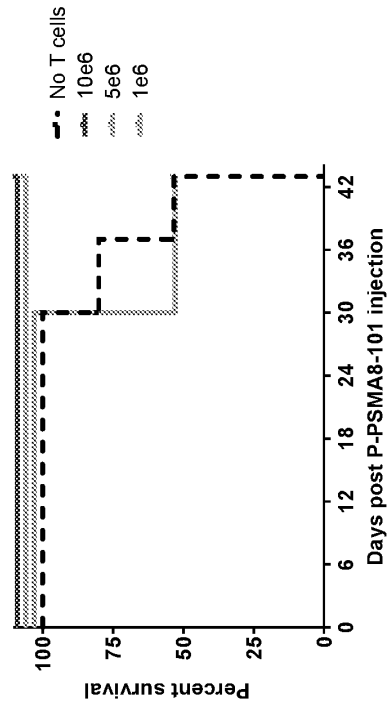
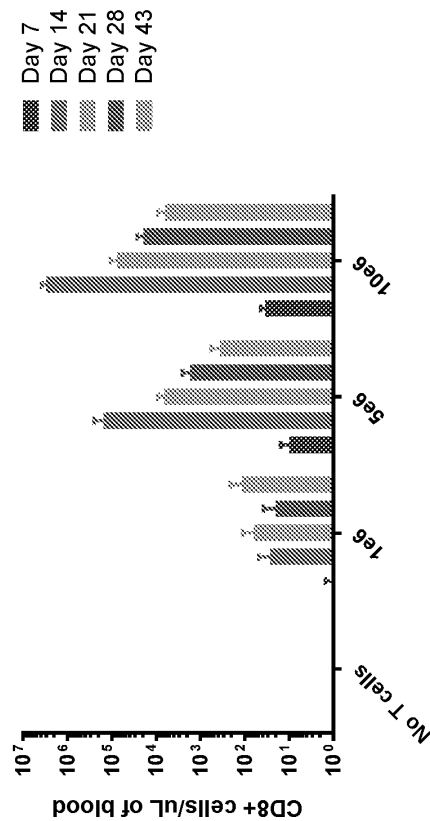


FIGURE 8B

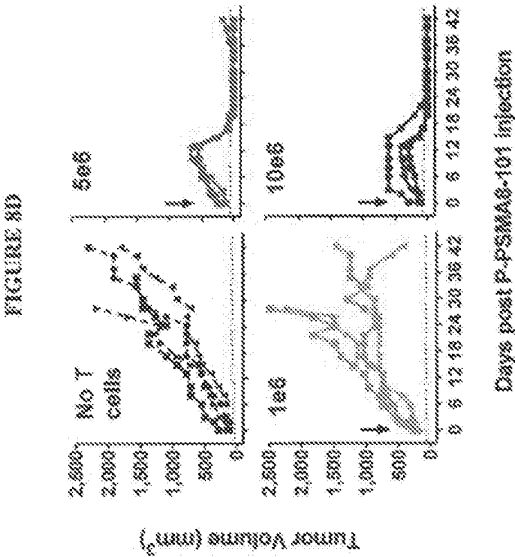


B) Survival data

FIGURE 8C

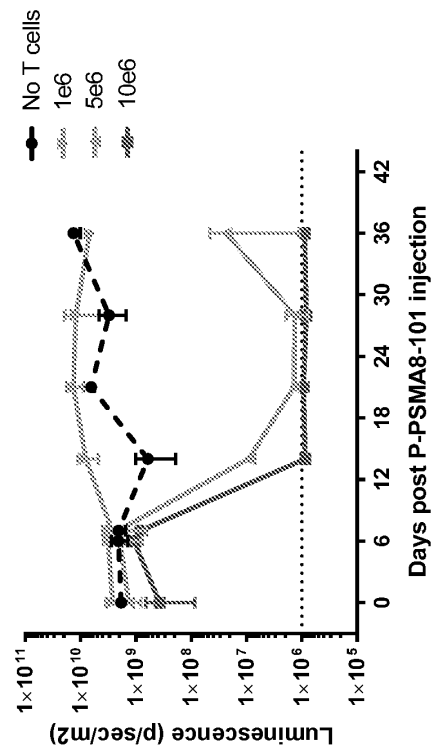


C) Enumeration of CD8+ T cells per microliter of peripheral blood



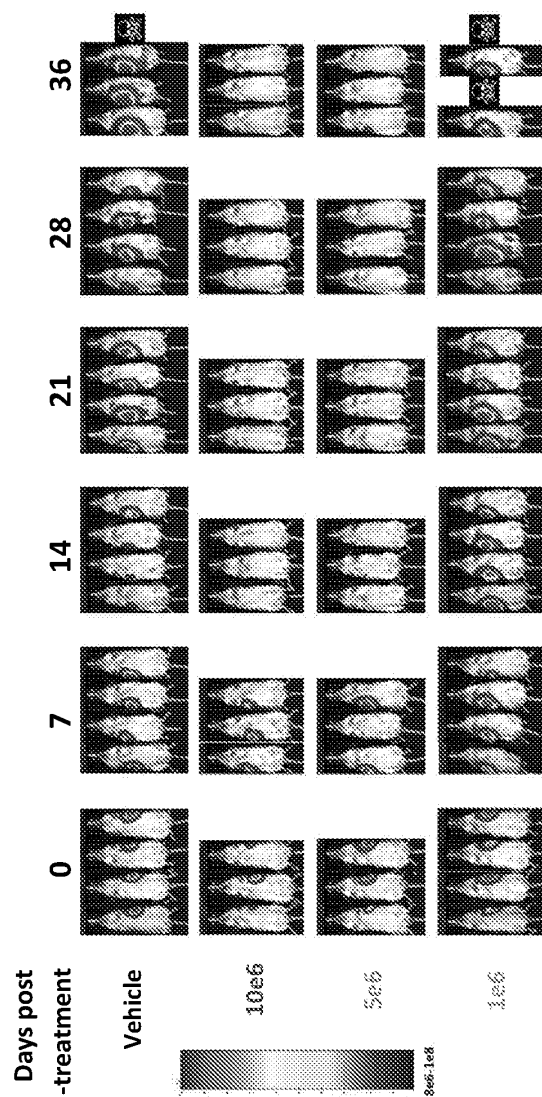
D) Tumor burden by caliper measurement

FIGURE 8E



E) Tumor burden by BLI (imaging quantified)

**FIGURE 8F**



F) Tumor burden by BLI (imaging)

FIGURE 9A

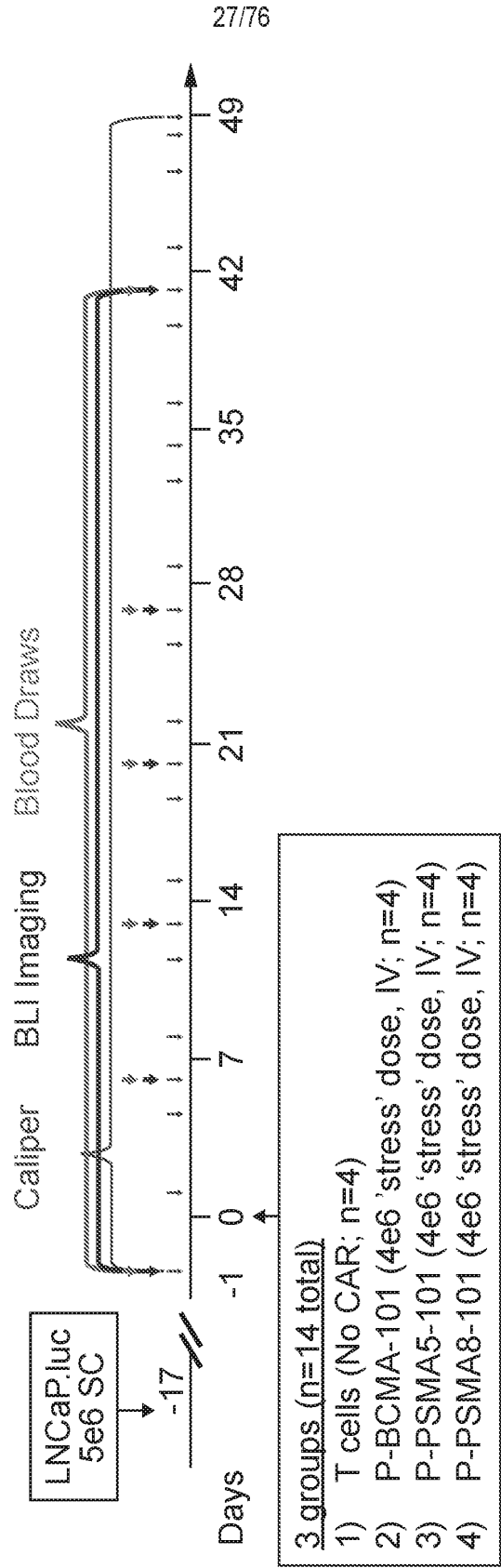


FIGURE 9B

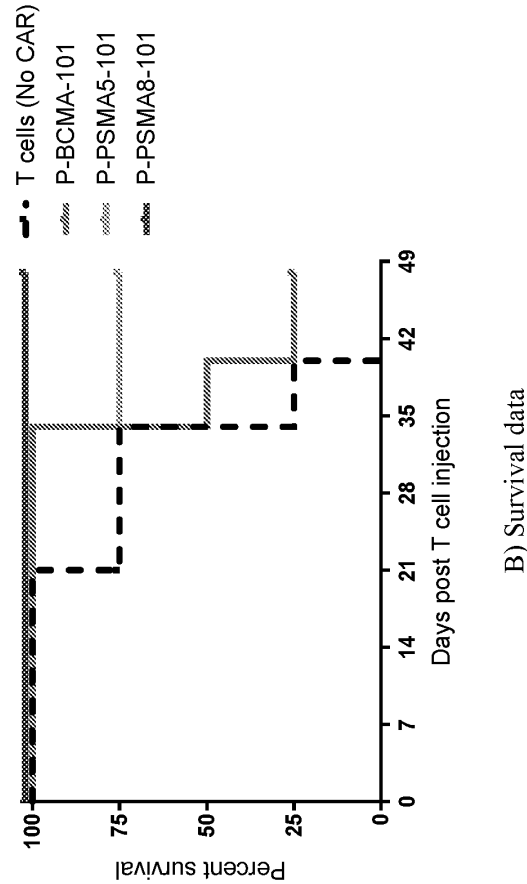
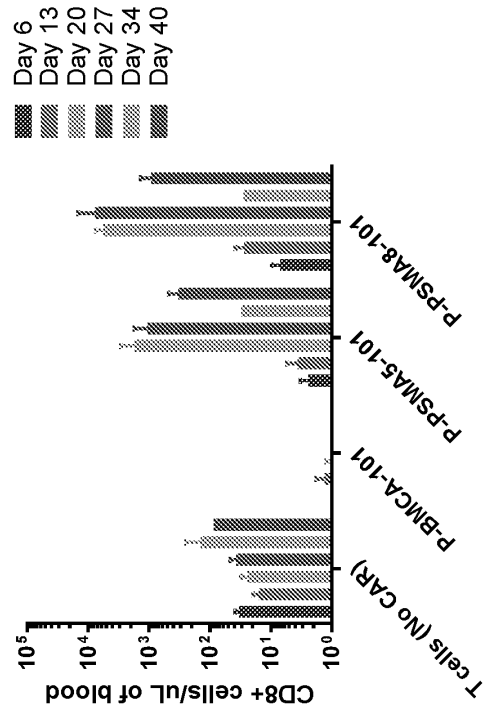
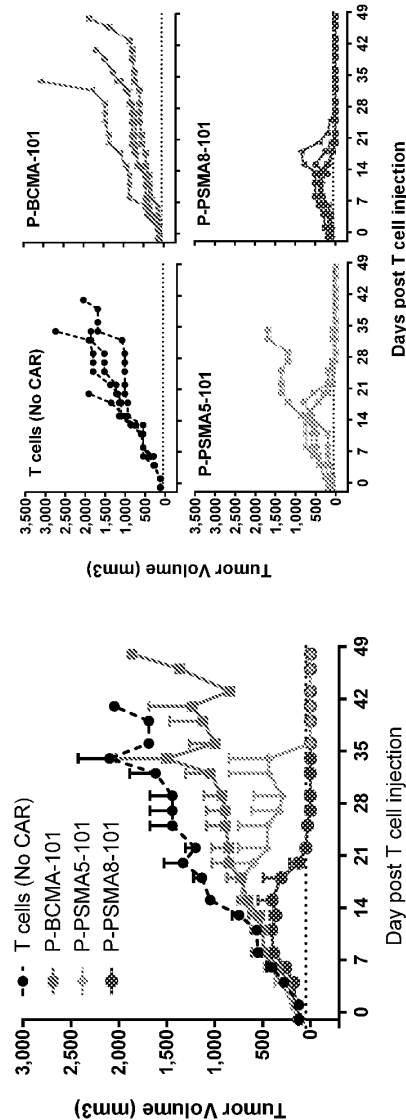


