```
1     MEPLRLLILLFVTELSGAHNTTVFQGVAGQSLQVSCPYDSMKHWGRRKAWCRQLGEKGPC    60
      + PL LL+LLF    + +    V Q VAGQ+L V C Y        +K WC++      C
6     LHPLLLLLLLFPGSQAQS-KAQVLQSVAGQTLTVRCQYPPTGSLYEKKGWCKEASAL-VC    63

61    QRVVSTHNLWLLSFLRRWNGSTAITDDTLGGTLTITLRNLQPHDAGLYQCQSLHGSEADT   120
      R+V++     ++    W     I DD   G  T+T+ +L+  D+G Y C+    S+
64    IRLVTSSKPRTMA----WTSRFTIWDDPDAGFFTVTMTDLREEDSGHYWCRIYRPSDNSV   119

121   LRKVLVEVLADP   132 TREM-2 Human
       + V   ++  P
120   SKSVRFYLVVSP   131 NCTR2_HUMAN
```

FIG. 1A

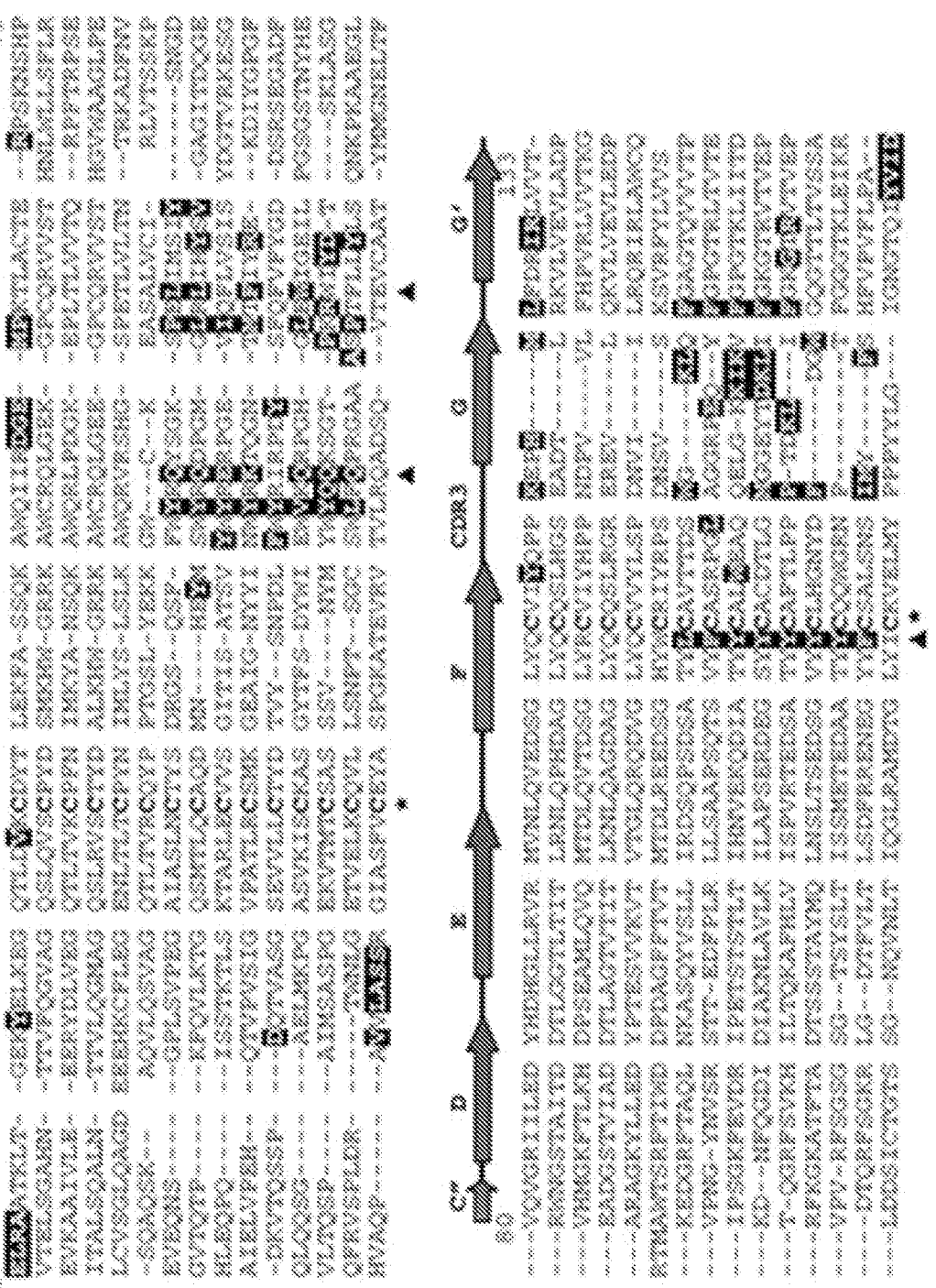


FIG. 1B

sp|Q9NZC2|TREM2_HUMAN Triggering receptor expressed on myeloid cells 2 OS=Homo sapiens GN=TREM2 PE=1 SV=1
Sequence ID: lcl|35715 Length: 230 Number of Matches: 1
Range 1: 6 to 110

Score	Expect	Method	Identities	Positives	Gaps	Frame
42.7 bits(99)	1e-09()	Compositional matrix adjust.	34/107(32%)	49/107(45%)	4/107(3%)	

Features:

```
TREM1    9    LLWMLFVSELRAATKLTEEKYELKEGQTLDVKCDYTLEKFASSQKAW--QIIRDGEMPKT  66
              LL +LFV+EL  A   T   ++   GQ+L V C Y   K    +KAW  Q+   G   +
TREM2    6    LLILLFVTELSGAHNTT--VFQGVAGQSLQVSCPYDSMKHWGRRKAWCRQLGEKGPCQRV  63

TREM1    67   LACTERPSKNSHPVQVGRIILEDYHDHGLLRVRMVNLQVEDSGLYQC  113
              ++       +      G   + D    G L + + NLQ  D+GLYQC
TREM2    64   VSTHNLWLLSFLRRWNGSTAITDDTLGGTLTITLRNLQPHDAGLYQC  110
```

FIG. 2

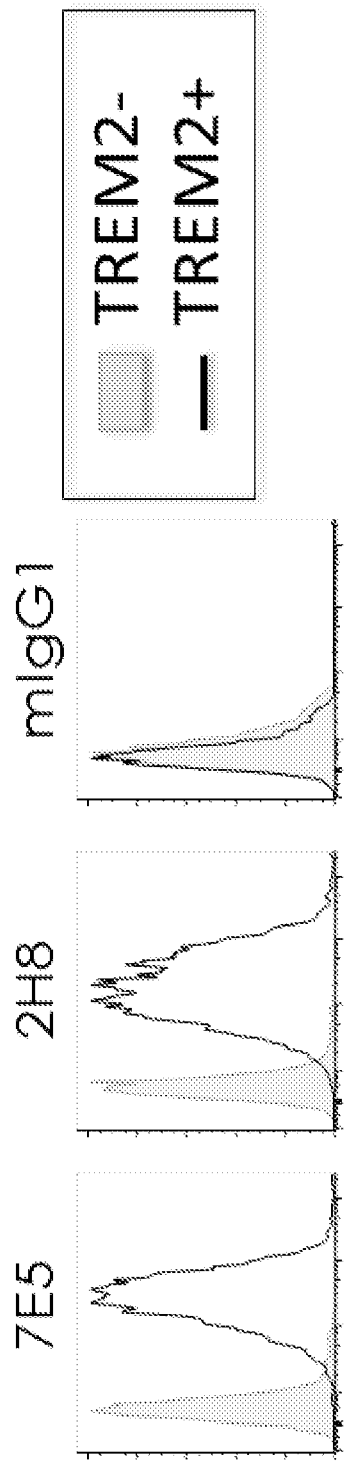

TREM2-
TREM2+
mIgG1
2H8
7E5

FIG. 3A

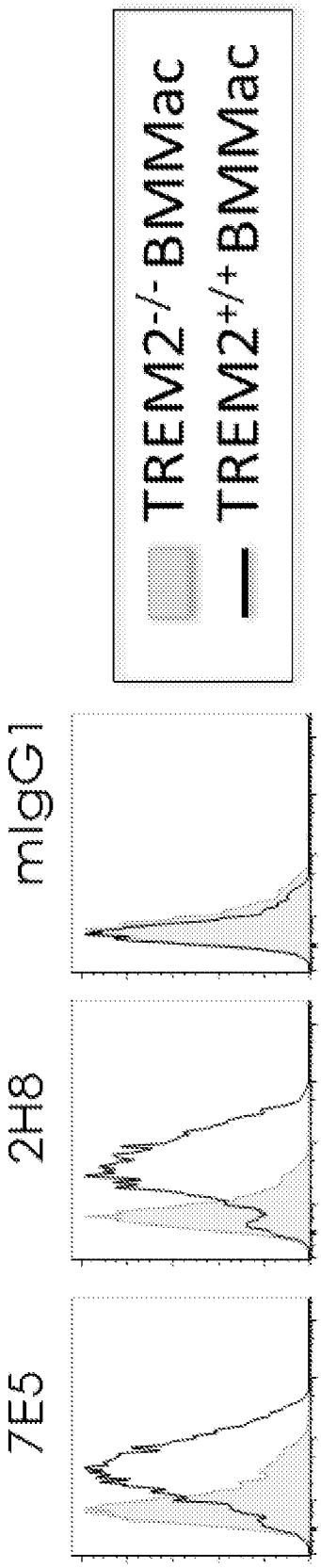

TREM2-/- BMMac
TREM2+/+ BMMac
mIgG1
2H8
7E5

FIG. 3B

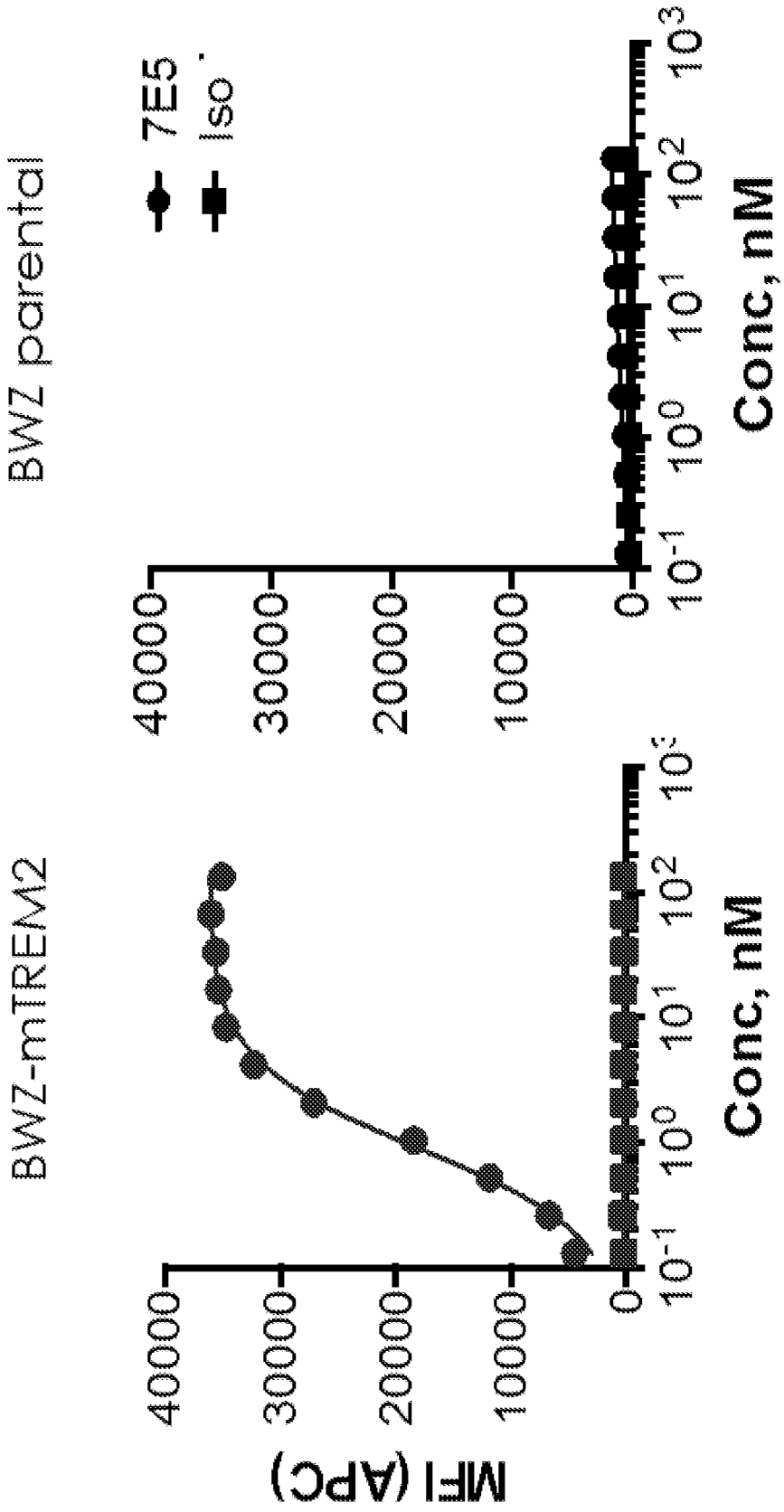

BWZ-mTREM2
BWZ parental
7E5
Iso
MFI (APC)
Conc, nM
Conc, nM
0
10000
20000
30000
40000
10^-1
10^0
10^1
10^2
10^3

