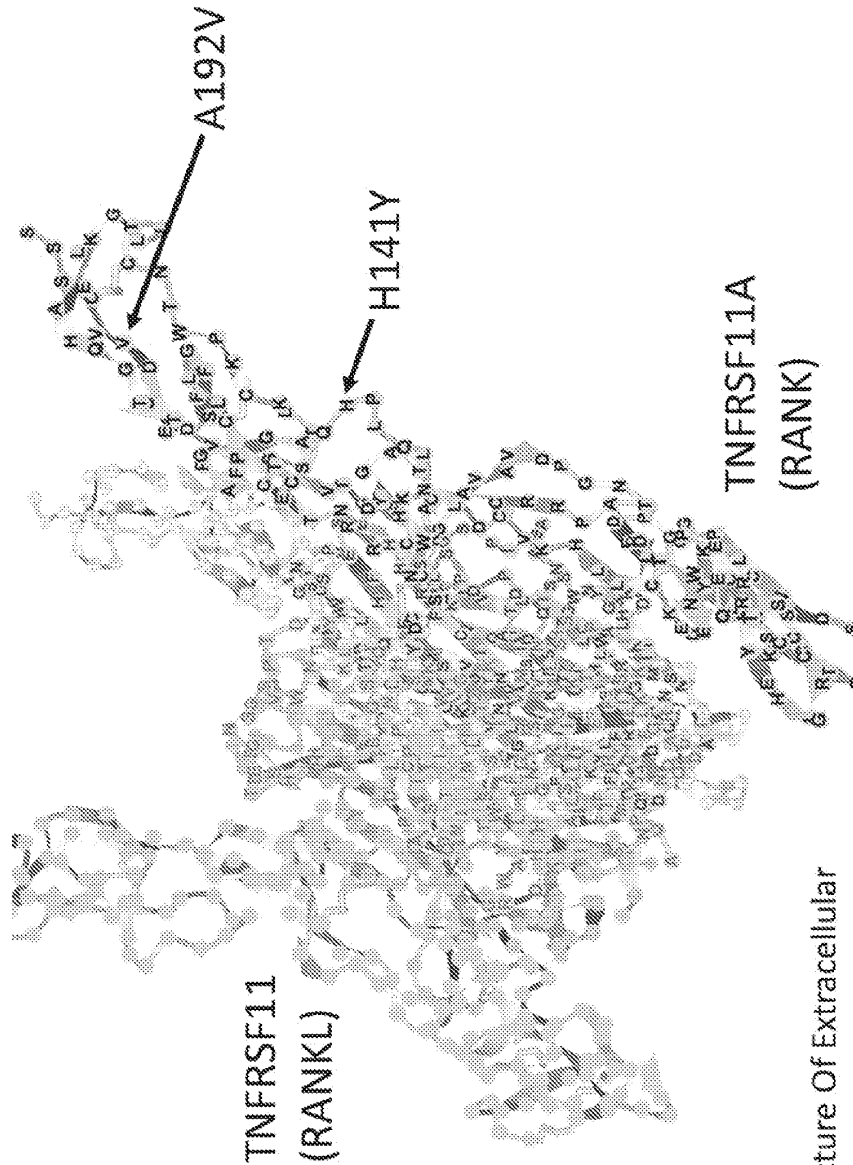


FIG. 1



3QBQ: Crystal Structure Of Extracellular
Domains
Of Mouse Rank-Rankl Complex
Ta et al., PNAS 2010

sp/P38570/ITAE_HUMAN/1-1179	1	-----MWLHTLLCIASALLAAPFVVARFWLTPKGGPVLSSLLHQDPSTNQTHLL
sp/P20702/ITAX_HUMAN/1-1163	1	MTRTRAALLTA-----TSLGELNLTTEELTAFRVDSAG-----GDSVVQVANSVVV
sp/P38570/ITAE_HUMAN/1-1179	139	ANFFDLENLLDPDAKVDTCGYSNKEGGEDDVNTARQPRALEKEEEEDEKEEEEAG
sp/P20702/ITAX_HUMAN/1-1163	138	-----VSRQECPROE
sp/P38570/ITAE_HUMAN/1-1179	291	SFTTSCHSSRKSSVMVVLADGGIFEIPNLTIVINSPKNOQVEFFAGVGEEAKSARTAR
sp/P20702/ITAX_HUMAN/1-1163	238	RLZHAAYCAEDAKILLIITTECKKEGSLDYKDVIPNADAAITIEYAGVGLAFONRNSWK
sp/P38570/ITAE_HUMAN/1-1179	440	GRINQTAATAAADAEAAQYVIGAVAVLHKTCSLVYIAGSPKTHGAVFELQKEGEASE
sp/P20702/ITAX_HUMAN/1-1163	389	-TIIAMS-----QENVDMRDVILSTELAIWKGVQLNLTAEHVOITKAVIFTQVSEWRM
sp/P38570/ITAE_HUMAN/1-1179	592	LIDVATGAPILGGFADGASESLIYINSHWD-GLNAPSPQIRASTVAPGQVMSMA
sp/P20702/ITAX_HUMAN/1-1163	536	ETAVVQNGCE-----ENRINILFHVLGPSTFHHQRAQQLSSRQVQOALS
sp/P38570/ITAE_HUMAN/1-1179	731	VVVKORRLOCSDVRS-CGCLKEWSSGSQLDLLMPTGELFECFSNASVKVSQV
sp/P20702/ITAX_HUMAN/1-1163	681	LPFRLSPATFOETNRNSSRVIVL-GLKANGNFNLL---PSVLSVTPTILRLNFT
sp/P38570/ITAE_HUMAN/1-1179	880	LKRMOKP-----PQNIQDDP-QPVASVLINNFPGPVLKRSSAHVSVV--WOLEENF
sp/P20702/ITAX_HUMAN/1-1163	829	YRYVAEGCKQKQGLRLHLTDSAPVGSQGTWSTSRLNLIIRGGAQ-TTFLATFDVSPKIV
sp/P38570/ITAE_HUMAN/1-1179	1016	LQVAVKKLTRLT-QATVCTWQERACVSSVQVVEEWHVSQVLT-----SD
sp/P20702/ITAX_HUMAN/1-1163	980	ERVMDVEVSHQPQNPRLRSSEKIAPESDFLAIQKNPVLDSACGLRERCDFESFSVQE
sp/P38570/ITAE_HUMAN/1-1179	1151	ETEEKCOLNLIRKKAQLKSLILEEN-----
sp/P20702/ITAX_HUMAN/1-1163	1132	ETEEKKENNEANGQI--APVGTQTFSPPEK

1019

FIG. 2

TS RTKR-----TEPHR SILVQDEILH VERHPI KGRH--RVTV---VRHHGV I IOVL RRPHSLSSE AGRH SAGE DLRF AQ 138
GA OKITAANOT GYO GYSTG--AEIIGLOVP EAVNMSL LSLASTT FSOI A GP-T HHCEGRMY TOL FLCE TOLT R- 137
TE ATIL SES DPPD ORAND ISNMNRN IEKCEECN A VYGGVIT E DLRDSQDVMA S ARVONIT VGSV KEI S MCHLD 290
QD VELI SES ISSRN ATMMN VRAVISQORP--STQ SLM FSNKFC H TFEERSSNP SLLASVH LOGFTYAT II NVH 237
TINL ASD DETHAEVINYNAIDGLLSKIRYNTISMGVV---GDALHYQI QICFSAQILDEROVILSGVBAFASGAIL DTRSR 439
EIND ASKESOEI ENVEDEDA KDIONQ KEK FAIEG EITSSSFELEMAGEFSAVFT-PDGPVLCVGSFHWSECAF LPPNMSP 388
LPVLE GEONESVSESE GPVHIMGES FLI VAEFF HVHGEER YMY SEQDGSFSLARI SEHFE TNA F FAMAANGILSQ 593
KAETVTH IESNEFAS ISDVVSDSESLV IIGEPHYEQTRG QMS CP FRGWRWNCDAVIMYEQ HPWGRF AALTIVL EDVNG 535
FISG ZIA IITVGTILCAVVE SH VRLKZ AFI SAL IIGFNG-----V NVRL FELSSTTASES IL EALLNF--D 730
Q LITC GIVLS AR VILL ITP LNVCS OFI AET RSAFECEQVNSEQIL OSNIIYDKRSKN-LL S DLOSSV LLA 680
Q-T EGOTDHPQ I I DRYTEPENAFQI YAAKNKLF VAE OLATIVS-QCE V GLTKELTILINILT SSSS M SMALNY ENNO 879
VGK LLAFRNLREM AADAORYFTAS FFEAN GADHI QDN GISFSFPGLKS LGSNLEI NAEVMMV DEDS G TITFESH AC S 828
PNRTADI VVTNSERRSLANEHT QFRHGF--VAAL K--PSIM VVTGQGLSHHKEFLF VHGENLF-----AEYOLQICVTKERG 1015
LGDRLLL ANESSENIPTSKT FQ ELPVYAVYT V SHEQFTR LTFSESEEEKESHVAMRYQVNI QRDLPVSINFWVEVE NO 979
KENV VAAEIAWDHSEEL KDVTIELQILGE SENK IYEG NAENHR--TKITV FL DEKYHSLEITIKG VGGIIV IIVILVILFC 1150
ELDF LKGNLSEFGWVRQI QKKVSVVSVAT TDT V SQ PGQEAFMRAQT I VLE YKVHNPTPLVGS I ELL LALATAV YVE 1131
1179
1163

FIG. 2 (Cont..)

FIG. 3

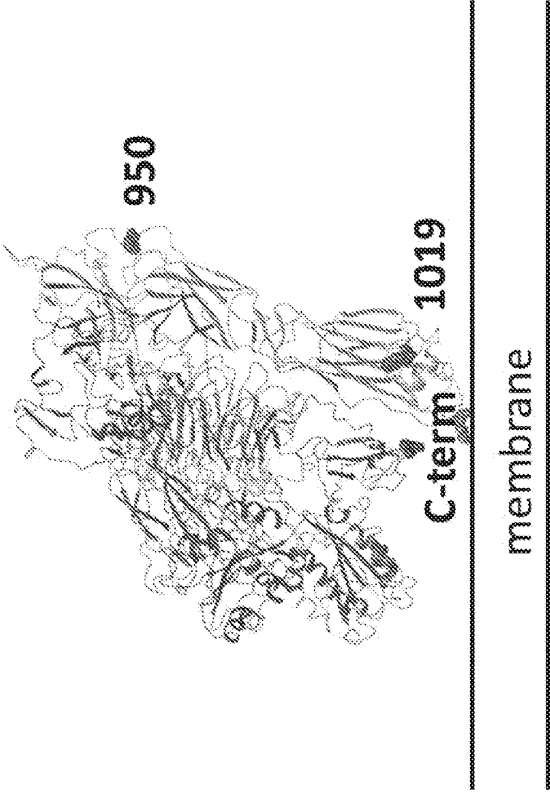
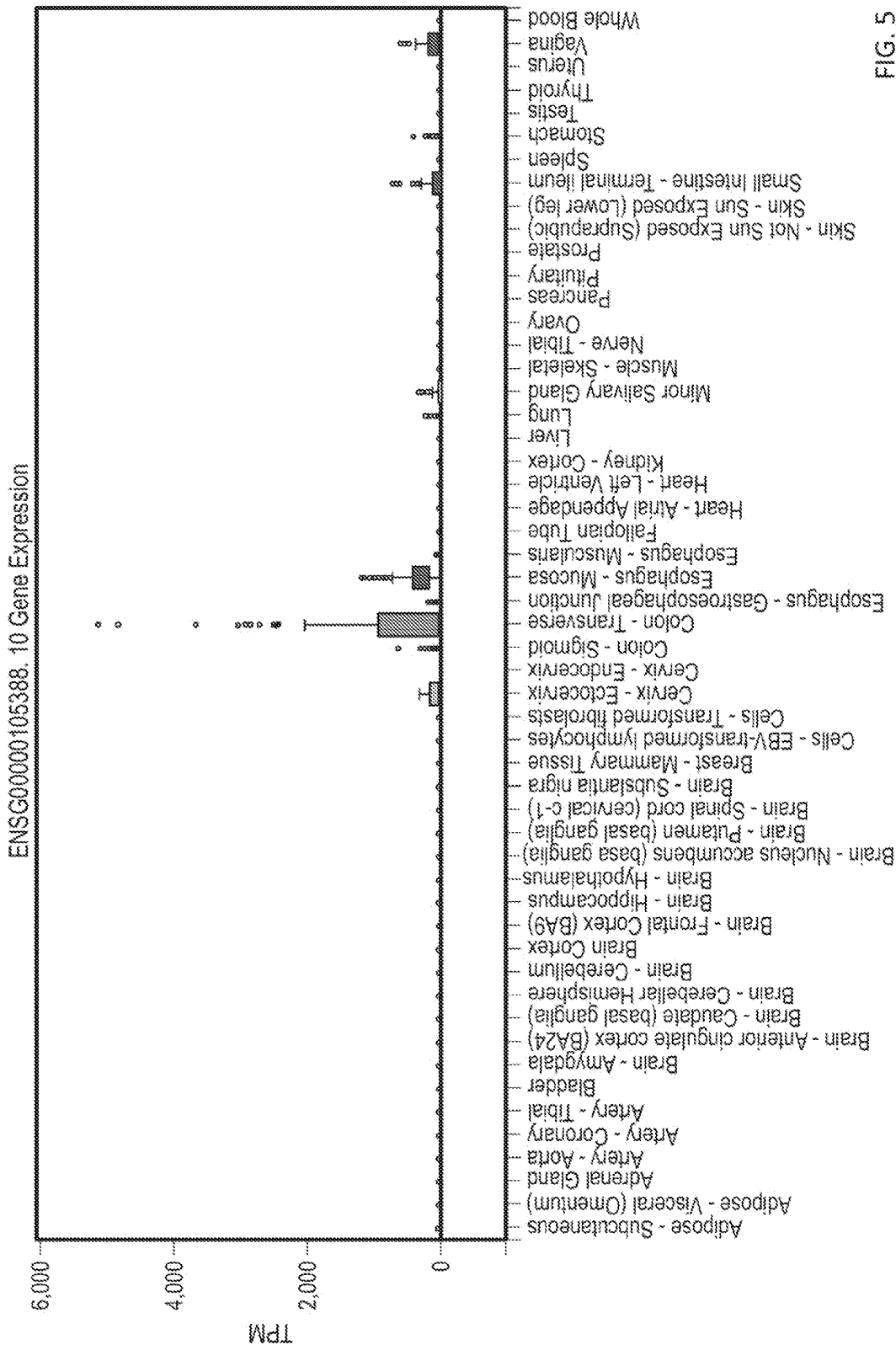


FIG. 4

Cancer (% CEA+; median >100 transcripts/cell)	Patient No.	RANK LOH Freq.	Treatable No. Range (CEA+) [MAF = 0.1 – 0.4]	NGS Dx: pass/tested [MAF = 0.1 – 0.4]
Rectal (100%) [30% subset of colorectal]	15K	0.87	0.8-1.6K	$2 \times [0.05 - 0.11] = [1/10 - 1/5]$
Colorectal (100%)	53K	0.70	2-5K	$2 \times [0.04 - 0.09] = [1/12 - 1/6]$
Pancreatic (50%)	43K	0.67	0.8-2.0K	$2 \times [0.04 - 0.09]$
Esophagael (50%)	16K	0.63	0.3-0.7K	$2 \times [0.03 - 0.08]$
Gastric (50%)	11K	0.47	0.2-0.3K	$2 \times [0.03 - 0.06]$
Lung adenocarcinoma (50%)	109K	0.47	1.5-3K	$2 \times [0.03 - 0.06] = [1/20 - 1/9]$
Head&Neck		0.53		
DLBCL		0.04		
AML		0.02		
All cancers		0.33		