FIGURE 9C



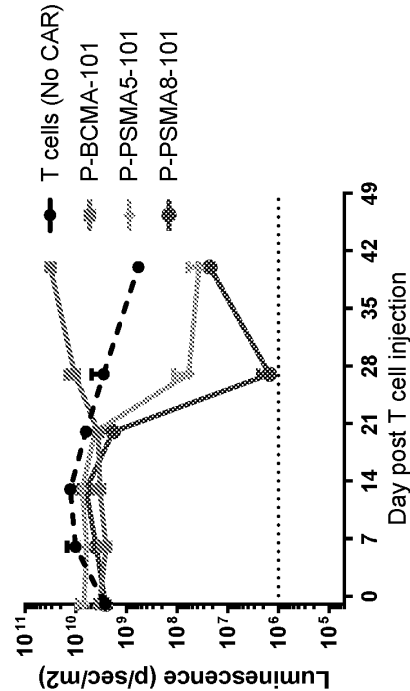
C) Enumeration of CD8+ T cells per microliter of peripheral blood

FIGURE 9D



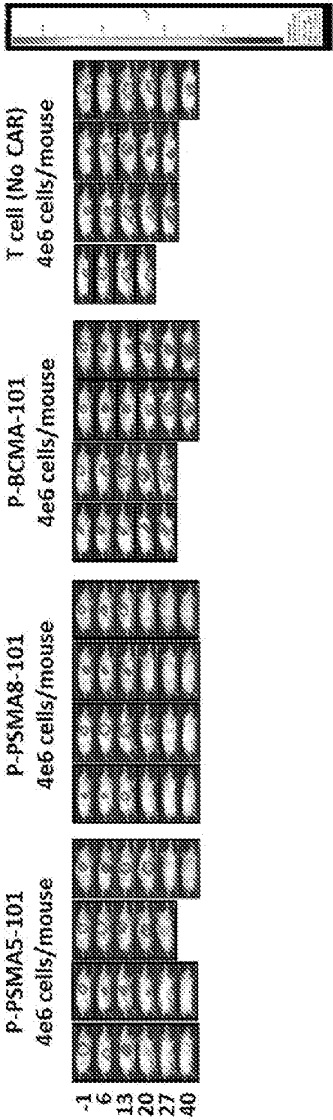
D) Tumor burden by caliper measurement

FIGURE 9E

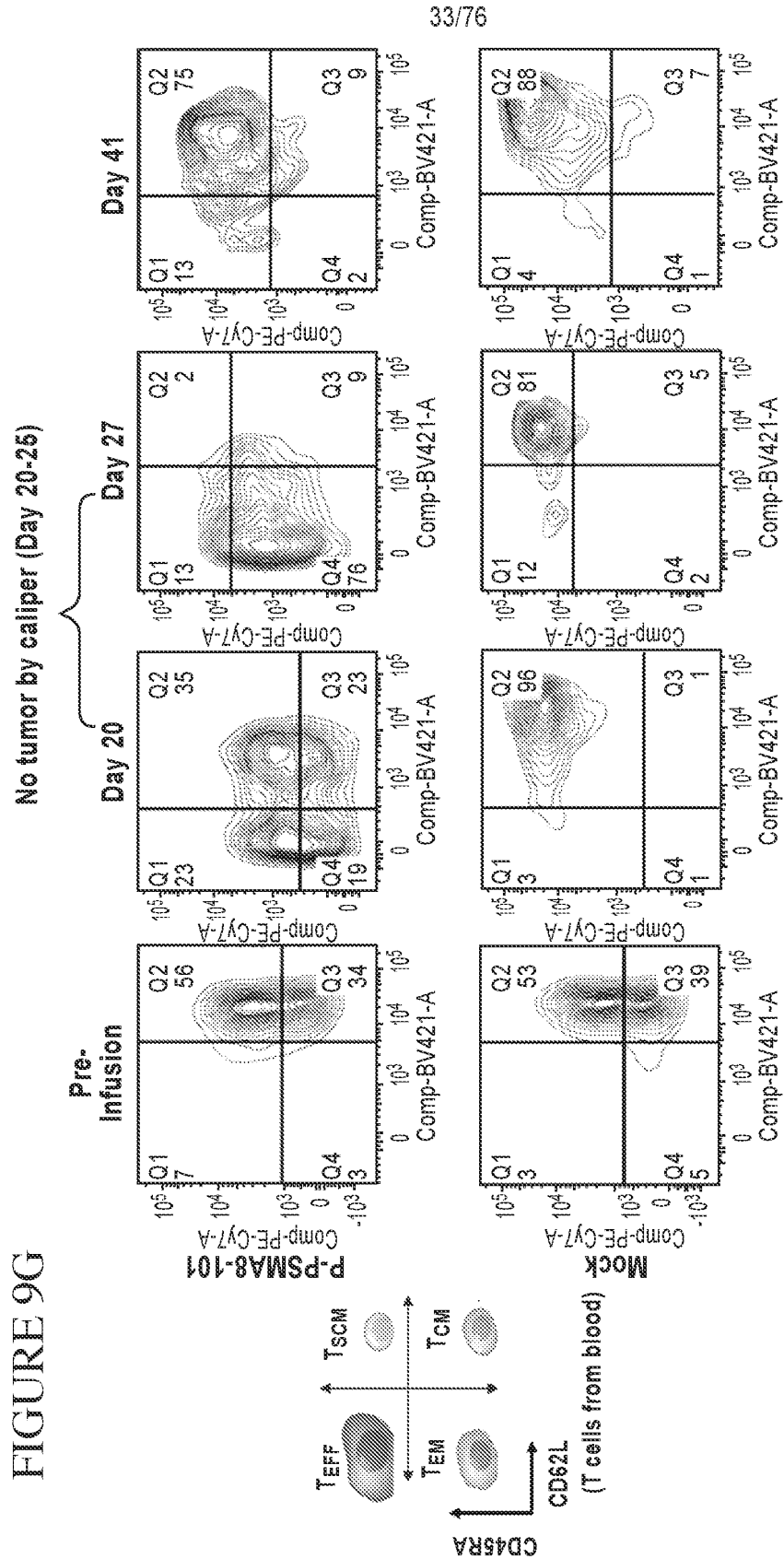


E) Tumor burden by BLI (imaging quantified)

FIGURE 9F



F) Tumor burden by BLI (imaging)



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## iC9/AP1903 Safety Switch Day 12

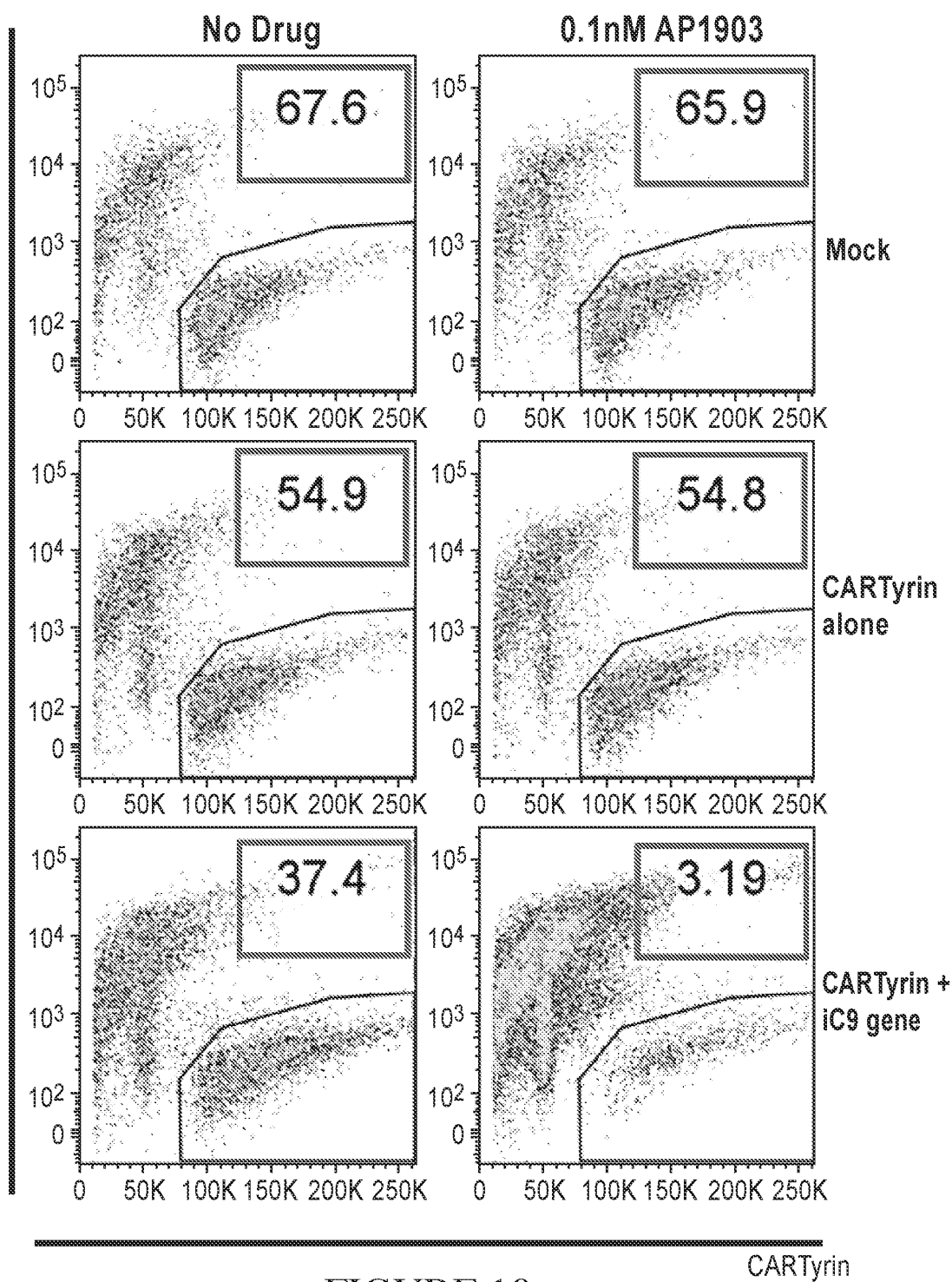


FIGURE 10

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## iC9/AP1903 Safety Switch Day 12