FIG. 3C

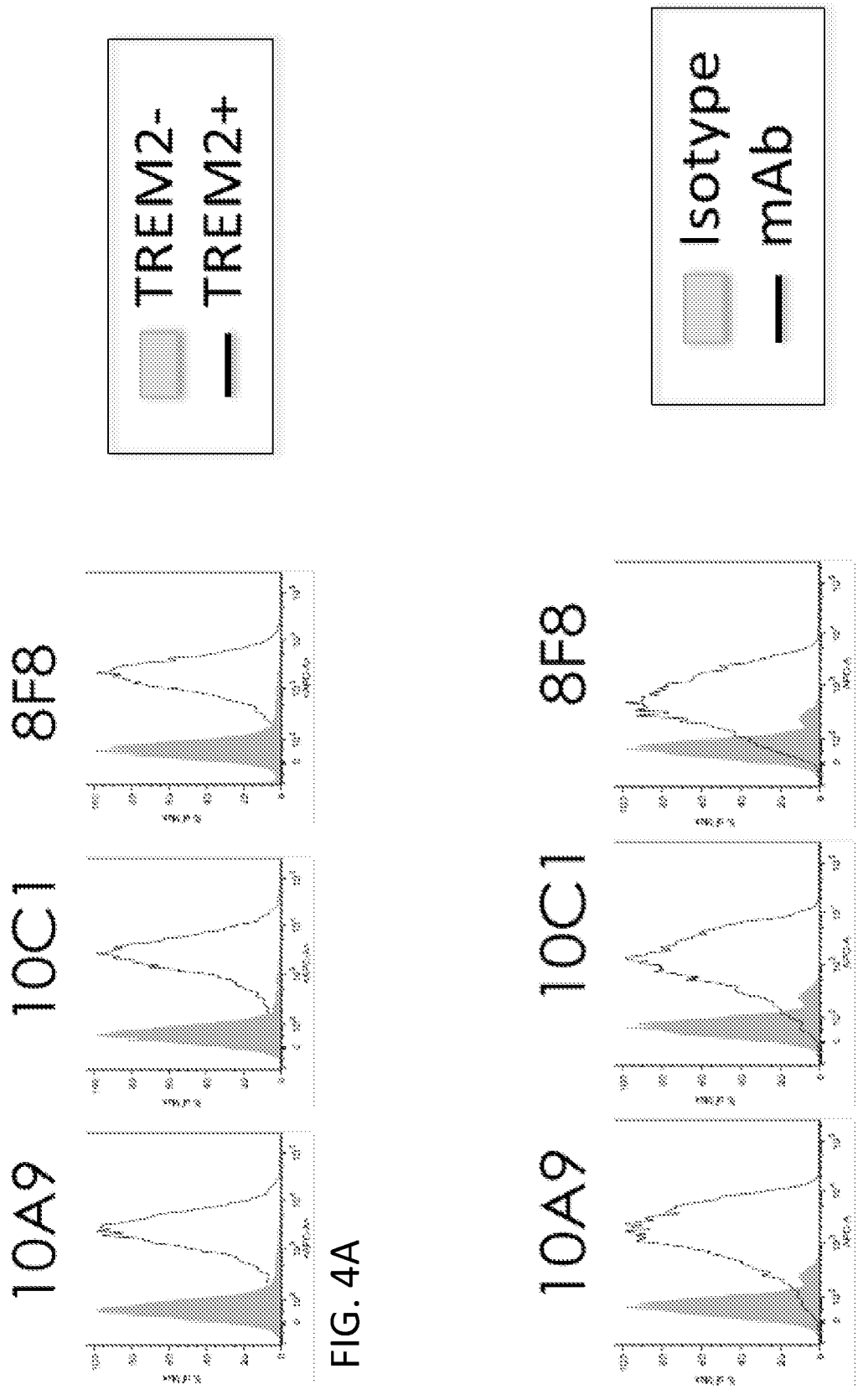


FIG. 4A

FIG. 4B

```
Potential humanized sequence based on IMGT IGKV2-29*02 acceptor framework (AbM CDR definition)
IGKV2-29*02 DIVMTQTPLSLSVTPGQPASISCKSSQSLLHSDGKTYLYWYLQKPGQSPQLLIYEVSNRFS
            GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYCMQSIQLPP
Joining region  IMGT J00242|IGKJ2*01|YTFGQGTKLEIK

seq                10        20        30        40        50        60
AbM                10        20        30abcde        40        50
            b b b    p p     p b b  b   b        bi bi i    ii ibbi      i
T2-9F5.1  DVVMTQTPLSLPVSLGDQASISC RSSQSLVHSNGYTYLH WYLQKPGQSPKLLIY KVSNRFS
            *         * ** **                                  *
2-29*02   DIVMTQTPLSLSVTPGQPASISC KSSQSLLHSDGKTYLY WYLQKPGQSPQLLIY EVSNRFS
h9F5-L1   DIVMTQTPLSLSVTPGQPASISC RSSQSLVHSNGYTYLH WYLQKPGQSPQLLIY KVSNRFS
h9F5-L2   DVVMTQTPLSLSVTPGQPASISC RSSQSLVHSNGYTYLH WYLQKPGQSPQLLIY KVSNRFS
                                                                    #

seq               70        80        90        100        110
AbM         60        70        80        90        100
            b   b        b b b  b    ib bib  ibi iib  i   b b b
T2-9F5.1  GVPDRFSGSGSGTDFTLKISRVEADDLGVYFC SQSTRVPYT FGGGTKLEIK
                                  * *   *              *
2-29*02   GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC MQSIQLPP  FGQGTKLEIK
h9F5-L1   GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC SQSTRVPYT FGQGTKLEIK
h9F5-L2   GVPDRFSGSGSGTDFTLKISRVEAEDVGVYYC SQSTRVPYT FGQGTKLEIK
                                    L   F

# deamidation substitutions: Q/S/A/D
@ isoaspartate substitutions: Q/S/A

h9F5-L1 is a "CDR-swap" with no changes to human framework.  Subsequent sequences alter framework changes
shown in red (compared to sequence above it).
```

(1) CDR sequences noted in bold. CDR definitions are AbM from website www.bioinf.org.uk/abs/.
(2) Human germline and joining sequences from IMGT® the international ImMunoGeneTics® information system www.imgt.org (founder and director: Marie-Paule Lefranc, Montpellier, France).
(3) Residue numbering shown as sequential (seq) or according to Chothia from website www.bioinf.org.uk/abs/ (AbM).
(4) "b" notes buried sidechain; "p" notes partially buried; "i" notes sidechain at interface between VH and VL domains.
(5) Sequence differences between human and murine germlines noted by asterisk (*). (6) Potential additional mutations in frameworks are noted below sequence.
(7) Potential changes in CDR sequences noted below each CDR sequence. These may prevent asparagine (N) deamidation or isoaspartate (DG) formation).

FIG. 4C

Potential humanized sequence based on IMGT IGHV1-46*01 acceptor framework (AbM CDR definition)
IGHV1-46*01 QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGIINPSGGSTS
YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR
Joining region IMGT J00256|IGHJ4*01|YFDYWGQGTLVTVSS

seq 10 20 30 40 50
AbM 10 20 30 40 50 **a**
b b b p b b b b b b b bi i i ibb b

T2-9F5.1	QVQLQQSGPELVKPGASLKISCKAS **GYAFSSSWMN** WVKQRPGKGLEWIG **RIYPGDGDTN**
	* * *# # # * * * #
1-46*01	QVQLVQSGAEVKKPGAS#K#SCKAS GYTFTSYYMH WVRQAPGQGLEW##G IINPSGGSTS
h9F5-H1	QVQLVQSGAEVKKPGASVKVSCKAS **GYAFSSSWMN** WVRQAPGQGLEWMG **RIYPGDGDTN**
h9F5-H2	QVQLVQSGAEVKKPGASVKVSCKAS **GYAFSSSWMN** WVRQAPGQGLEW#G **RIYPGDGDTN**
h9F5-H3	QVQLVQSGAEVKKPGAS#K#SCKAS **GYAFSSSWMN** WVRQAPGQGLEW**I**G **RIYPGDGDTN**
	V ^ @ #

seq 60 70 80 90 100 110 120
AbM 60 70 80 **abc** 90 110
i b b b b x b b b b bibibb i b b b

T2-9F5.1	YNGEFRVRATLTADTSSTTAYMQLSSLTSEDSAVYFCAR **LLRNQPGESYAMDY** WGQGASVTVSS
	#** ** # # # ** # * * * # **
1-46*01	YAQKFQGR#T#T#DTSTST#YMELSSLRSEDTAVYYCAR WGQG#LVTVSS
h9F5-H1	YAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCAR **LLRNQPGESYAMDY** WGQGTLVTVSS
h9F5-H2	YAQKFQGRVTMT#DTSTSTVYMELSSLRSEDTAVYYCAR **LLRNQPGESYAMDY** WGQGTLVTVSS
h9F5-H3	YAQKFQGR#T#T**A**DTSTST#YMELSSLRSEDTAVYYCAR **LLRNQPGESYAMDY** WGQG#LVTVSS
	N F #

deamidation substitutions: Q/S/A
^ tryptophan oxidation substitutions: H/Y/F
@ isoaspartate substitutions: Q/S/A

h9F5-H1 is a "CDR-swap" with no changes to human framework. Subsequent sequences alter framework changes shown in red (compared to sequence above it).

(1) CDR sequences noted in bold. CDR definitions are AbM from website www.bioinf.org.uk/abs/.
(2) Human germline and joining sequences from IMGT® the international ImMunoGeneTics® information system www.imgt.org (founder and director: Marie-Paule Lefranc, Montpellier, France).
(3) Residue numbering shown as sequential (seq) or according to Chothia from website www.bioinf.org.uk/abs/ (AbM).
(4) "b" notes buried sidechain; "p" notes partially buried; "i" notes sidechain at interface between VH and VL domains.
(5) Sequence differences between human and murine germlines noted by asterisk (*). (6) Potential additional mutations in frameworks are noted below sequence.
(7) Potential changes in CDR sequences noted below each CDR sequence. These may prevent asparagine (N) deamidation, tryptophan (W) oxidation, or isoaspartate (DG) formation.

FIG. 4D

Binding Reactivity (% WT)				
Mutation	**T21-9 Fab**	**T22 Fab**	**T45-10 Fab**	**9F5 MAb**
K42A	2.0 (2)	0.0 (0)	70.1 (22)	130.8 (26)
G45A	46.1 (9)	9.7 (1)	128.8 (34)	145.0 (19)
R77A	170.0 (24)	138.7 (12)	15.4 (2)	123.8 (22)
H114A	29.1 (0)	8.0 (2)	70.6 (8)	114.5 (29)
E151A	238.0 (21)	148.7 (22)	96.8 (9)	4.8 (6)
D152A	191.8 (86)	140.9 (32)	98.3 (15)	2.7 (1)
H154A	250.8 (59)	138.0 (33)	82.6 (0)	3.0 (2)
E156A	162.0 (20)	154.7 (61)	103.8 (12)	17.7 (13)