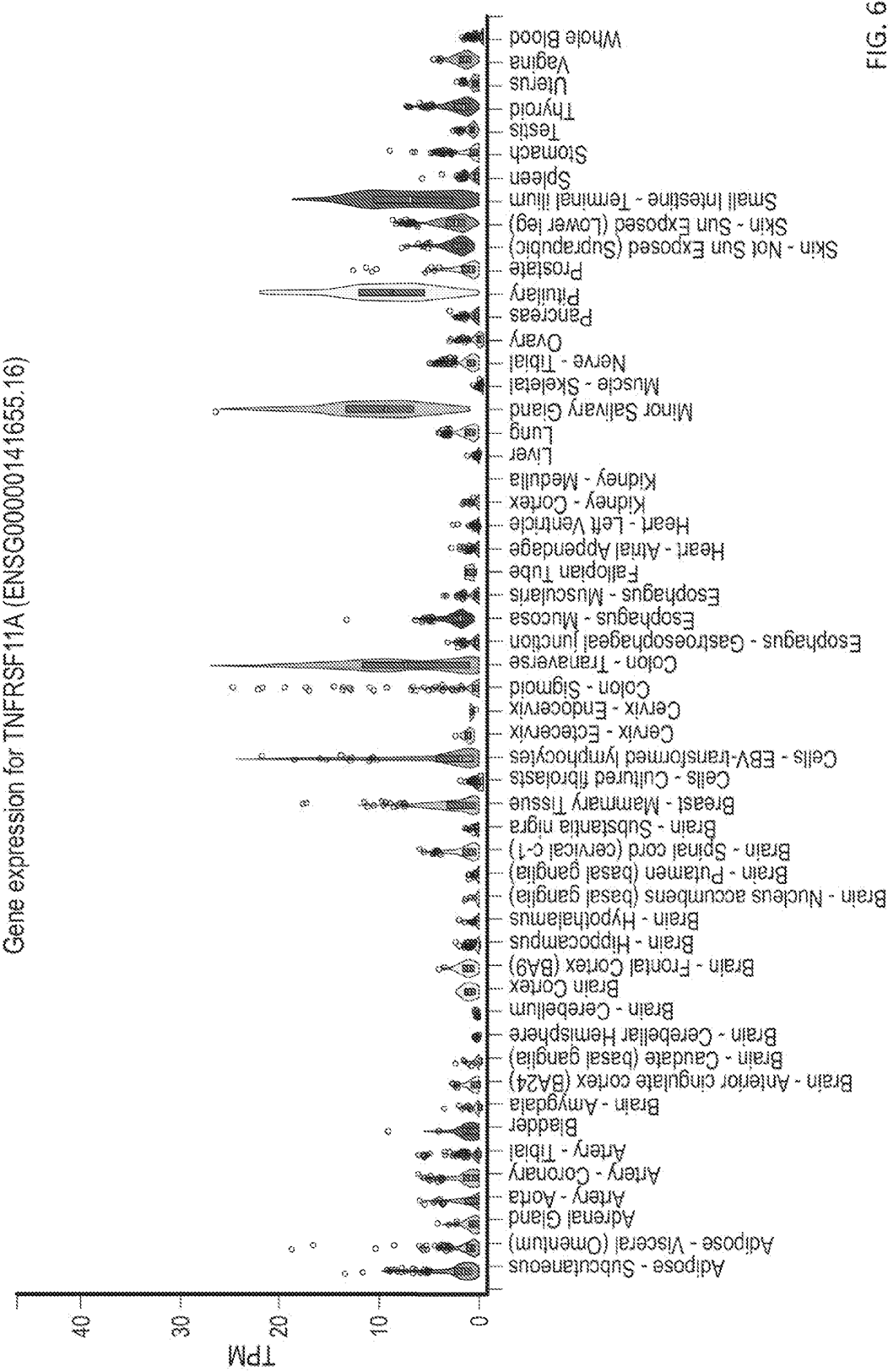


FIG. 6

FIG. 7

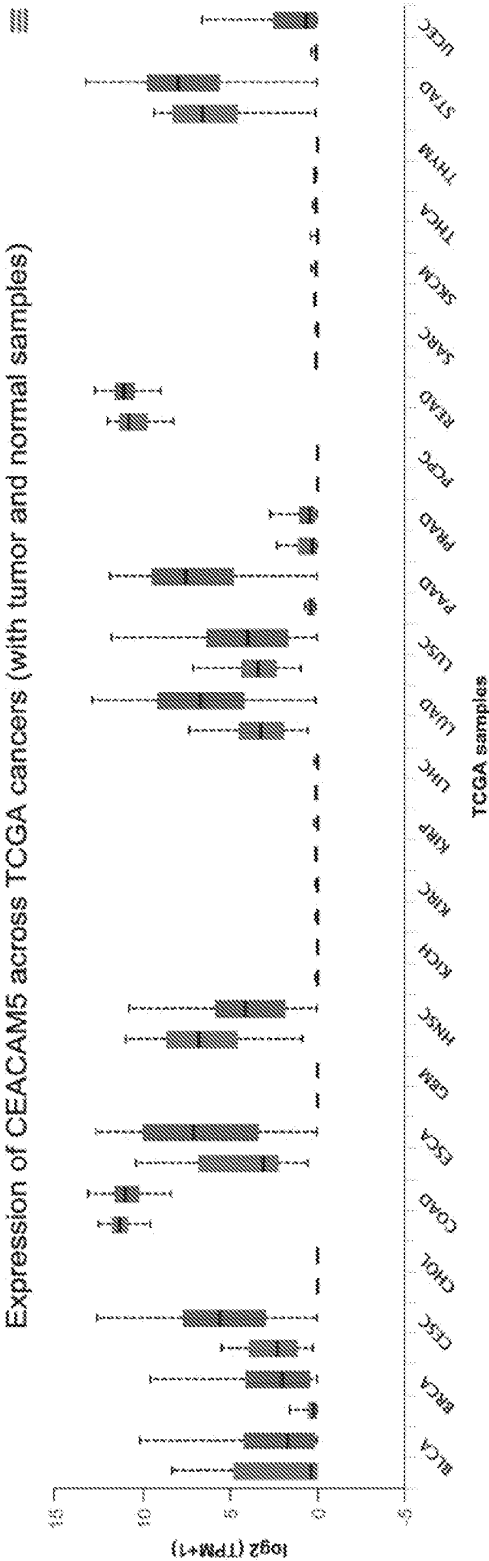


FIG. 8

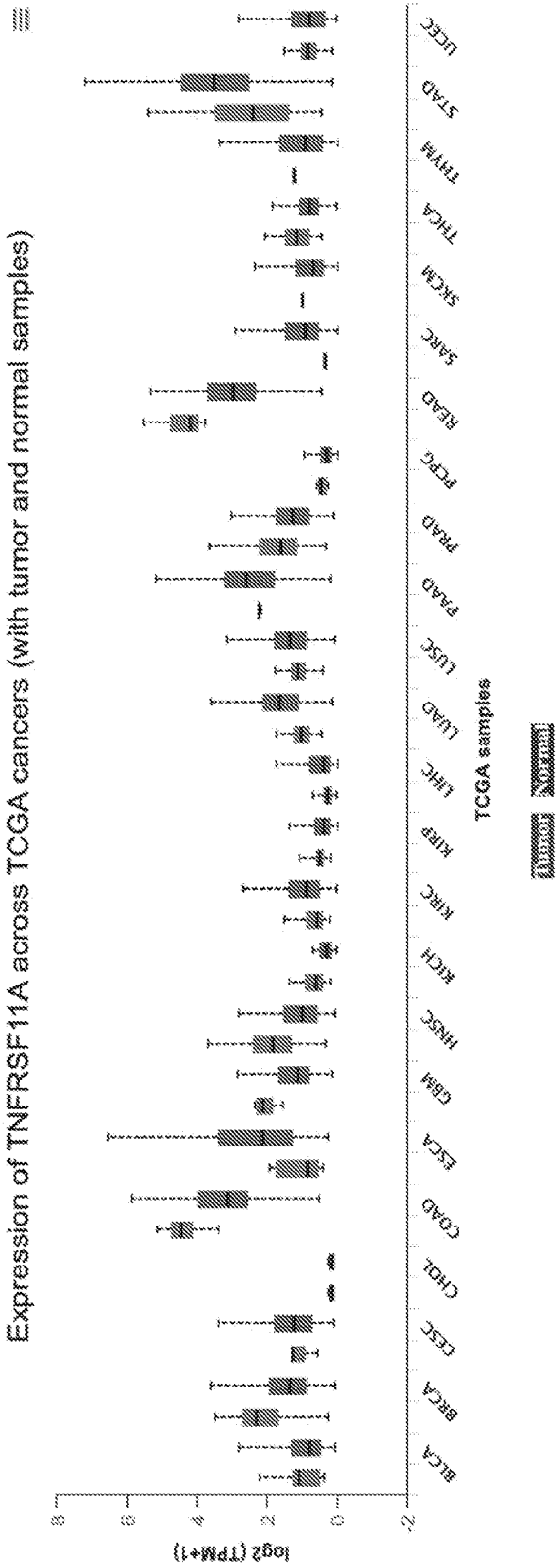


FIG. 9

CANCER TYPE	DEATHS	CANCER TYPE	DEATHS
Lung and bronchus	155,870	Melanoma of the skin	9,730
Colorectum	50,260	Oral cavity and pharynx	9,700
Pancreas	43,090	Soft tissue (including heart)	4,990
Breast	41,070	Cervix	4,210
Liver and intrahepatic bile duct	28,920	Gallbladder and other biliary	3,830
Prostate	26,730	Larynx	3,660
Leukemia	24,500	Thyroid	2,010
Non-Hodgkin lymphoma	20,140	Bones and joints	1,550
Urinary bladder	16,870	Small intestine	1,390
Brain and other nervous system	16,700	Vagina and other female genital	1,240
Esophagus	15,690	Vulva	1,150
Kidney and renal pelvis	14,400	Anus, anal canal and anorectum	1,100
Ovary	14,080	Hodgkin lymphoma	1,070
Myeloma	12,590	Ureter and other urinary organs	920
Stomach	10,960	Testis	410
Uterine corpus	10,920	Penis and other male genital	360

FIG. 10

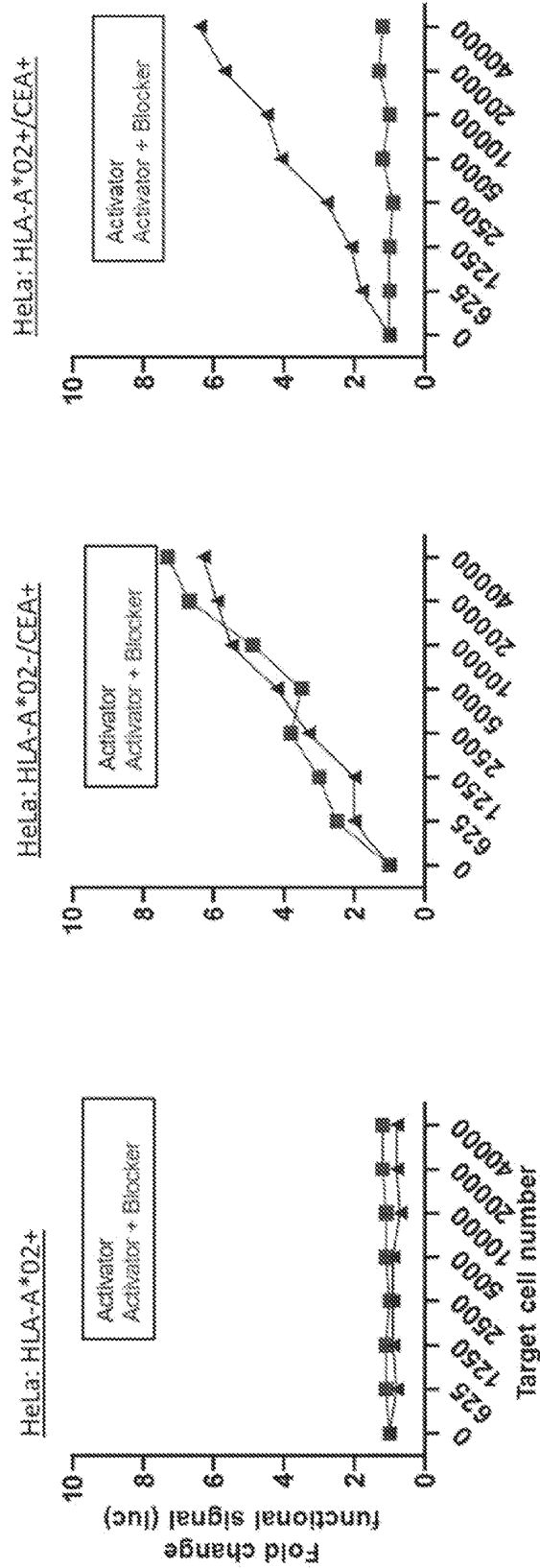


FIG. 11

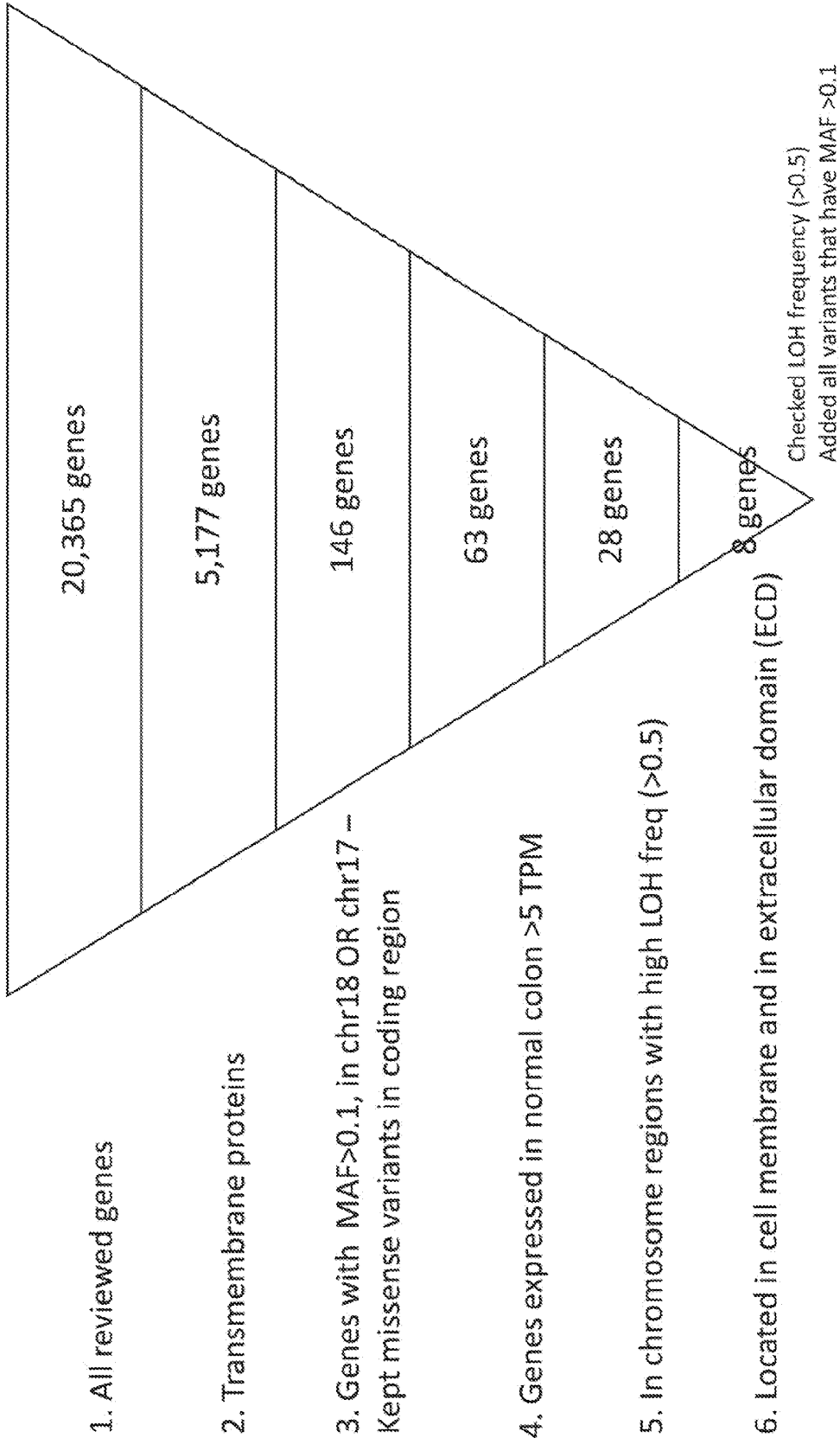
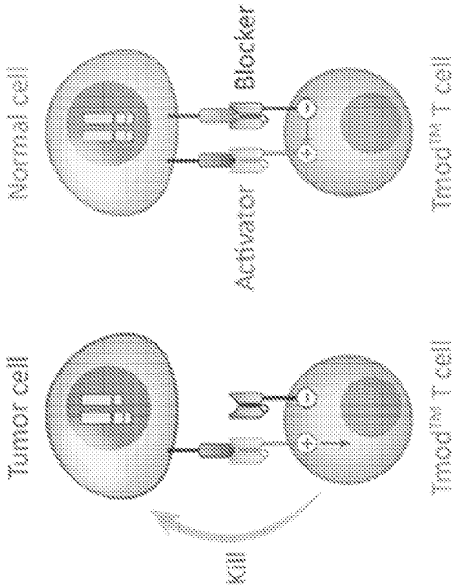