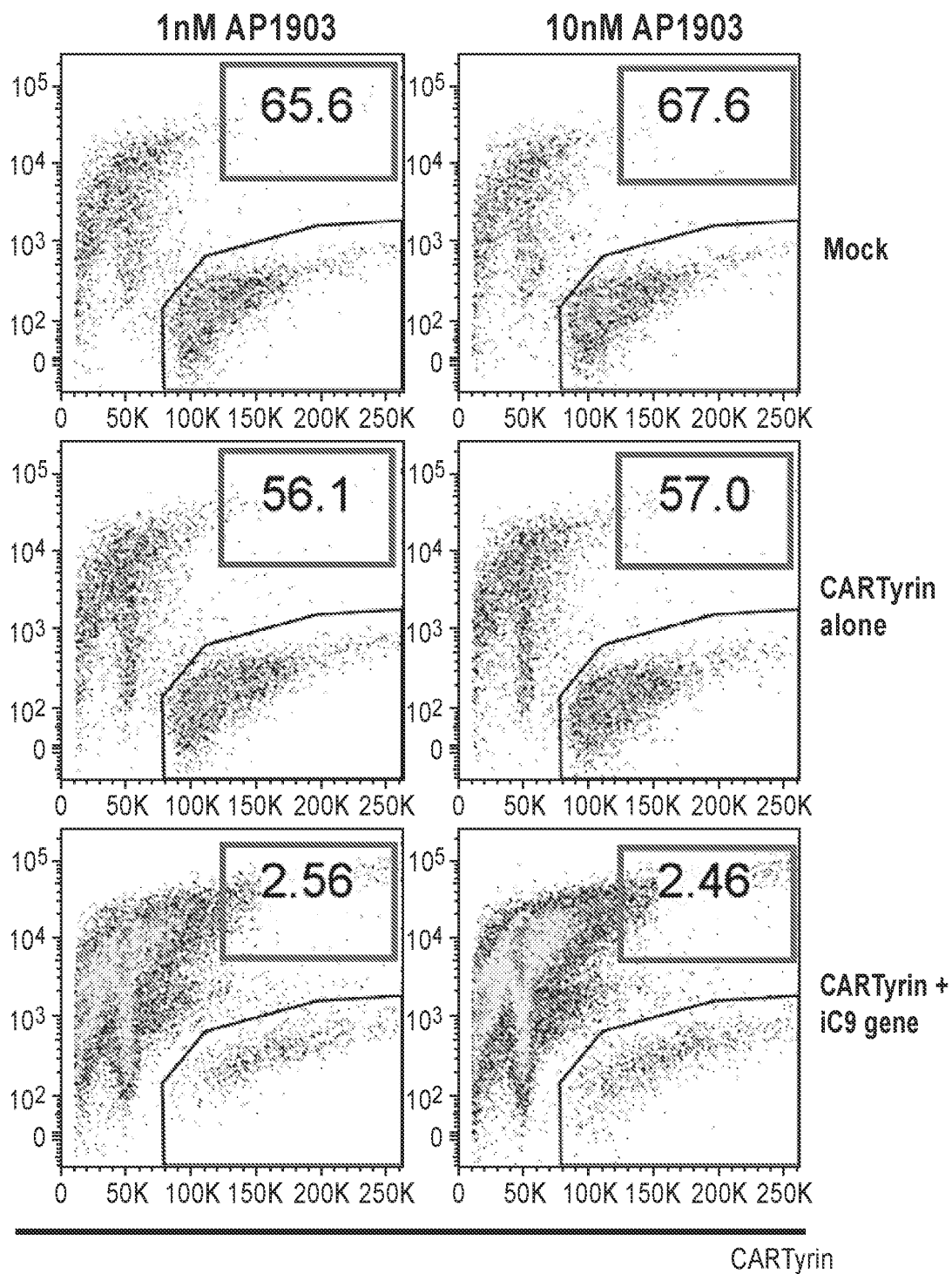


FIGURE 10 (cont.)

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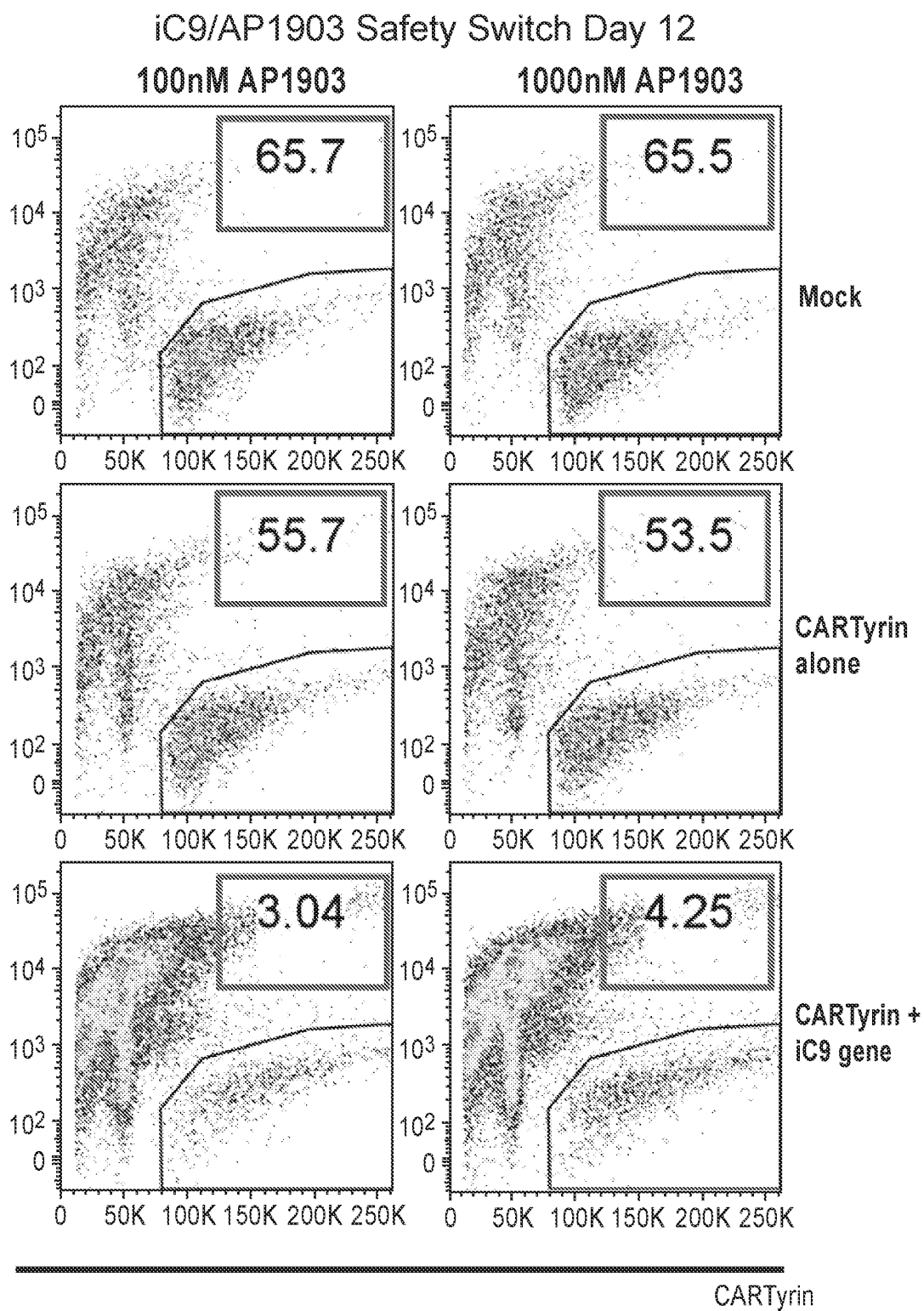


FIGURE 10 (cont.)

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## iC9/AP1903 Safety Switch Day 12

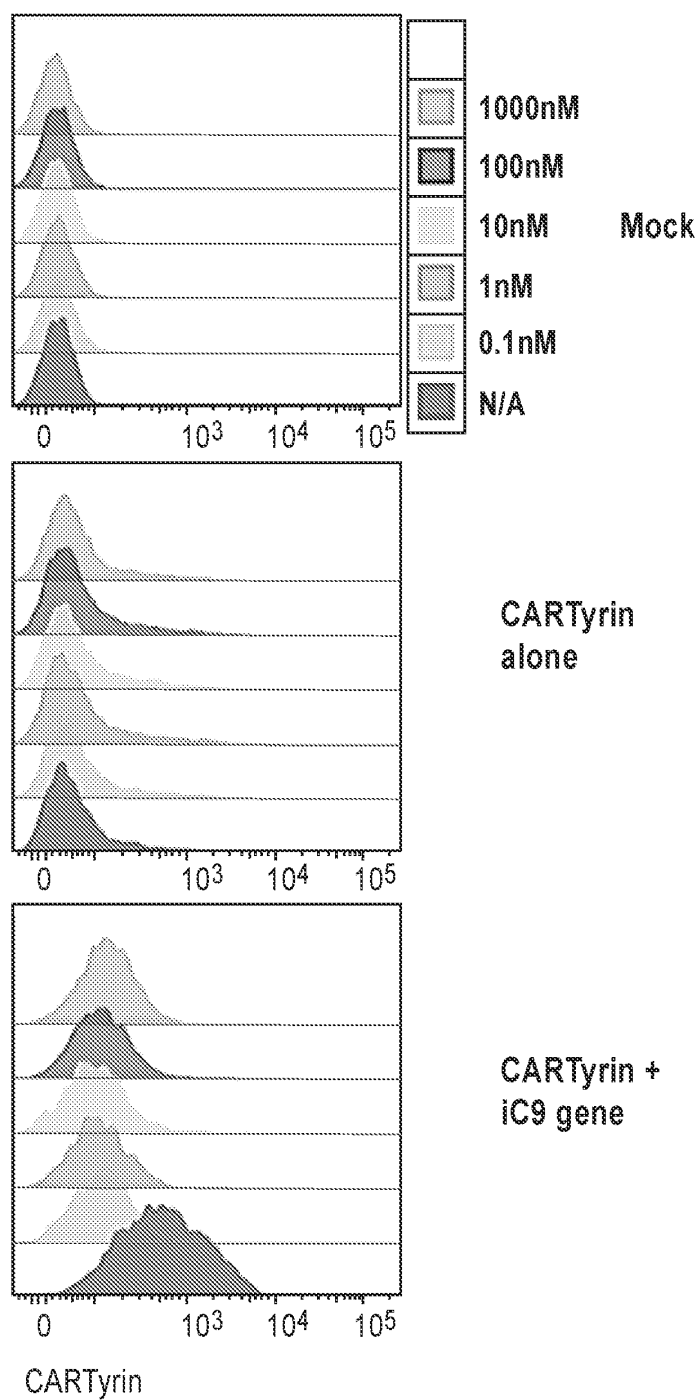


FIGURE 10 (cont.)

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## iC9/AP1903 Safety Switch Day 19

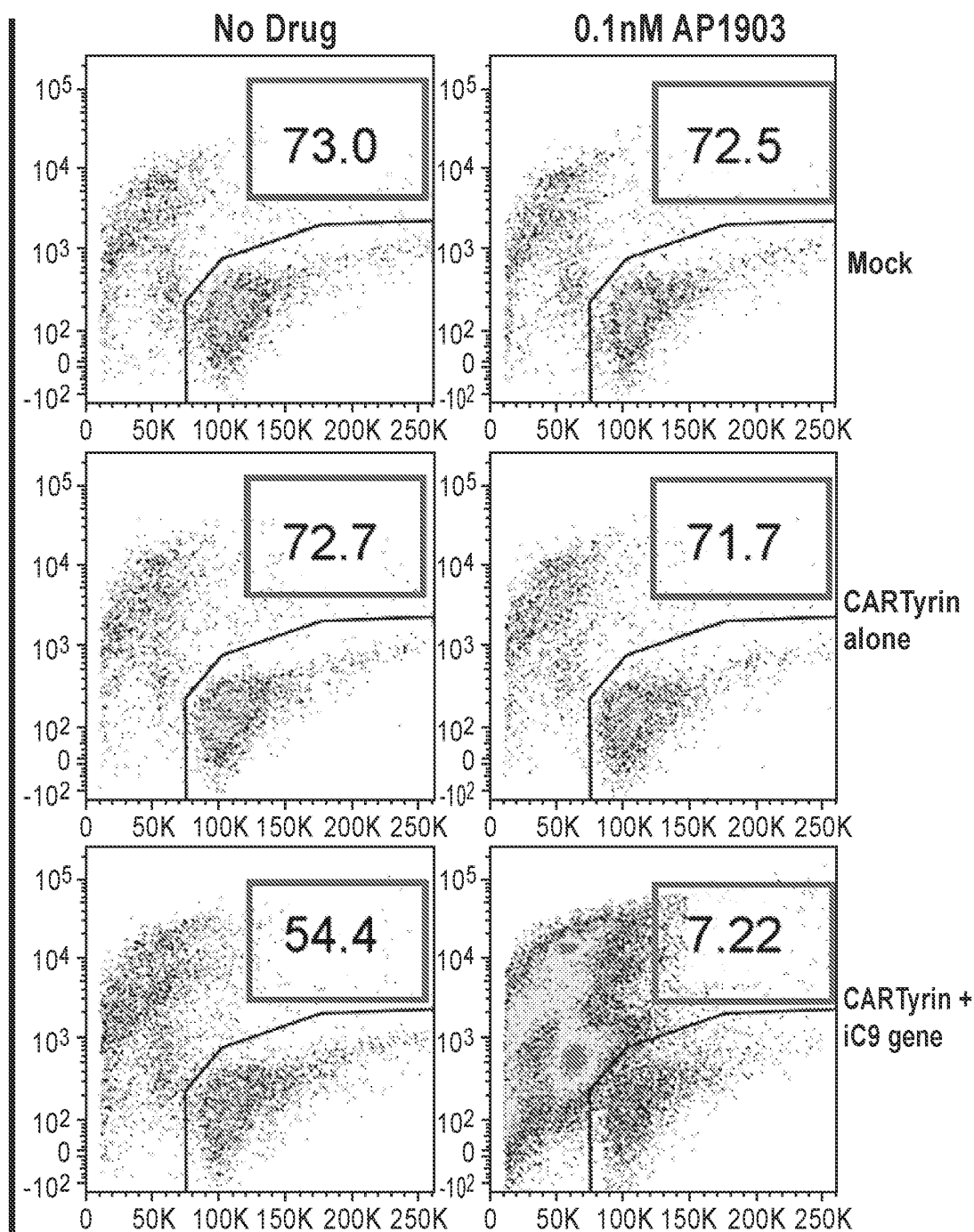


FIGURE 11

CARTyrin

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iC9/AP1903 Safety Switch Day 19