FIG. 4E

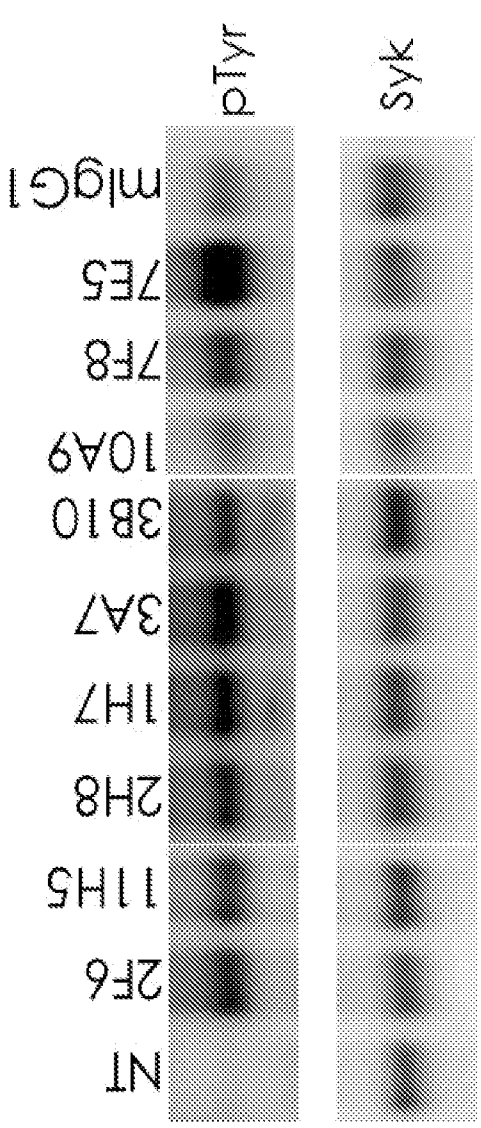

pTyr
Syk
mIgG1
7E5
7F8
10A9
3B10
3A7
1H7
2H8
11H5
2F6
NT

FIG. 5A

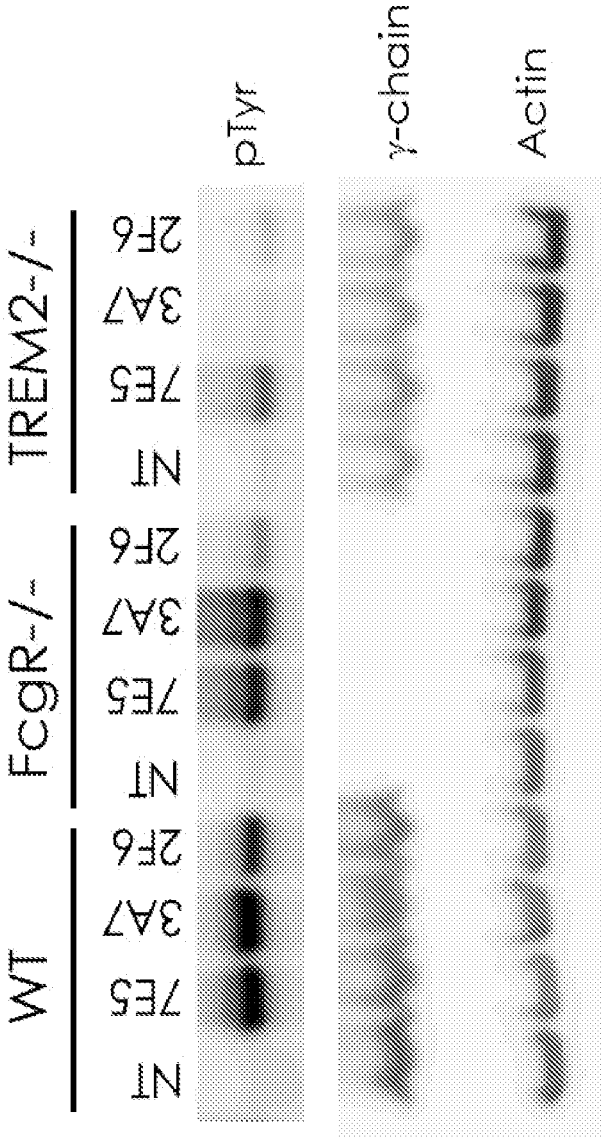

pTyr
γ-chain
Actin
WT
FcgR-/-
TREM2-/-
NT
7E5
3A7
2F6

FIG. 5B

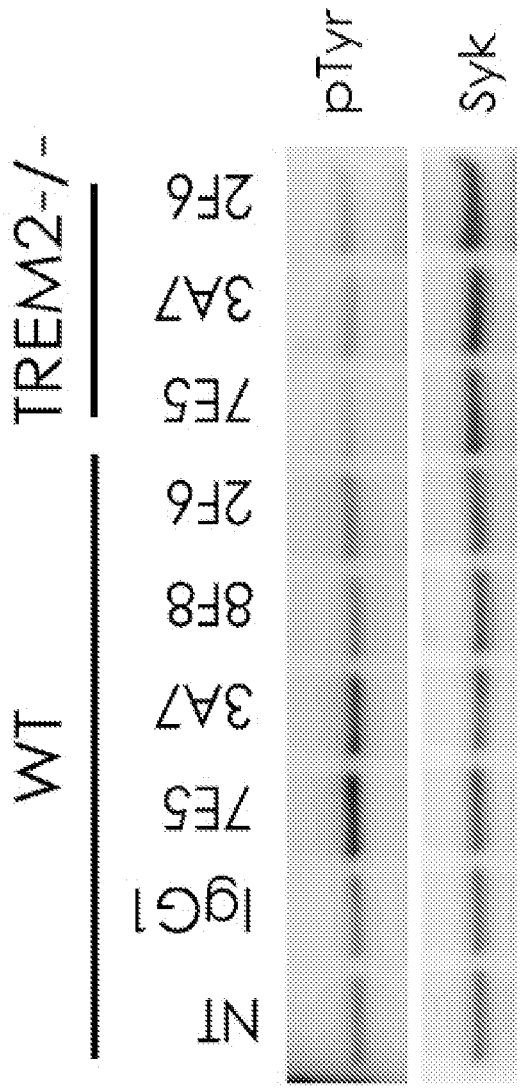

WT
TREM2-/-
NT
IgG1
7E5
3A7
8F8
2F6
7E5
3A7
2F6
pTyr
Syk

FIG. 6A

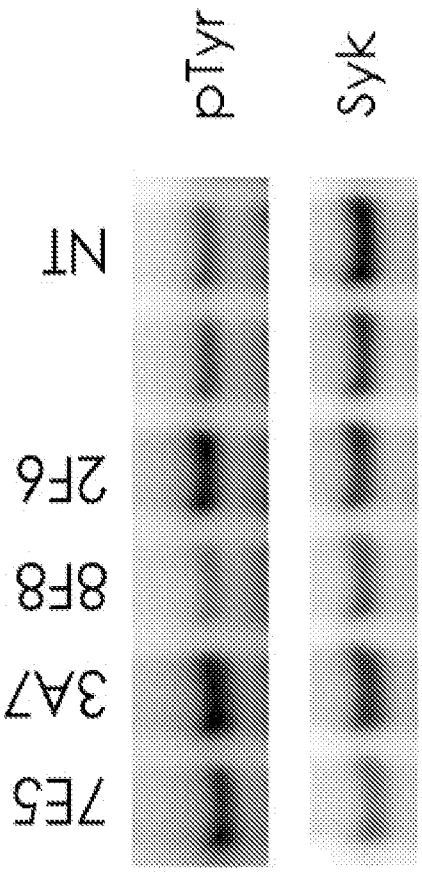

NT
2F6
8F8
3A7
7E5
pTyr
Syk

FIG. 6B

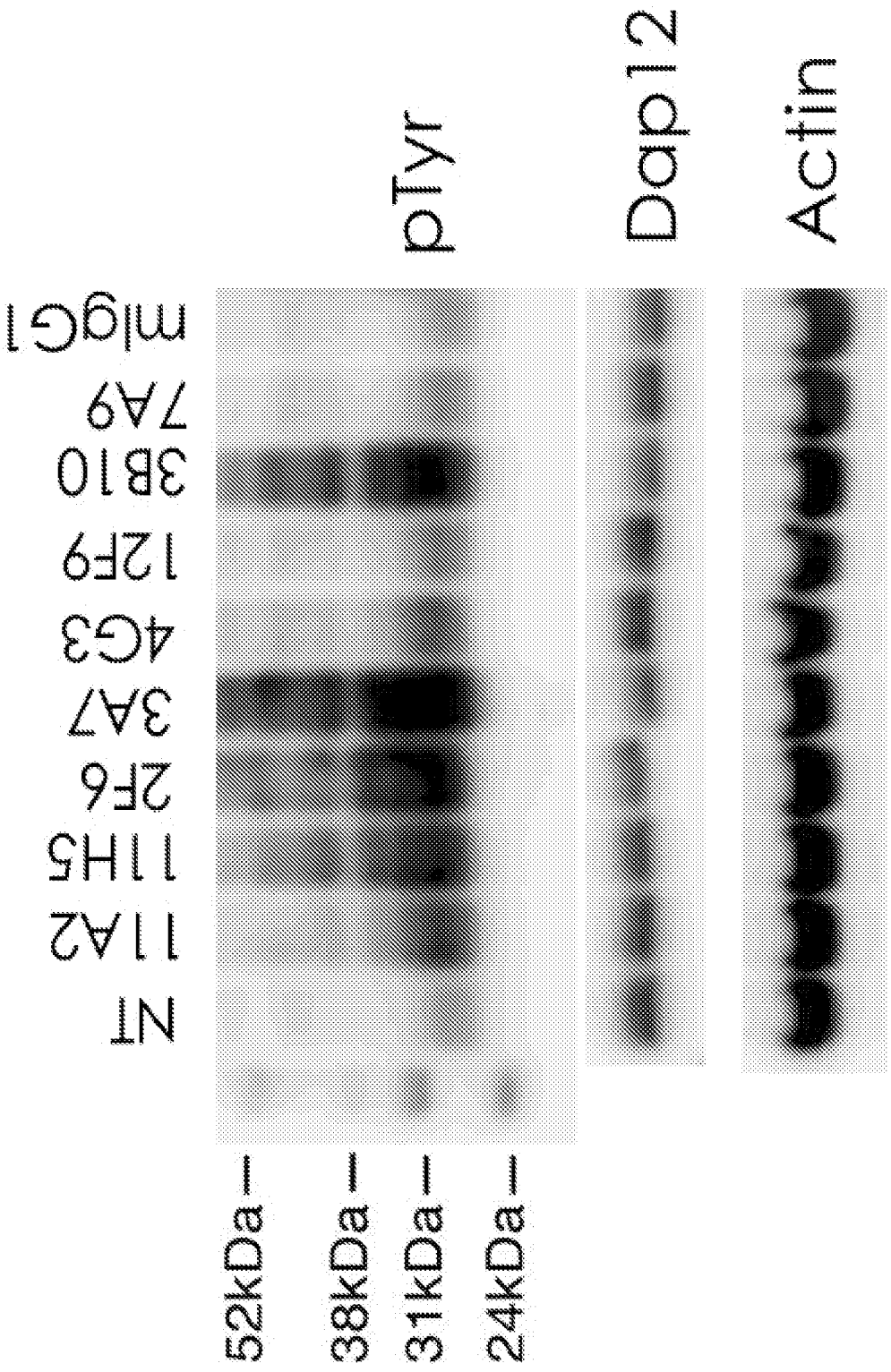

pTyr
Dap12
Actin
NT
11A2
11H5
2F6
3A7
4G3
12F9
3B10
7A9
mIgG1
52kDa
38kDa
31kDa
24kDa