FIG. 12

Tmod™ mechanism for selectivity



Selected patients

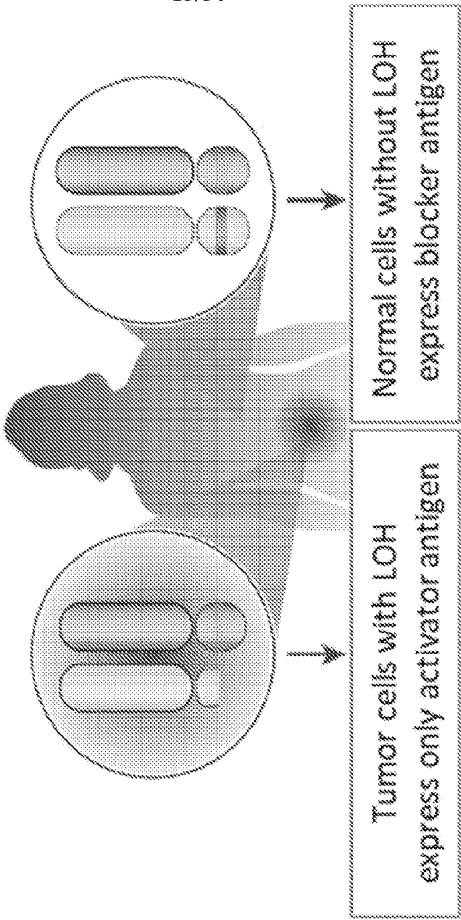


FIG. 13

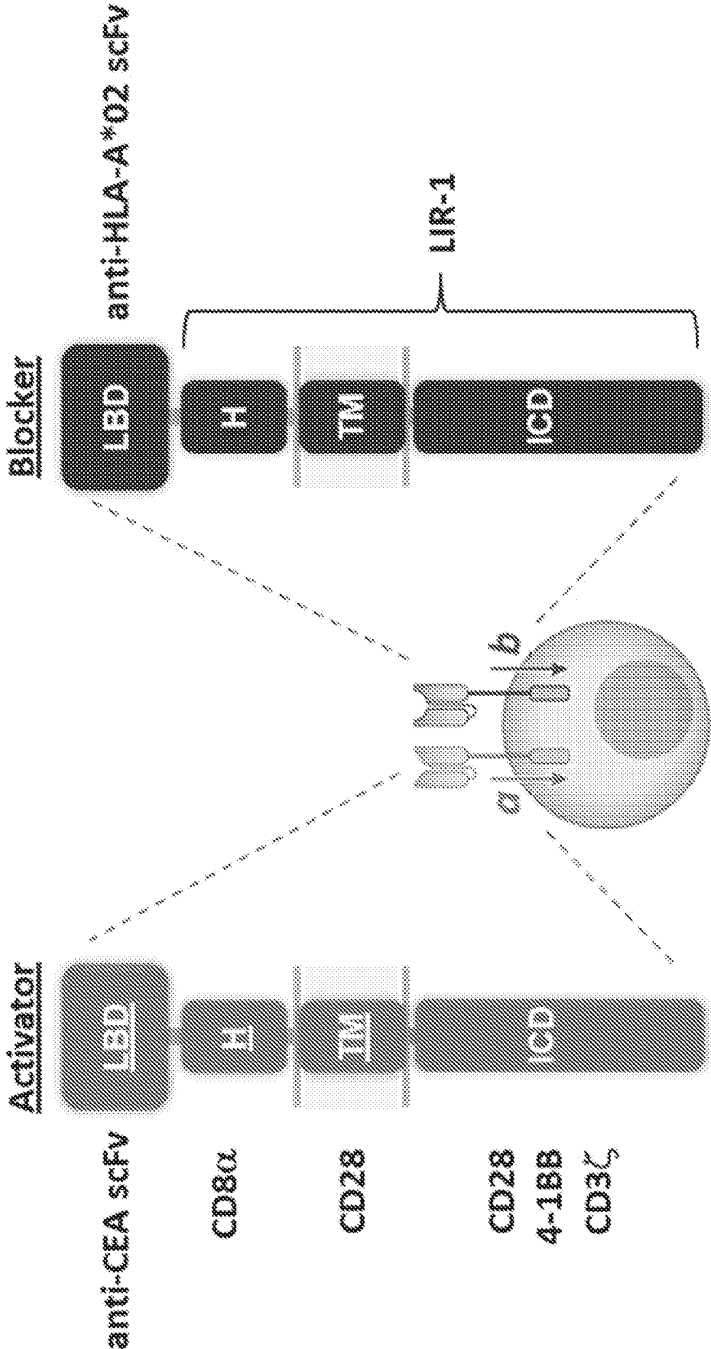


FIG. 14

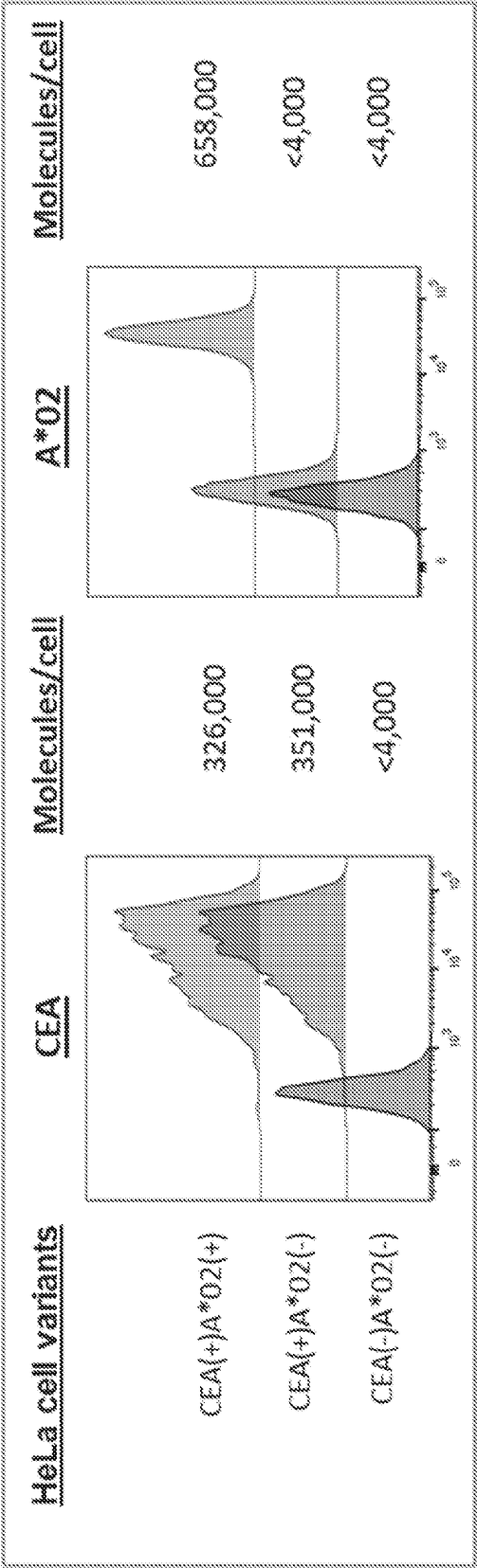


FIG. 15

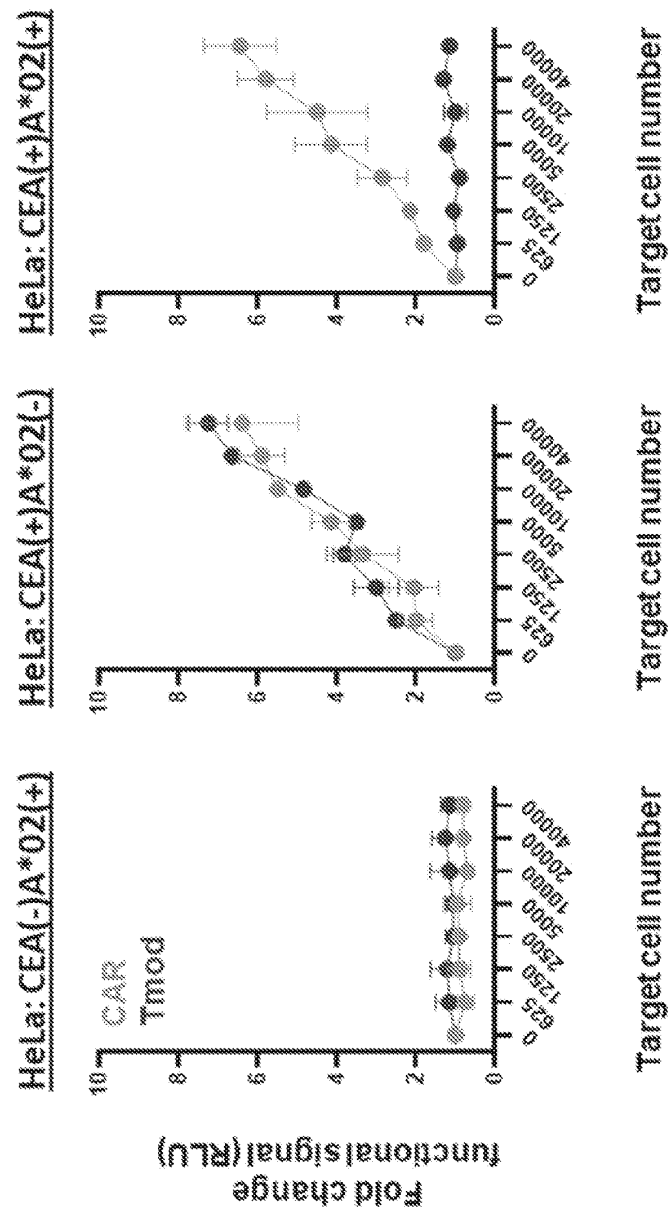


FIG. 16

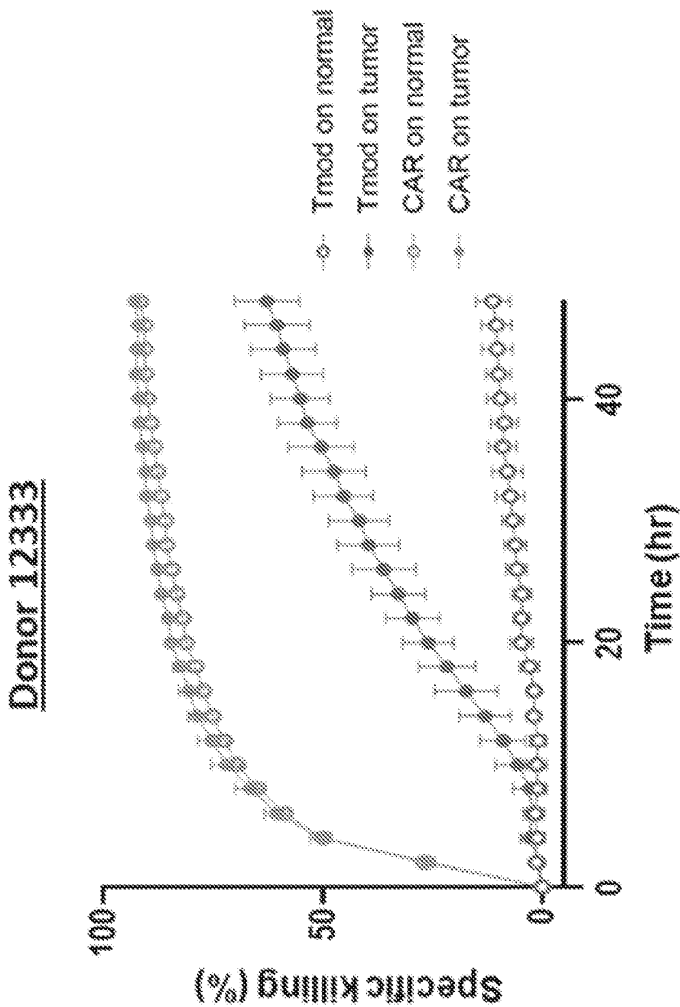


FIG. 17

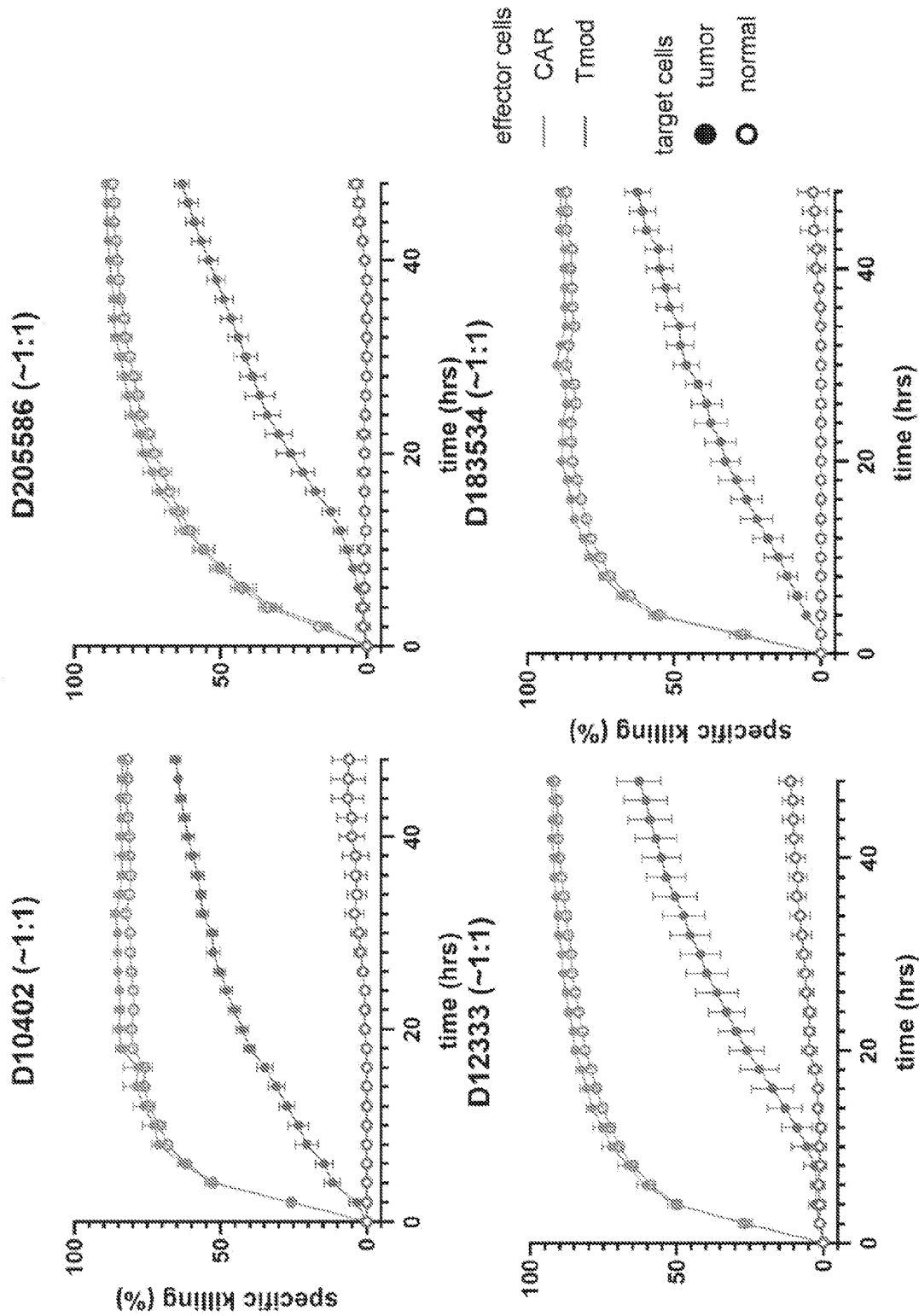


FIG. 19

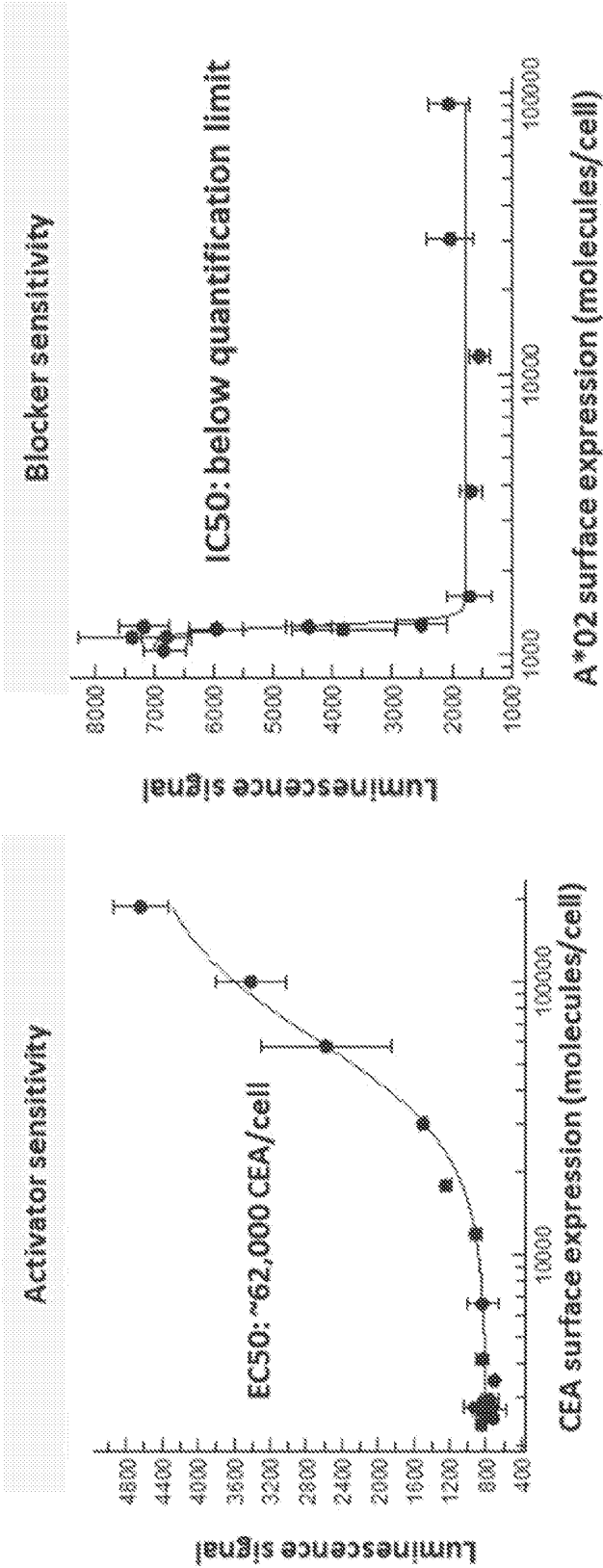


FIG. 20

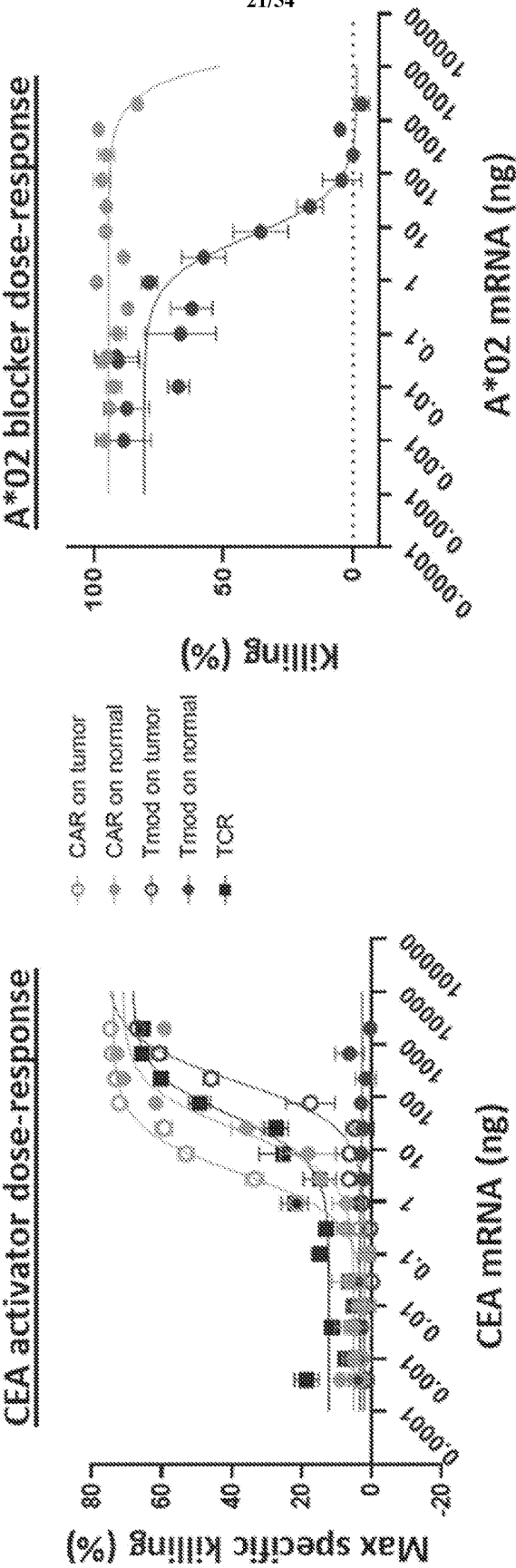


