

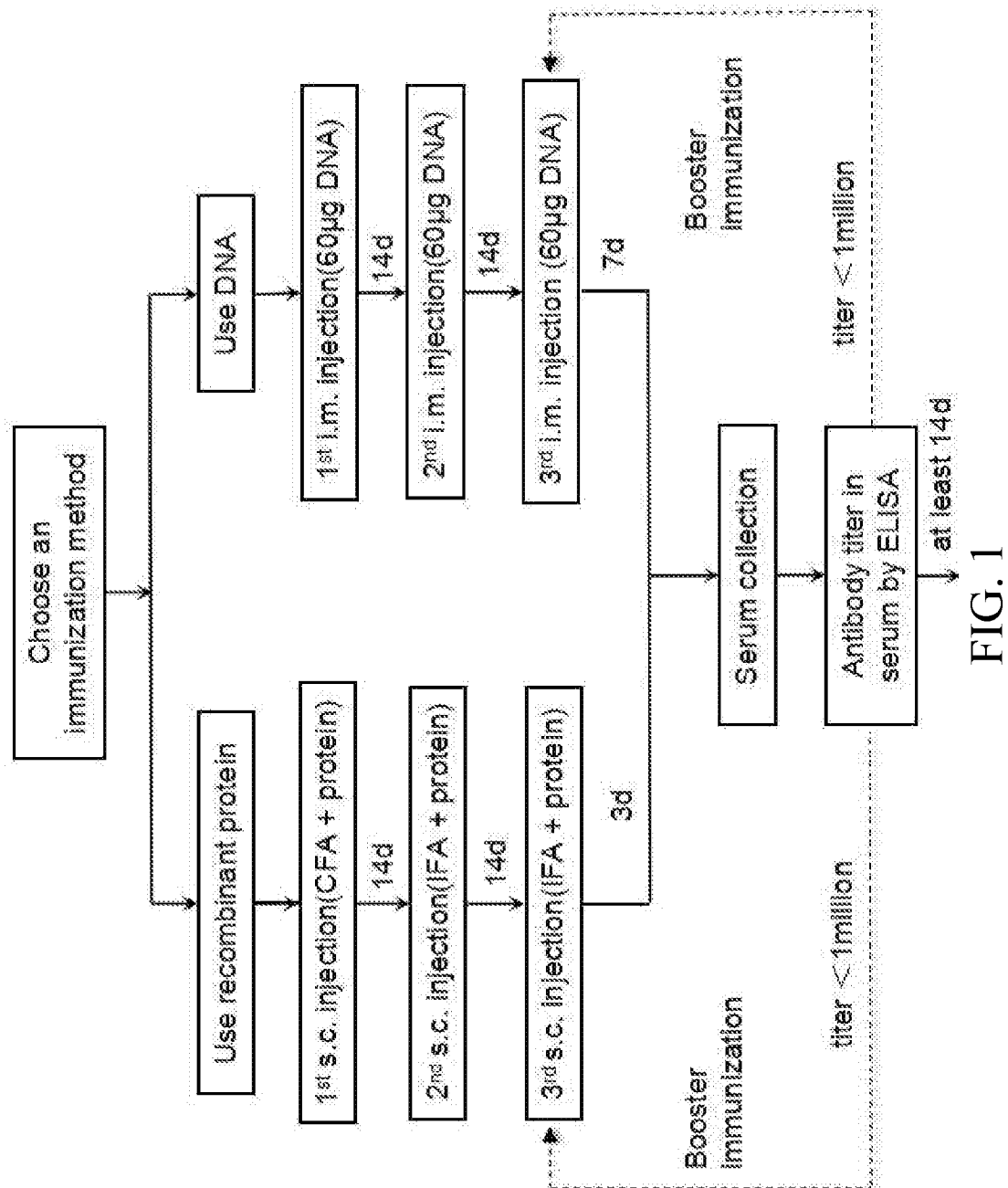


FIG. 1

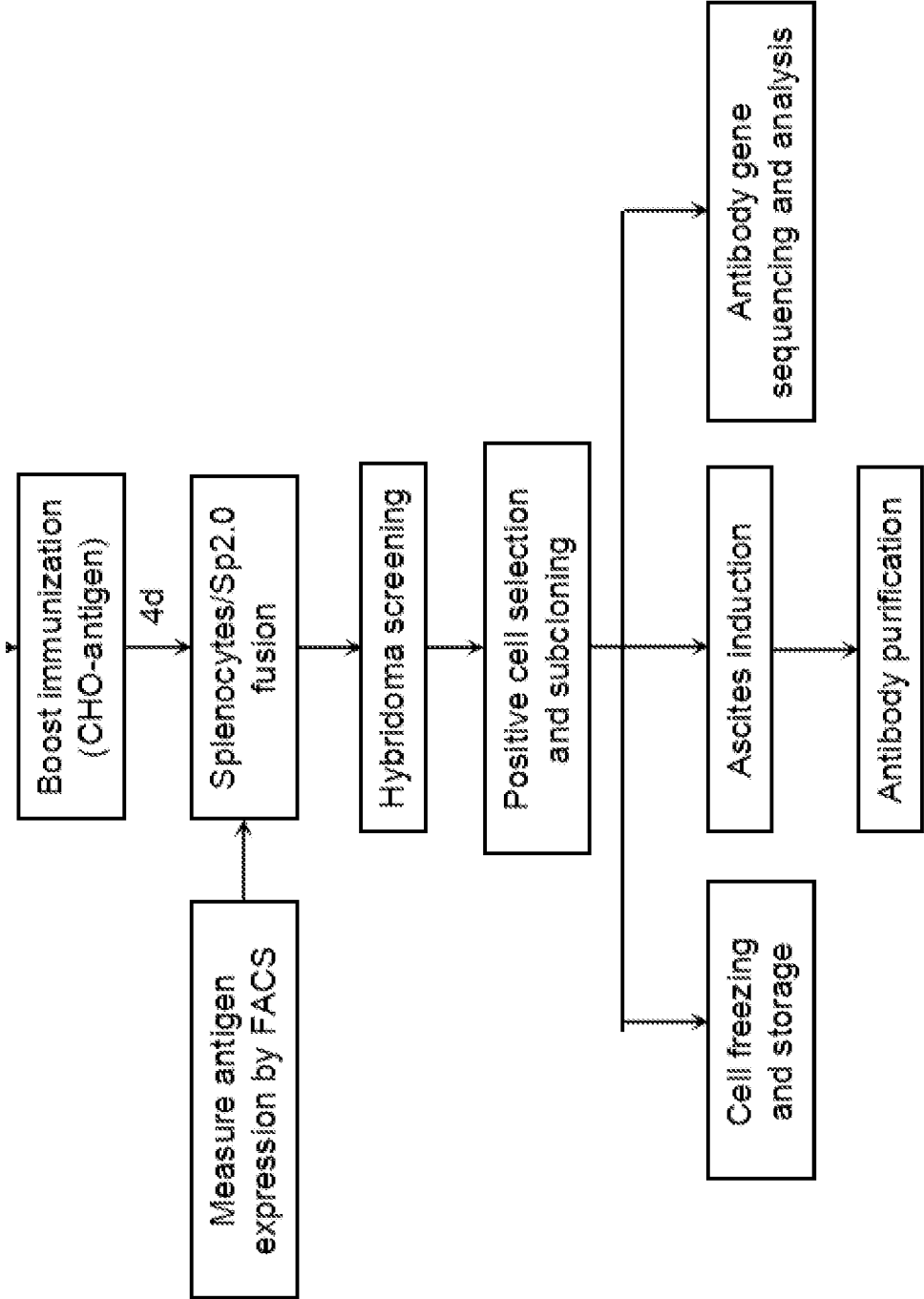


FIG. 2

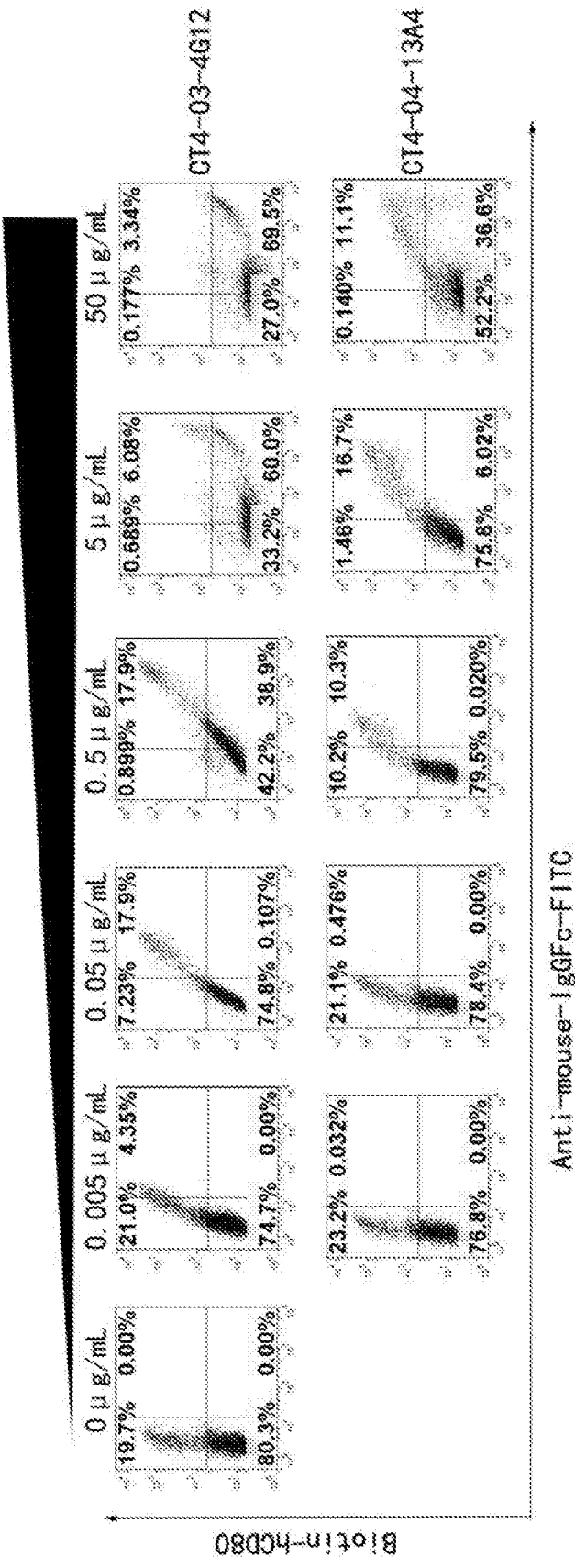


FIG. 3

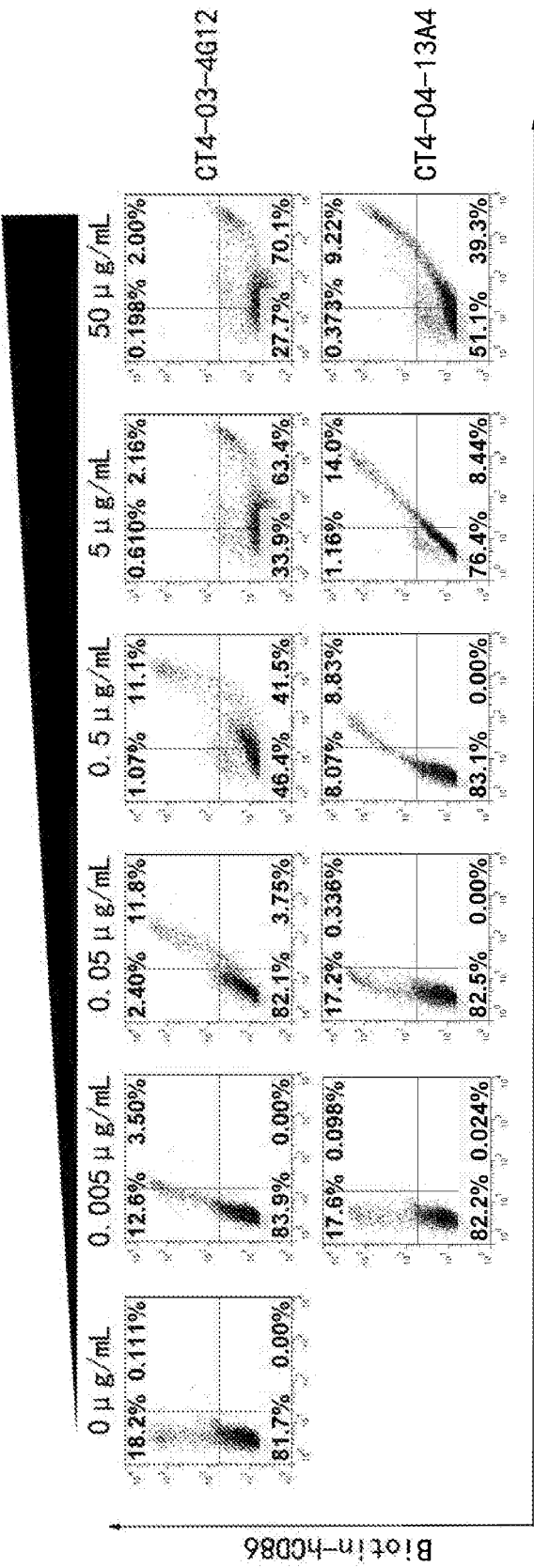
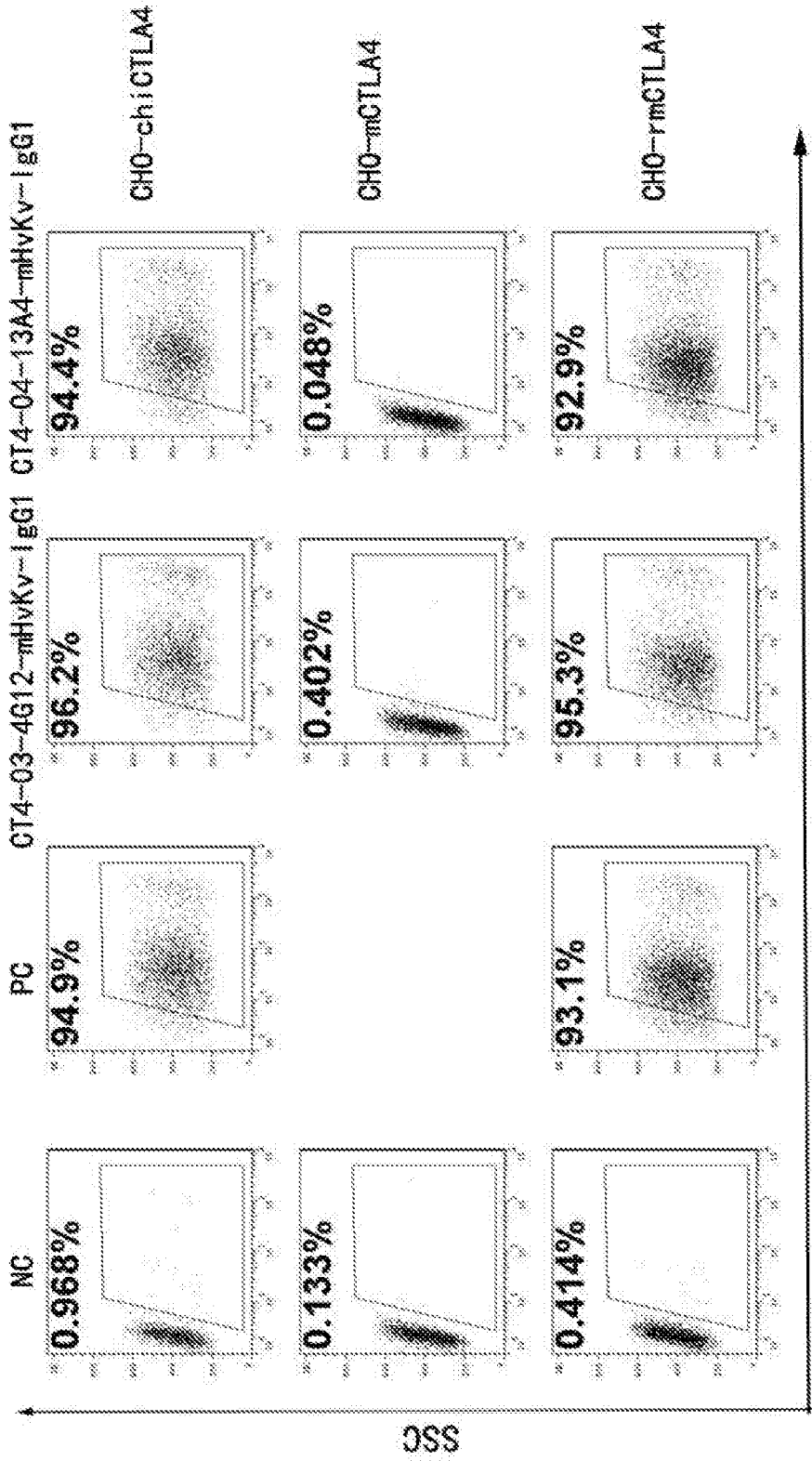