1nM AP1903

10nM AP1903

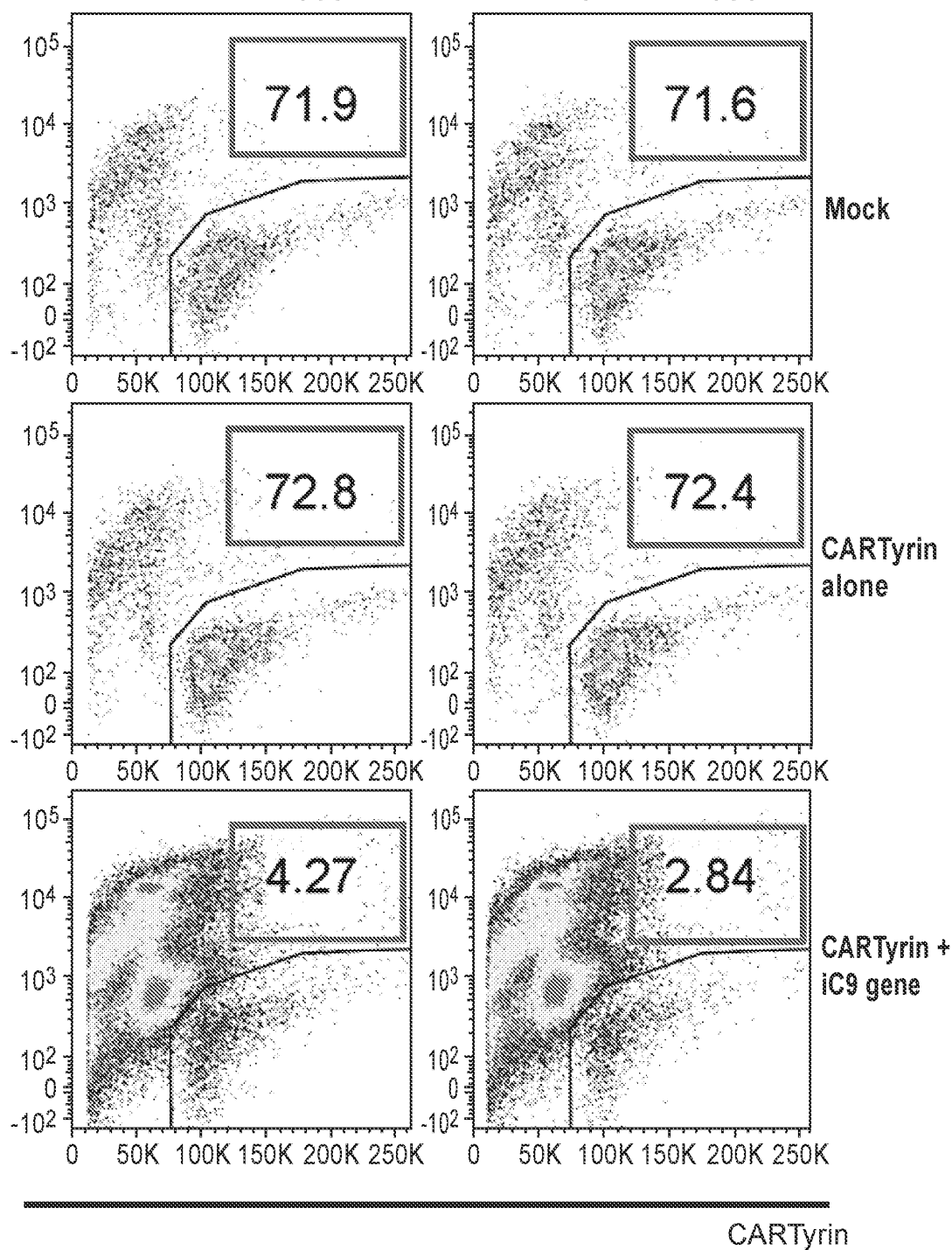


FIGURE 11 (cont.)

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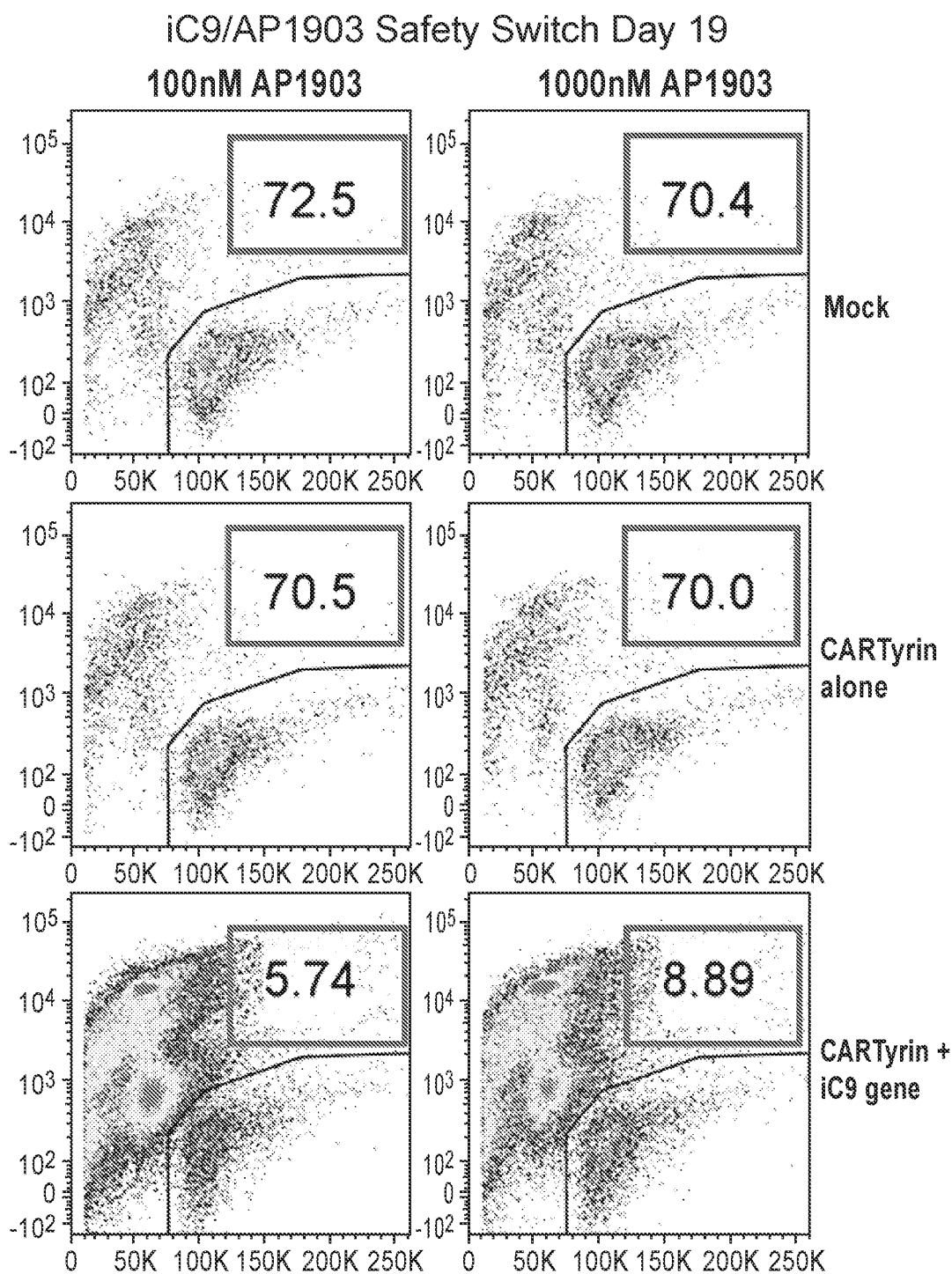


FIGURE 11 (cont.)