FIG. 21
CEA CAR Tmod sensitivity mapped on CEA and A*02 expression

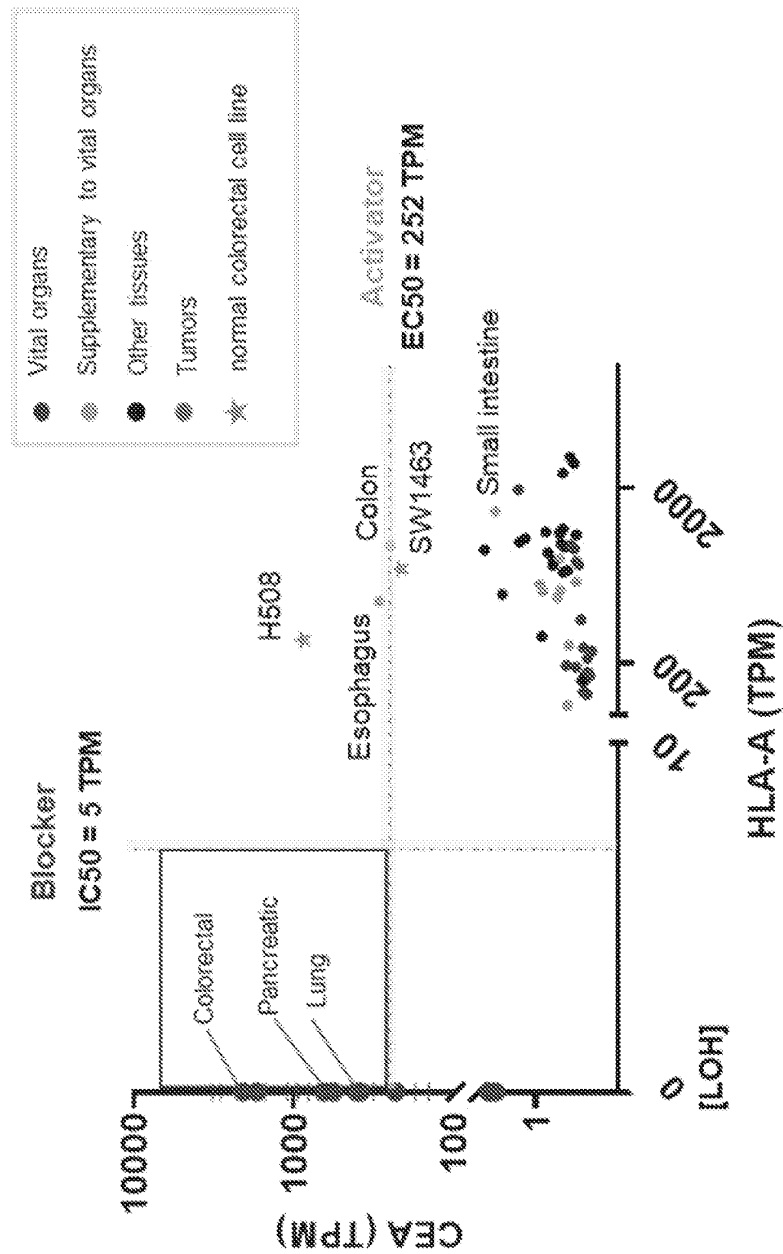


FIG. 22

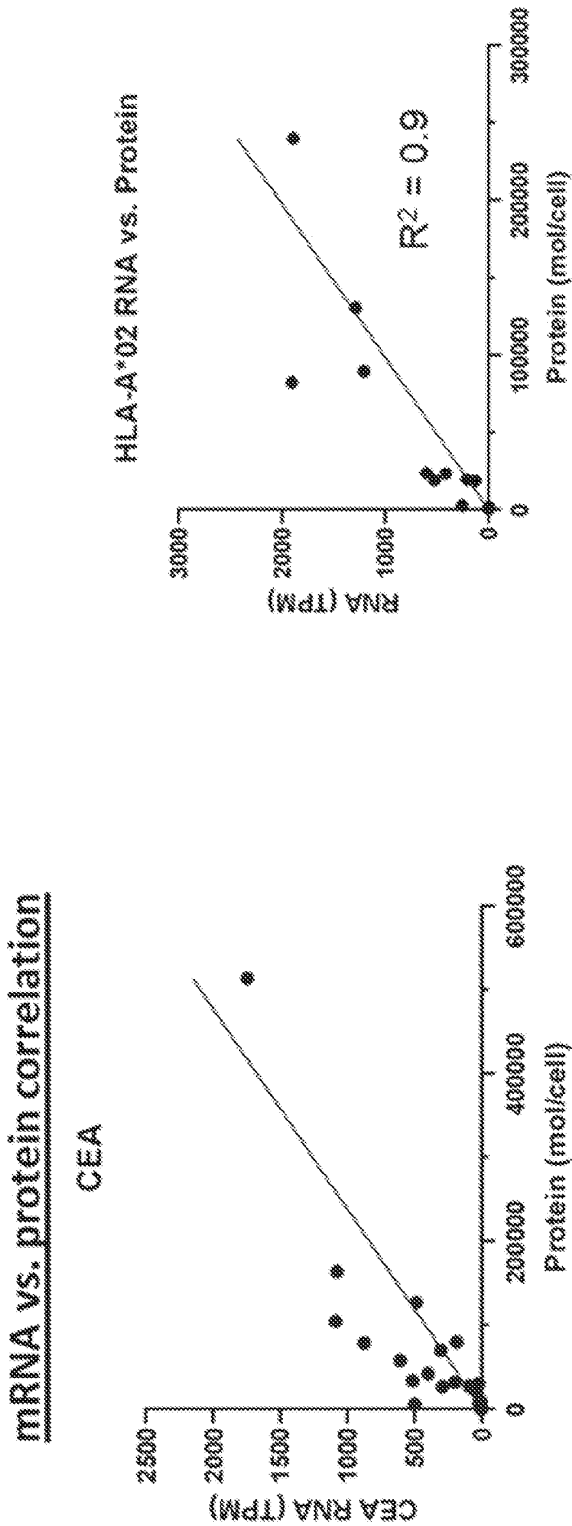


FIG. 23

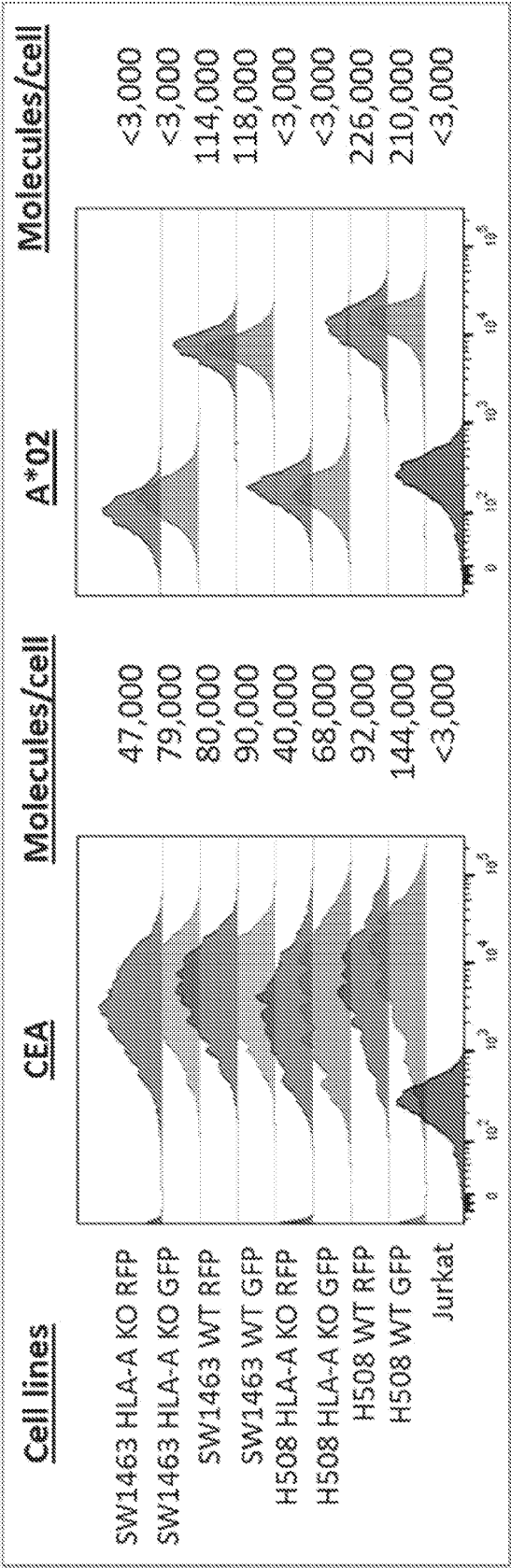


FIG. 24

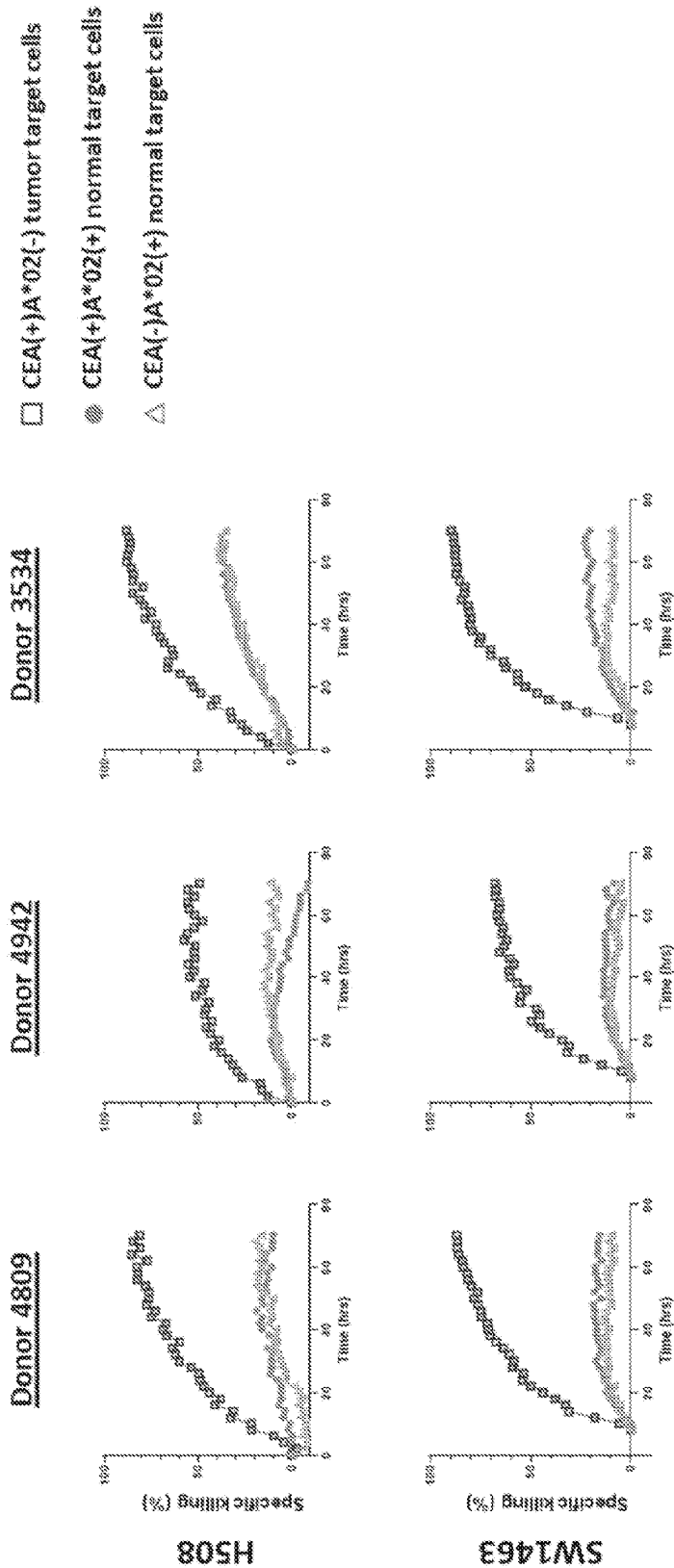


FIG. 25

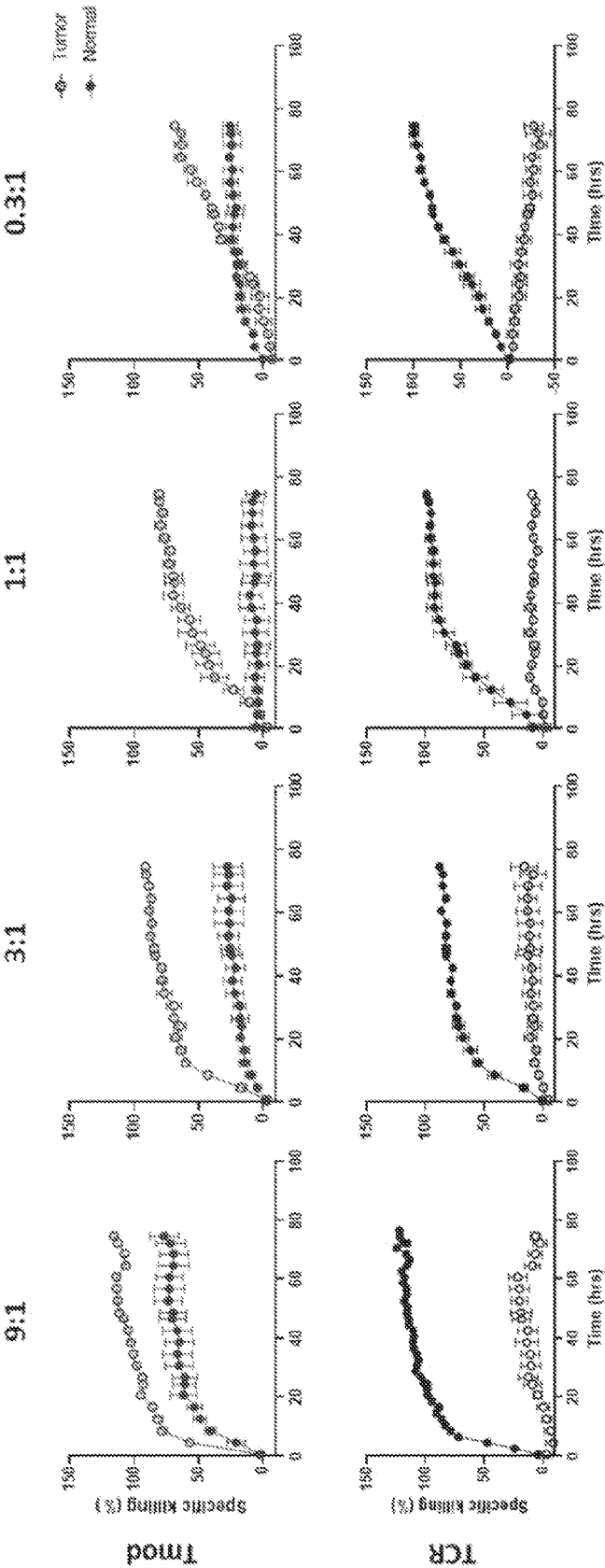
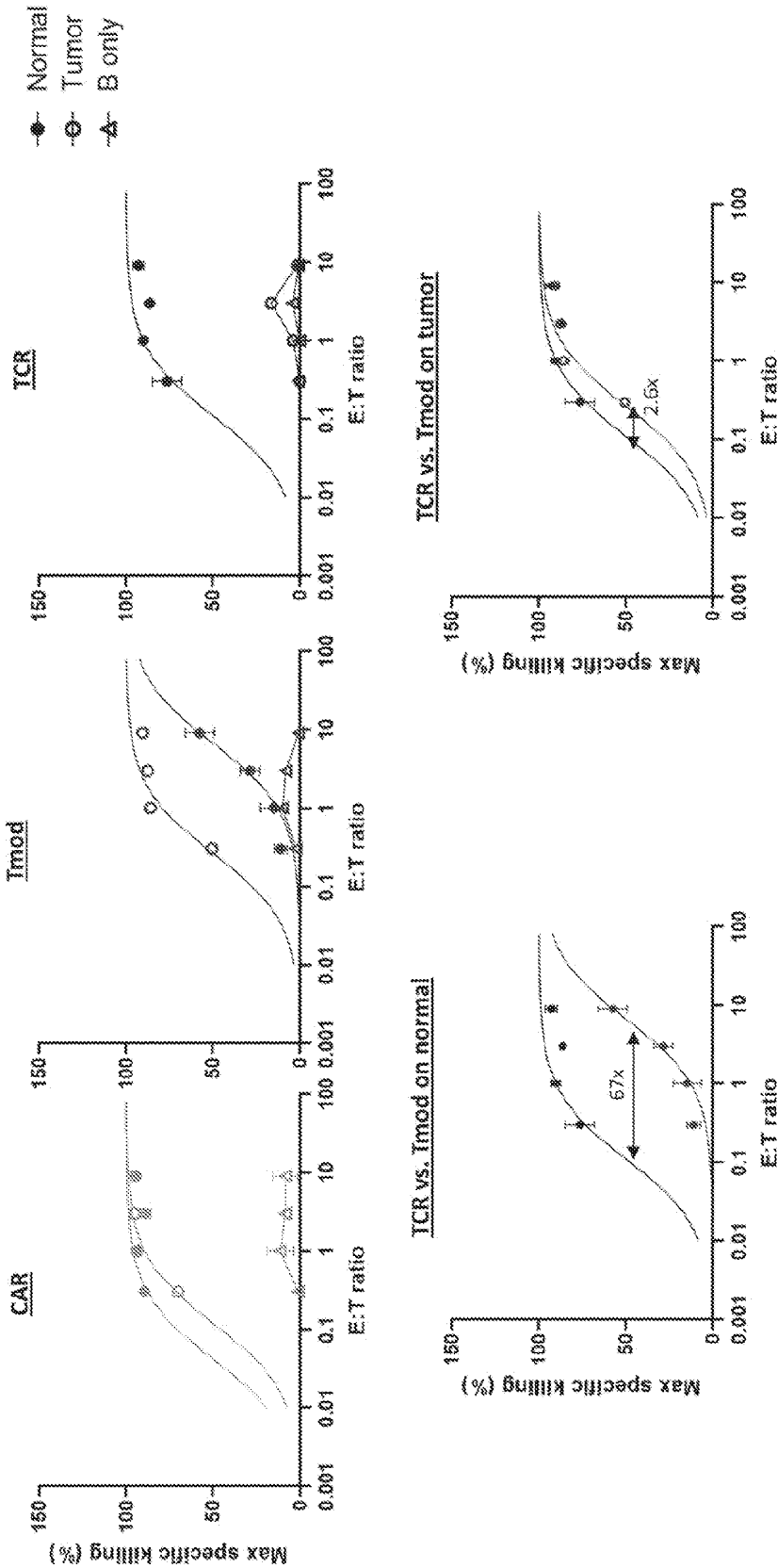


FIG. 26



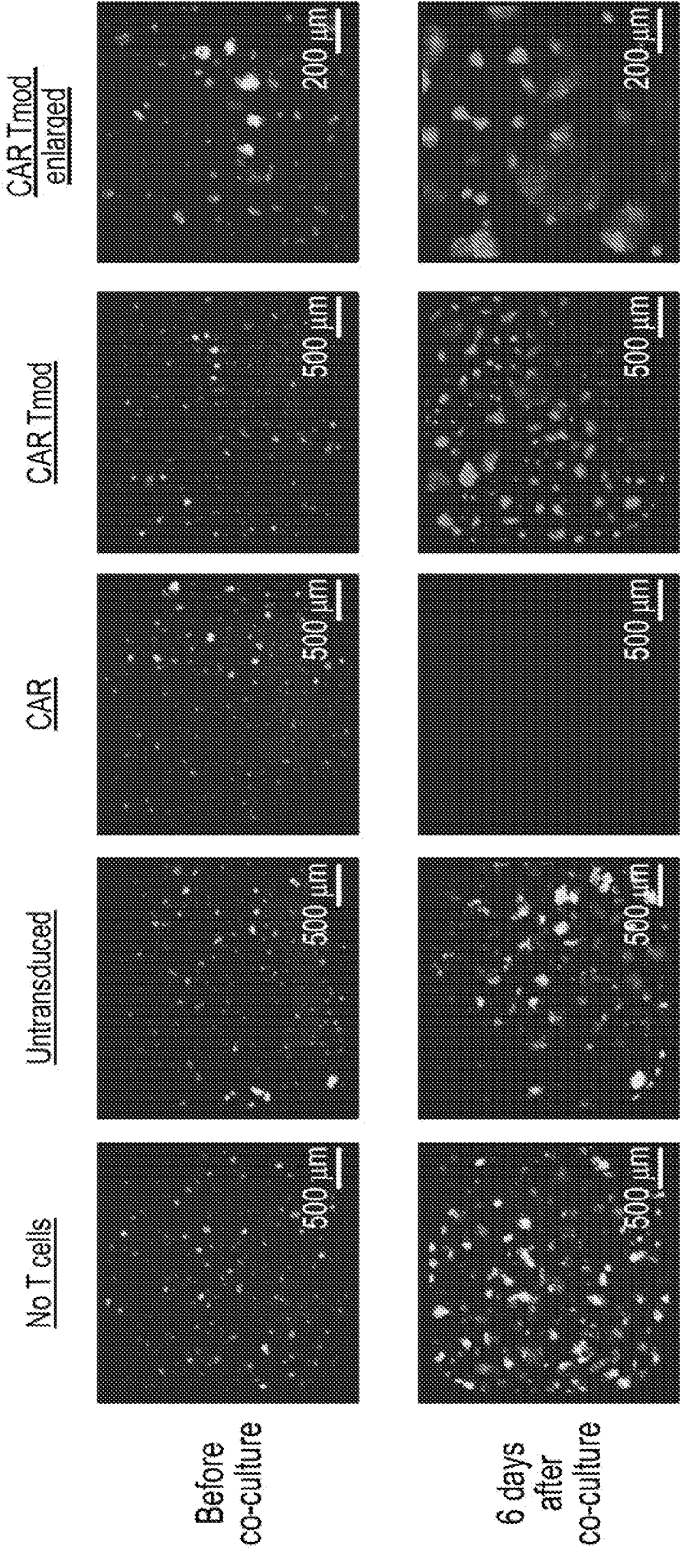
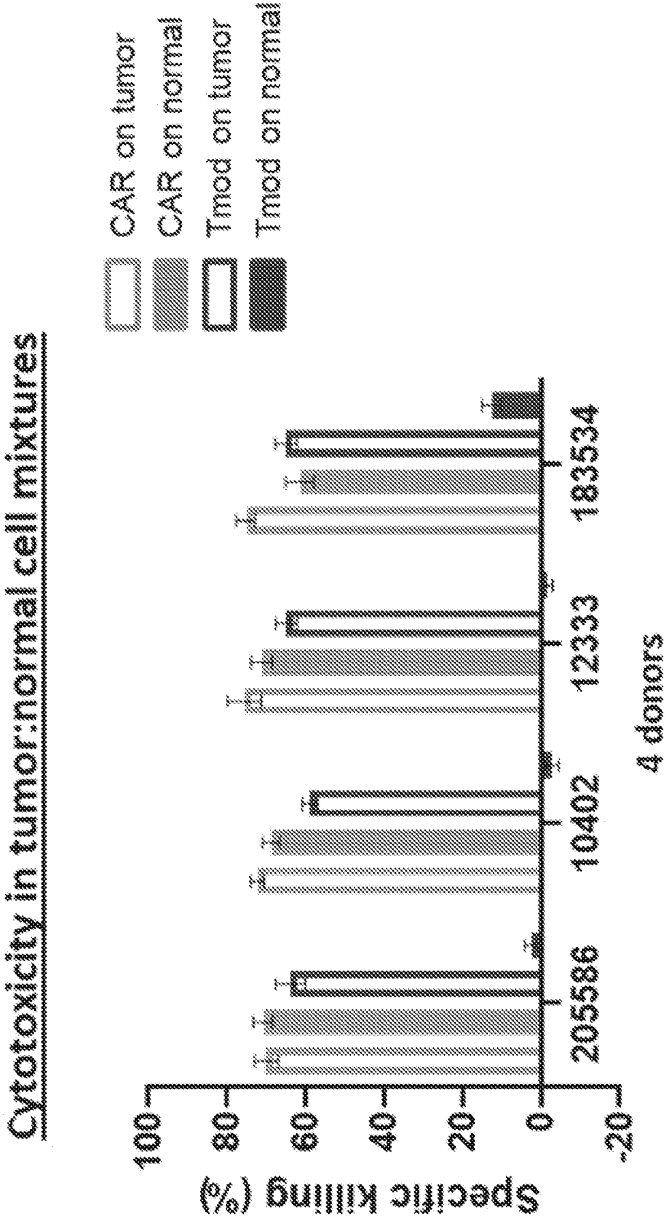