FIG. 4



Anti-Human-IgGc-FITC
FIG. 5

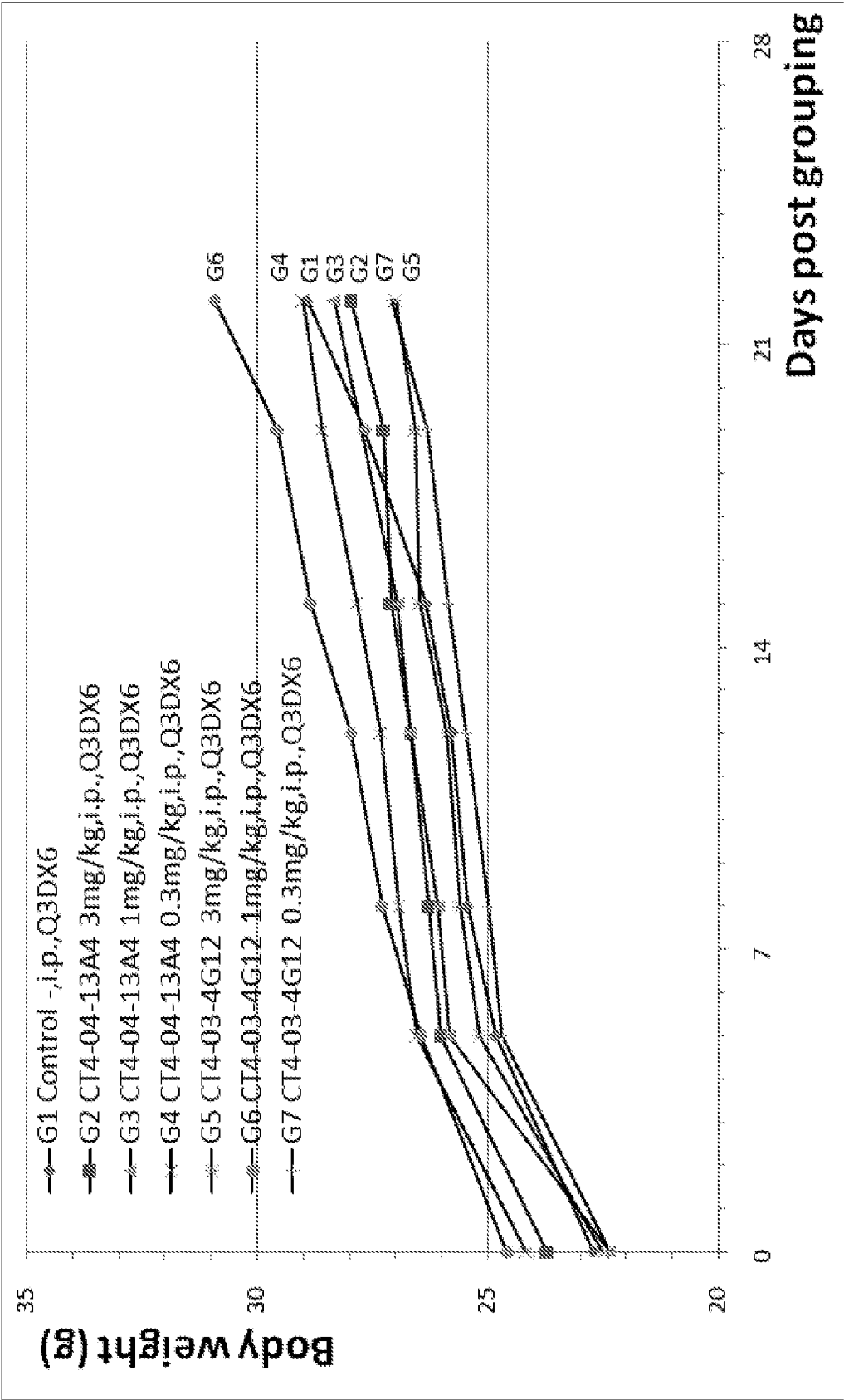


FIG. 6

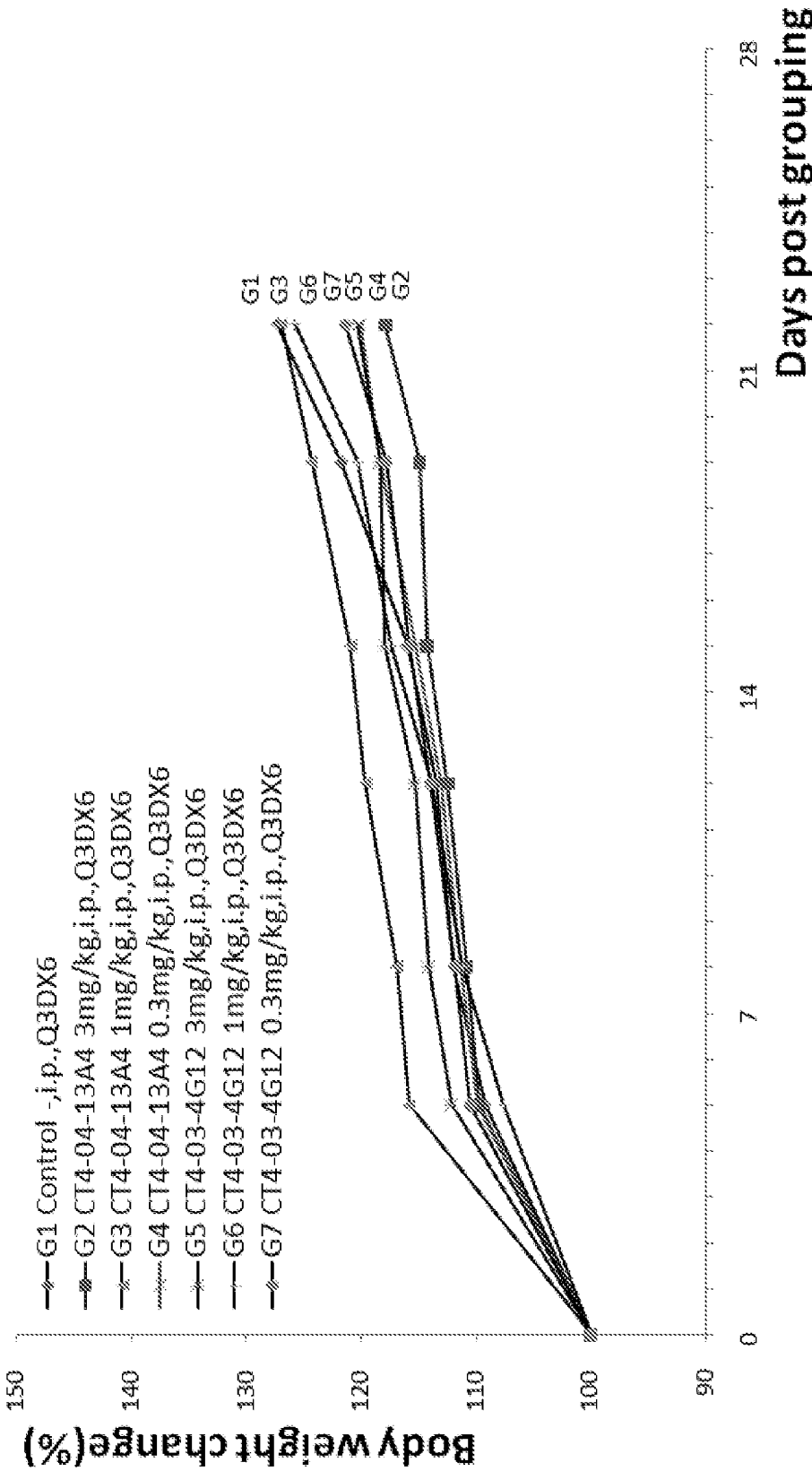


FIG. 7

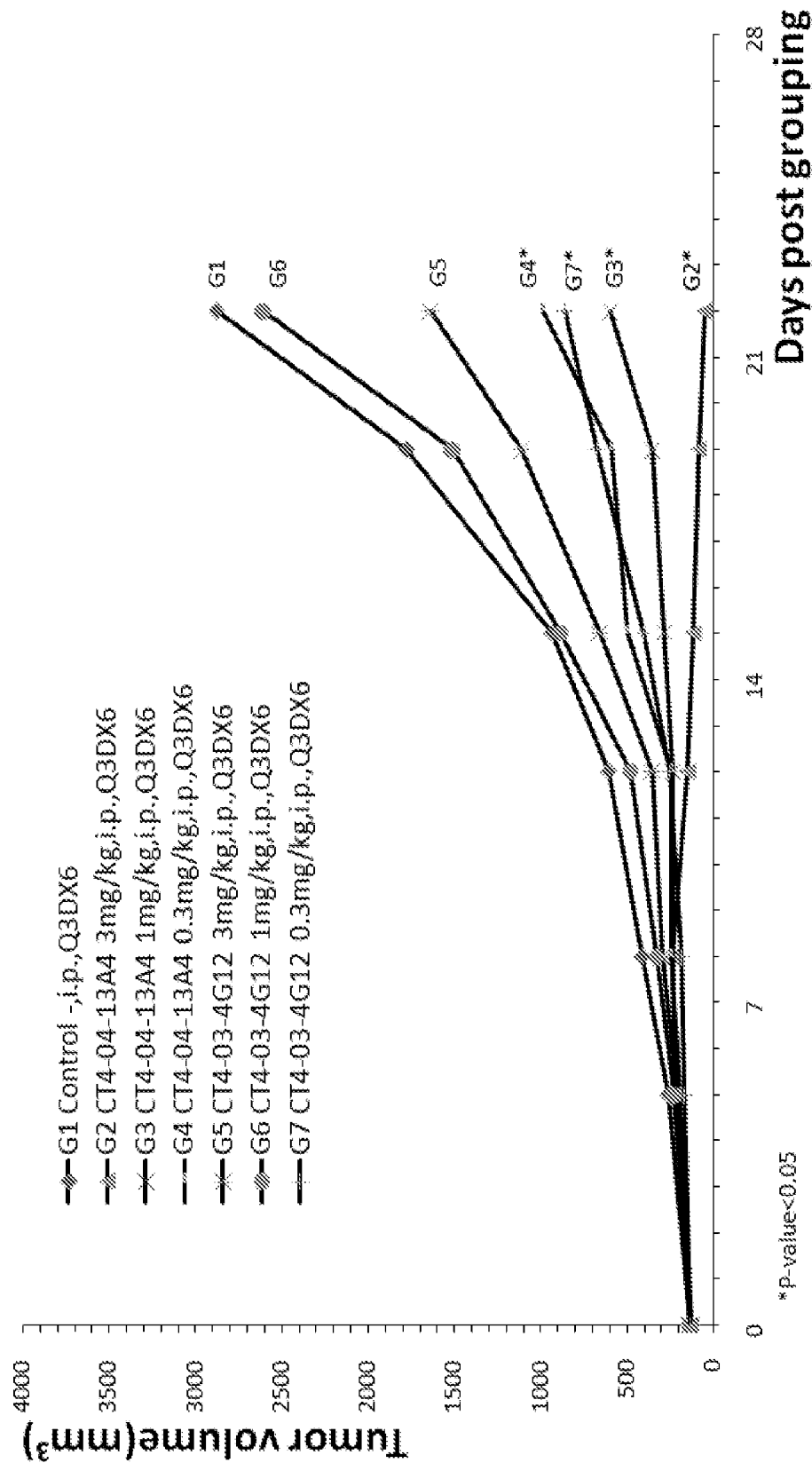


FIG. 8

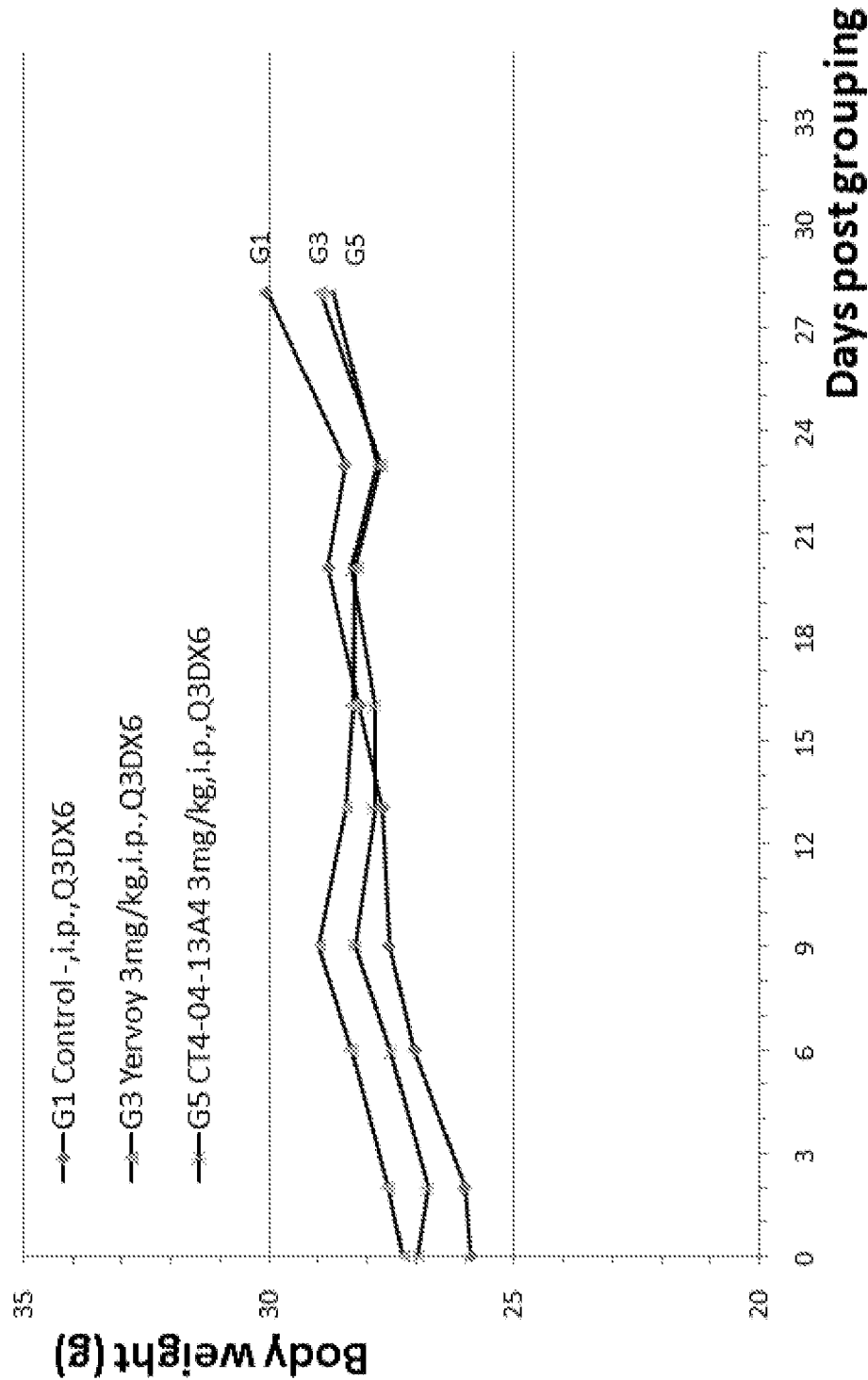


FIG. 9

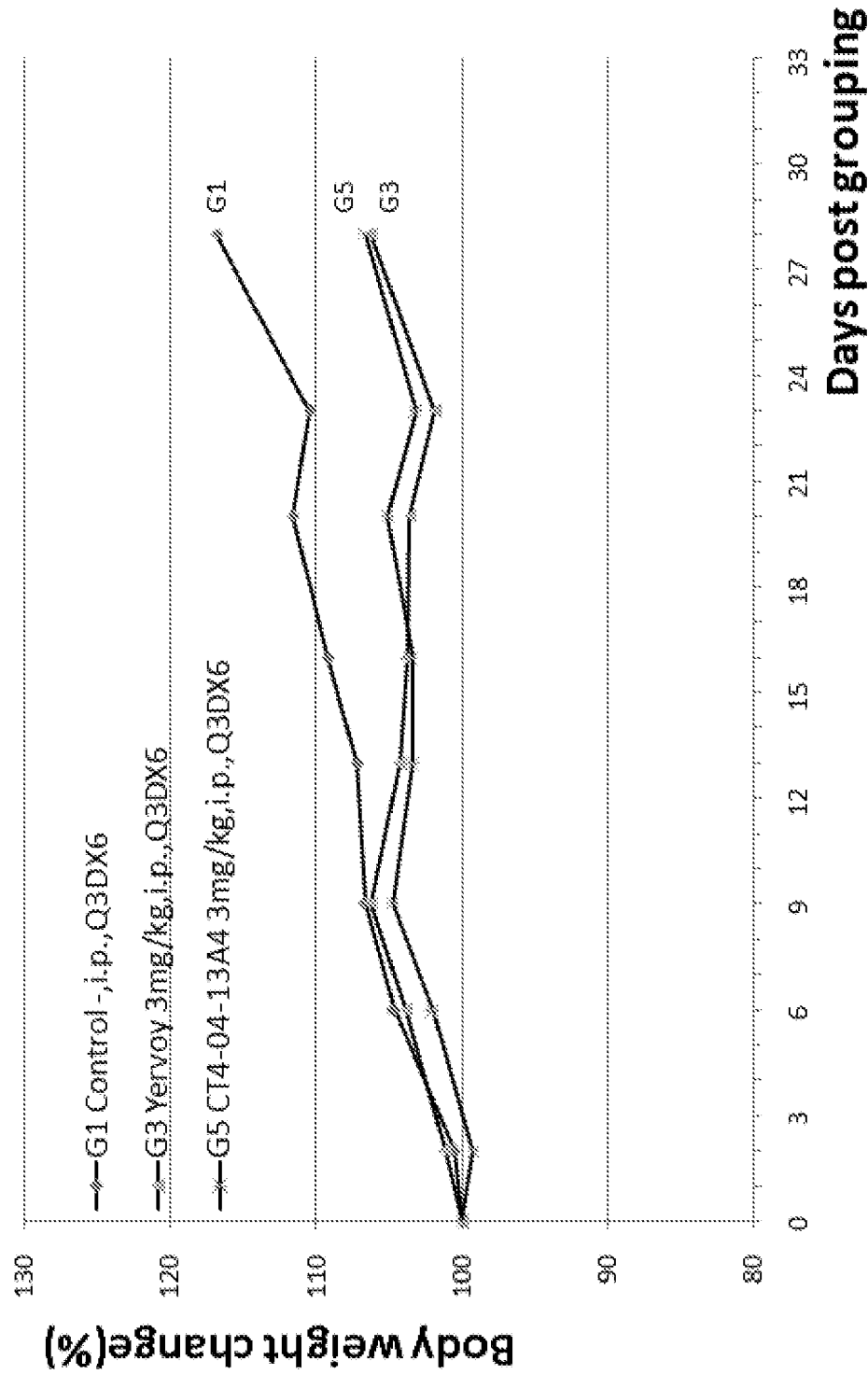


FIG. 10

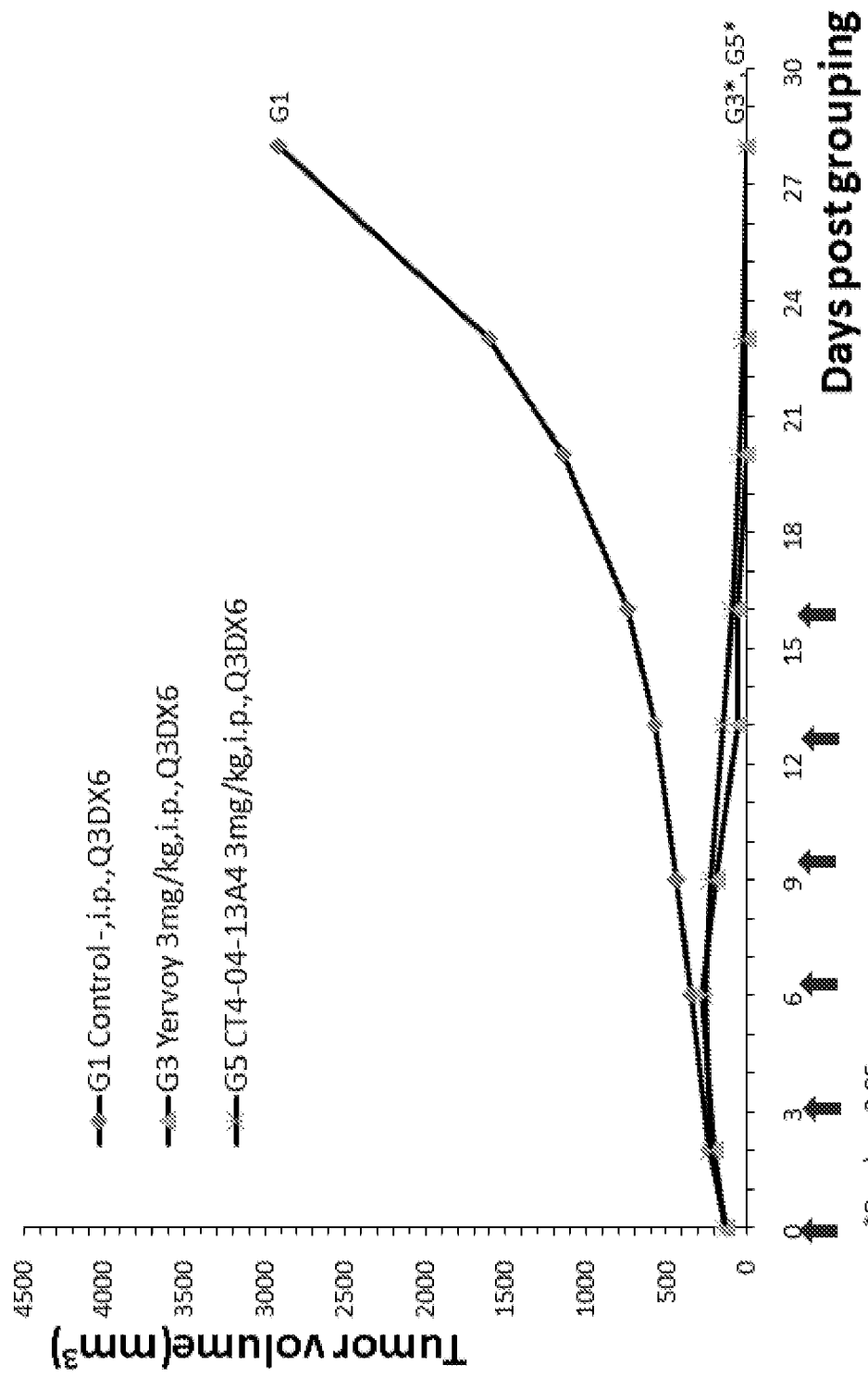