FIG. 7A

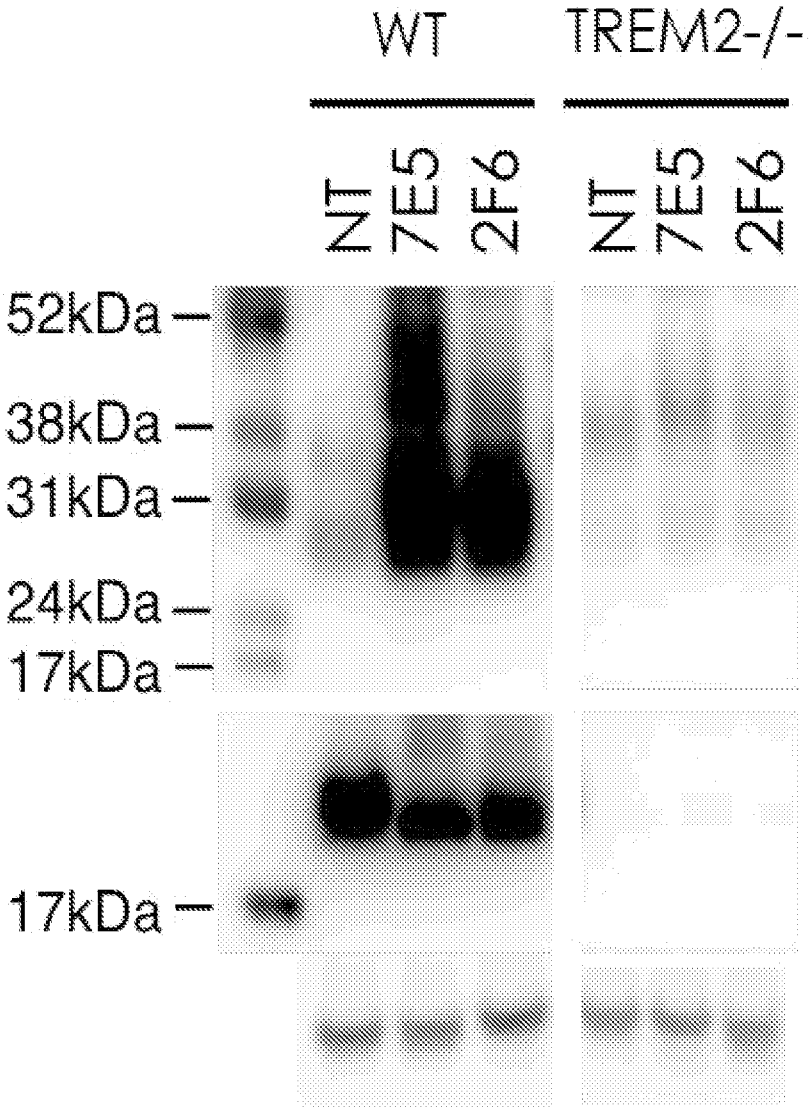

WT
TREM2-/-
NT
7E5
2F6
NT
7E5
2F6
52kDa
38kDa
31kDa
24kDa
17kDa
17kDa

FIG. 7B

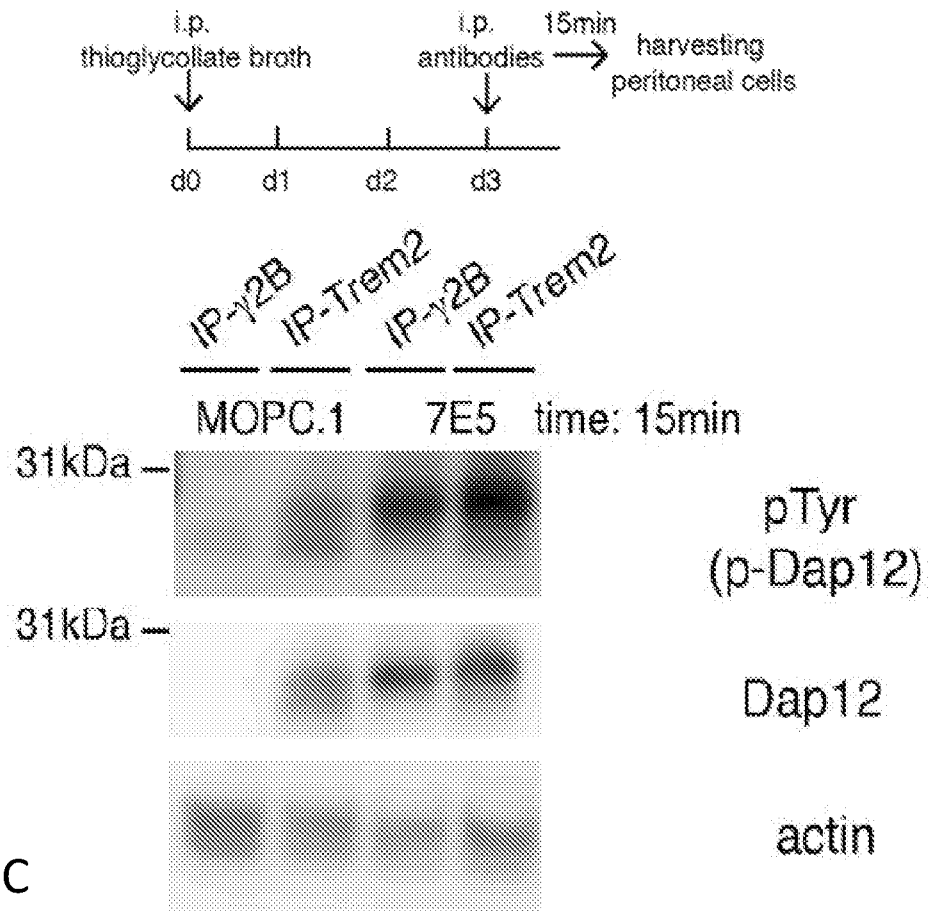

i.p.
thioglycollate broth
i.p.
antibodies
15min
harvesting
peritoneal cells
d0
d1
d2
d3
IP-γ2B
IP-Trem2
IP-γ2B
IP-Trem2
MOPC.1
7E5
time: 15min
31kDa
31kDa
pTyr
(p-Dap12)
Dap12
actin

FIG. 7C

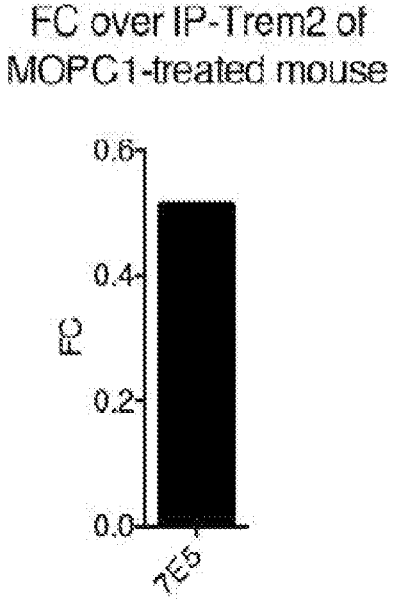

FC over IP-Trem2 of
MOPC1-treated mouse
0.6
0.4
0.2
0.0
FC
7E5

FIG. 7D

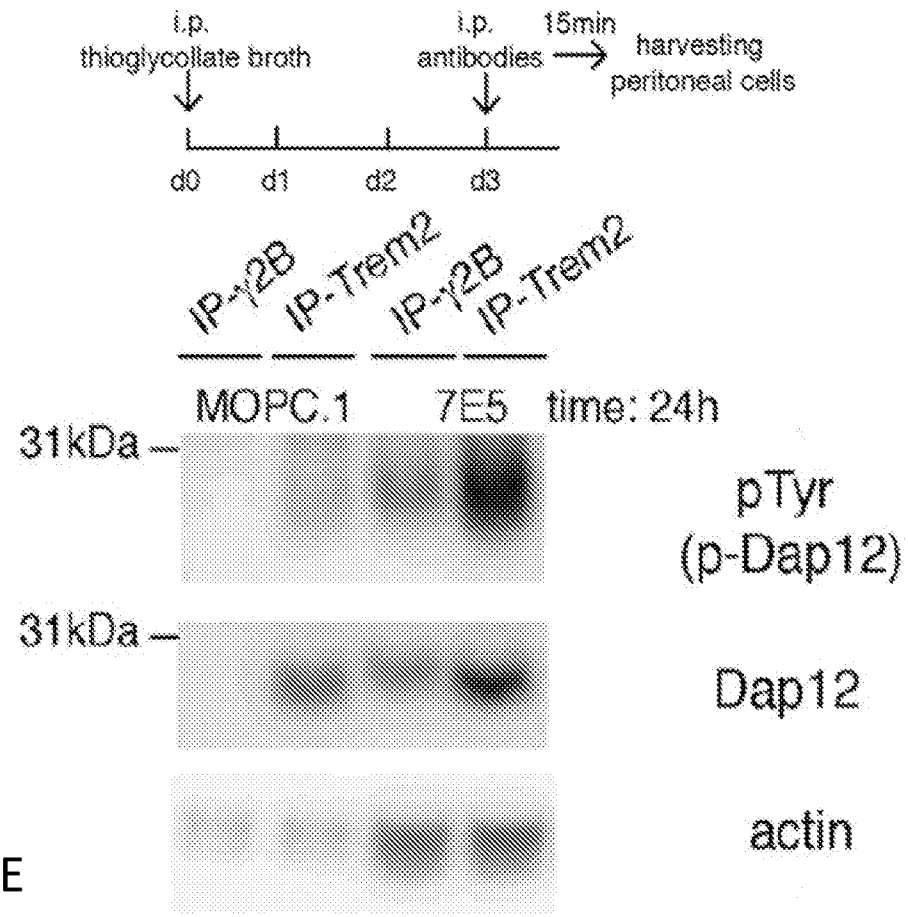

i.p.
thioglycollate broth
i.p.
antibodies
15min
harvesting
peritoneal cells
d0
d1
d2
d3
IP-γ2B
IP-Trem2
IP-γ2B
IP-Trem2
MOPC.1
7E5
time: 24h
31kDa
pTyr
(p-Dap12)
31kDa
Dap12
actin

FIG. 7E

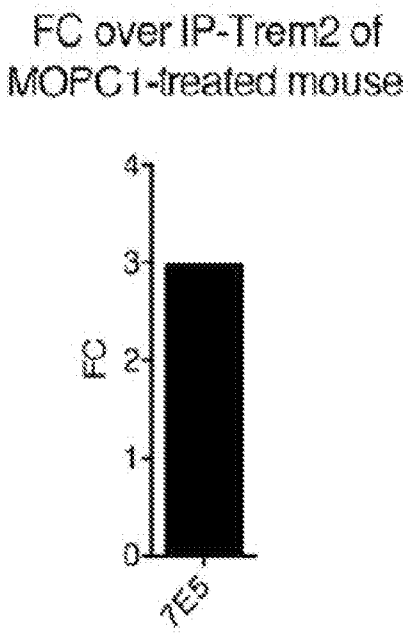

FC over IP-Trem2 of
MOPC1-treated mouse
FC
0
1
2
3
4
7E5

FIG. 7F

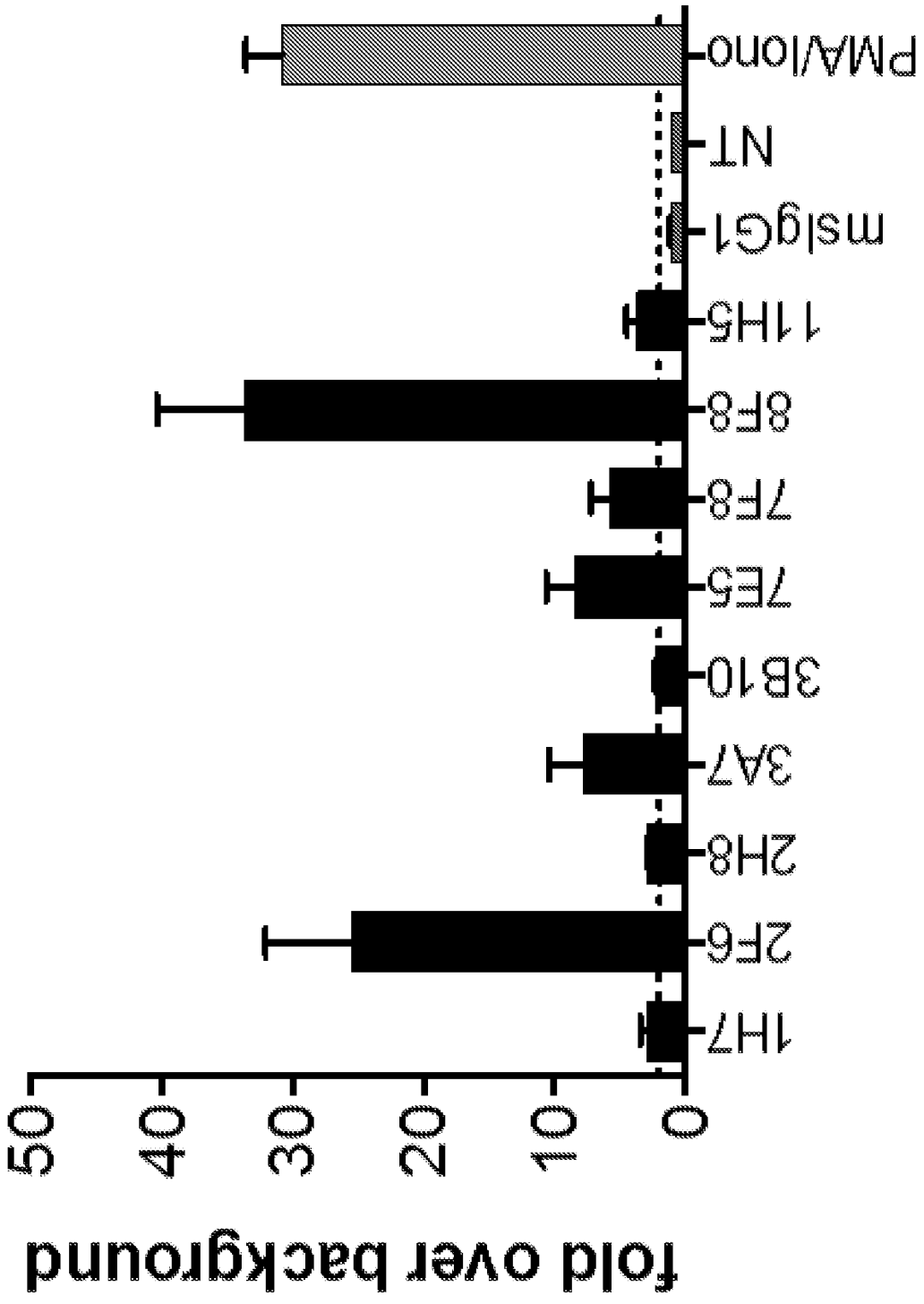

fold over background
0
10
20
30
40
50
1H7
2F6
2H8
3A7
3B10
7E5
7F8
8F8
11H5
mIgG1
NT
PMA/Iono