FIG. 27

FIG. 28



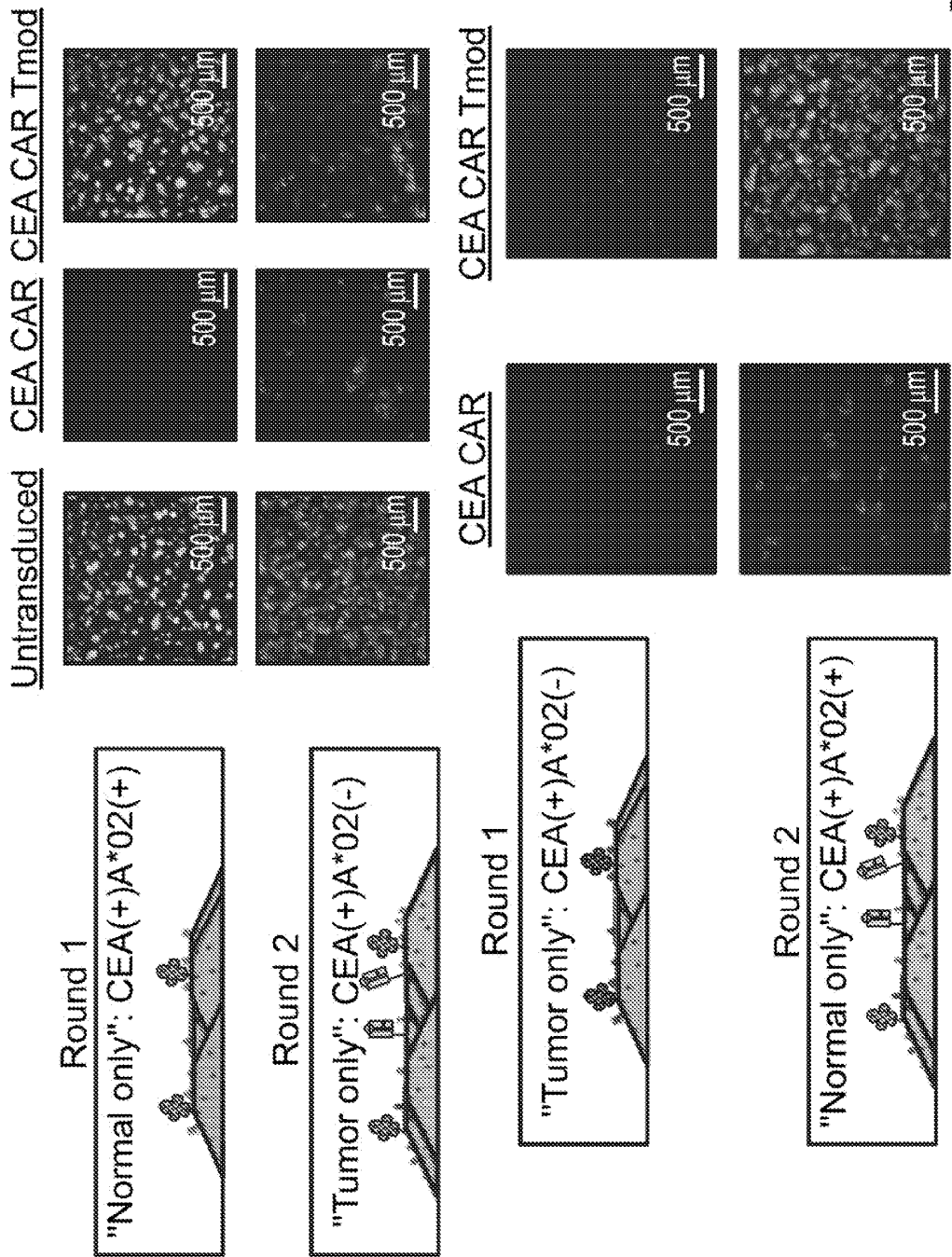


FIG. 29

FIG. 31

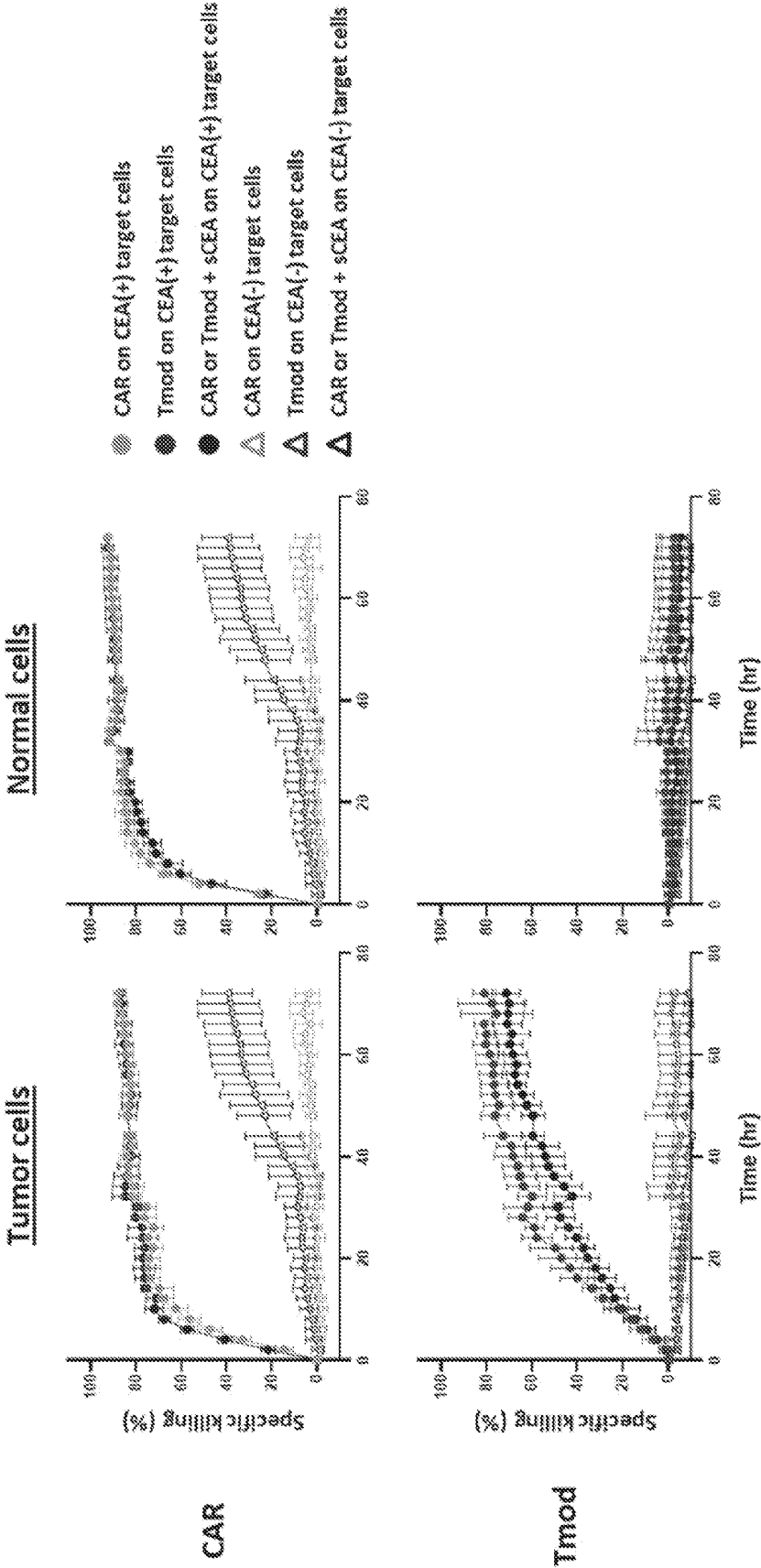
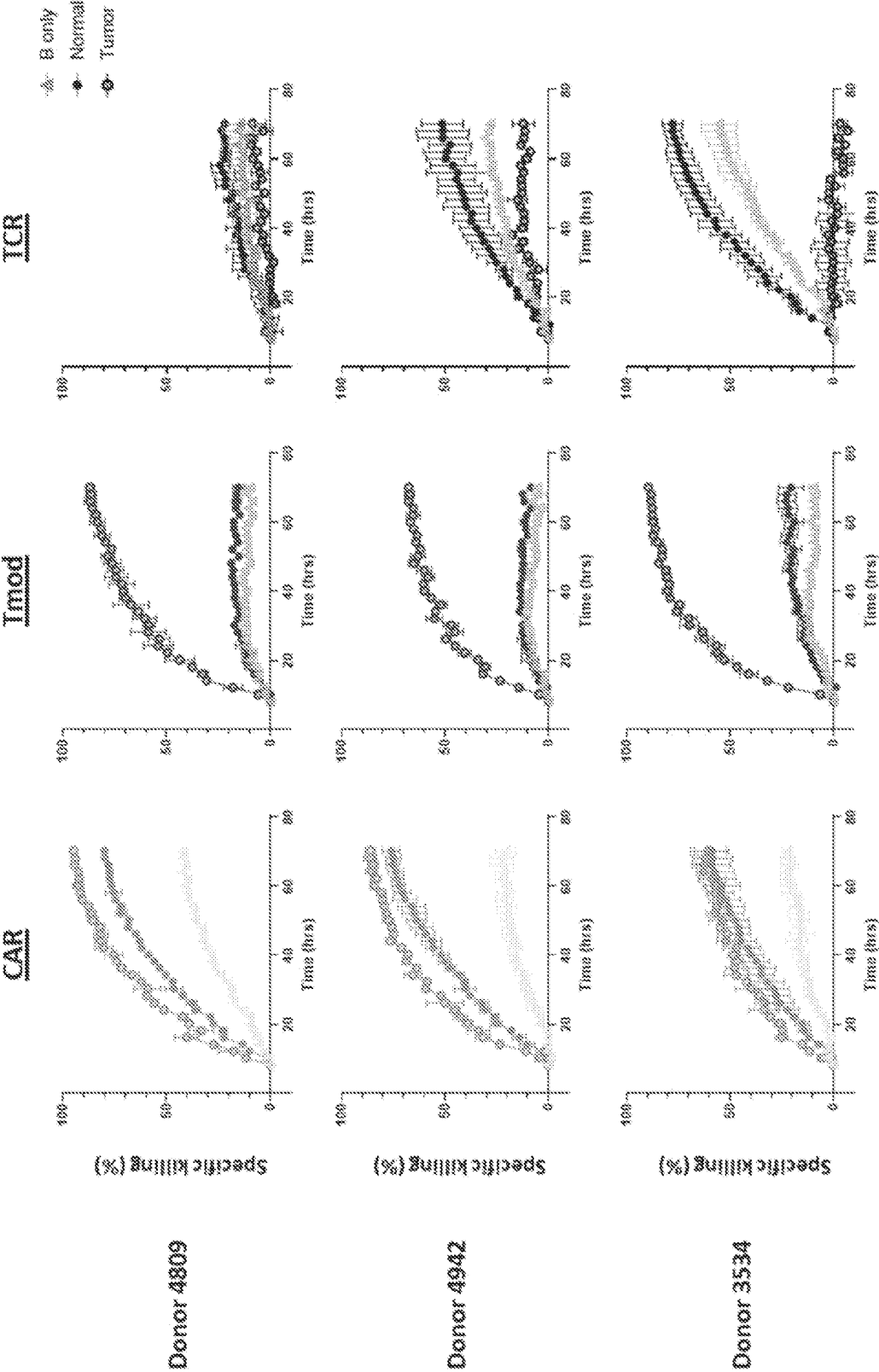