CARTyrin

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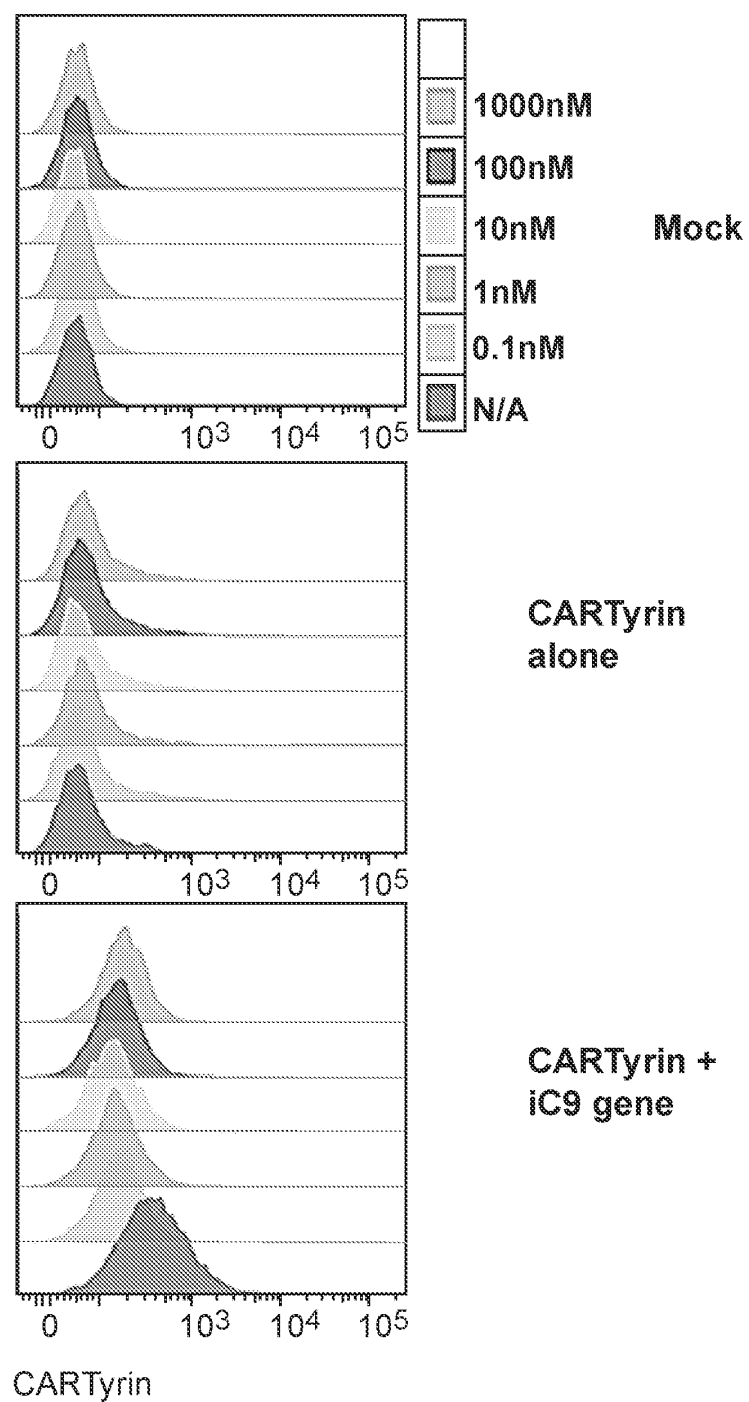
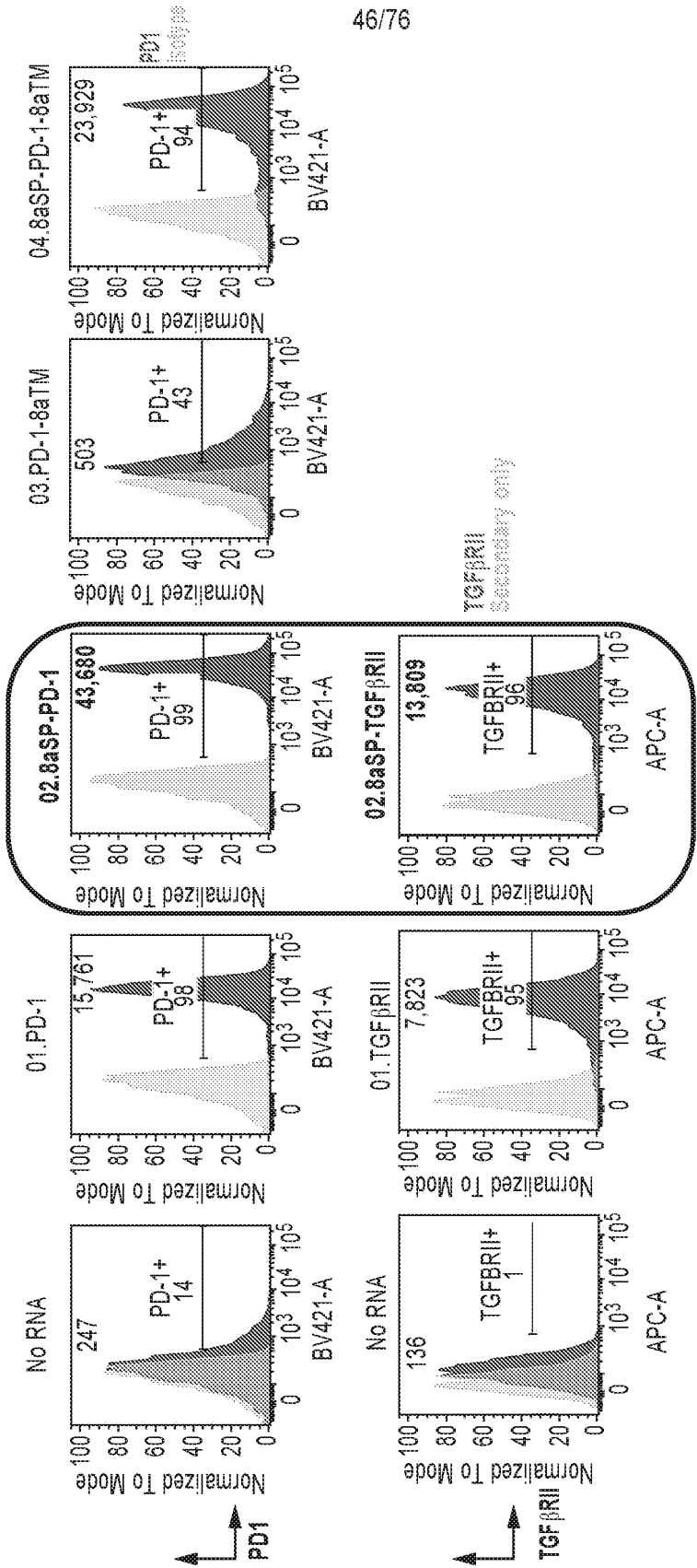


FIGURE 11 (cont.)

FIGURE 15B



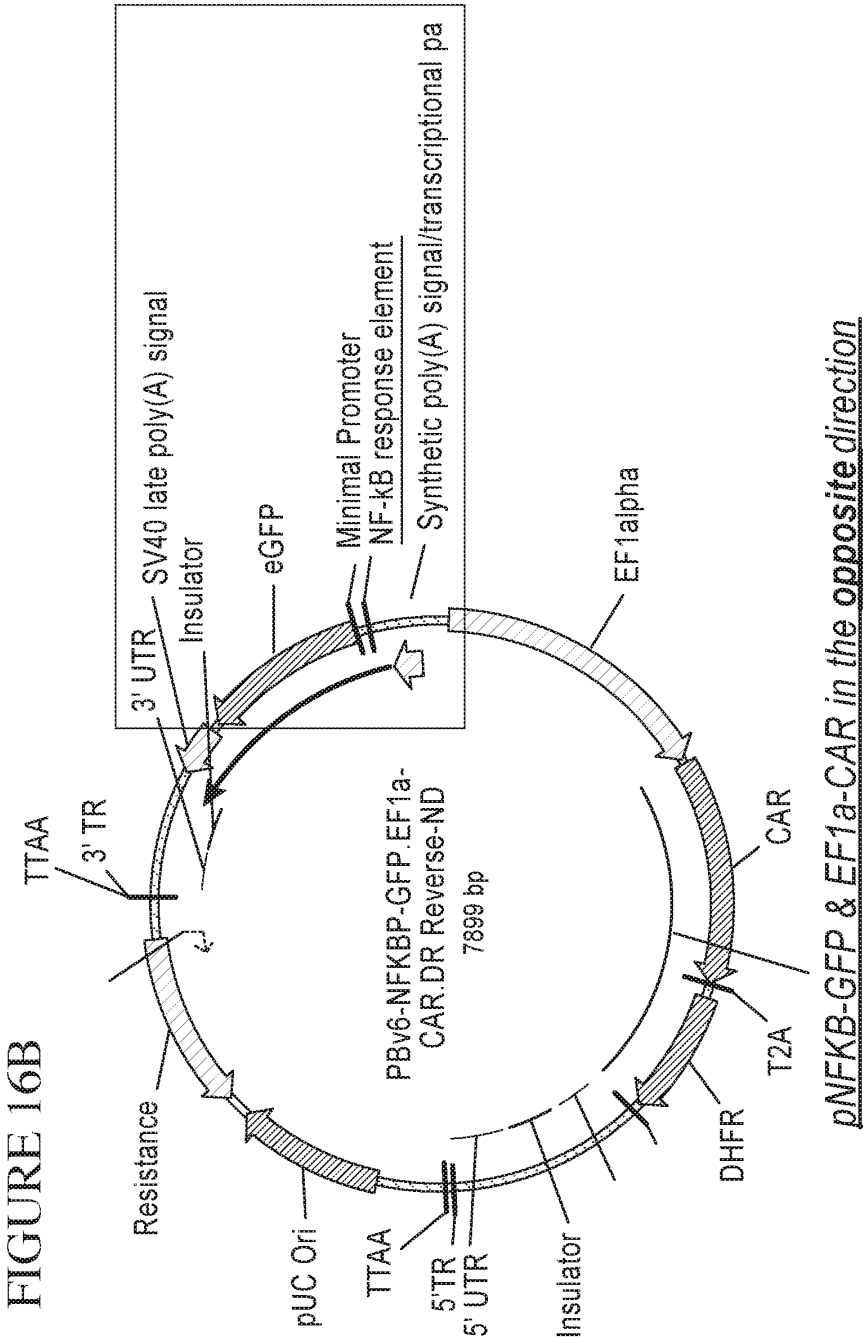
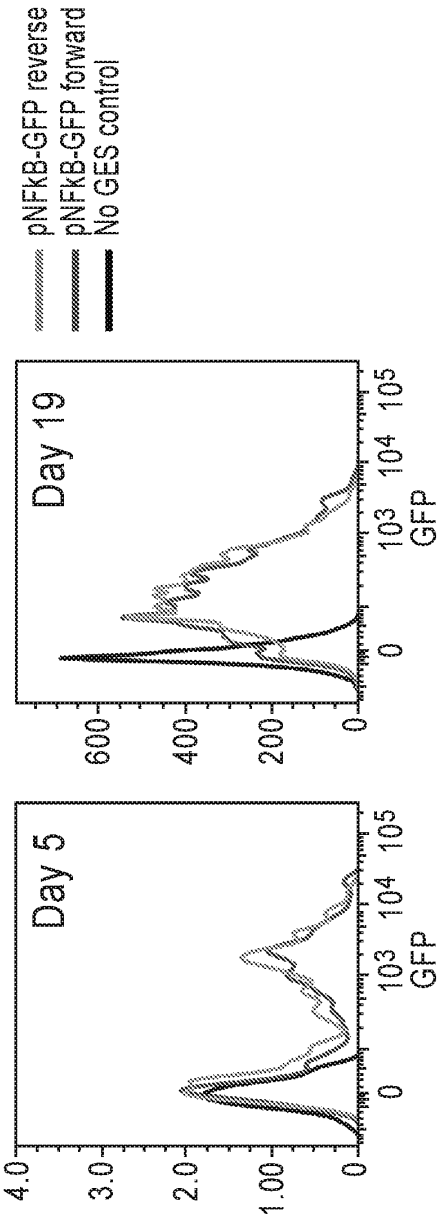
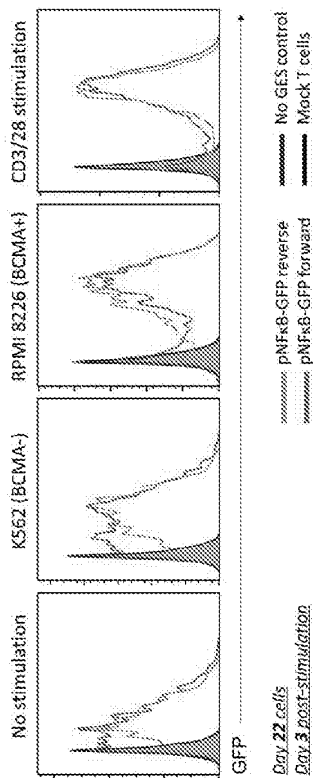


FIGURE 17



- At Day 5-post T cell activation (Day 5), T cells are proliferating and are highly stimulated; GFP expression is strong since NF-κB activity is high
- By Day 19, T cells are almost fully resting; GFP expression is significantly lower than Day 5 (~1/8 MFI), since NF-κB activity is low
- GFP expression is still observed at Day 19, which may be due to the long half life of GFP protein (~30hr), or, basal level of NF-κB activity through TCR, CAR, cytokine, growth factor, etc...