FIG. 8A

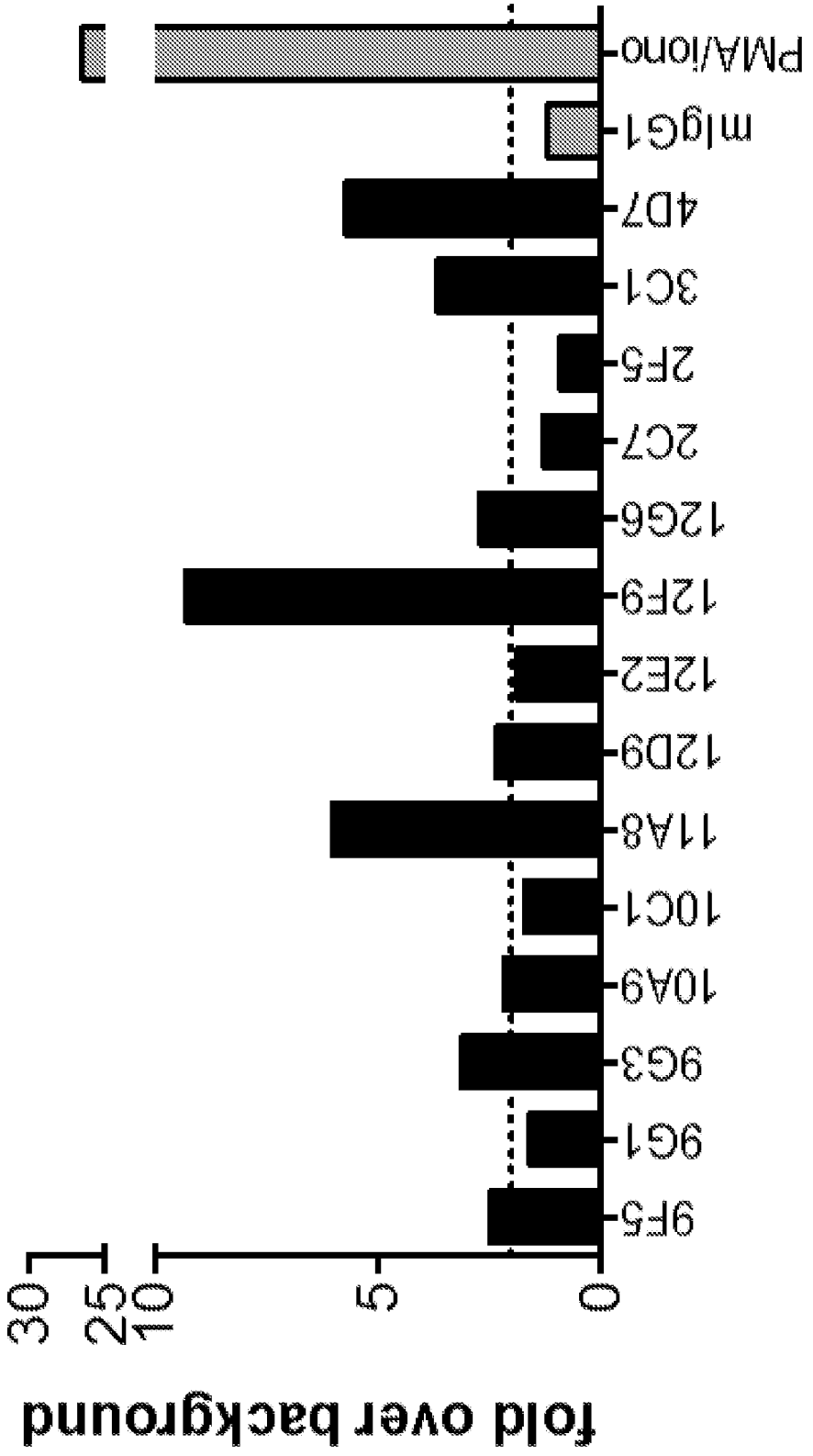

fold over background
30
25
10
5
0
9F5
9G1
9G3
10A9
10C1
11A8
12D9
12E2
12F9
12G6
2C7
2F5
3C1
4D7
mIgG1
PMA/iono

FIG. 8B

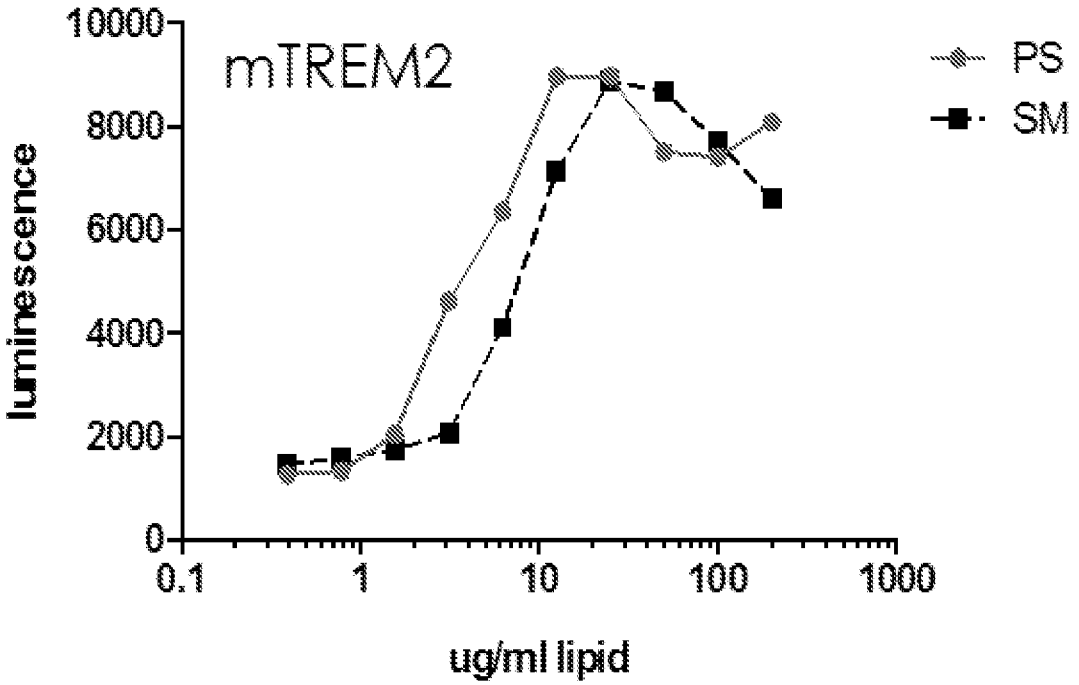

mTREM2
PS
SM
luminescence
10000
8000
6000
4000
2000
0
0.1
1
10
100
1000
ug/ml lipid

FIG. 8C

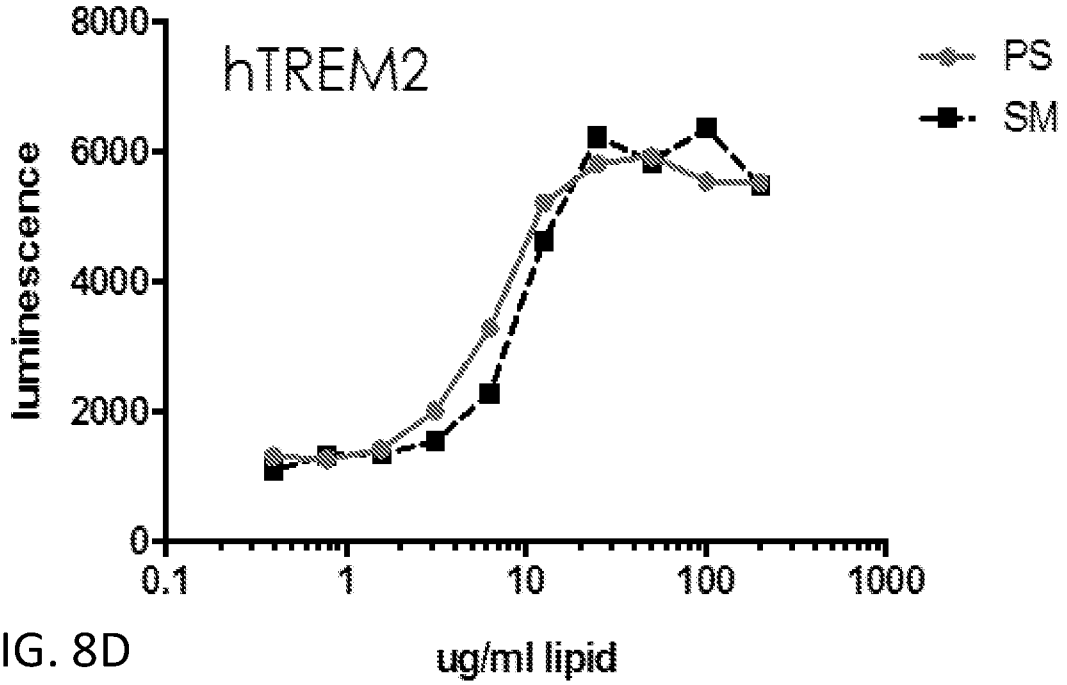

hTREM2
PS
SM
luminescence
8000
6000
4000
2000
0
0.1
1
10
100
1000
ug/ml lipid

FIG. 8D

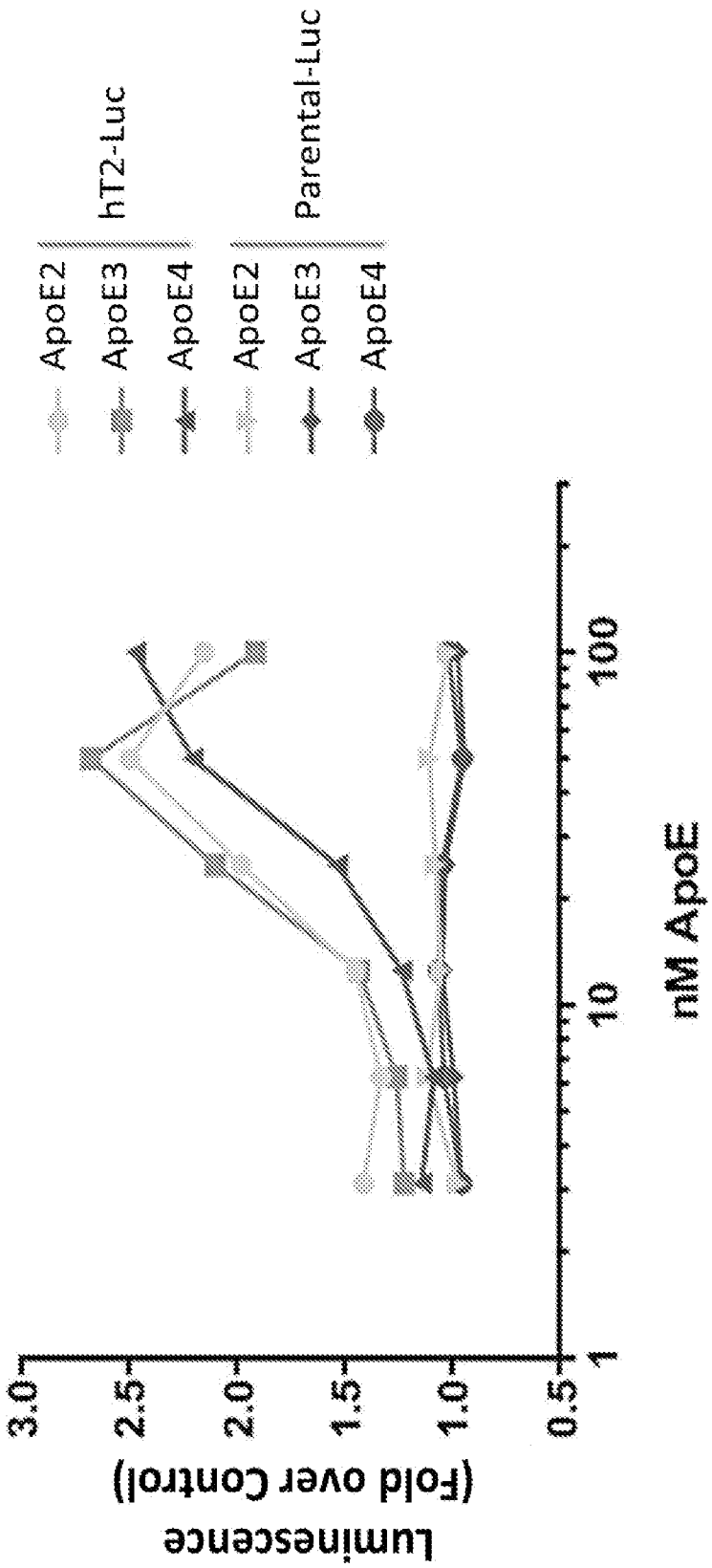

ApoE2
ApoE3
ApoE4
hT2-Luc
ApoE2
ApoE3
ApoE4
Parental-Luc
Luminescence
(Fold over Control)
3.0
2.5
2.0
1.5
1.0
0.5
1
10
100
nM ApoE