FIG. 32



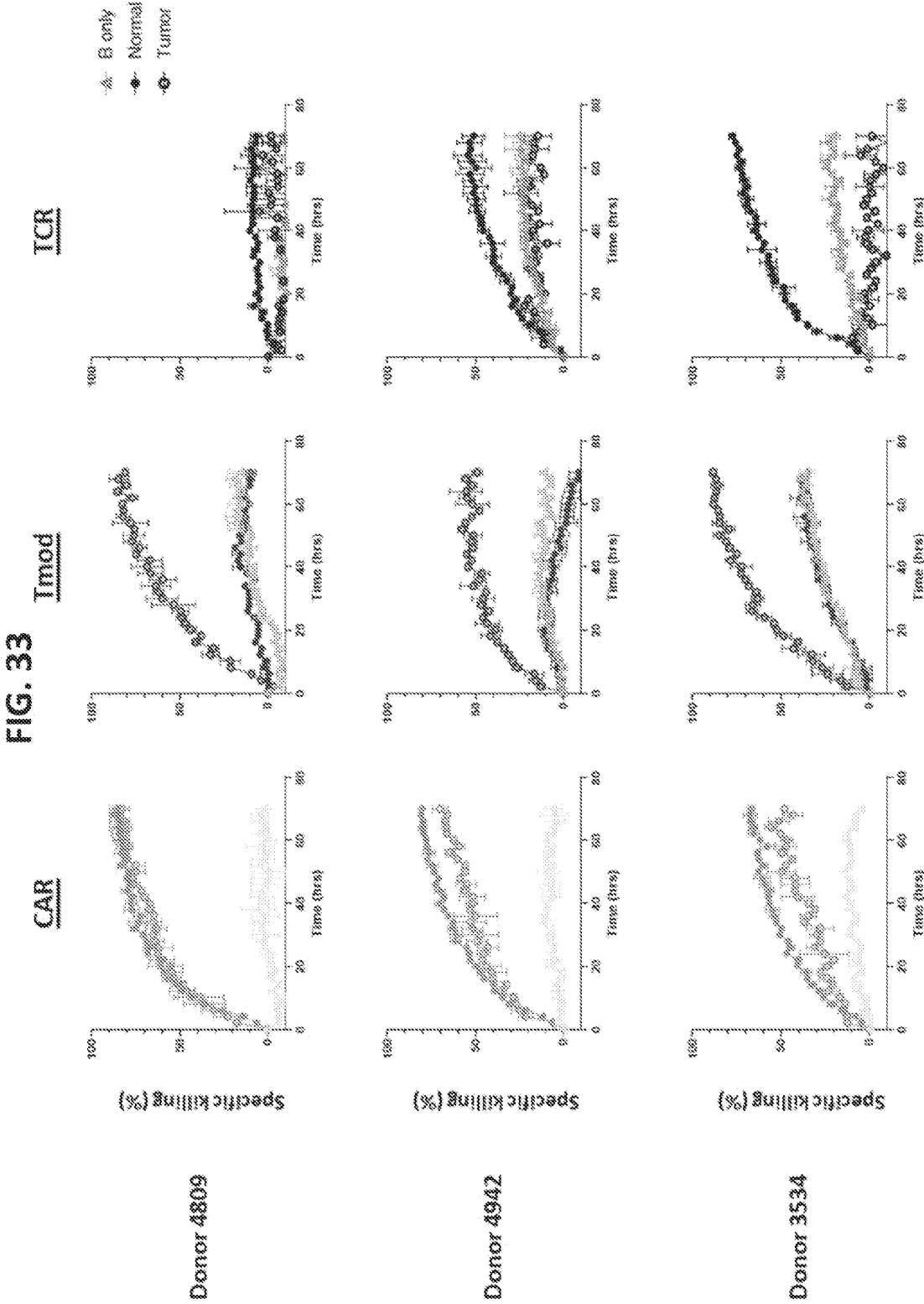


FIG. 34

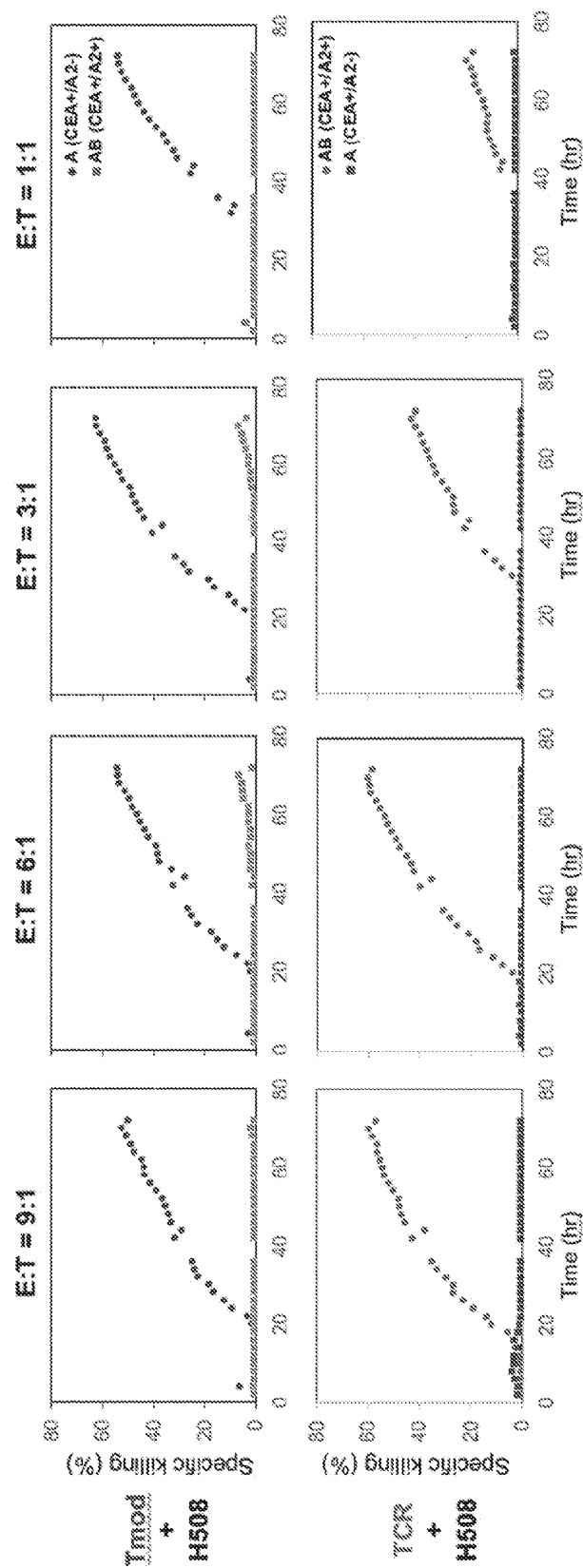


FIG. 35

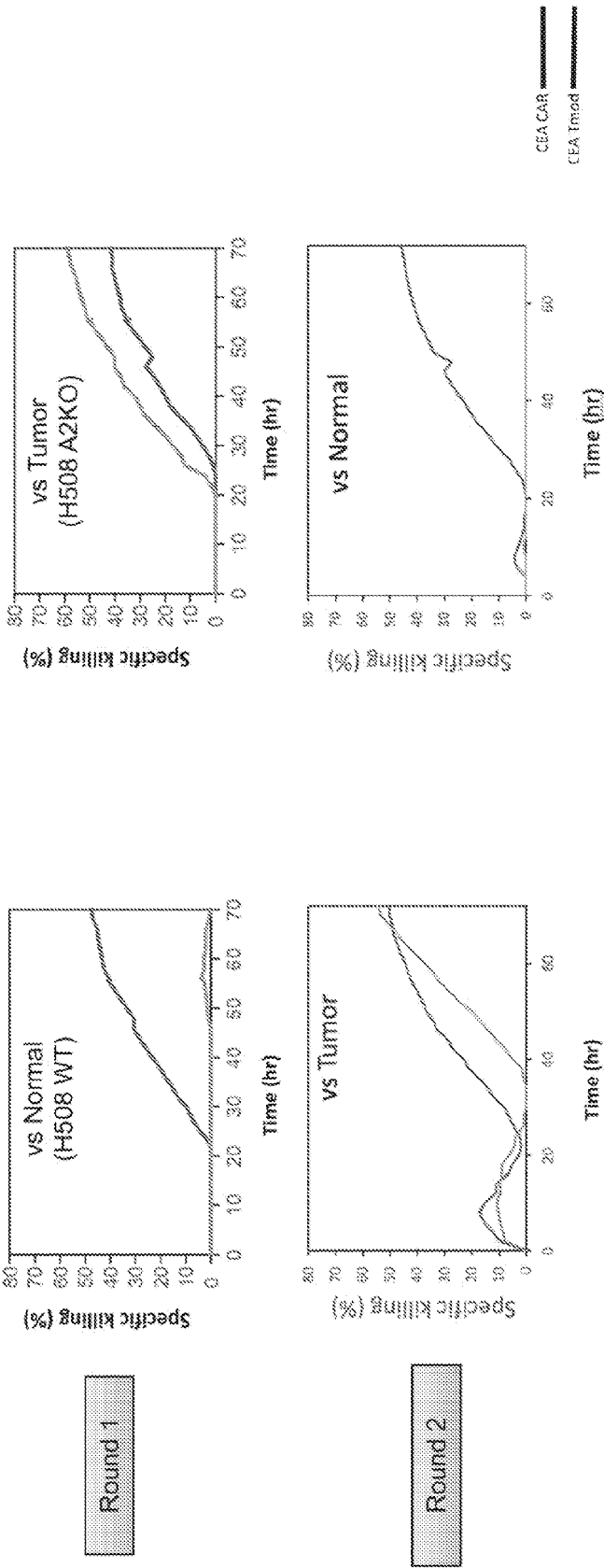


FIG. 36

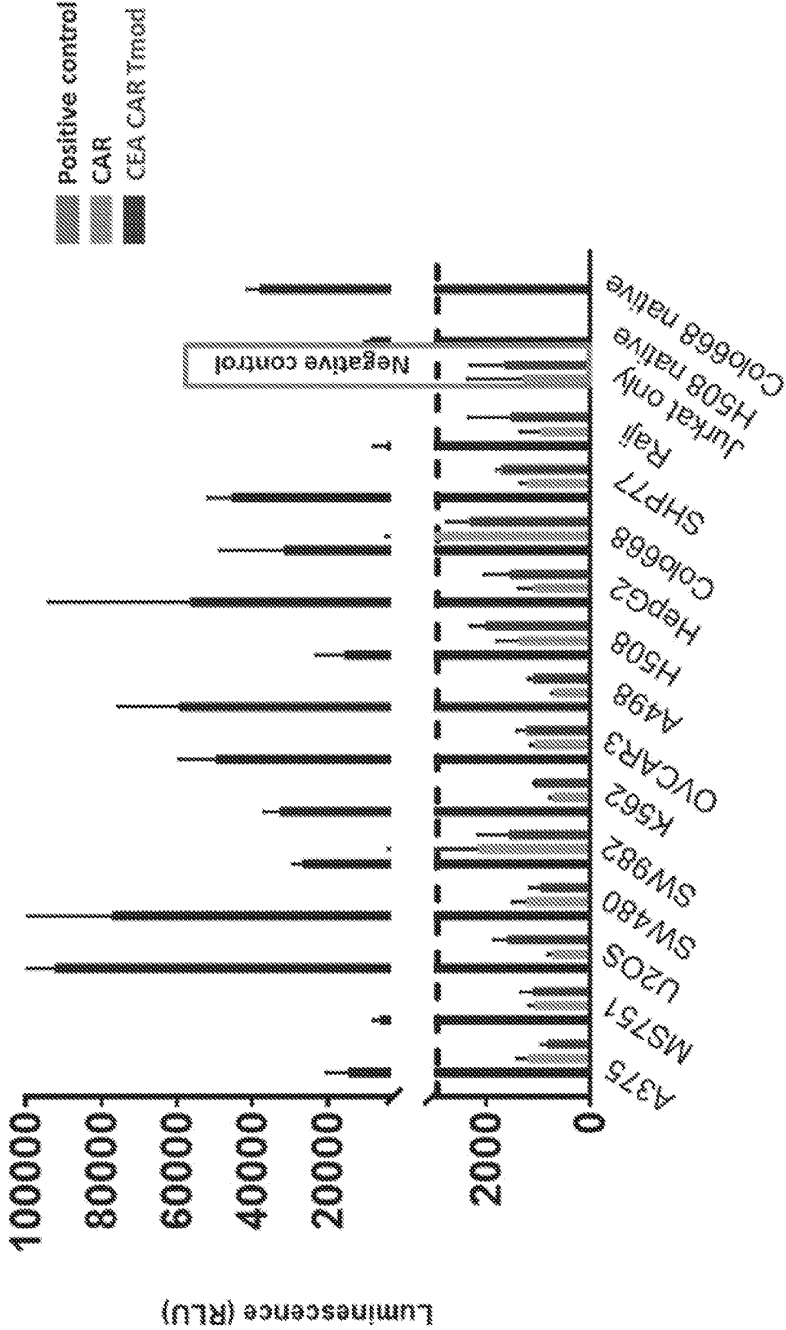


FIG. 37

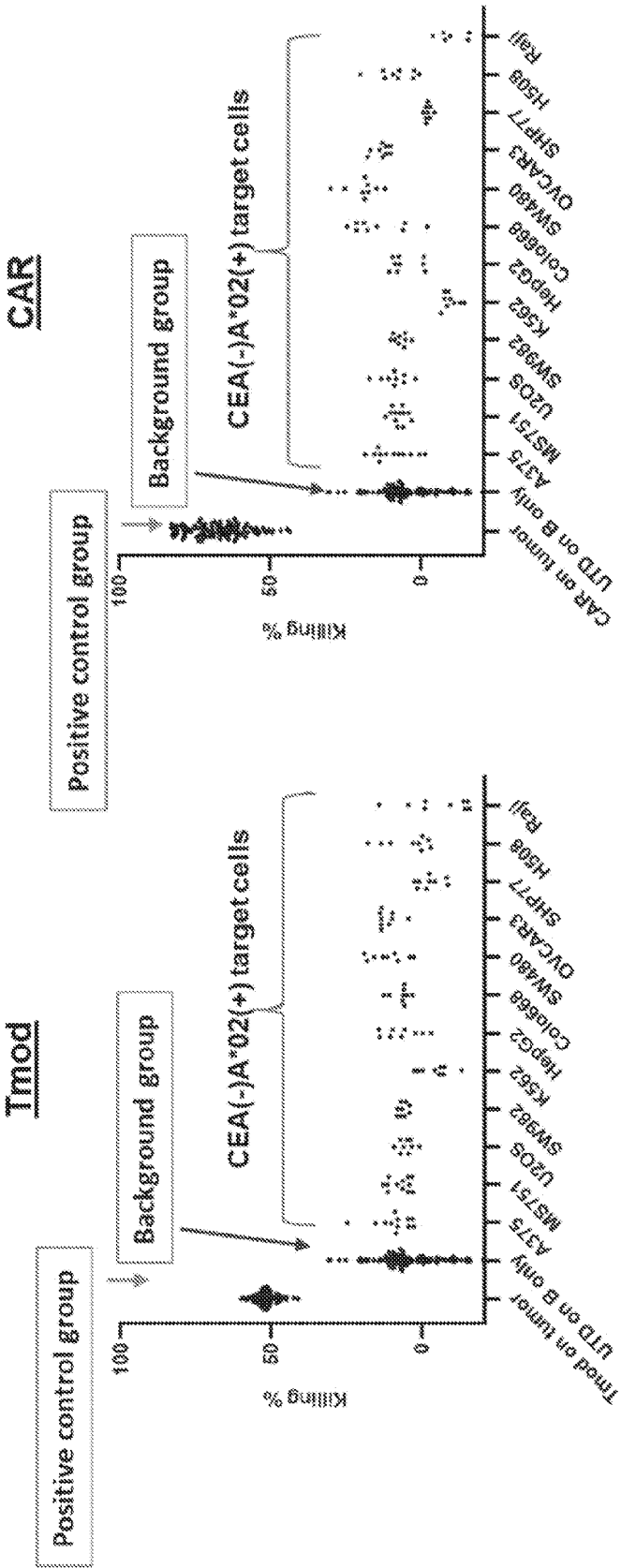


FIG. 38

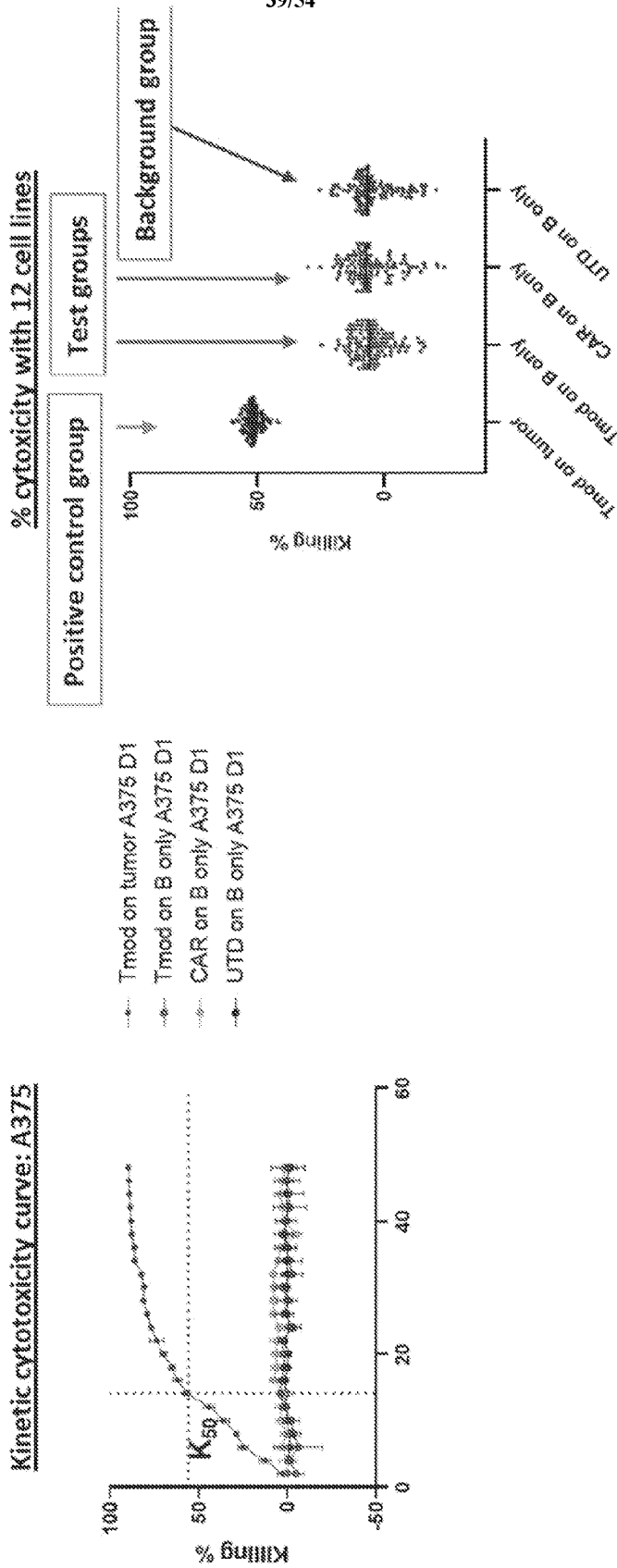


FIG. 39

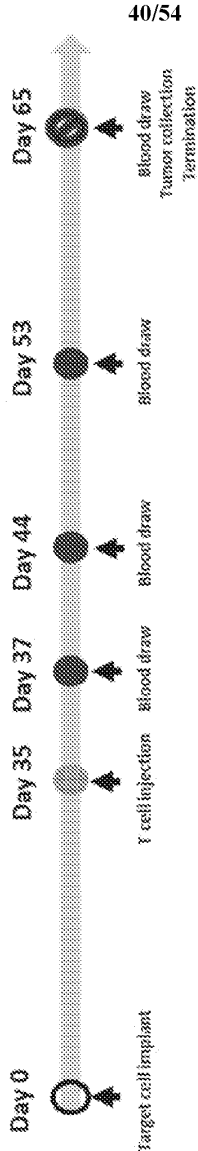
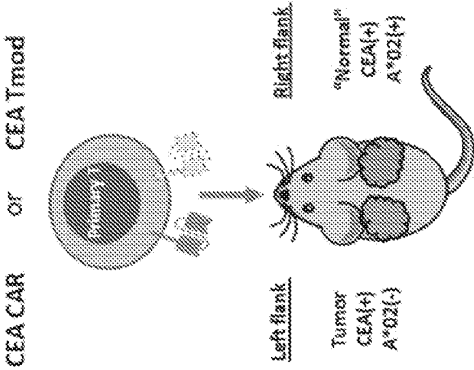