FIGURE 18



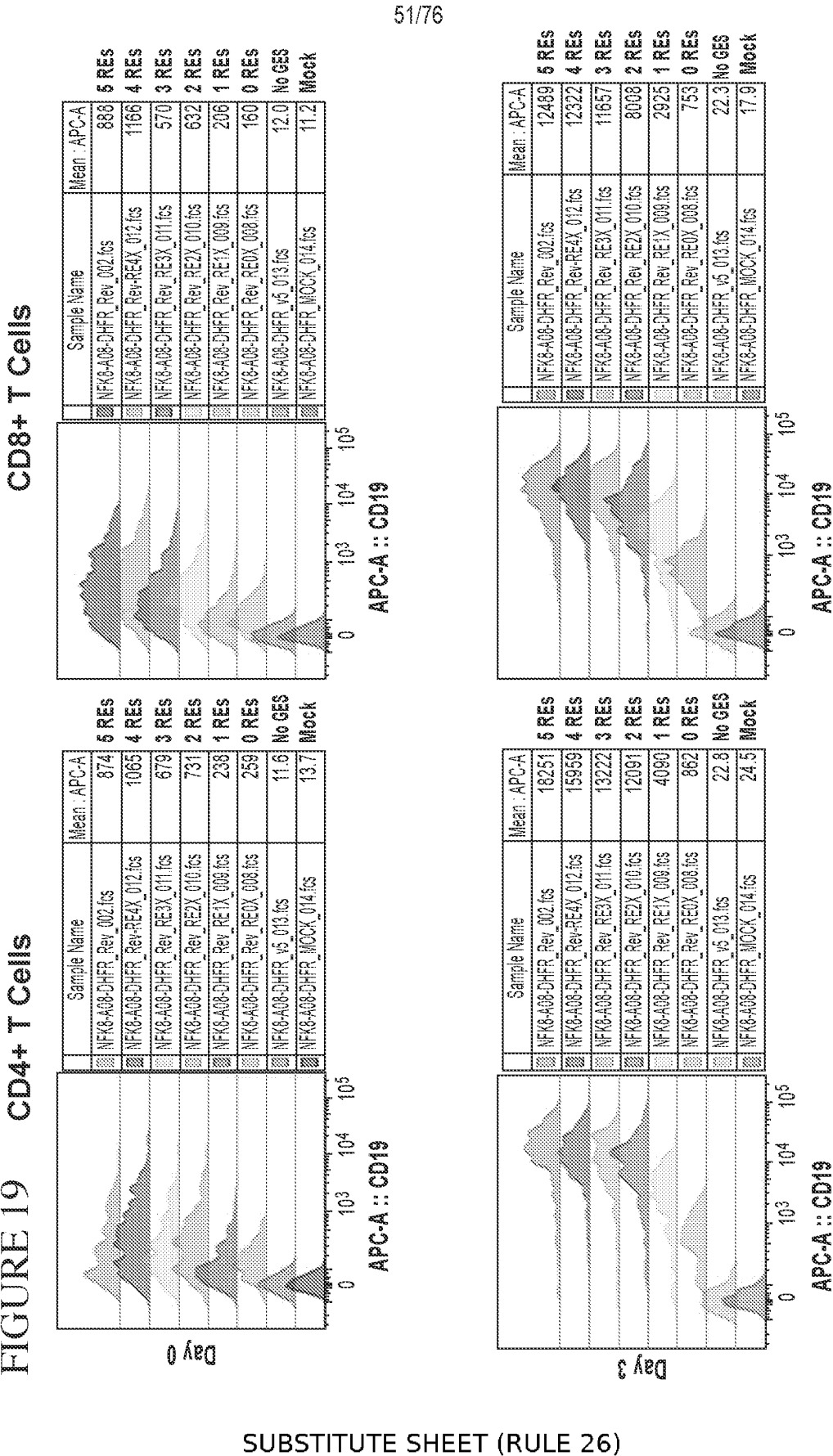


FIGURE 19 (cont.)

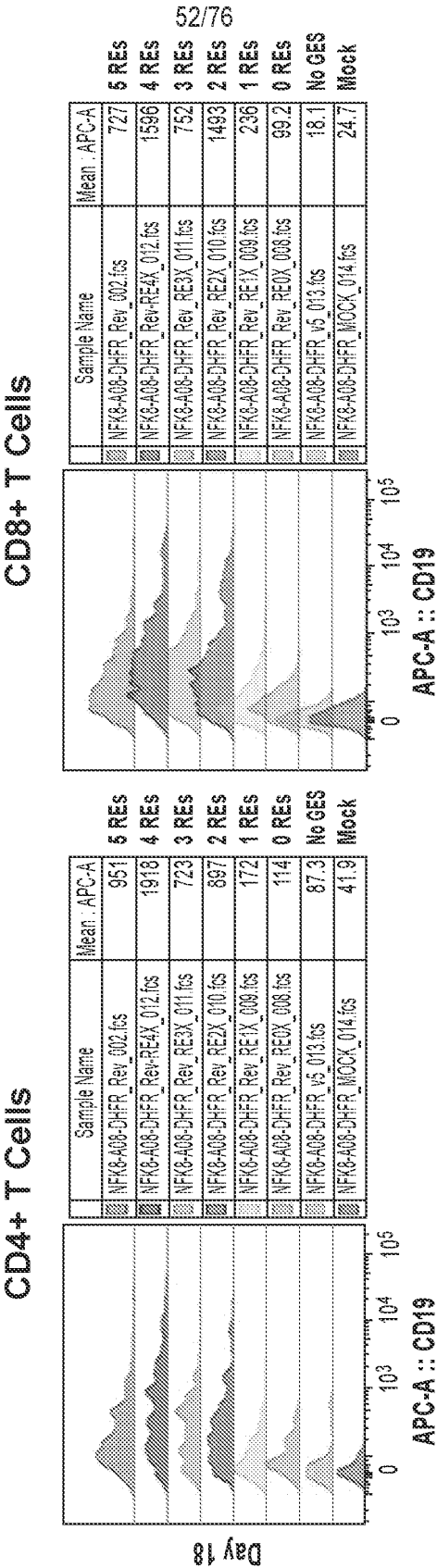


FIGURE 19 (cont.)

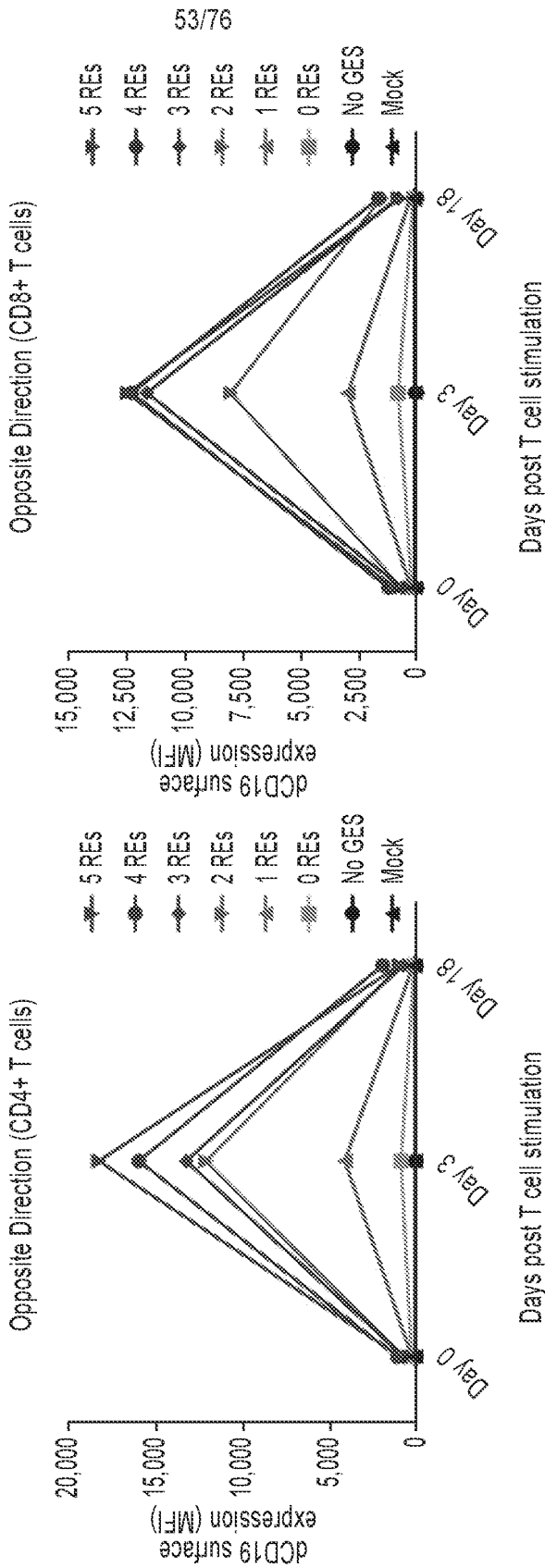


FIGURE 20

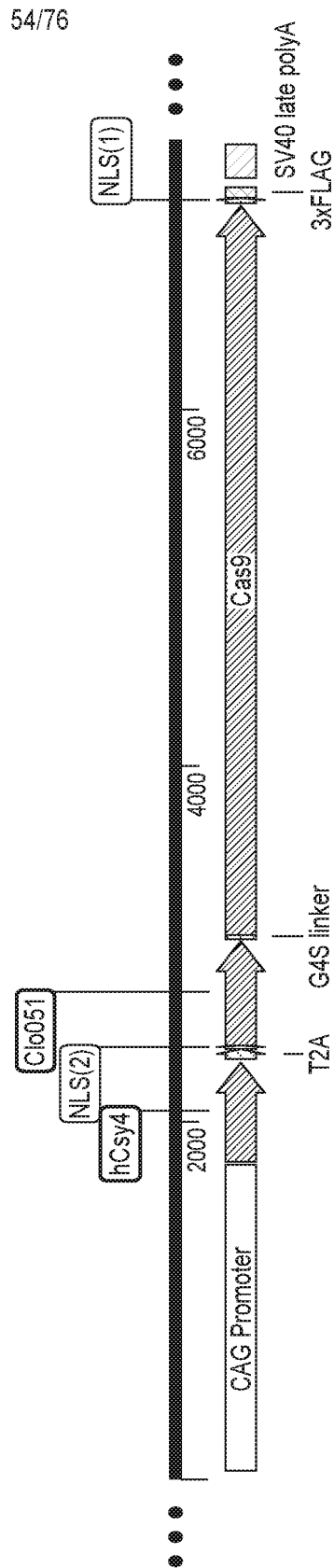
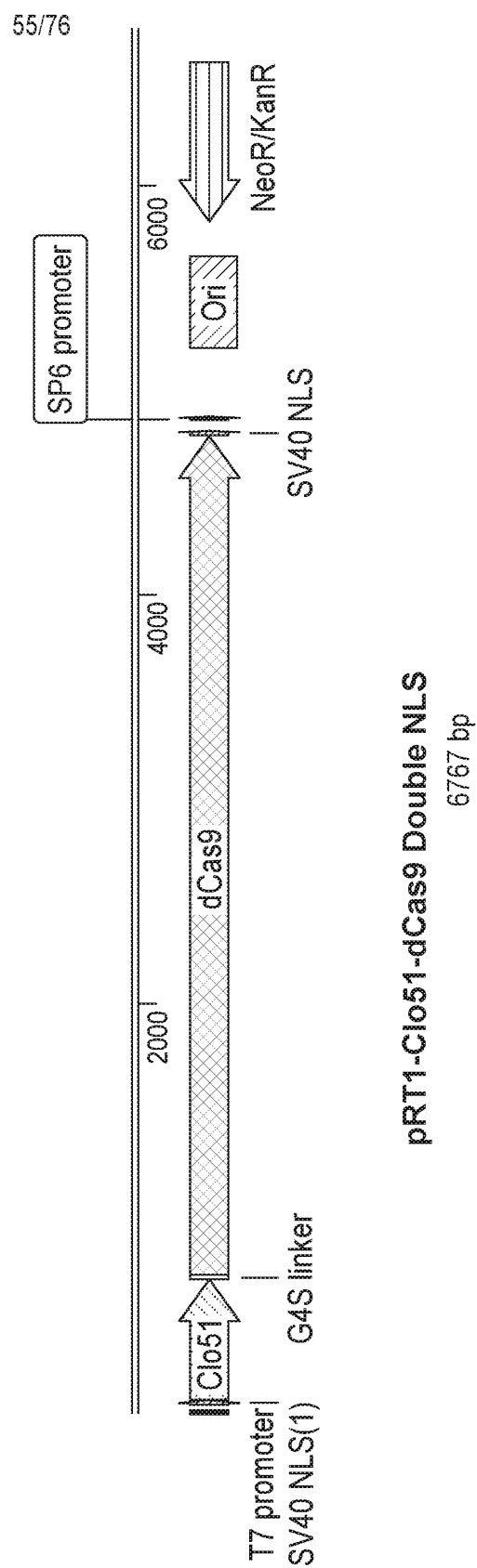