FIG. 8E

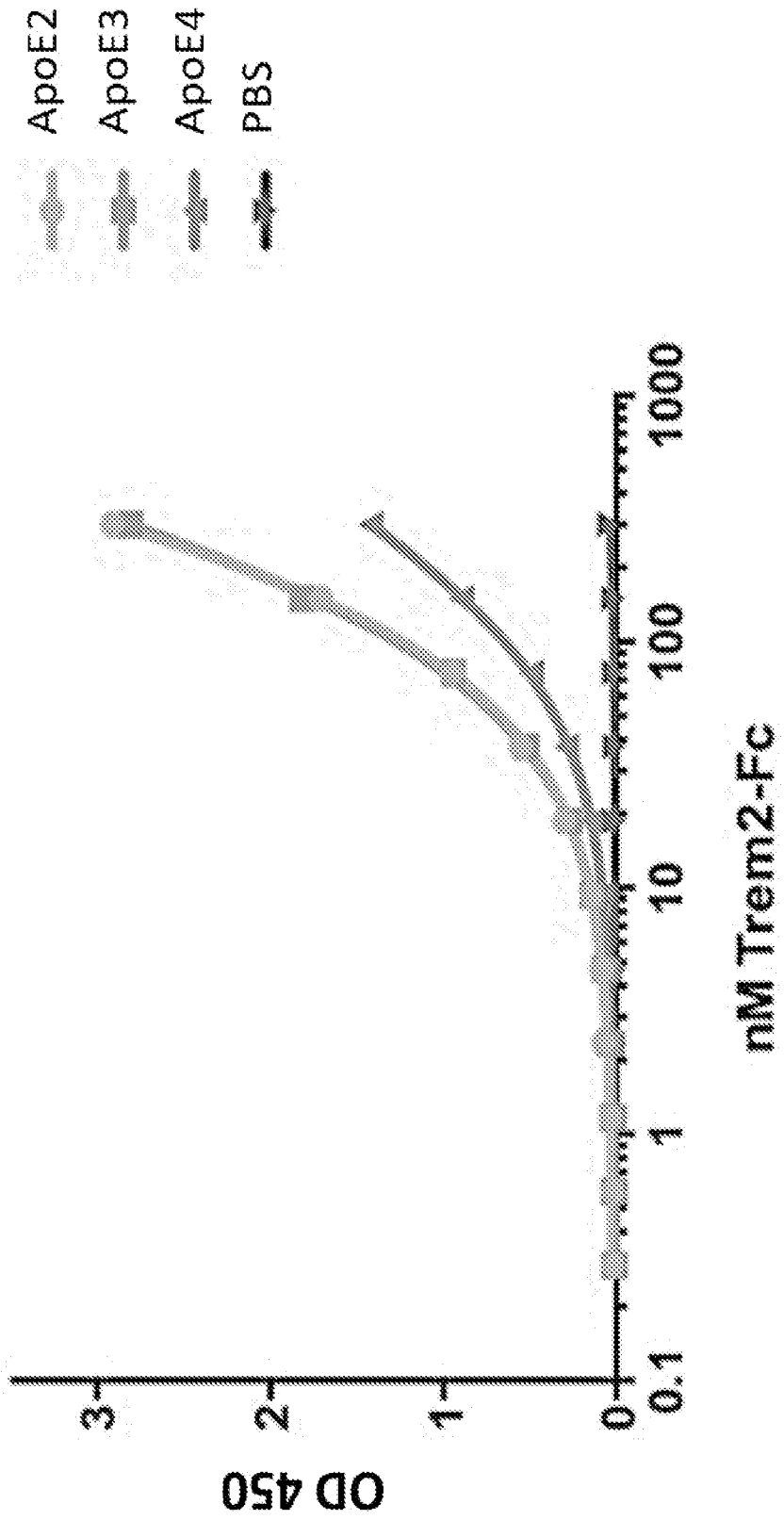


FIG. 8F

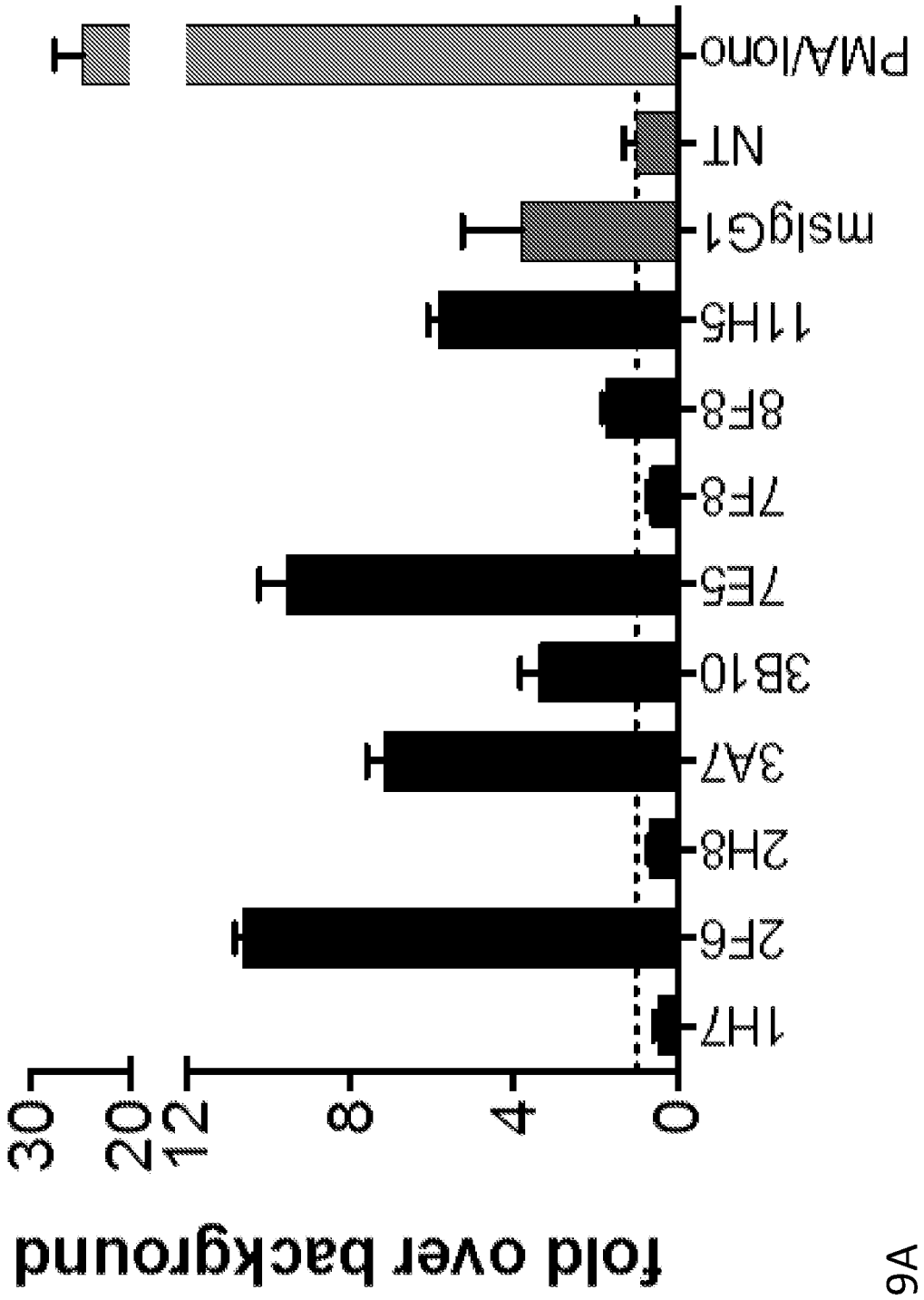

fold over background
30
20
12
8
4
0
1H7
2F6
2H8
3A7
3B10
7E5
7F8
8F8
11H5
msIgG1
NT
PMA/Iono

FIG. 9A

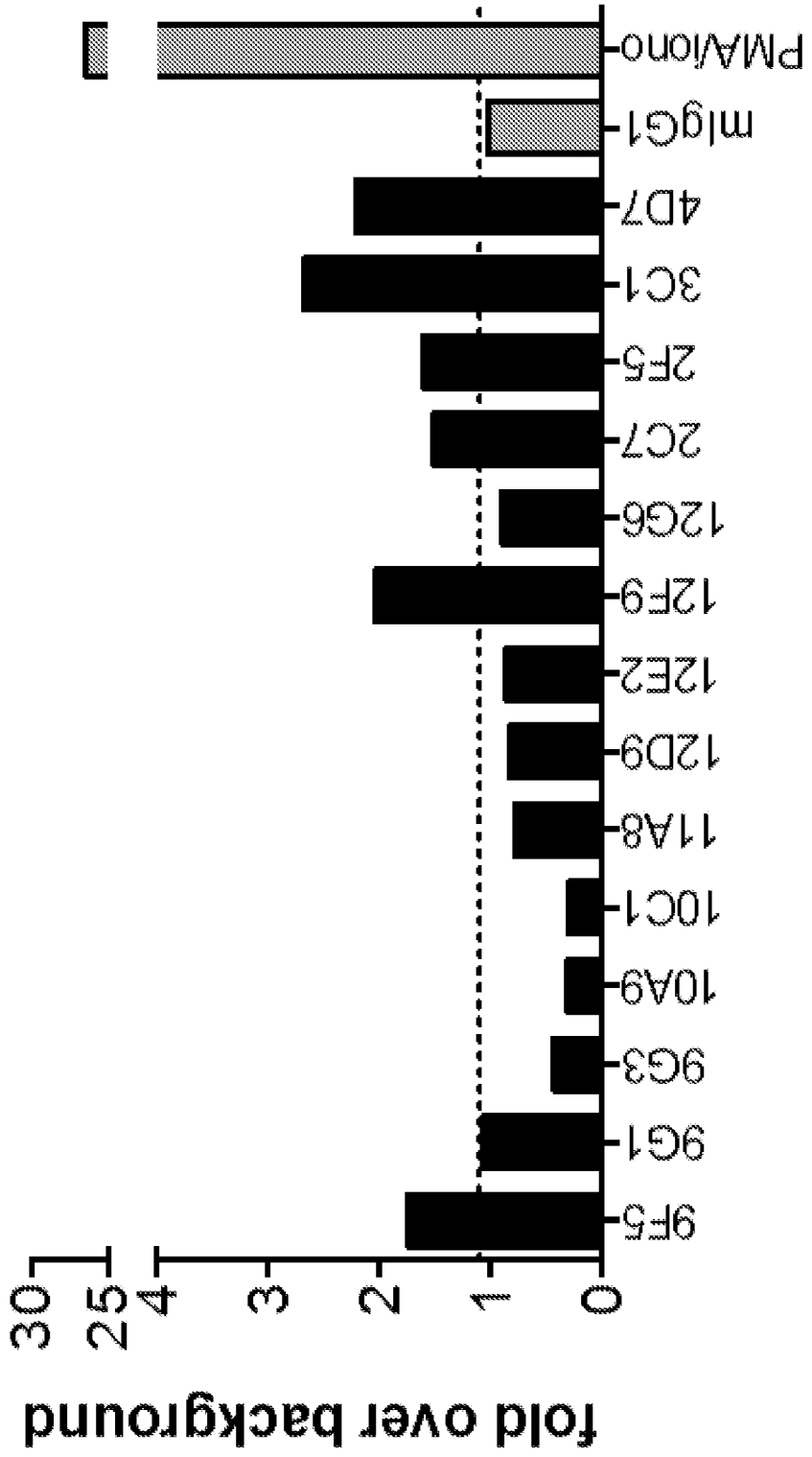

fold over background
30
25
4
3
2
1
0
9F5
9G1
9G3
10A9
10C1
11A8
12D9
12E2
12F9
12G6
2C7
2F5
3C1
4D7
mIgG1
PMA/iono