FIG. 11

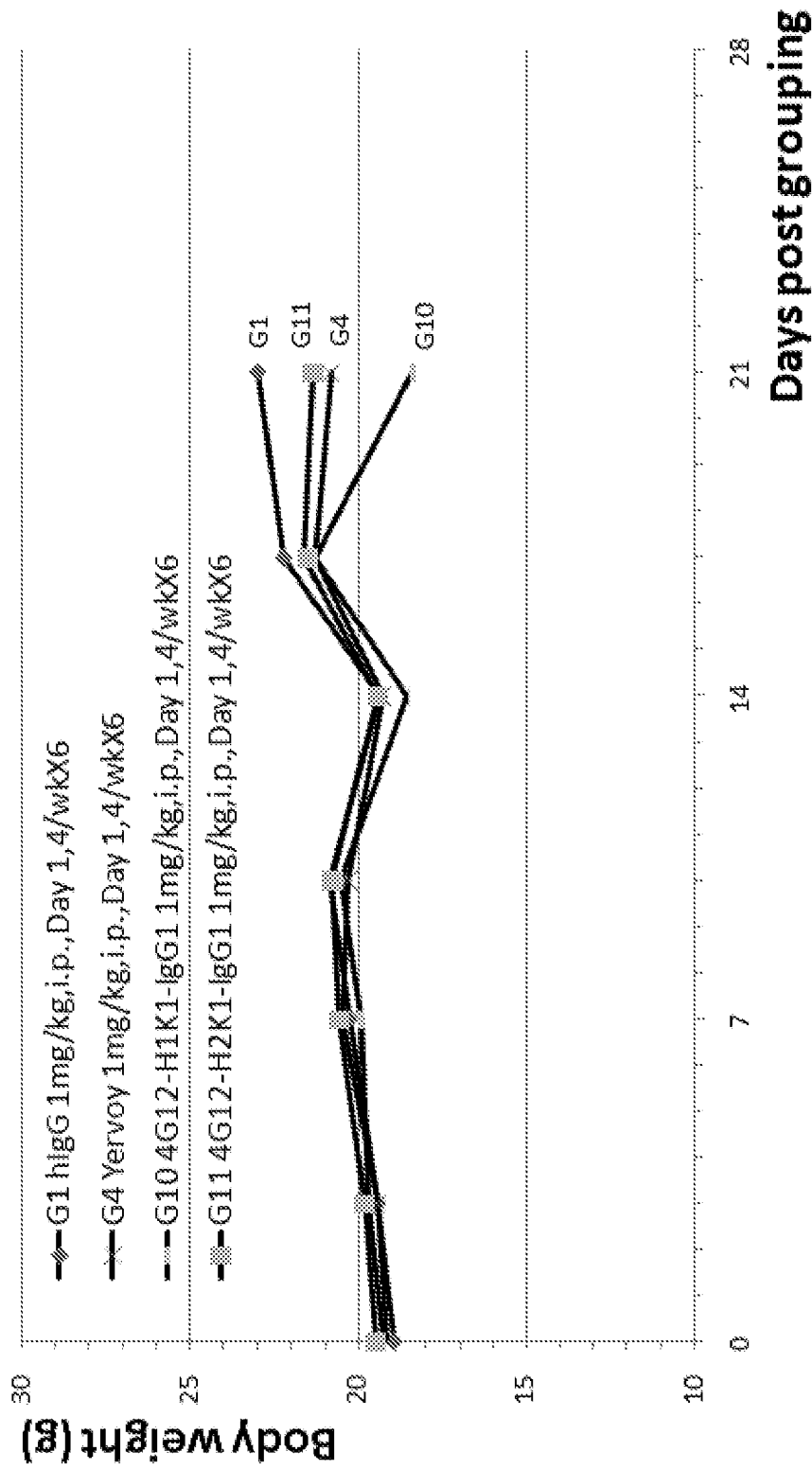


FIG. 12

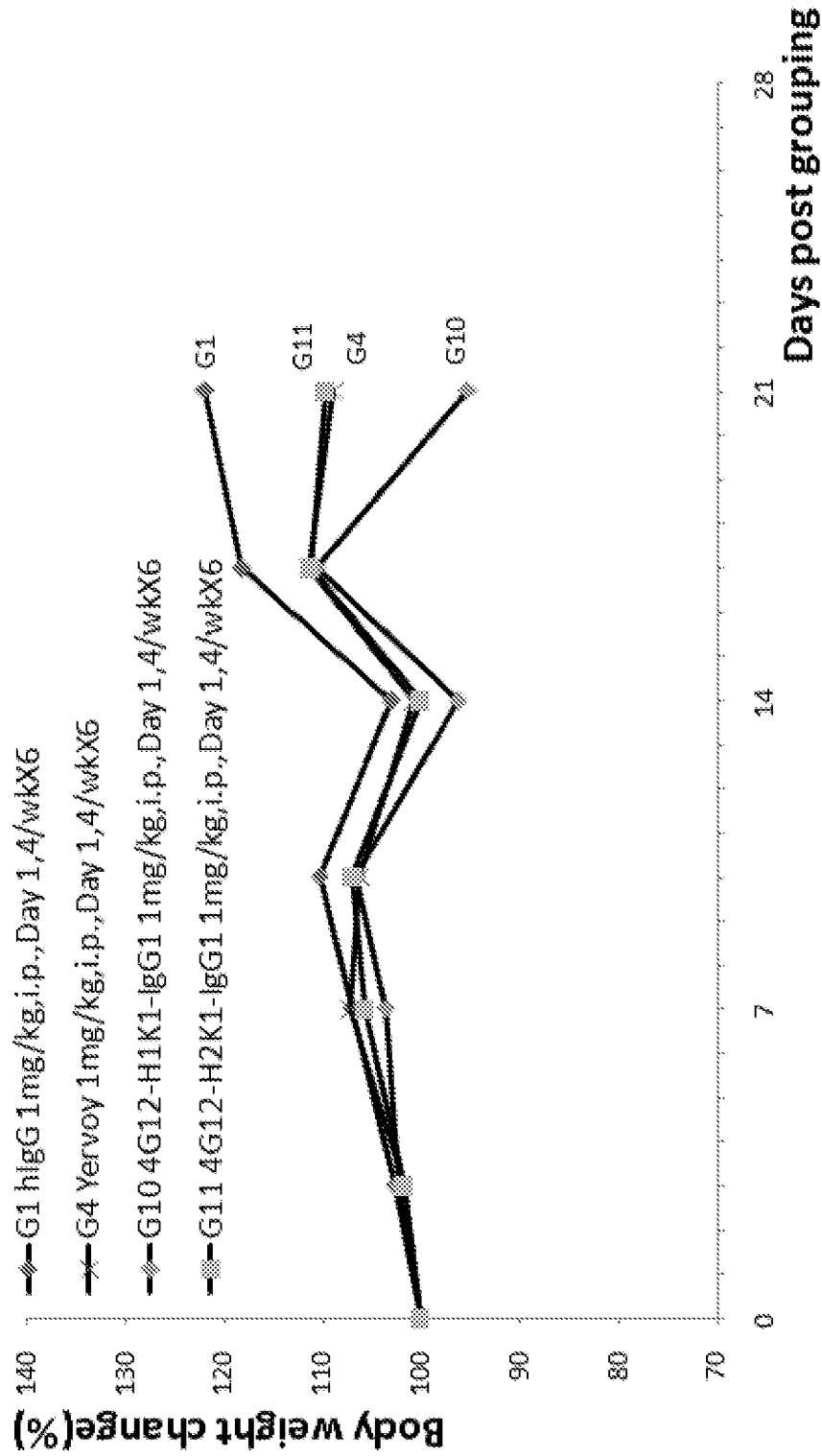


FIG. 13

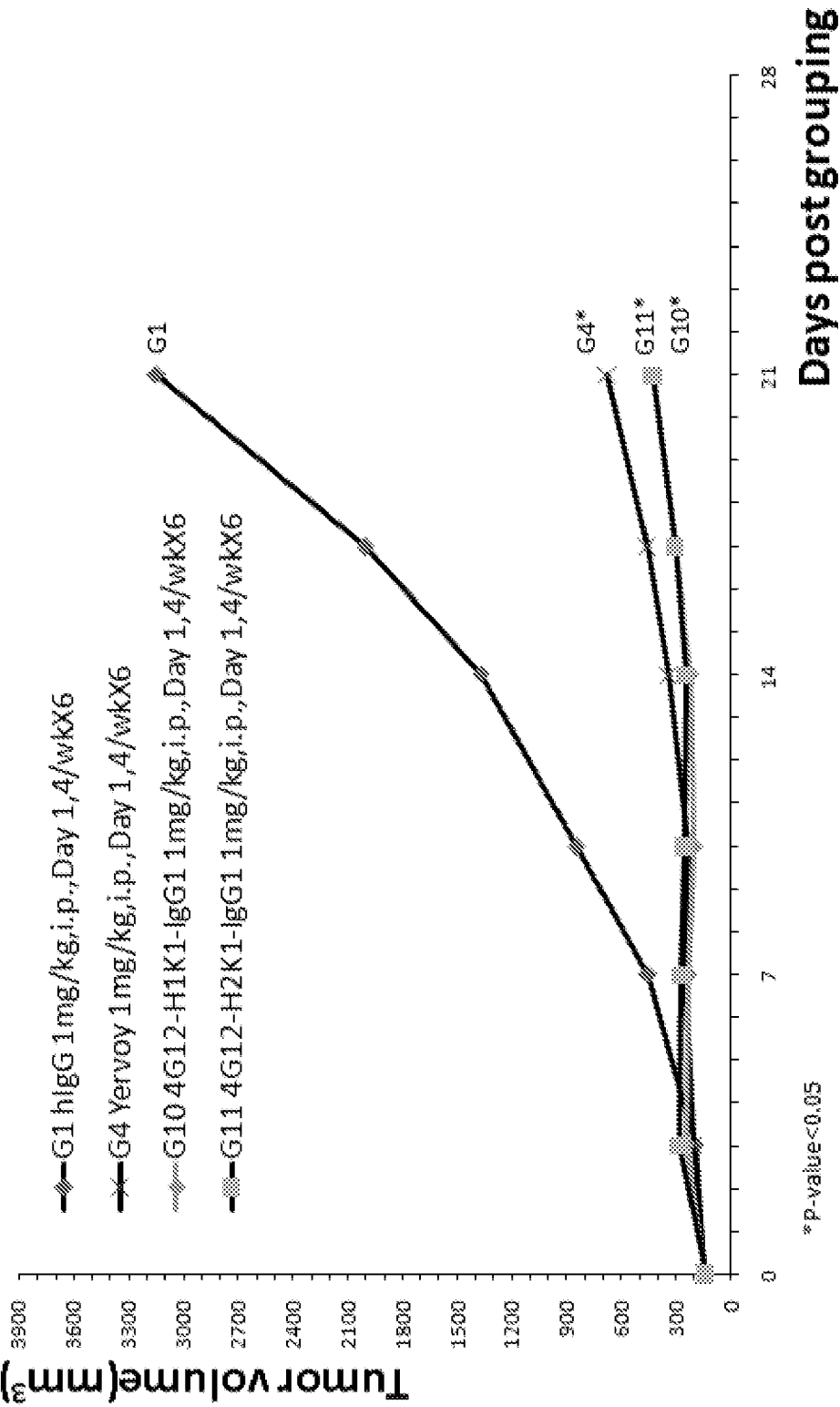


FIG. 14

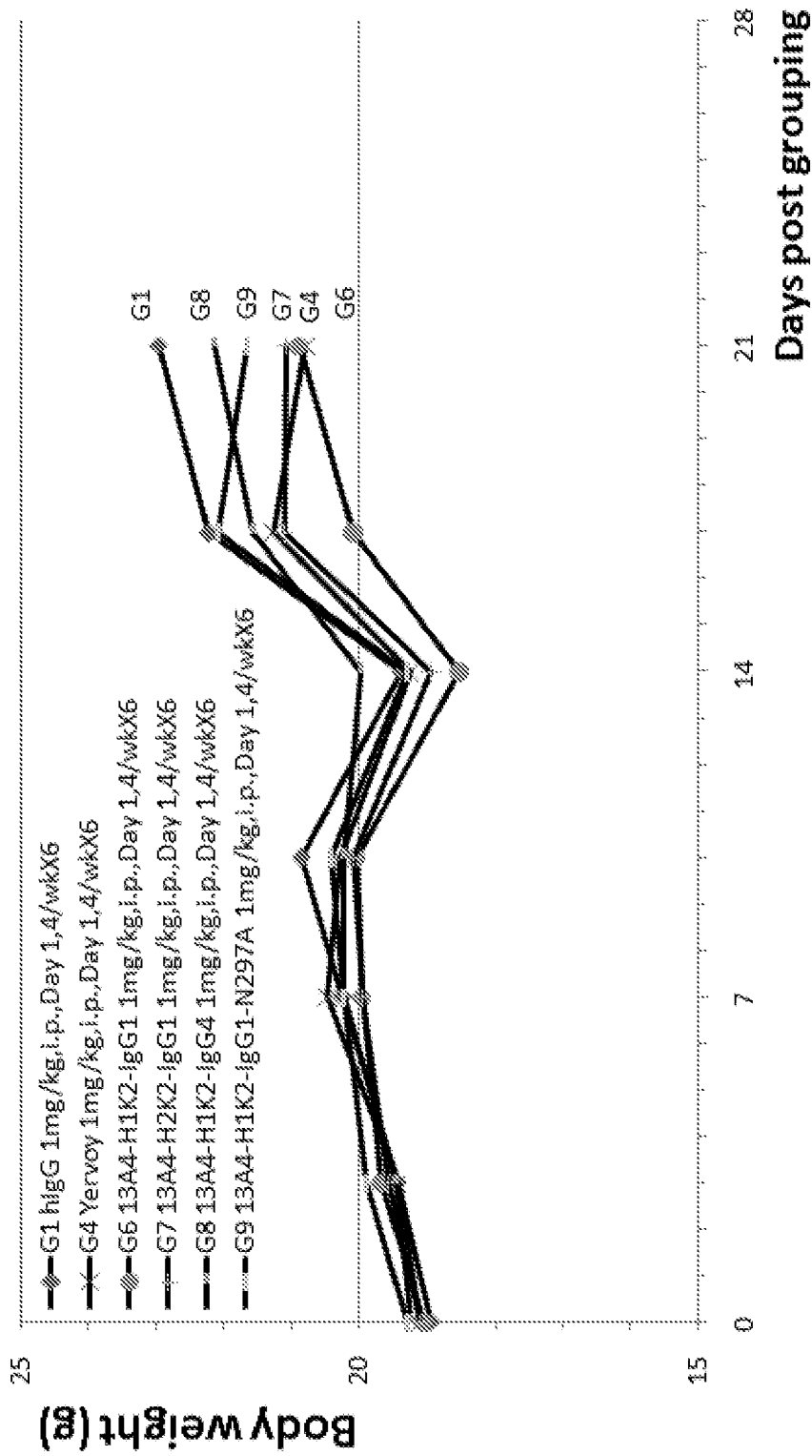


FIG. 15

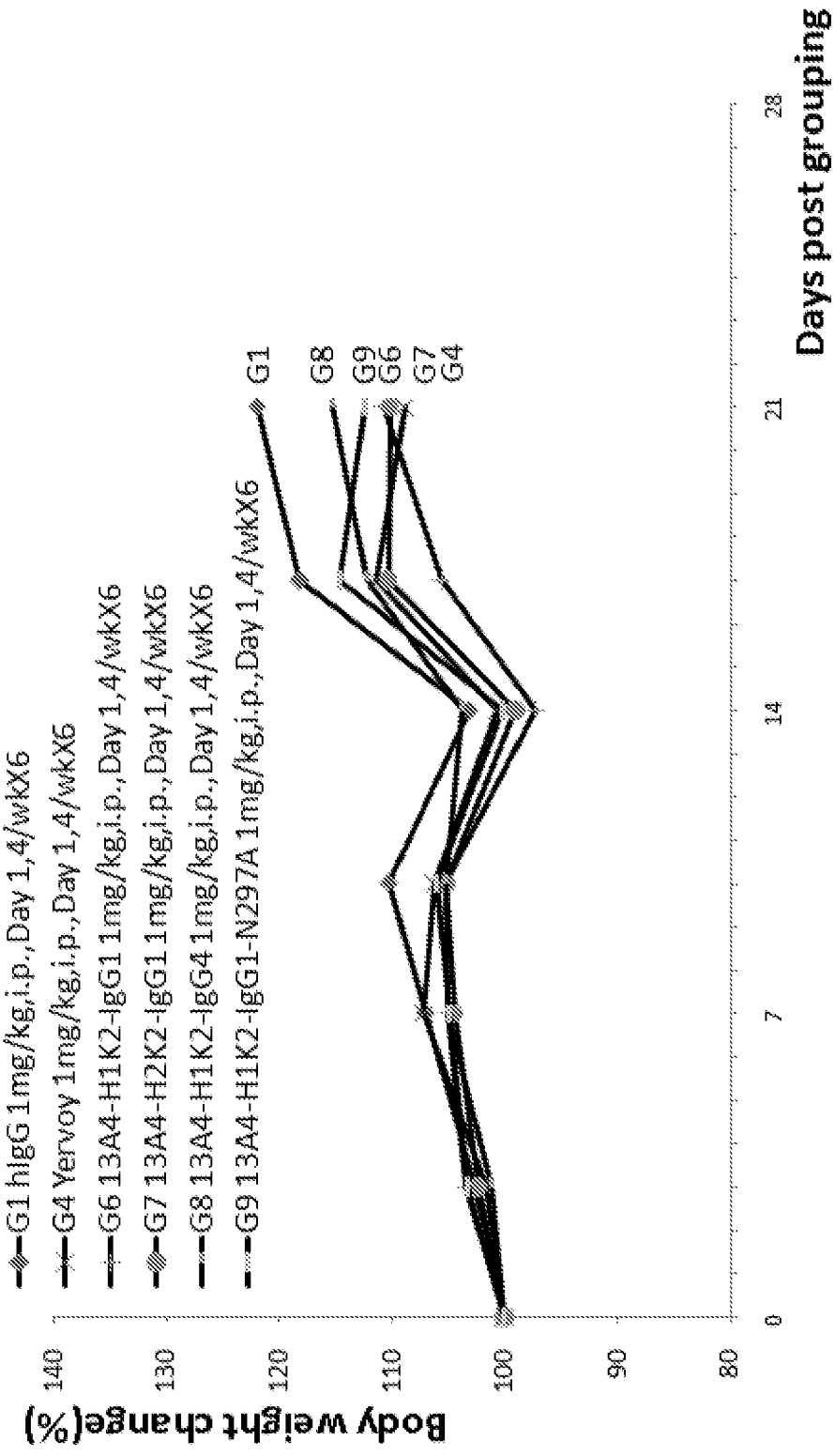


FIG. 16

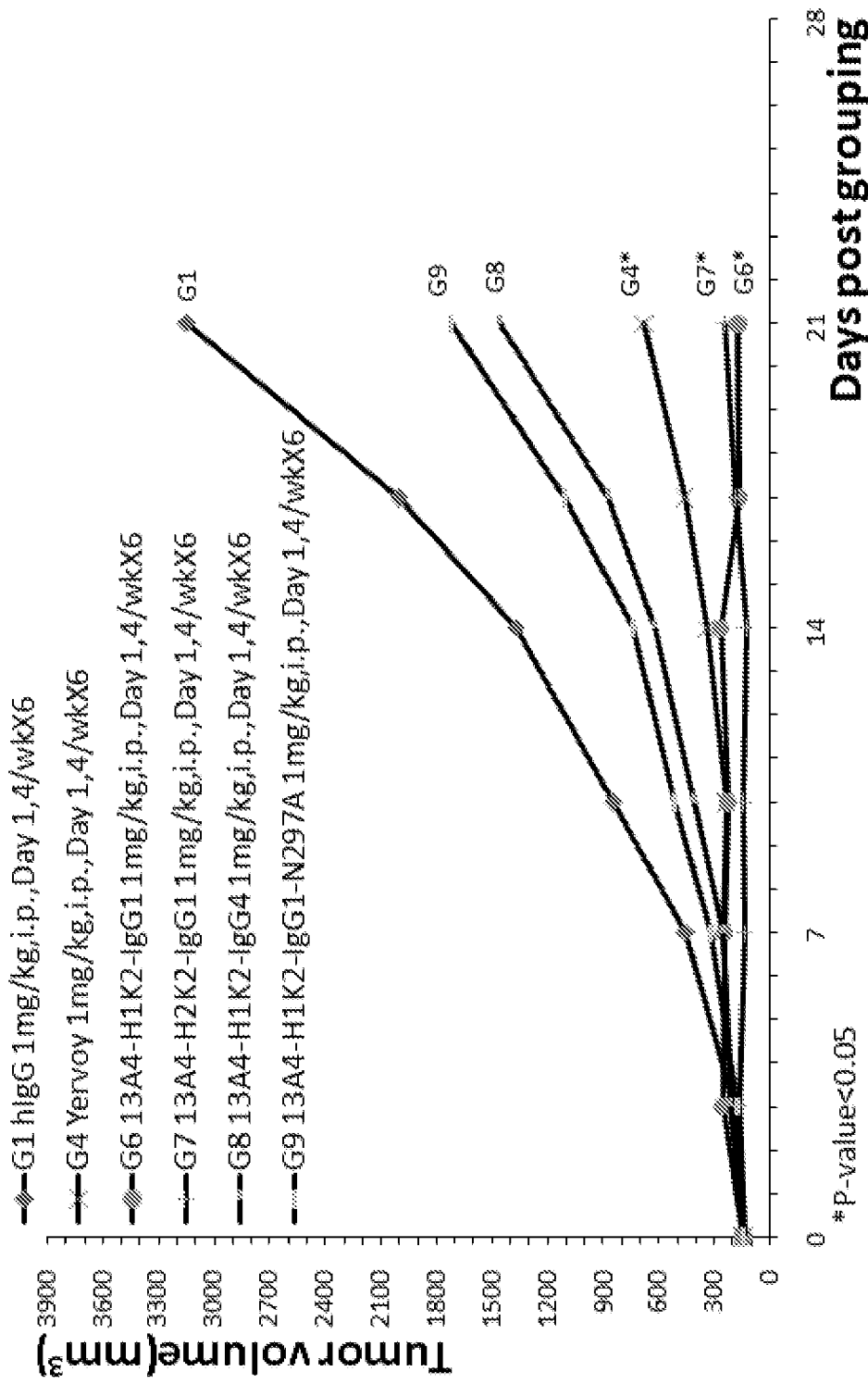


FIG. 17