FIGURE 21



**pRT1-Clo51-dCas9 Double-NLS**

6767 b9

FIGURE 24

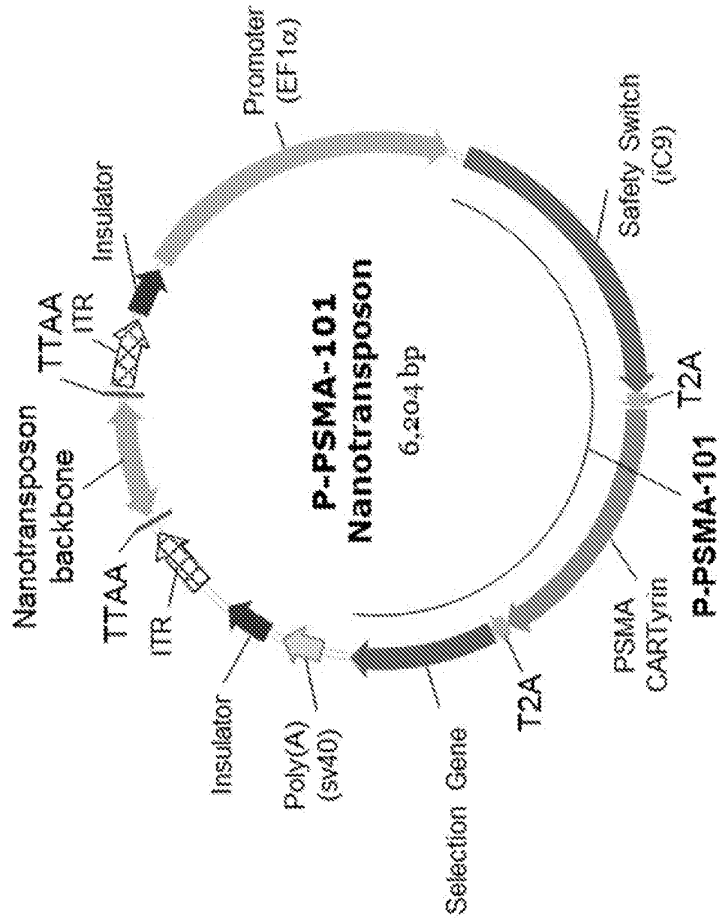
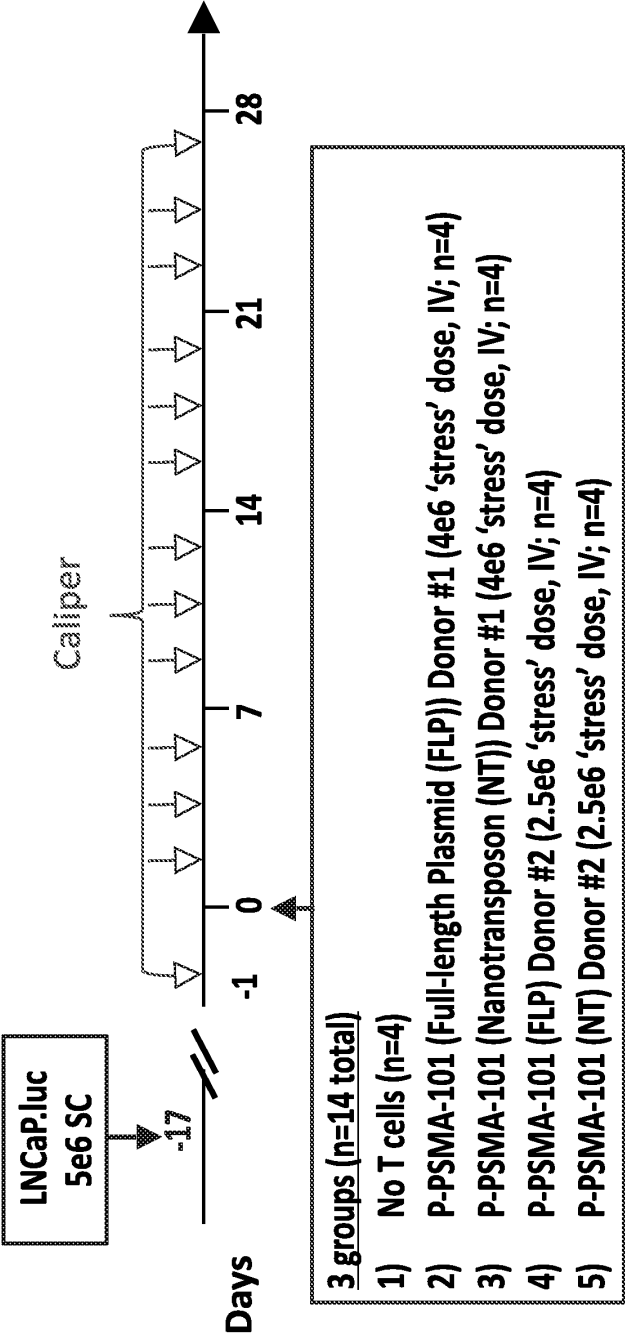
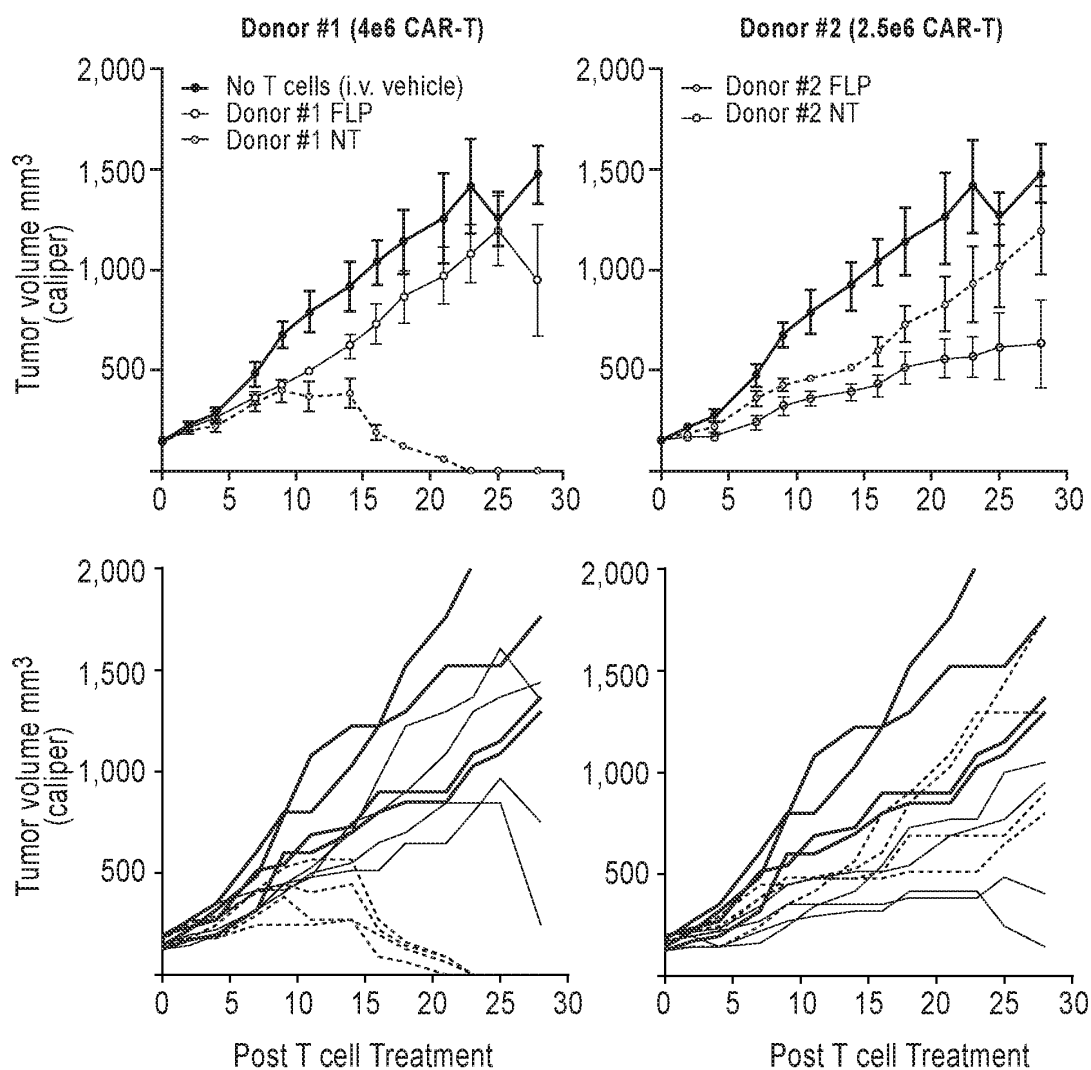


FIGURE 29A



A) Study design

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B) Caliper Measurements

FIGURE 29B

FIGURE 30  
T-cell receptor (TCR) and co-receptors CD28 and CD2

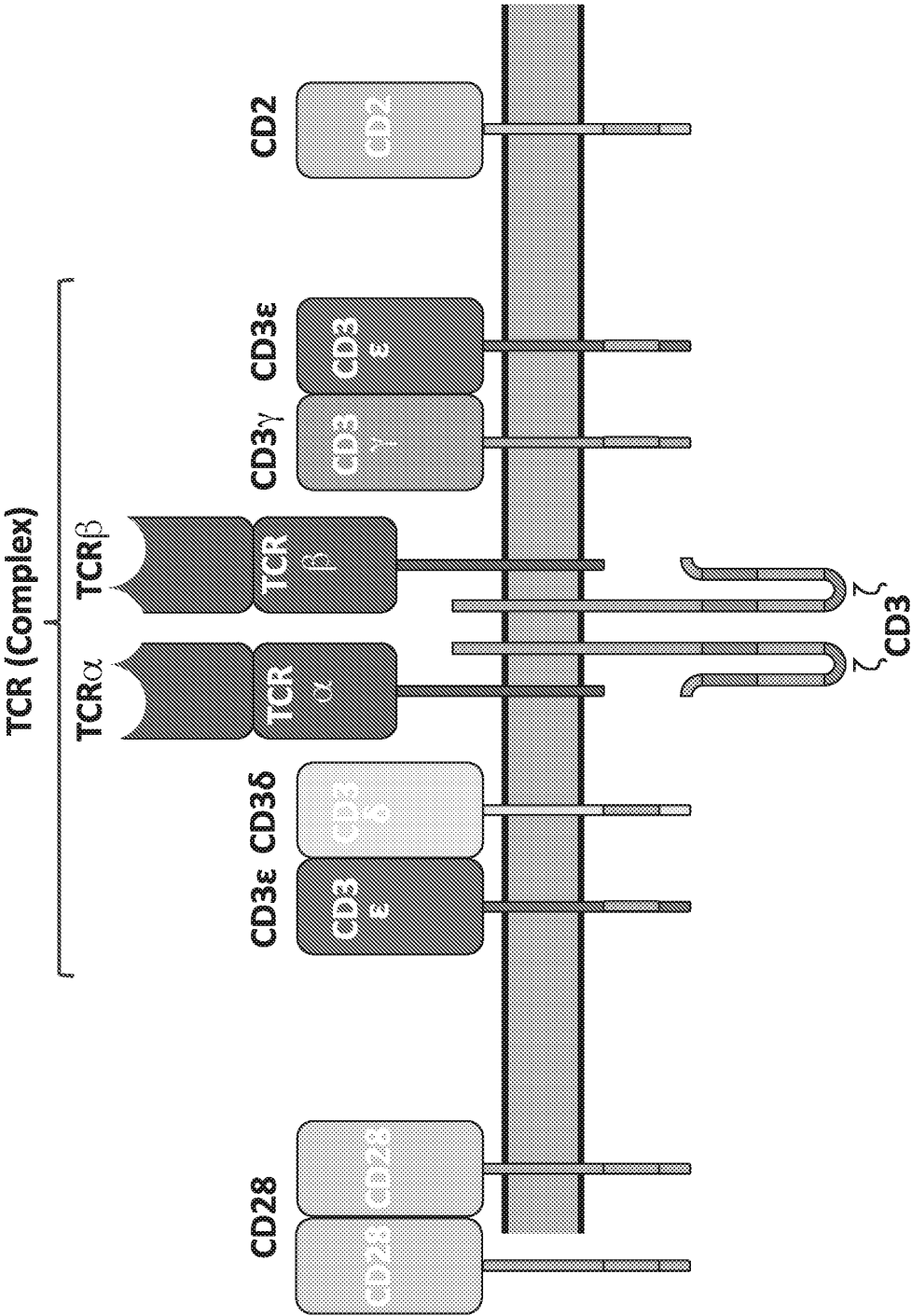


FIGURE 31

Primary and secondary co-stimulation is delivered to T-cell via binding of agonist mAbs (anti-CD3, anti-CD28, and anti-CD2)