FIG. 9B

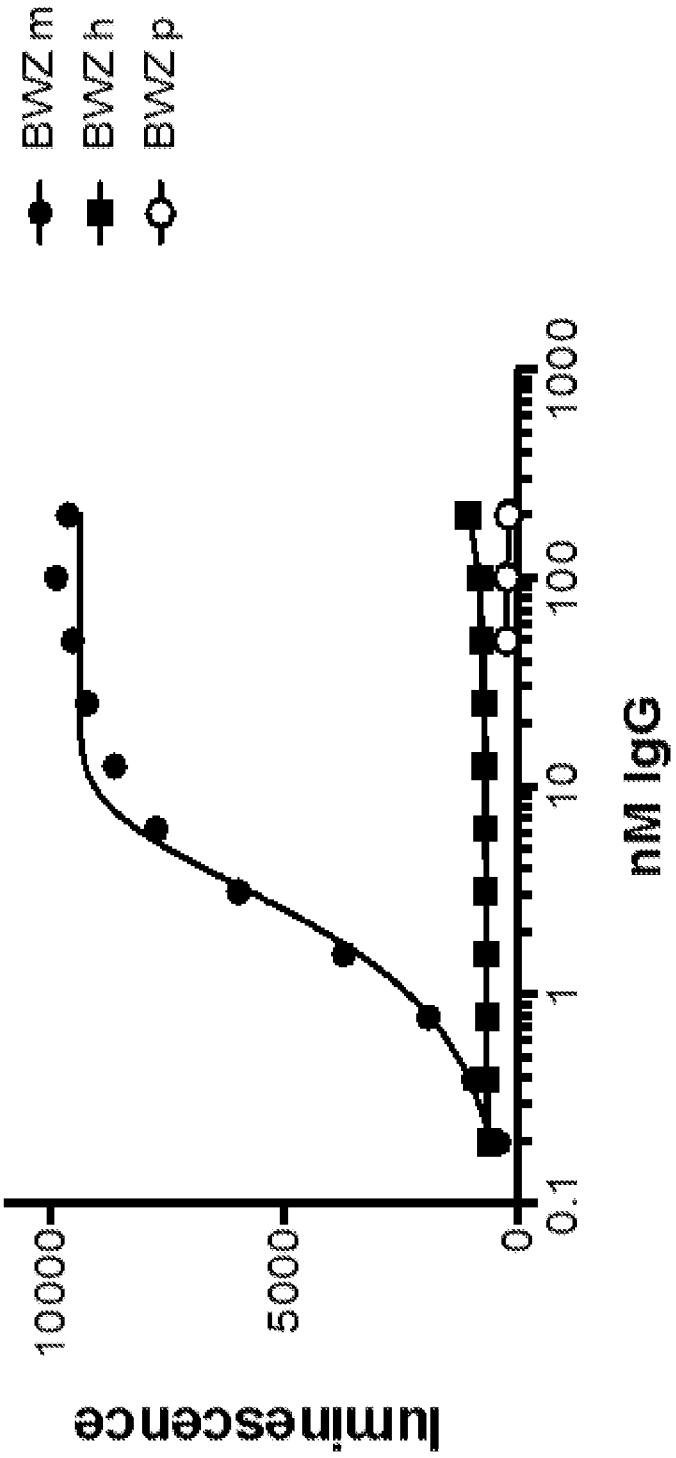

BWZ m
BWZ h
BWZ p
luminescence
10000
5000
0
0.1
1
10
100
1000
nM IgG

FIG. 9C

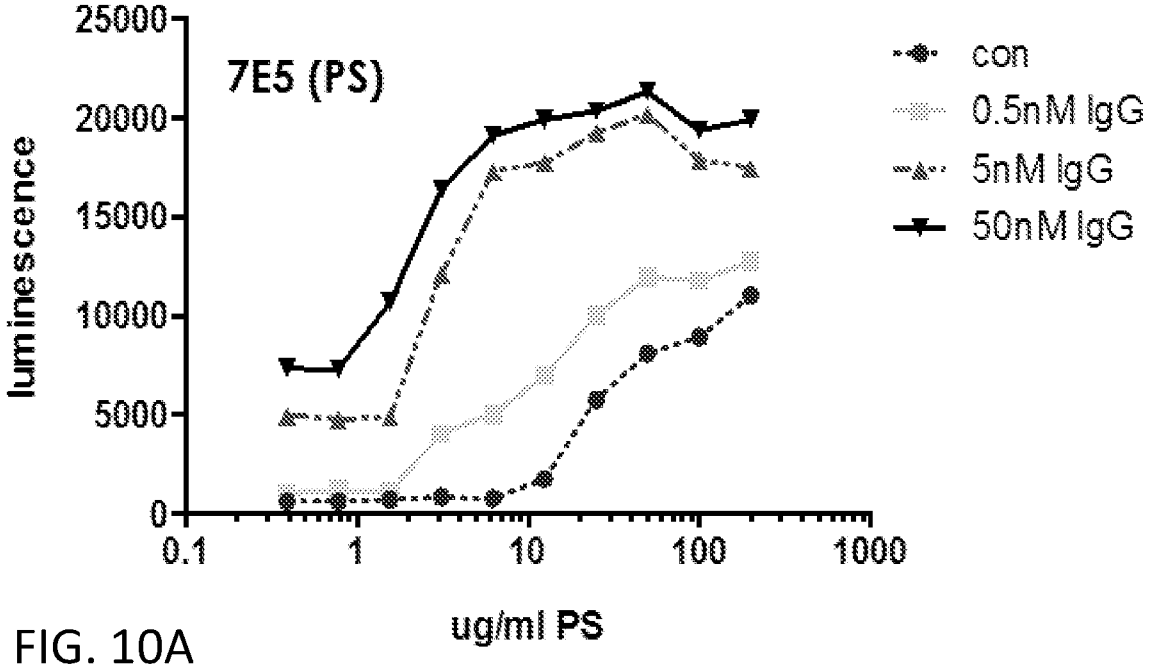


FIG. 10A

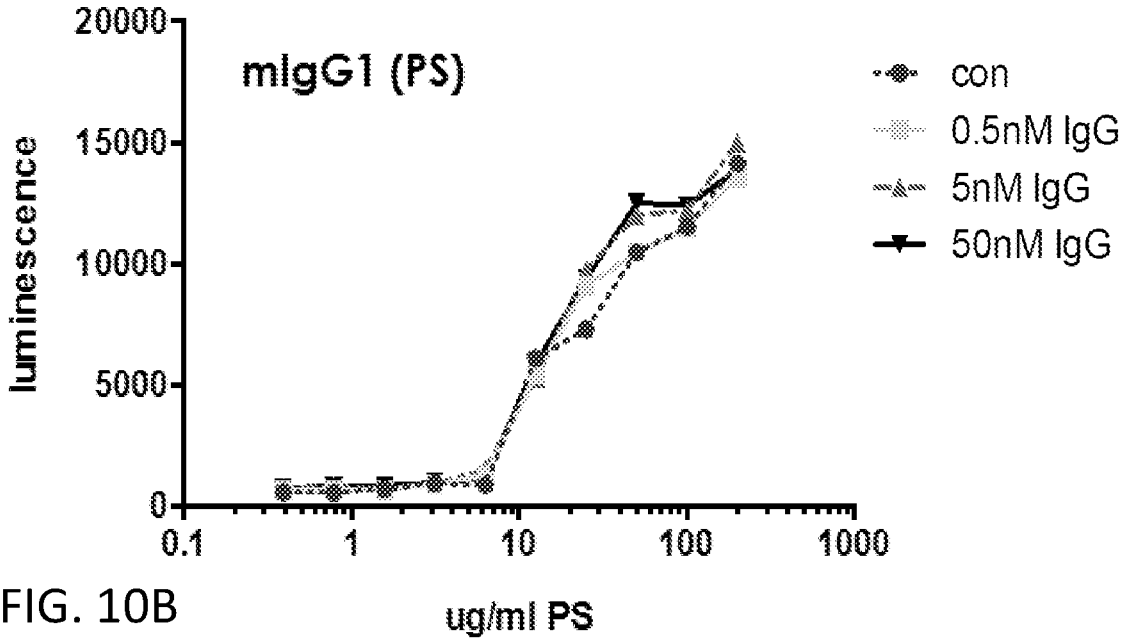


FIG. 10B

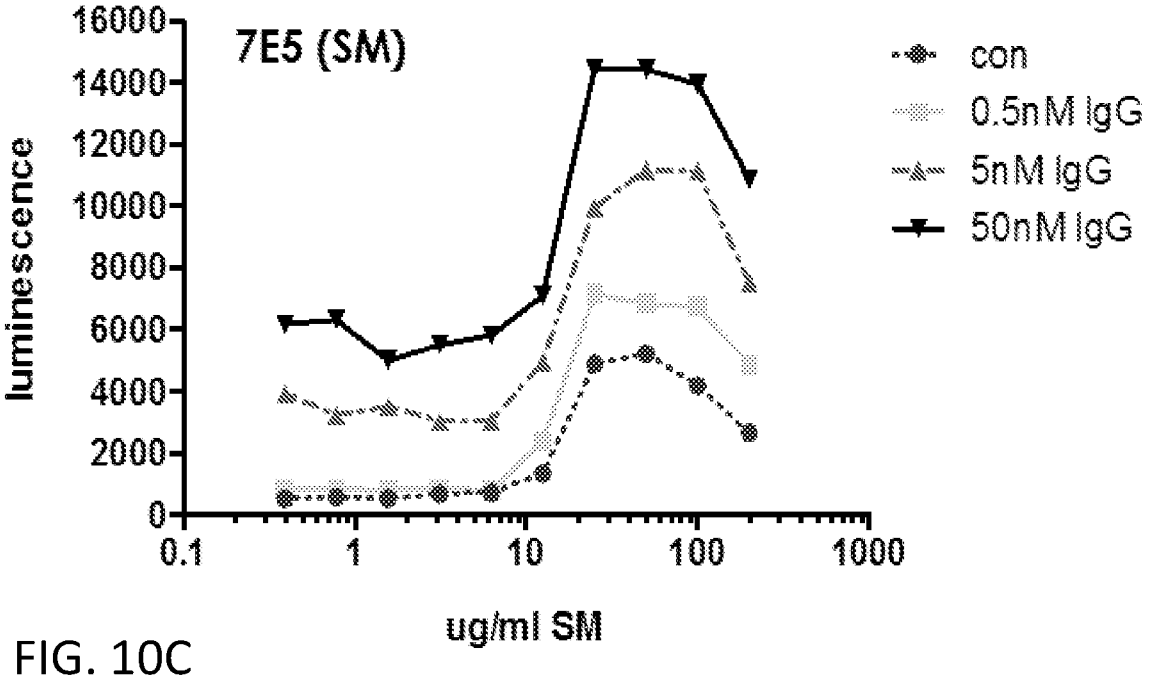


FIG. 10C