FIG. 40

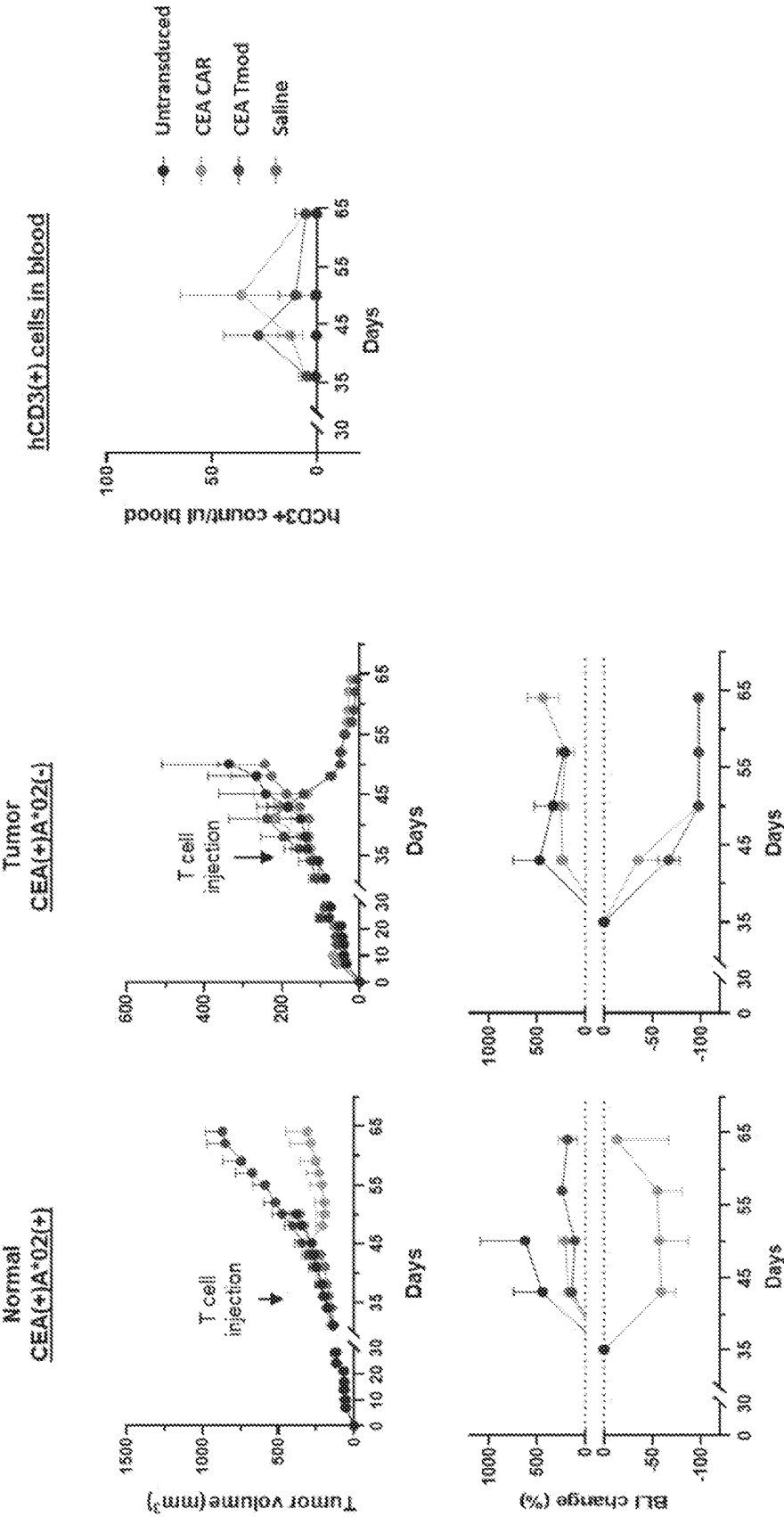


FIG. 41

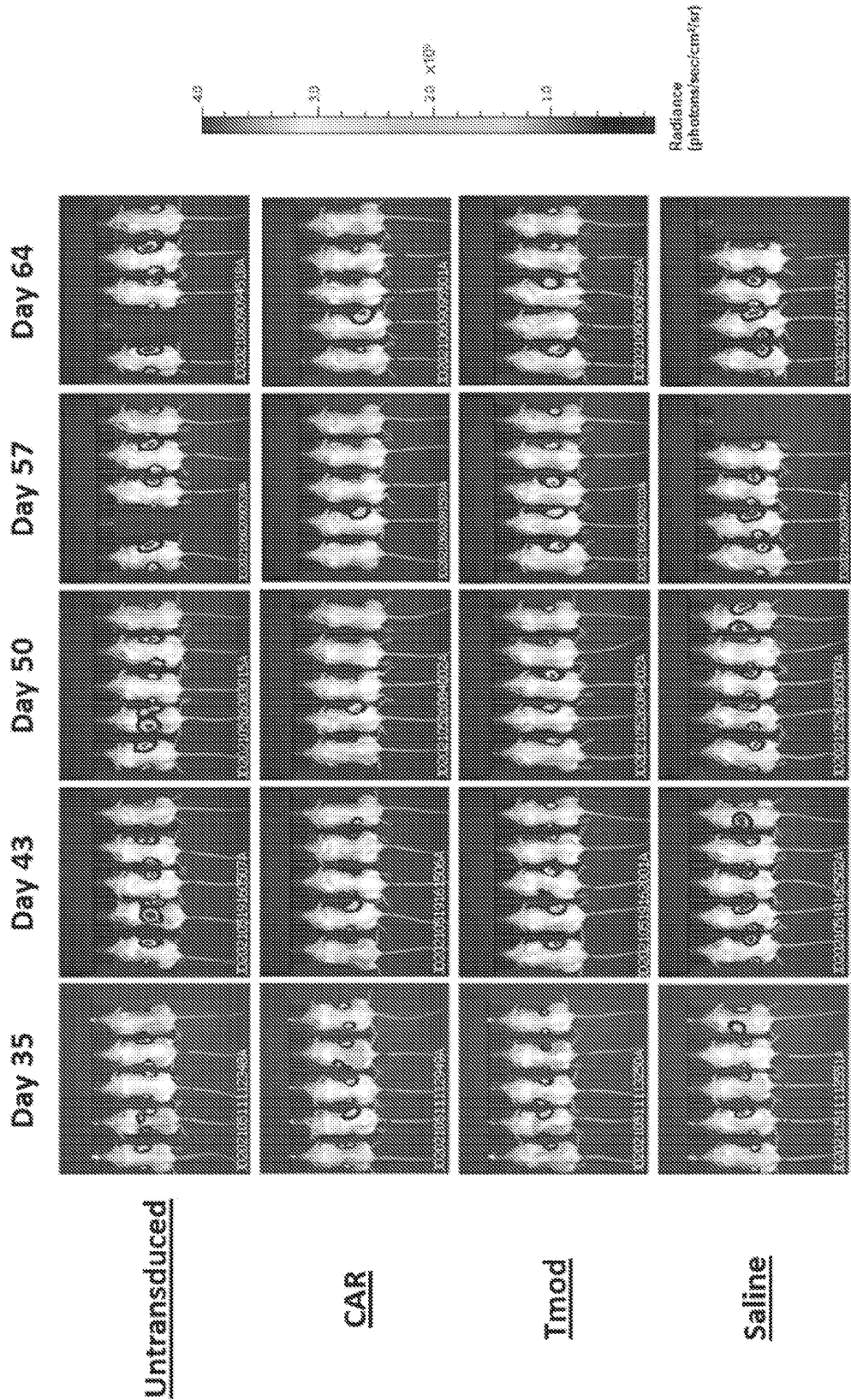


FIG. 42

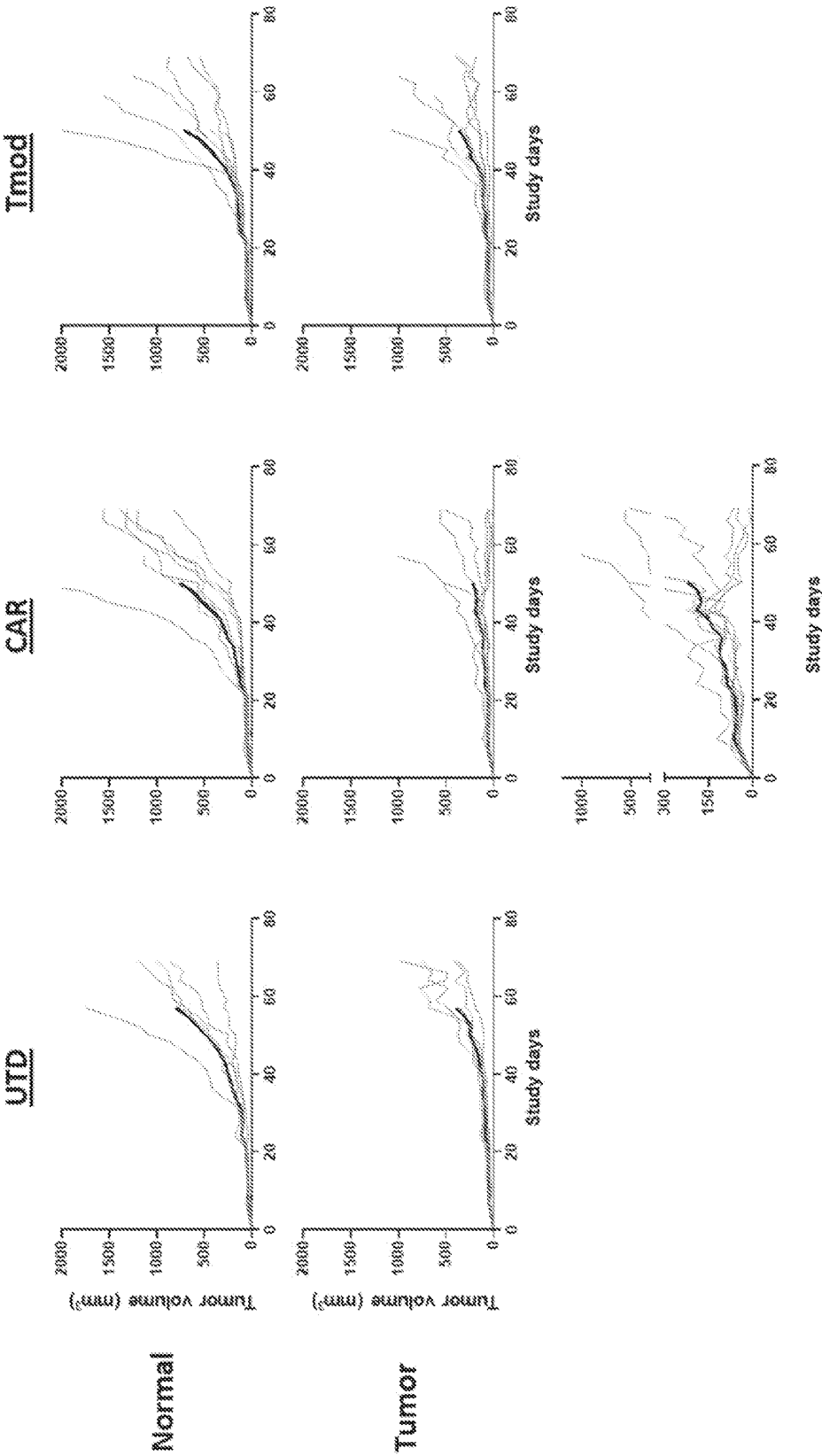


FIG. 43

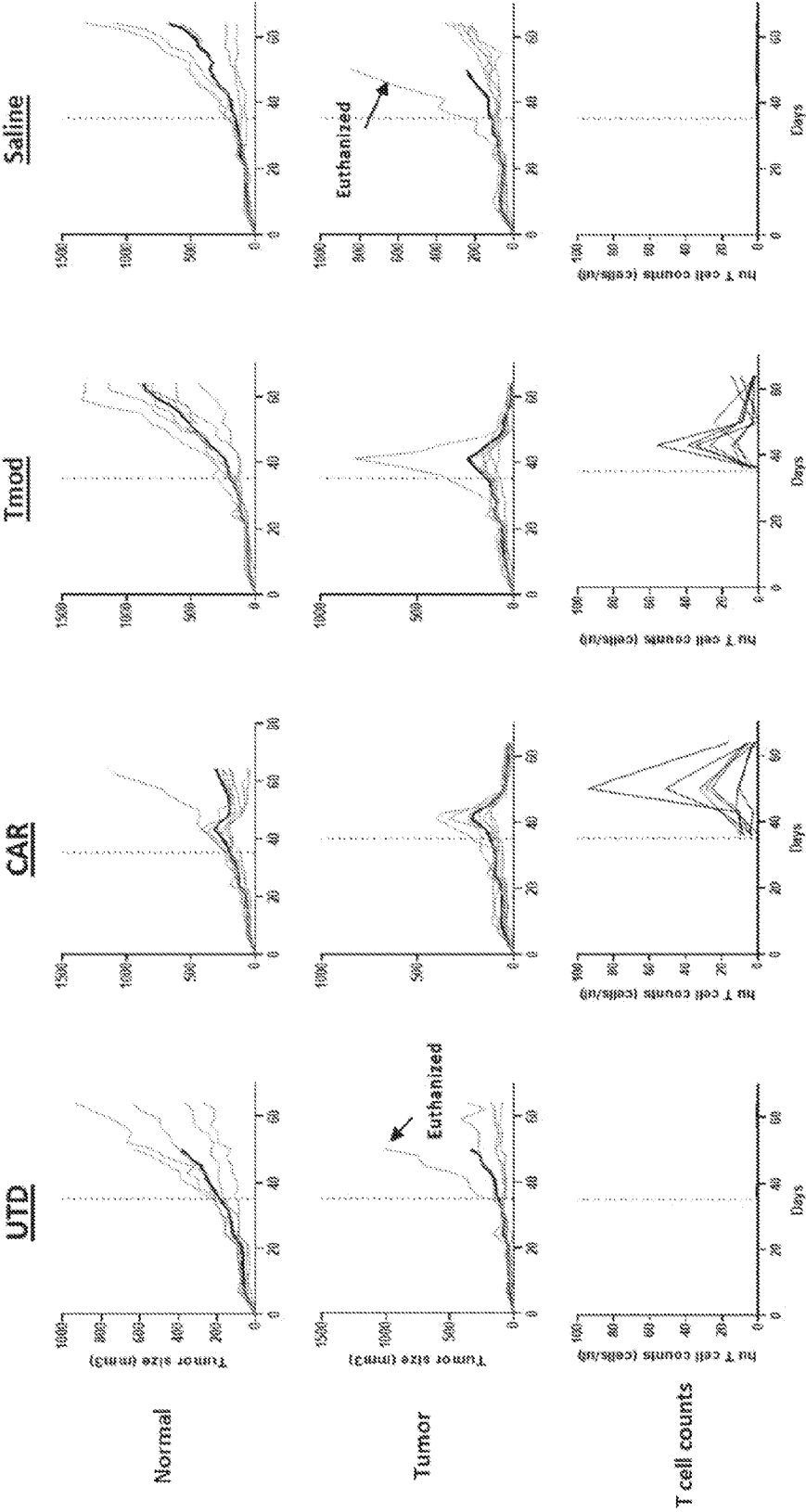
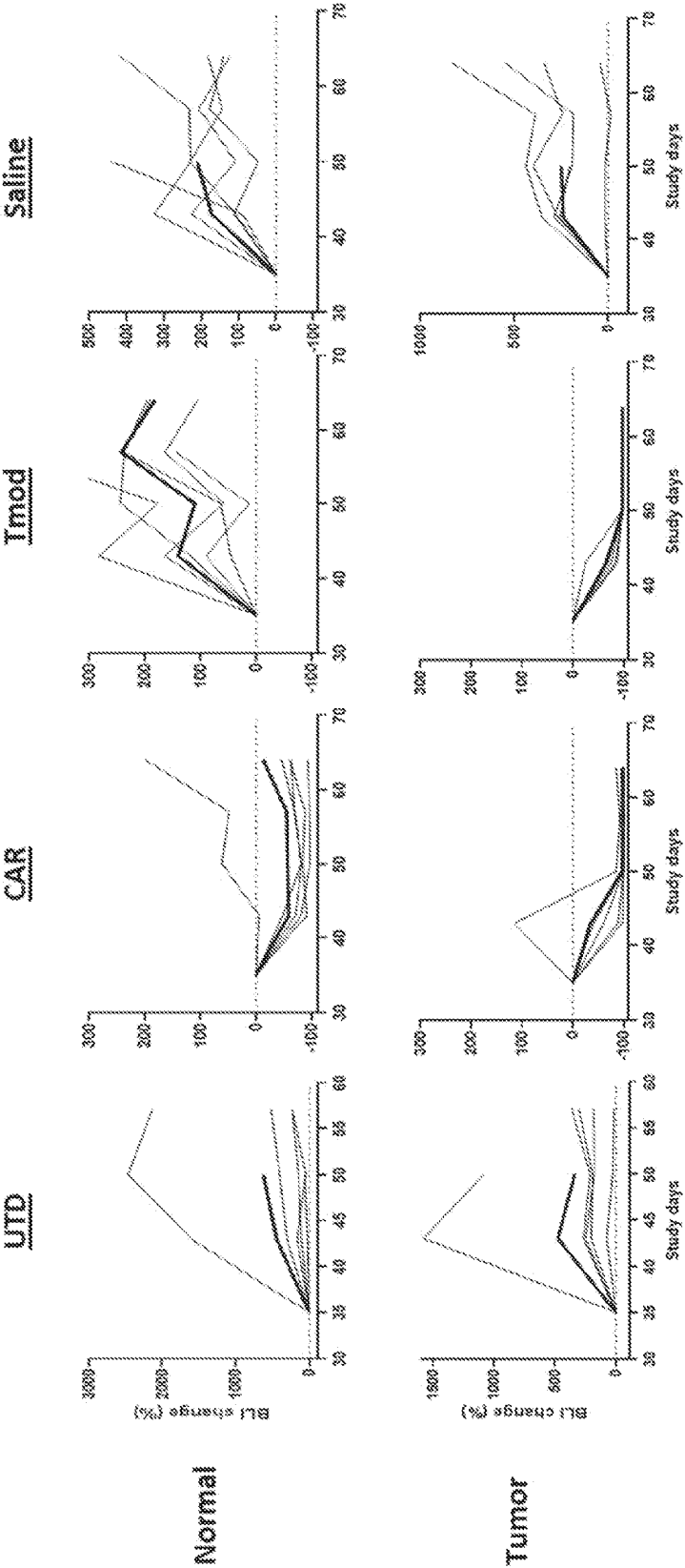


FIG. 44



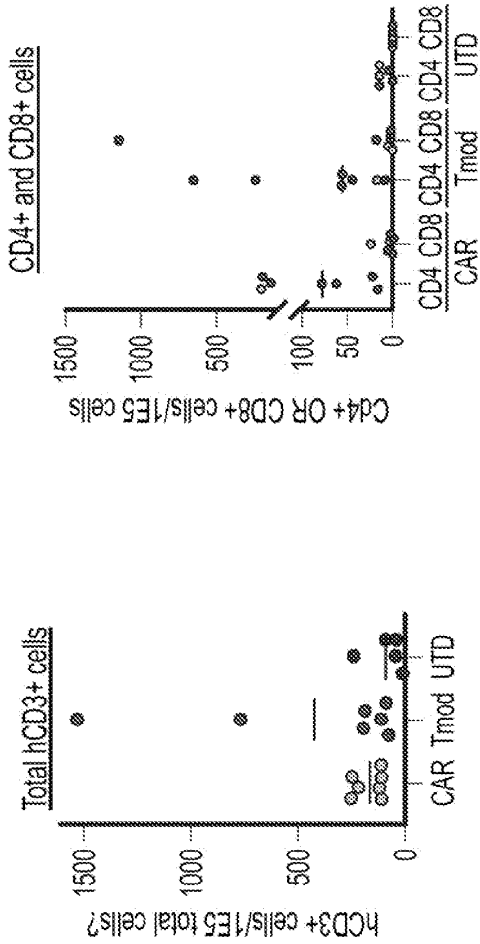
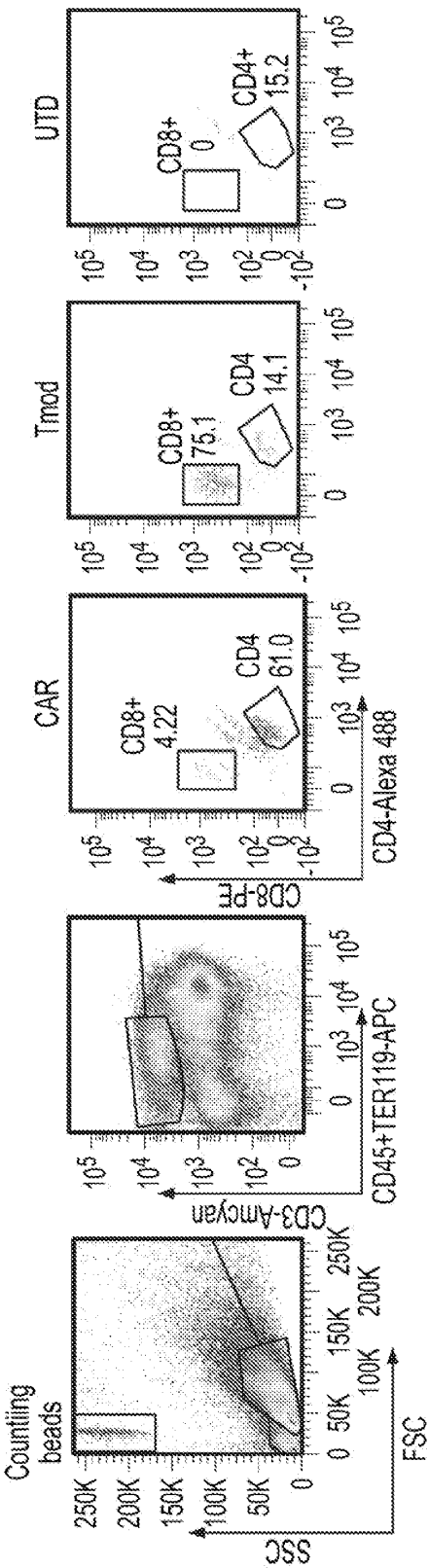