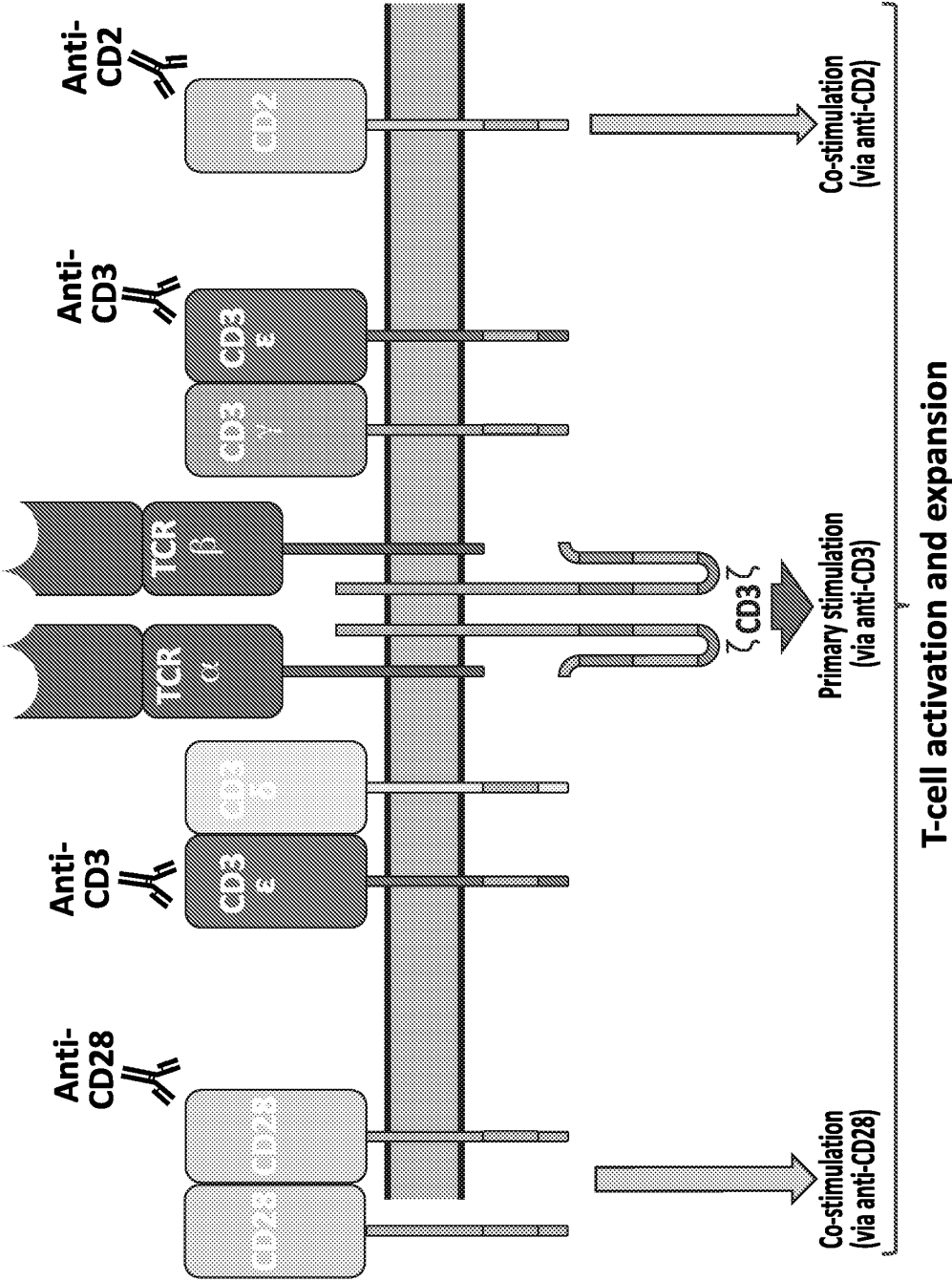


FIGURE 32

Enhanced stimulation by expression of Chimeric Stimulatory Receptors (CSR)s

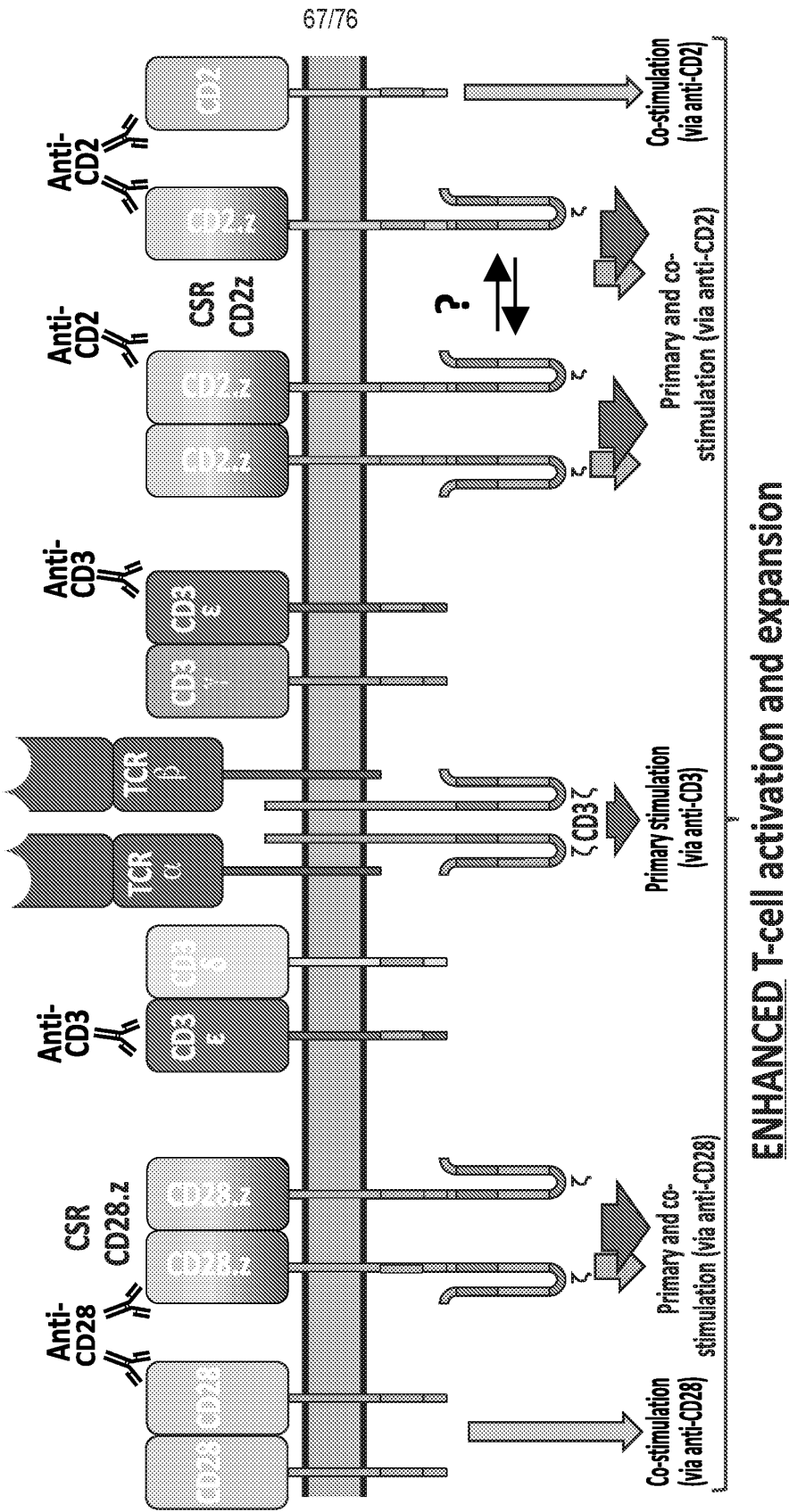


FIGURE 33A

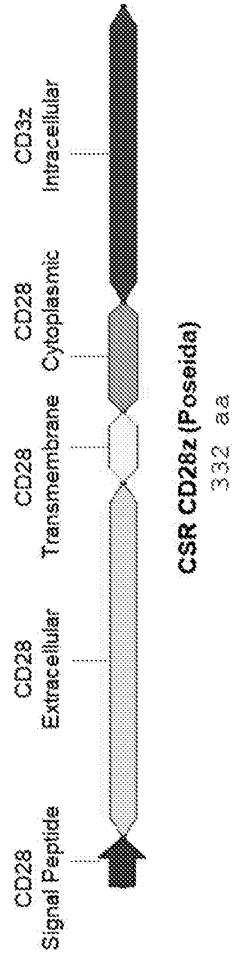


FIGURE 33B

MLRLLALNLFPSIQVTGNKILVKQSPMLVAYDNAVNLSCKYSYNLFSREFRSLHKGLDSAVE  
VCVWYGNYSQQLQVYSKTGFNC DGKLGNE SVTFYLNQNLVWNQTDIYFCKIEVMYPPPYLDN  
EKSNGTIIHVKGKHLCPSPLPFGPSKPFWVLVWVGVLACYSLLVTVAFIIFWVRSKRSRLHS  
DYMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYKQGQNQLYNELNLGRR  
EEYDVLDKRRGRDPGMPGKPRKNPQEGLYNELQDKMAEAYSEIGMKGERRRGKGHDG  
LYQGLSTATKDTYDALHMQALPPR (SEQ ID NO: 17910)

FIGURE 33C

ATGCTGAGACTGCTGGCCCTGAATCTGTTCCCCAGCATCCAAAGTGACCGGCAACAAGA  
TCCTGGTCAAGCAGAGCCCTATGCTGGTGGCCTACGACAACGCCGTGAACCTGAGCTGCAA  
GTACAGCTACAACCTGTTACGACAGAGAGTCCGGGCCAGCTGCACAAGGACTGGATTCT  
GCTGTGGAAGTGTGCGTGGTACGGCAACTACAGCCAGCAGCTGCAGGTCTACAGCAAG  
ACCGCTTCAACTCGACGGCAAGCTGGGCAATGAGAGCGTGACCTTCTACCTGCAAAACC  
TGTACGTGAACCAAGCCGACATCTATTTCTGCAAGATCGAAAGTGATGACCCGCTCCTTAC  
CTGGACAACGAGAAGTCCAACGGCACCATCATCCACGTGAAGGGCAAGCACCTGTGTCTT  
CTCCACTGTTCCCCGGACCTAGCAAGCCTTCTGGGTGCTCGTTGTTGGGTCGGAAGCAAGCGGA  
GCCTGTTATAGCTGCTGGTTACAGTGGCCTTCATCATCTTTTGGGTCCGAAGCAAGCGGA  
GCCGGCTGCTGCACAGCGACTACATGAACATGACCCCTAGACGGGCCCGGACCAACCAGAA  
AGCACTACCAAGCCTACGCTCCTCTAGAGACTTCGCCGCCTACCGGTCCAGAGTGAAGTTC  
TCCAGATCCGCCGATGCTCCCGCCTAAGCAGGGGCCAGAACCGCTGTACAACGAGCTGA  
ACCTGGGGAGAAGAGAAGAGTACGATGTGCTGGACAAGCGGAGAGGCAGAGATCCTGAG  
ATGGCGGCAAGCCAGACGGAAGAAATCCTCAAGAGGGCCTGTACAATGAACGACAGAAA  
GACAAGATGGCCGAGGCTACAGCGAGATCGGAATGAAGGGCGAGCGCAGAGAGGCA  
AGGGACACGATGGACTGTACCAGGGCCTGAGCACCGCCACCAAGGATACCTATGATGCC  
TGACATGCAGGCCCTGCCTCAAAGA (SEQ ID NO: 17911)

FIGURE 37