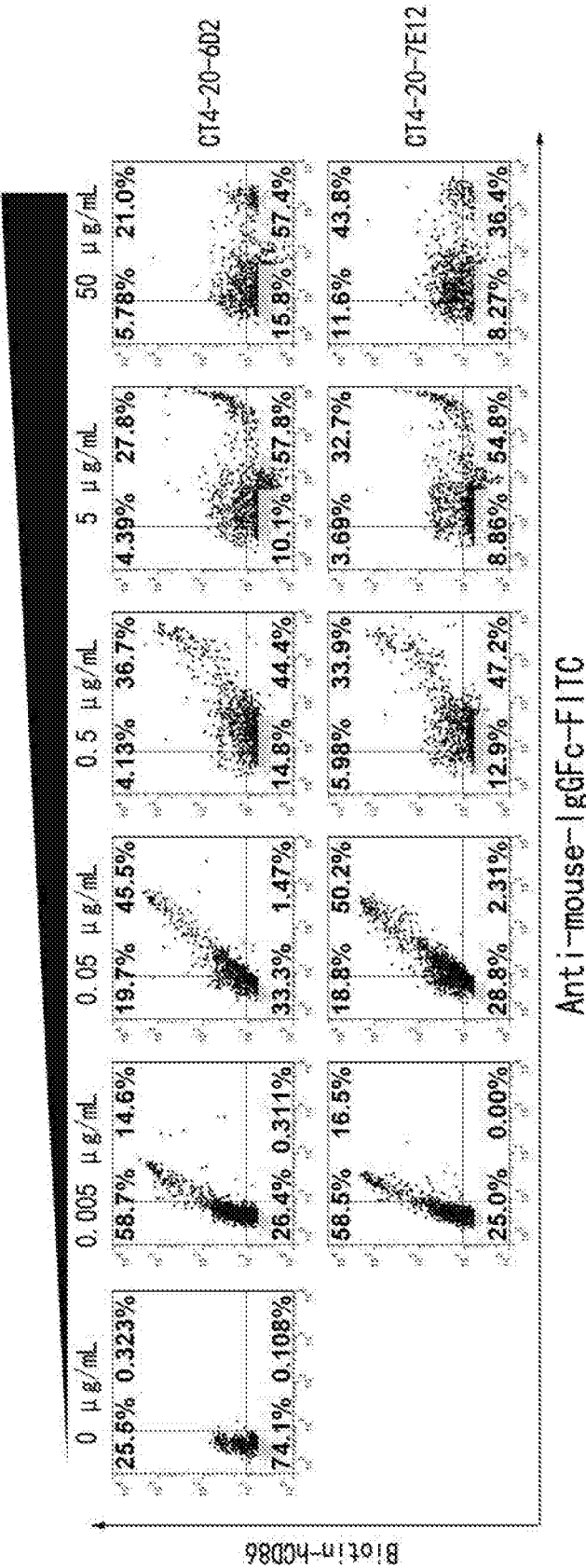


FIG. 18

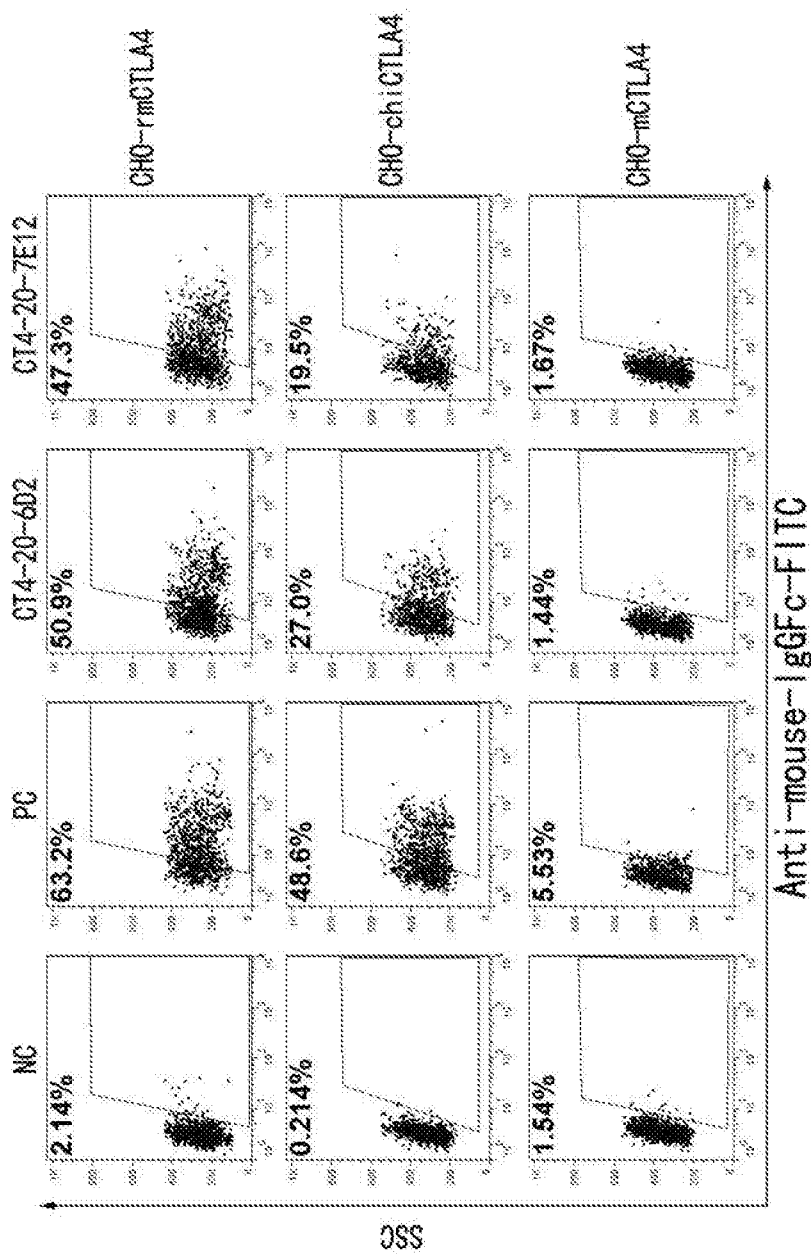


FIG. 19

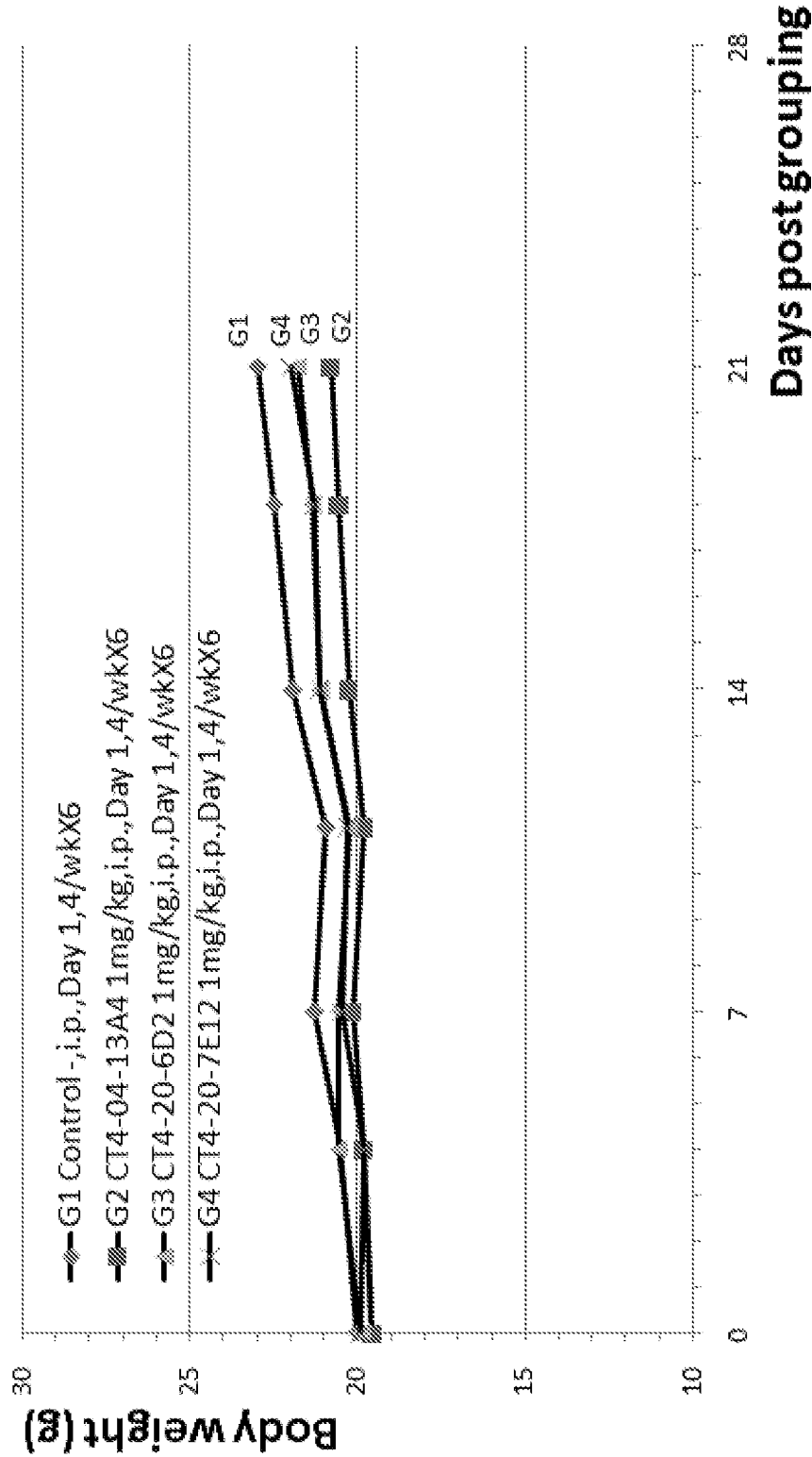


FIG. 20

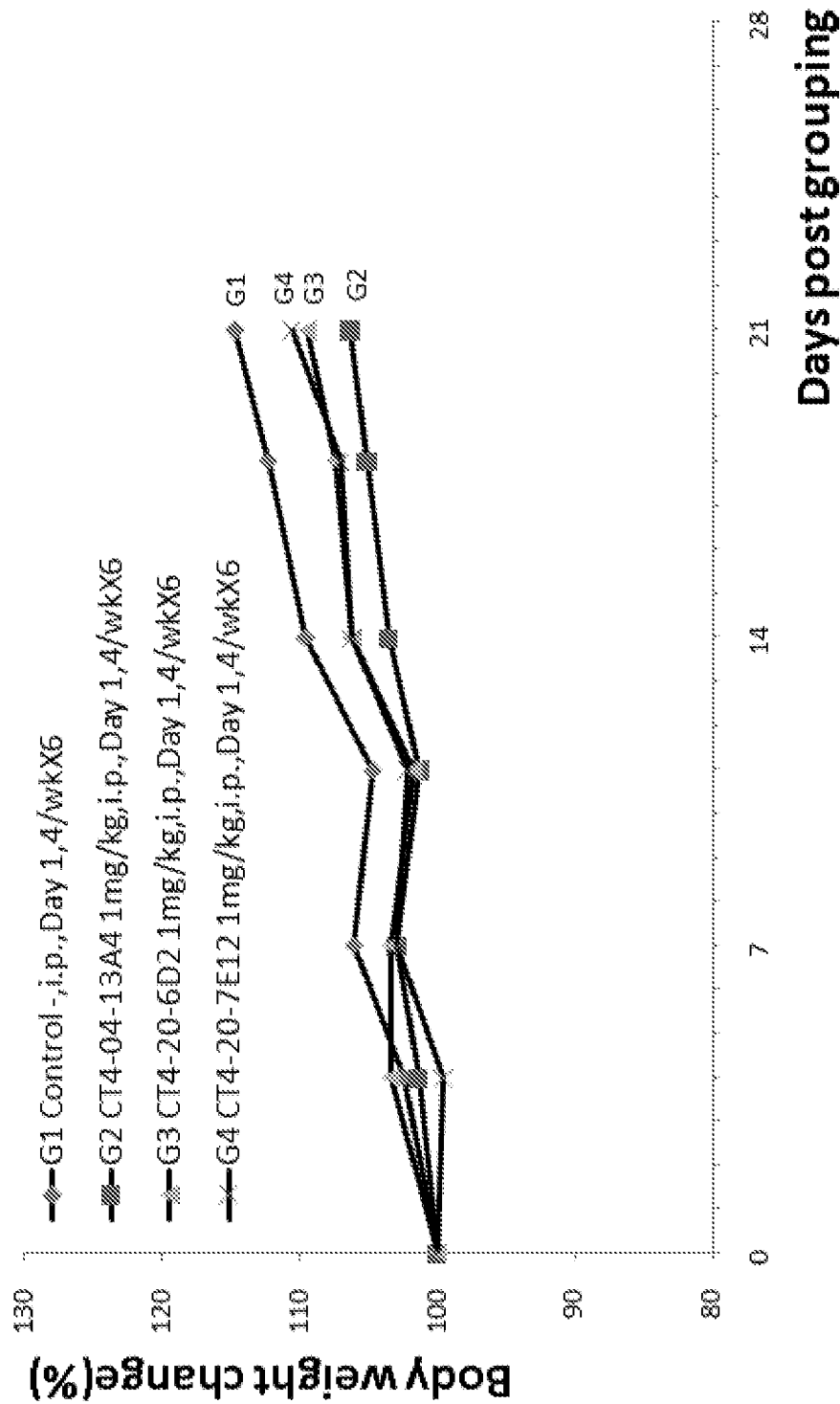


FIG. 21

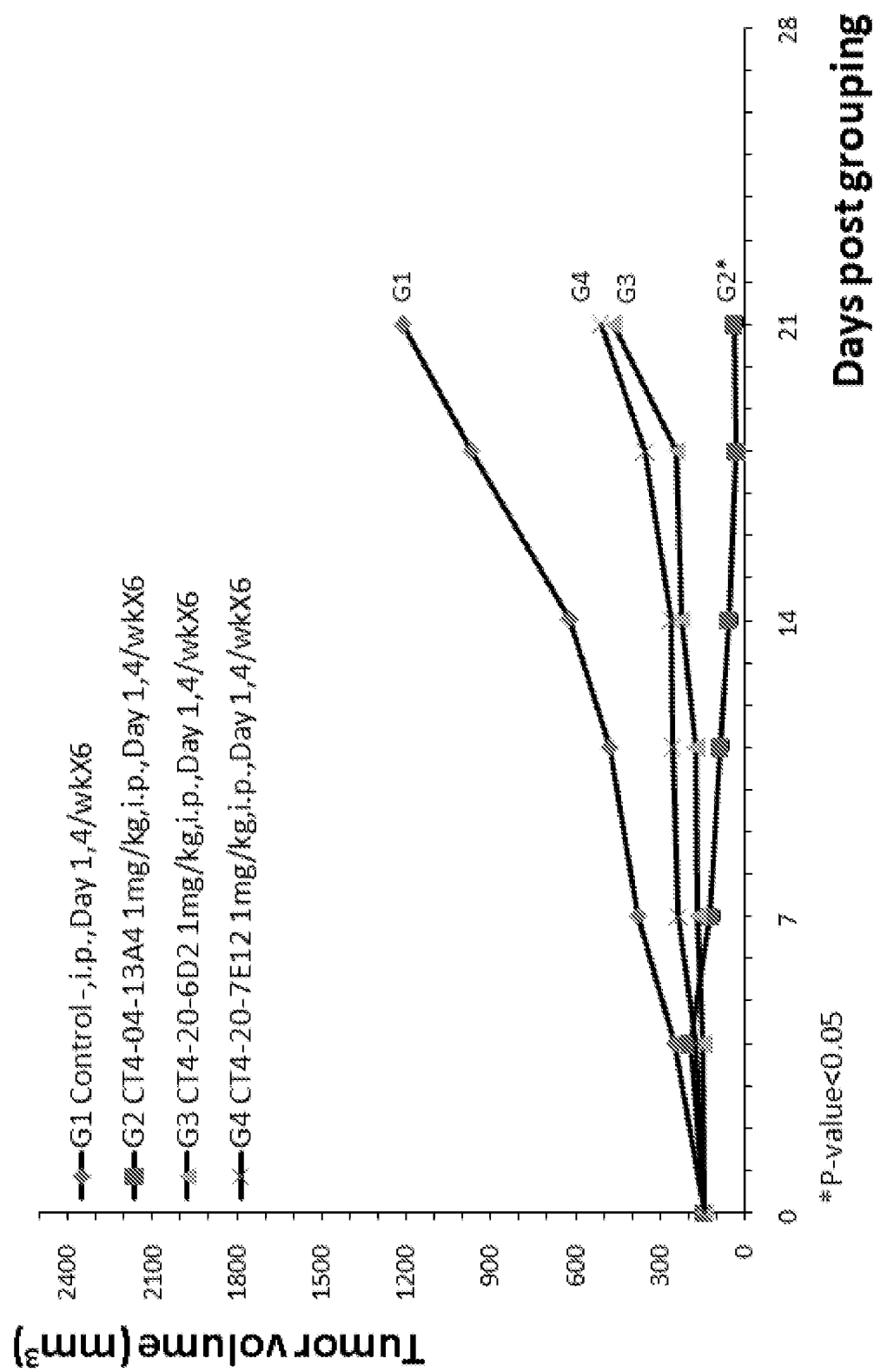


FIG. 22

Kabat CDR

Ab	VH CDR1	SEQ ID:	VH CDR2	SEQ ID:	VH CDR3	SEQ ID:	VL CDR1	SEQ ID:	VL CDR2	SEQ ID:	VL CDR3	SEQ ID:
13A4 or humanized 13A4	DYEM H	1	VIDPETGGTAYN QKFKG	2	GTTWGLDY	3	RASGNIHNYLA	4	KEKTLTD	5	QHFWST PWT	6
4G12 or humanized 4G12	SYTMS	7	TISRGGGYTSYDP SVKG	8	EDYGSSVH WFAY	9	RAGENIYSYLA	10	NARTLAE	11	QHHYGSP RT	12
6D2 or humanized 6D2	DYEM H	45	TIDPETGGTAYN QKFKG	46	RGKYGNYDY VMDY	47	RASGNIHNYLA	48	NAKTLAD	49	QHFWST PWT	50
7E12 or humanized 7E12	DYW MN	51	QIRNKPNYETH YSDSVKG	52	TFAY	53	GTSENIYGGLN	54	GATNLAD	55	QNVLSTP YT	56

FIG. 23

Chothia CDR

Ab	VH CDR1	SEQ ID:	VH CDR2	SEQ ID:	VH CDR3	SEQ ID:	VL CDR1	SEQ ID:	VL CDR2	SEQ ID:	VL CDR3	SEQ ID:
13A4 or humanized 13A4	GYTFT DYEM H	29	DPETGG	30	GTTVWGLDY	31	RASGNIHNYLA	32	KEKTLTD	33	QHFWST PWT	34
4G12 or humanized 4G12	GFTFS SYTMS	35	SRGGGY	36	EDYGSSVH WFAY	37	RAGENIYSYLA	38	NARTLAE	39	QHLYGSP RT	40
6D2 or humanized 6D2	GYTFT DYEM H	57	DPETGG	58	RGKYGNVDY VMDY	59	RASGNIHNYLA	60	NAKTLAD	61	QHFWST PWT	62
7E12 or humanized 7E12	GFTFS DYW MN	63	RNKPYNYE	64	TFAY	65	GTSENIYGGLN	66	GATNLAD	67	QNVLSTP YT	68