FIG. 45

47/54

FIG. 46

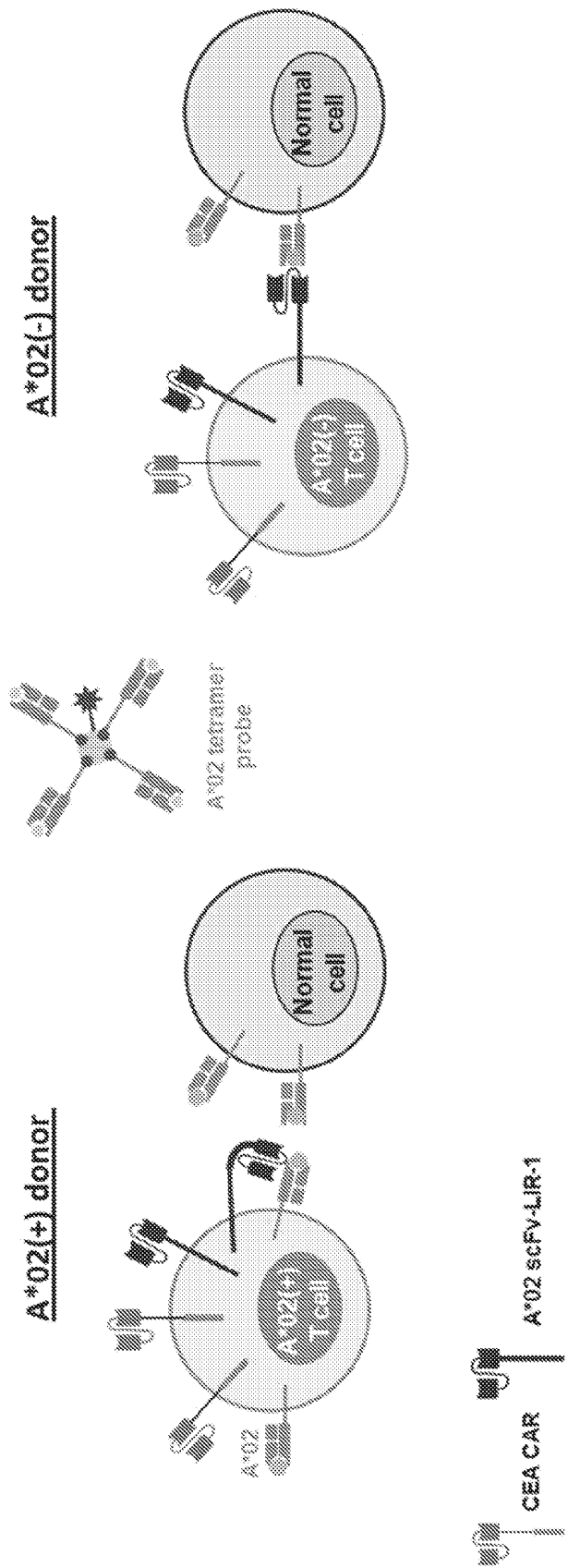


FIG. 47

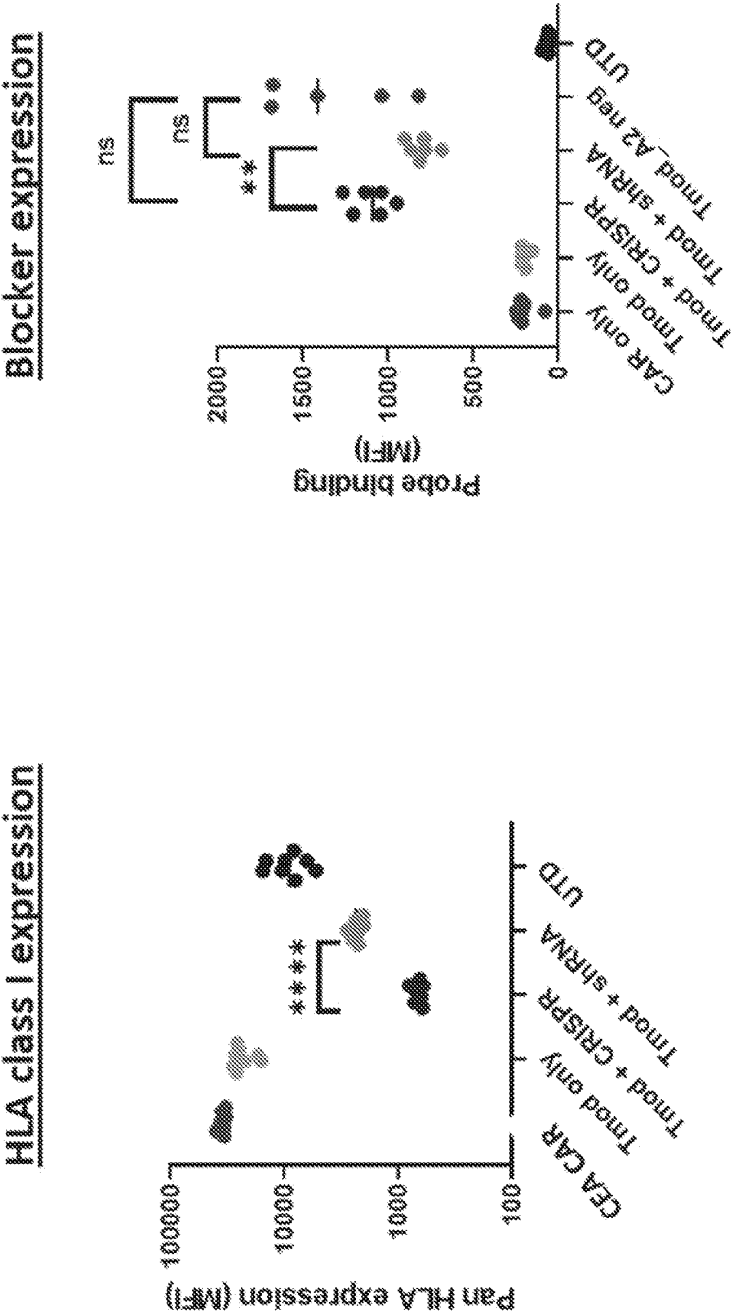


FIG. 48

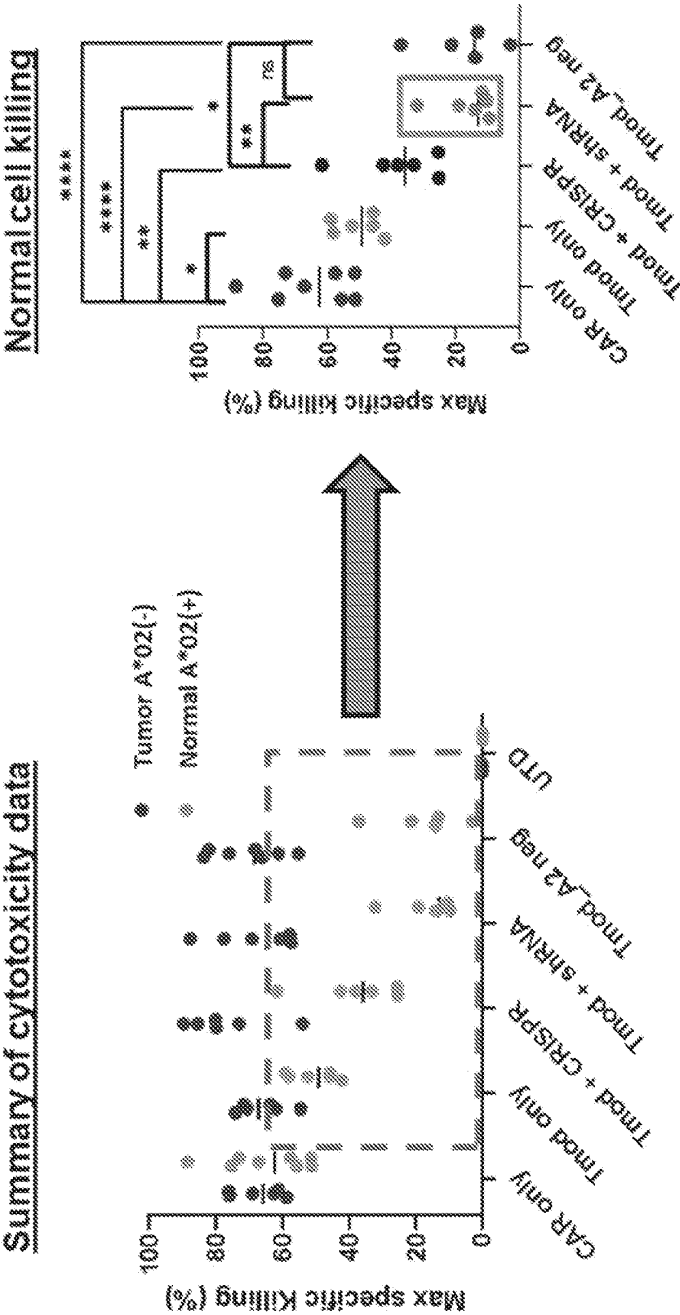
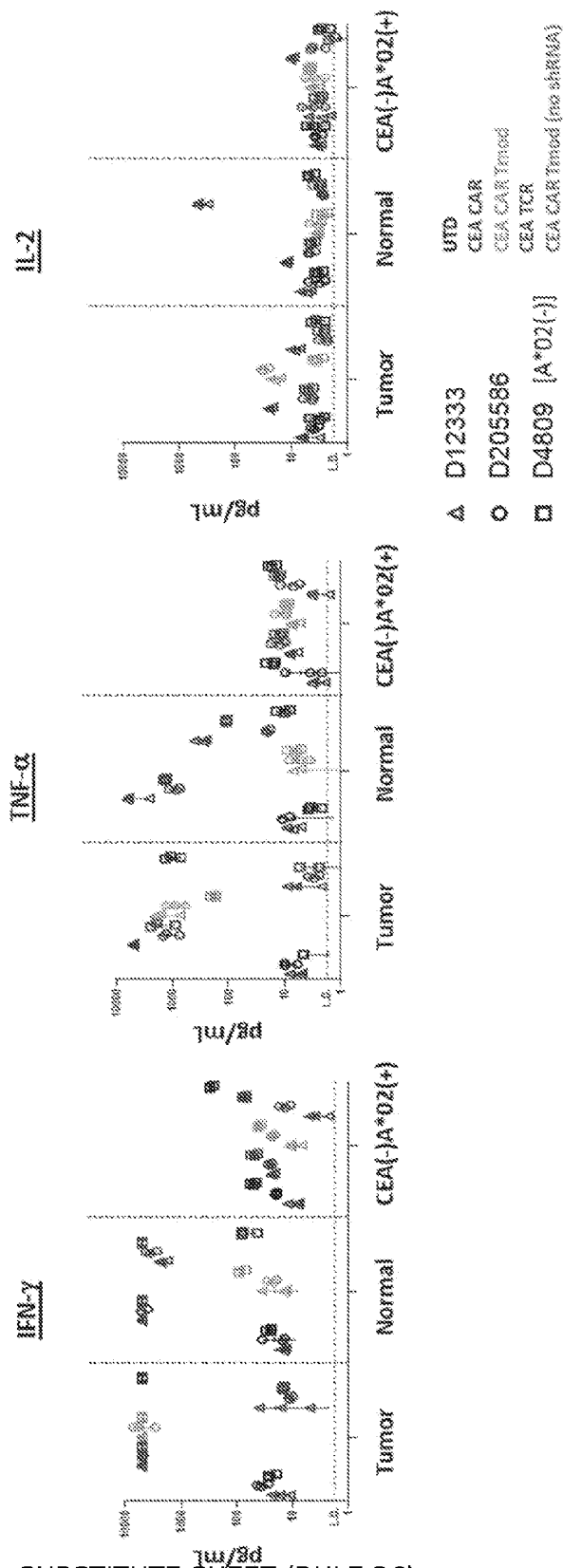


FIG. 49



SUBSTITUTE SHEET (RULE 26)

SUBSTITUTE SHEET (RULE 26)

Summary of blocker IC50 vs. CEA antigen level

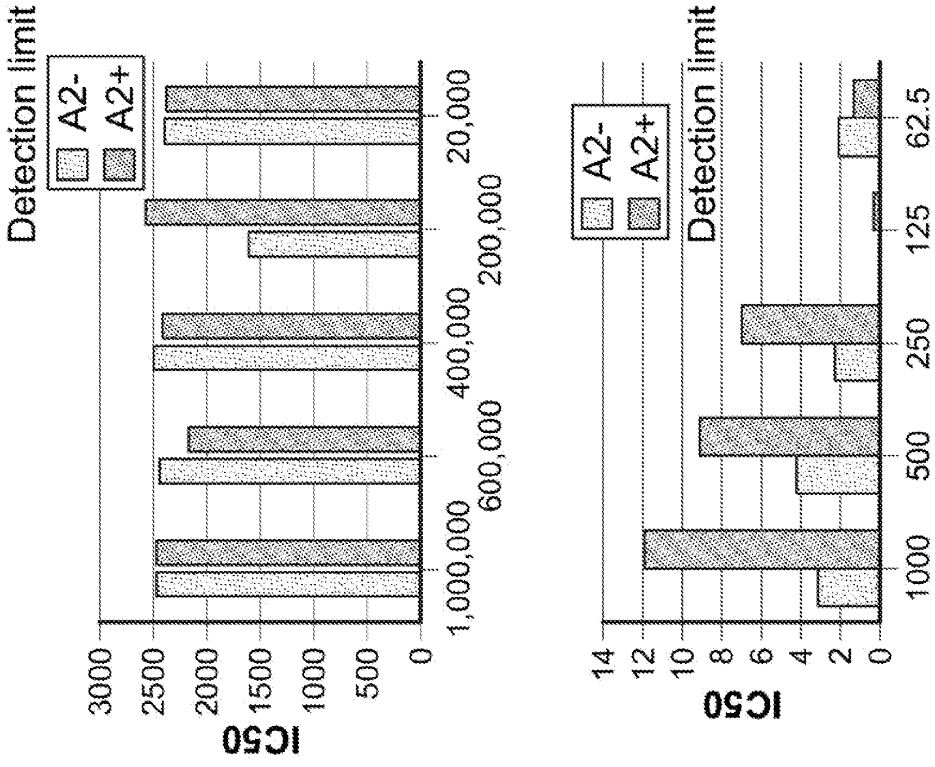


FIG. 51

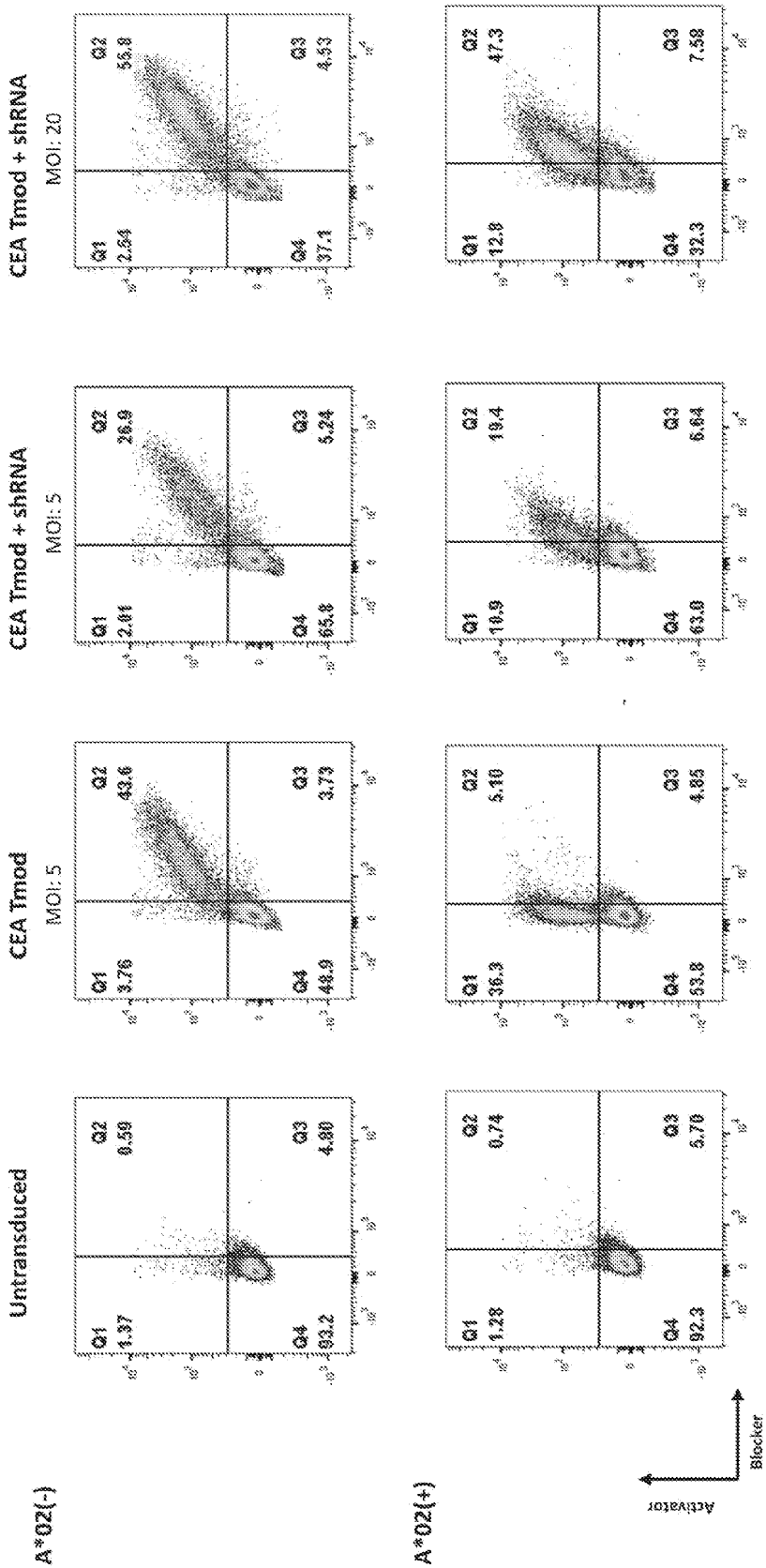


FIG. 52

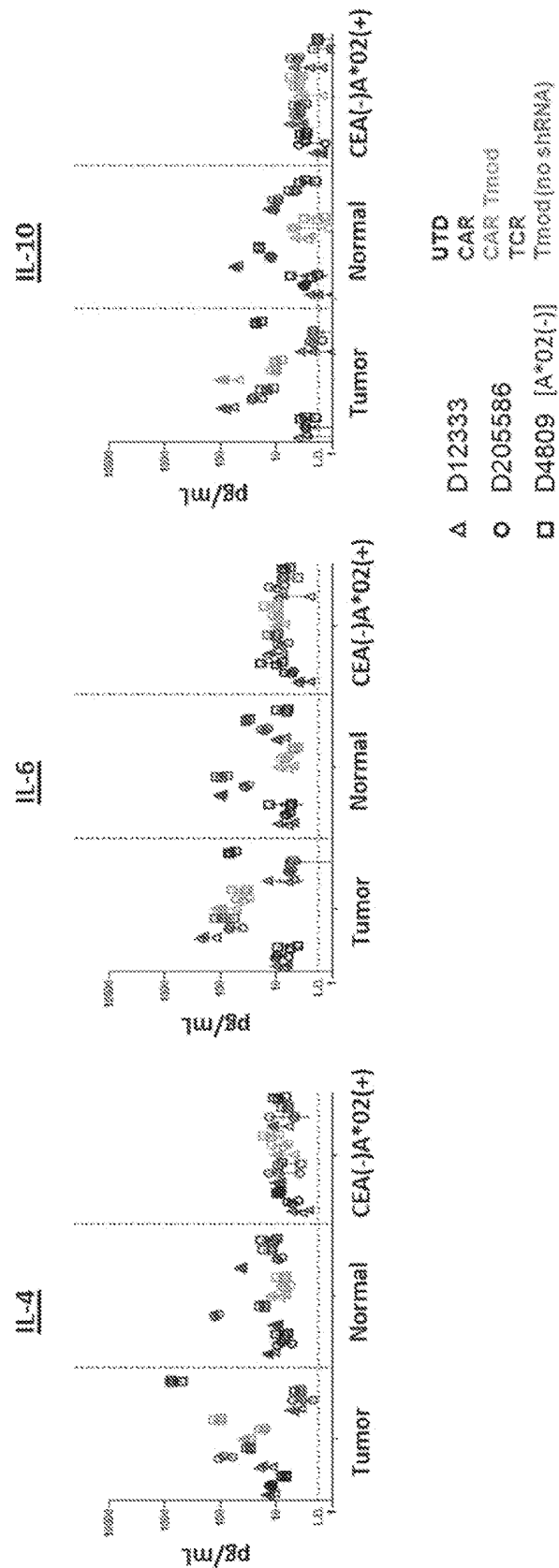


FIG. 53

CEA CAR Tmod properties	Supporting data
High on-target, off-tumor selectivity	• CEA CAR Tmod (CEA CAR paired with an HLA-A*02-specific blocker receptor) has >10x selectivity for CEA(+)/A*02(-) tumor cells relative to CEA(+)/A*02(+) normal cells • Comparable to TCR-T cells in cytotoxicity assays • Selectivity confirmed in mouse xenograft experiments
High potency	• CEA CAR Tmod cells specifically kill a tumor cell line with native CEA and HLA-A*02 expression • Similar potency to a benchmark clinical CEA TCR
Reversible activity	• CEA CAR Tmod cell activation is reversible in vitro, cycling between ON and OFF states
No inhibition from soluble CEA	• in vitro, CEA CAR Tmod cells are not inhibited by elevated levels of sCEA
Suitable for allogeneic or autologous	• With shRNA expression module, CEA CAR Tmod dual receptors function equivalently in HLA-A*02(+) and HLA-A*02(-) donor T cells