FIG. 24

Ab	Description	Amino acid sequence	SEQ ID NO:
Humanized 13A4	HuVHv1: (humanization percentage 86.5%; top hit to human and <i>Macaca fascicularis</i>)	QVQLVQSGAEVKKPGASVKVSCKVSGYTFITDYEMHWVRQAPGKGLEWMGVDPETGG TAYNQKFKGRVTLTADTSTDTAYMELSSLRSEDTAVYYCTRGTTVVGLDYWGQGTTLT VSS	13
Humanized 13A4	HuVHv2: (humanization percentage 85.4%; top hit to human and <i>Macaca fascicularis</i>)	QVQLVQSGAEVKKPGASVTVSCKVSGYTFITDYEMHWVRQAPGKGLEWMGVDPETGG TAYNQKFKGRVTLTADTSTDTAYMELSSLRSEDTAVYYCTRGTTVVGLDYWGQGTTLT VSS	14
Humanized 13A4	HuVHv3: (humanization percentage 84.4%)	QVQLVQSGAEVKKPGASVTVSCKASGYTFITDYEMHWVRQAPGKGLEWMGVDPETGG TAYNQKFKGRVTLTADTSTDTAYMELSSLRSEDTAVYYCTRGTTVVGLDYWGQGTTLT VSS	15
Humanized 13A4	HuVHv4: (humanization percentage 82.3%)	QVQLVQSGAEVKKPGASVKVSCKASGYTFITDYEMHWVKQAPGKGLEWIGVIDPETGGT AYNQKFKGRVTLTADRSTSTAYMELSSLRSEDTAVYYCTRGTTVVGLDYWGQGTTLTV SS	16
Humanized 13A4	HuVHv5: (humanization percentage 81.2%)	QVQLVQSGAEVKKPGASVTVSCKASGYTFITDYEMHWVRQAPGKGLEWIGVIDPETGGT AYNQKFKGRATLTADRSTSTAYMELSSLRSEDTAVYYCTRGTTVVGLDYWGQGTTLTV SS	17
Humanized 13A4	HuVLv1: (humanization percentage 85.3%; top hit to human)	DIQMTQSPSSLSASVGDRVTITCRASGNIHNLYAWYQQKPGKAPKLLLYKEKTLTDGVPS RFGSGSGTQYTLTISSLQPEDFATYYCQHFWSHPWTFGGGTNLEIKR	18
Humanized 13A4	HuVLv2: (humanization percentage 83.2%)	DIQMTQSPSSLSASVGDRVTITCRASGNIHNLYAWYQQKPGKAPKLLVYKEKTLTDGVPS RFGSGSGTQFTLTISSLQPEDFATYYCQHFWSHPWTFGGGTNLEIKR	19
Humanized 13A4	HuVLv3: (humanization percentage 82.1%)	DIQMTQSPSSLSASVGDRVTITCRASGNIHNLYAWYQQKPGKSPQLLVYKEKTLTDGVPS RFGSGSGTQFTLTISSLQPEDFATYYCQHFWSHPWTFGGGTNLEIKR	20
Humanized 4G12	HuVHv1: (humanization percentage 90.8%; top hit to human)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISRGGGYTS YPDSVKGRFTISRDNKNTLYLQMNSLR AEDTAVYYCAREDDYSSVHWFAFWYWGQGT L VTVSA	21
Humanized	HuVHv2: (humanization)	EVQLVESGGGLVQPGGSLRLSCAASGFTFSYTMWVRQAPGKGLEWVATISRGGGYTS	22

4G12	percentage 89.8%; top hit to human)	YPDSVKGRFTISRDNKNTLYLQMNSLRAEDTAMYYCAREDYGSSYVHWFAYWGQGT VTVSA	
Humanized 4G12	4G12 hu VHv3: (humanization percentage 87.8%)	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYTMWVRQTPGKRLEWVATISRGGGYS YPDSVKGRFTISRDNKNTLYLQMNSLRAEDTAMYYCAREDYGSSYVHWFAYWGQGT VTVSA	23
Humanized 4G12	4G12 hu VHv4: (humanization percentage 85.7%)	EVKLVESGGGLVQPGGSLRLSCAASGFTSSYTMWVRQTPGKRLEWVATISRGGGYS YPDSVKGRFTISRDNKNTLYLQMNSLRAEDTAMYYCAREDYGSSYVHWFAYWGQGT VTVSA	24
Humanized 4G12	4G12 hu VLv1: (humanization percentage 85.3%; top hit to human)	DIQMTQSPSFLSASVGDRVTITCRAGENIYSLAWYQQKPKAPKLLIYNARTLAEGVPS RFGSGSGTEFTLTISLQPEDFATYYCQHHYGSPTFGGGTKLEIKR	25
Humanized 4G12	4G12 hu VLv2: (humanization percentage 82.1%, using IGKV1- 39*01 as template)	DIQMTQSPSSLASVGDRVTITCRAGENIYSLAWYQQKQKSPKLLVYNARTLAEGVPS RFGSGSGTDFTLTISLQPEDFATYYCQHHYGSPTFGGGTKVEIKR	26
Humanized 4G12	4G12 hu VLv3: (humanization percentage 81.1%)	DIQMTQSPSSLASVGDRVTITCRAGENIYSLAWYQQKQKSPKLLVYNARTLAEGVPS RFGSGSGTQFTLTISLQPEDFATYYCQHHYGSPTFGGGTKLEIKR	27
Humanized 4G12	4G12 hu VLv4: (humanization percentage 80%, using IGKV1- 39*01 as template)	DIQMTQSPSSLASVGDRVTITCRAGENIYSLAWYQQKQKSPKLLVYNARTLAEGVPS RFGSGSGTDFTLTISLQPEDFATYYCQHHYGSPTFGGGTKLEIKR	28

FIG. 25

Protein	Amino acid sequence	SEQ ID NO:
Human CTLA4 (hCTLA4)	MACLGFRHKAQLNLATRTWPCTLLFFLLFIPVFCAMHVA QPAVVLASSRGIA SFVCEYASPGKATEVRVTVLRQADSQVTE VCAATYMMGNELTFLDDSICTGSSGNQVNLTIQGLRAMDT GLYICKVELMYPPPYL GIGNGTQIYVIDPECPDSDFLWIL AAVSSGLFFYSFLLTAVSLSKMLKKRSPLTTGVYVKMPPTPE ECKQFPYFIPIN	41
Mouse CTLA4 (mCTLA4)	MACLGLRRYKAQLQLPSRTWPFVALLTLLFIPVFSEAIQVTQP SVVLASSHGVA SFVCEYSPSHNTDEVRTVTVLRQNDQMTEVC ATTFTEKNTVGFLDYFPCSGTFNDSRVNLTIQGLRAVDTGly LCKVELMYPPPYFVGMNGTQIYVIDPECPDSDFLWILVA VSLGLFFYSFLLTAVSLSKMLKKRSPLTTGVYVKMPPTPEEC ECKQFPYFIPIN	42
Monkey CTLA4 (mCTLA4)	MACLGFRHKAQLNLATRTRPYTLFSLFIPVFSKAMHVAQ PAVLANSRGIA SFVCEYASPGKATEVRVTVLRQADSQVTEV CAATYMMGNELTFLDDSICTGSSGNQVNLTIQGLRAMDTGL YICKVELMYPPPYL GIGNGTQIYVIDPECPDSDFLWILAA VSSGLFFYSFLLTAVSLSKMLKKRSPLTTGVYVKMPPTPEEC ECKQFPYFIPIN	43
Chimeric CTLA4 (chiCTLA4) (Humanized CTLA4)	MACLGLRRYKAQLQLPSRTWPFVALLTLLFIPVFSEAIQVAQ PAVVLASSRGIA SFVCEYASPGKATEVRVTVLRQADSQVTEV CAATYMMGNELTFLDDSICTGSSGNQVNLTIQGLRAMDTGL YICKVELMYPPPYL GIGNGTQIYVIDPECPDSDFLWILVA VSLGLFFYSFLLTAVSLSKMLKKRSPLTTGVYVKMPPTPEEC ECKQFPYFIPIN	44

FIG. 26

CT4-04-13A4 (13A4) Heavy chain variable region (SEQ ID NO: 69)
 QVQLQQSGAELVRPGASVTLSCCKASGYTFTDYE¹MHWVKQTPVHGLEWIGVIDPETGGTA²
 YNQKFKGKATLTADRSSSTAYMELRSLTSEDSAVYYCTRGTTVVGLDYWGQGTTLTVSS³

CT4-04-13A4 (13A4) Light chain variable region (SEQ ID NO: 70)
 DIQMTQSPASLSASVGESVTITCRASGNIHN¹YLA²WYQQKQKSPQLLVYKEKTLTDTPPS³
 RFGSGSGTQFSLKINSLQPEDFGSY⁴YQC⁵HF⁶WSTP⁷WTFGGGTNLEIK⁸

CT4-03-4G12 (4G12) Heavy chain variable region (SEQ ID NO: 71)
 DVKLVESGGGLVKPGGSLKLSCTASGFTFSSYT¹MSWVRQTPEKRLEWVATISRGGGYTS²
 YPDSVKGRFTISRDN³AKNTLYLQMSLQSEDTAMYYCARD⁴DY⁵GSS⁶YV⁷HW⁸FAY⁹WGQGT¹⁰L¹¹
 VT¹²VSA¹³

CT4-03-4G12 (4G12) Light chain variable region (SEQ ID NO: 72)
 DIQMTQSPASLSASVGETVTITCRAGENIYSYL¹AWYQQKQKSPQLLVYNARTLAE²GVP³
 SRFGSGSGTQFSLKINSLQPEDFGSY⁴YC⁵QH⁶Y⁷GS⁸PR⁹T¹⁰FGG¹¹G¹²TKLEIK¹³

CT4-20-6D2 (6D2) Heavy chain variable region (SEQ ID NO: 73)
 MEWSVVFLLSVIAGVQSQVLQQSGAELVRPGASV¹TLSC²KASGYTFTDYE³MHWVKQTPVHG⁴LEWIG⁵TIDPETGGTA⁶YN⁷
 QKFKGKATLTTDKSSSTAYMELRSLTSEDSAVYYCTRRGKYGNYDYVMDYWGQTSVT⁸VSS⁹

CT4-20-6D2 (6D2) Light chain variable region (SEQ ID NO: 74)
 MSVL¹TQVLALLLWLTGARC²DIQMTQSPASLSASVGETVTITCRASGNIHN³YLA⁴WYQQKQKSPQLLVFNA⁵KT⁶LADGV⁷PSR⁸
 FSGSGSGTQYSLKINSLQPEDFGNY⁹YC¹⁰QH¹¹FWSTP¹²WTFGGGT¹³KLEIK¹⁴

CT4-20-7E12 (7E12) Heavy chain variable region (SEQ ID NO: 75)
 MYLGLSCVFIVFLKGVQCEVKLDETGGGLVQPGRPMKLS¹CVASGFTFSDYWMN²WVRQ³SPEKGLEWVAQIRN⁴KPYN⁵YETH⁶
 YSDSVKGRFTISRDDSKSSVYLQMNNLRGDMGIYYCTGT⁷FAYWGQGT⁸LVTVSA⁹

CT4-20-7E12 (7E12) Light chain variable region (SEQ ID NO: 76)
 MGVP¹TQLLLLLWLT²VVVRCDIQMTQSP³TSLSASVGETVTITCGTSEN⁴YGGLN⁵WYQR⁶KQKSPQLLIYGATNLADGMSS⁷RF⁸S⁹
 GSGGRQYSLKISSLHPDDVATYYCQNV¹⁰LSPT¹¹YTFGGGT¹²KLEIK¹³

FIG. 27