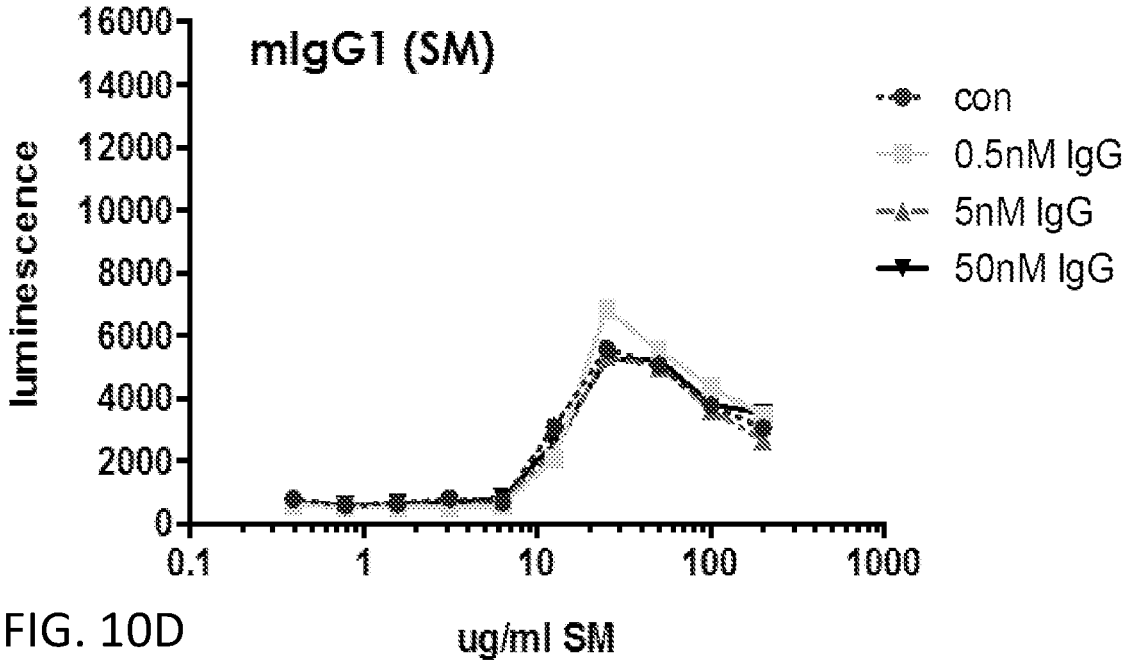


FIG. 10D

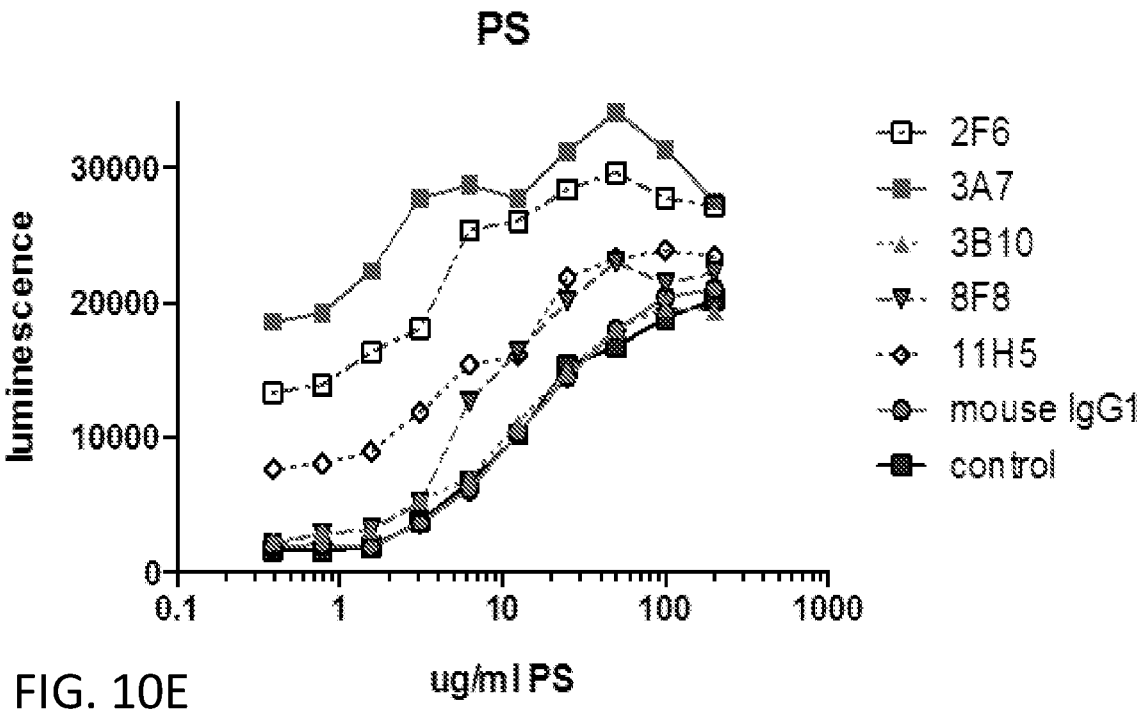


FIG. 10E

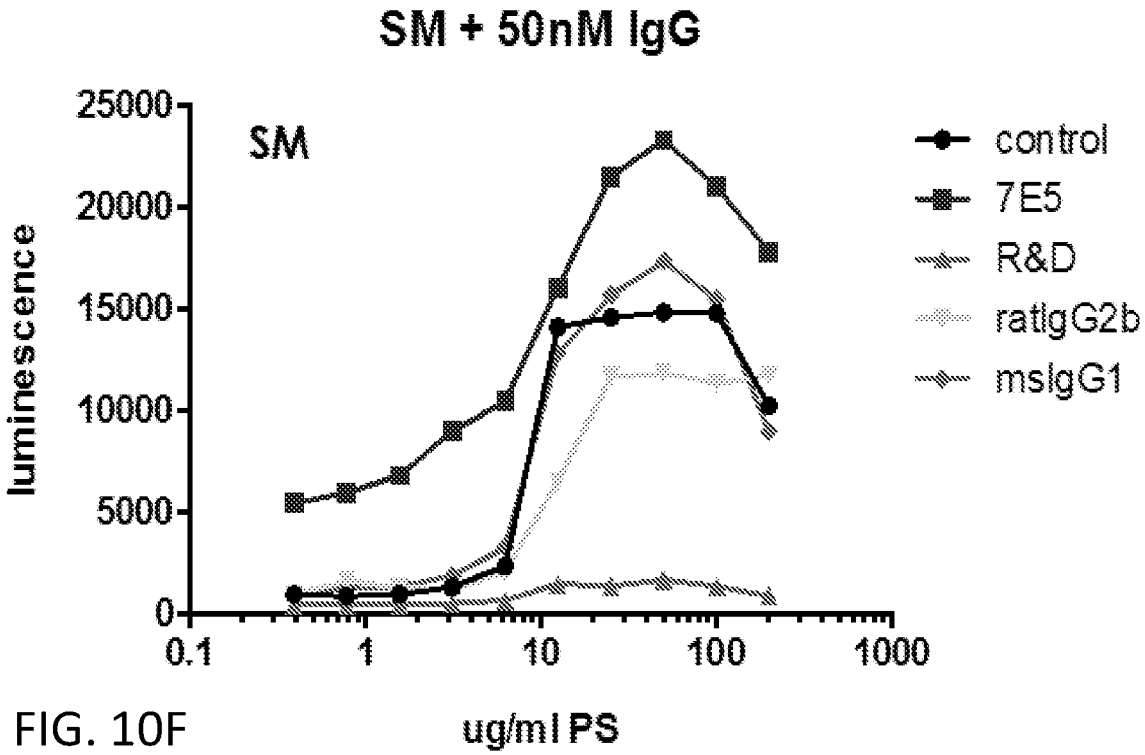


FIG. 10F

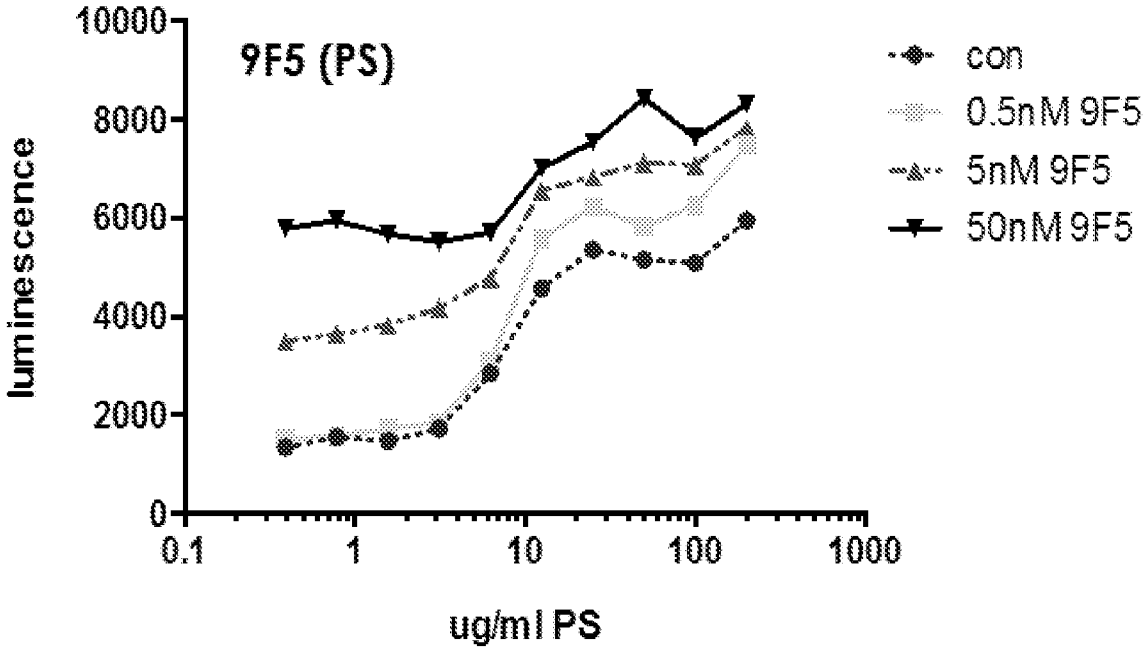


FIG. 11A

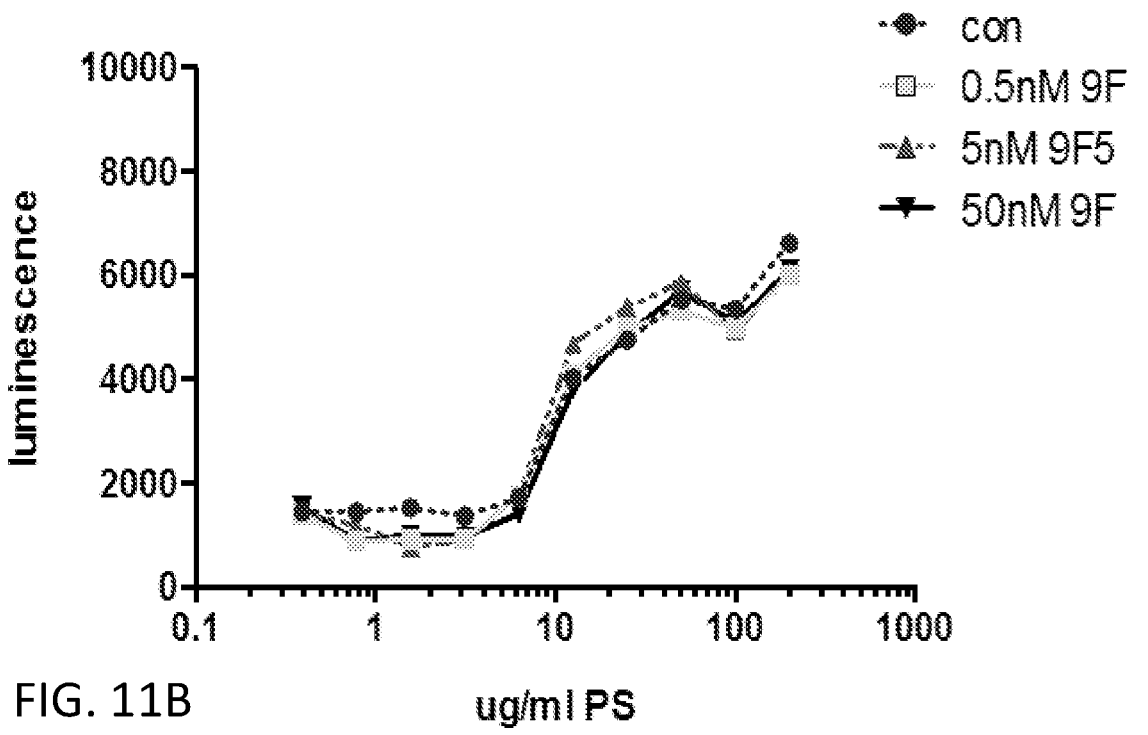


FIG. 11B

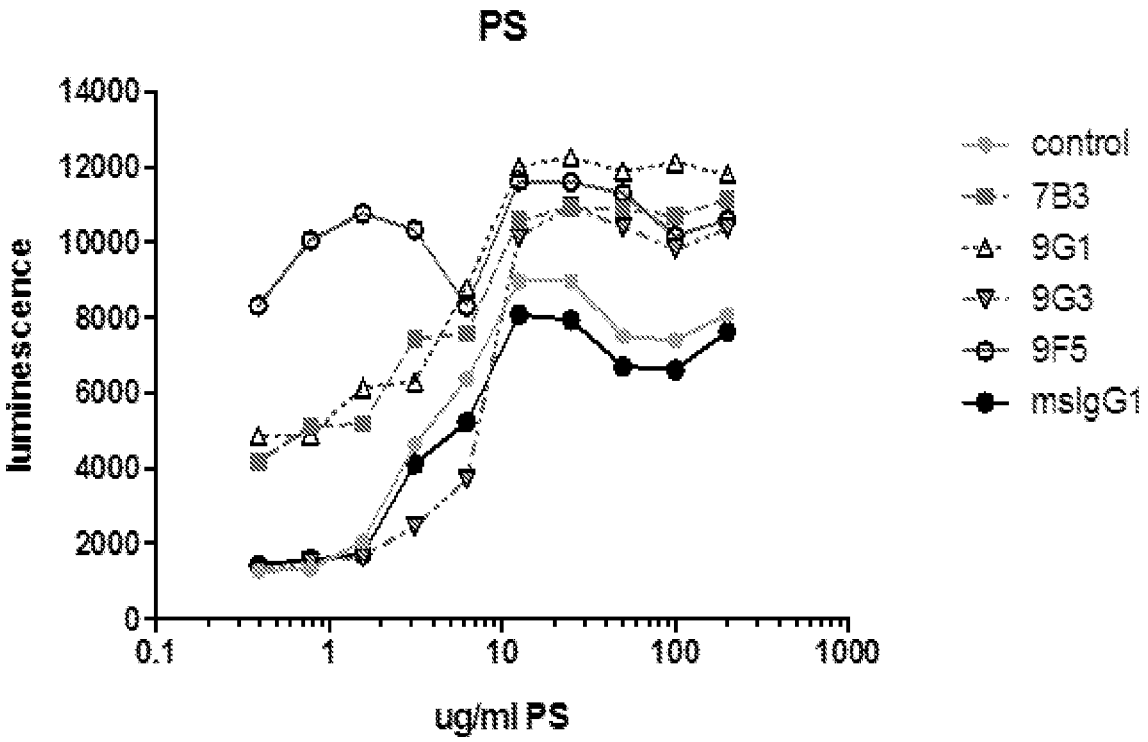


FIG. 11C

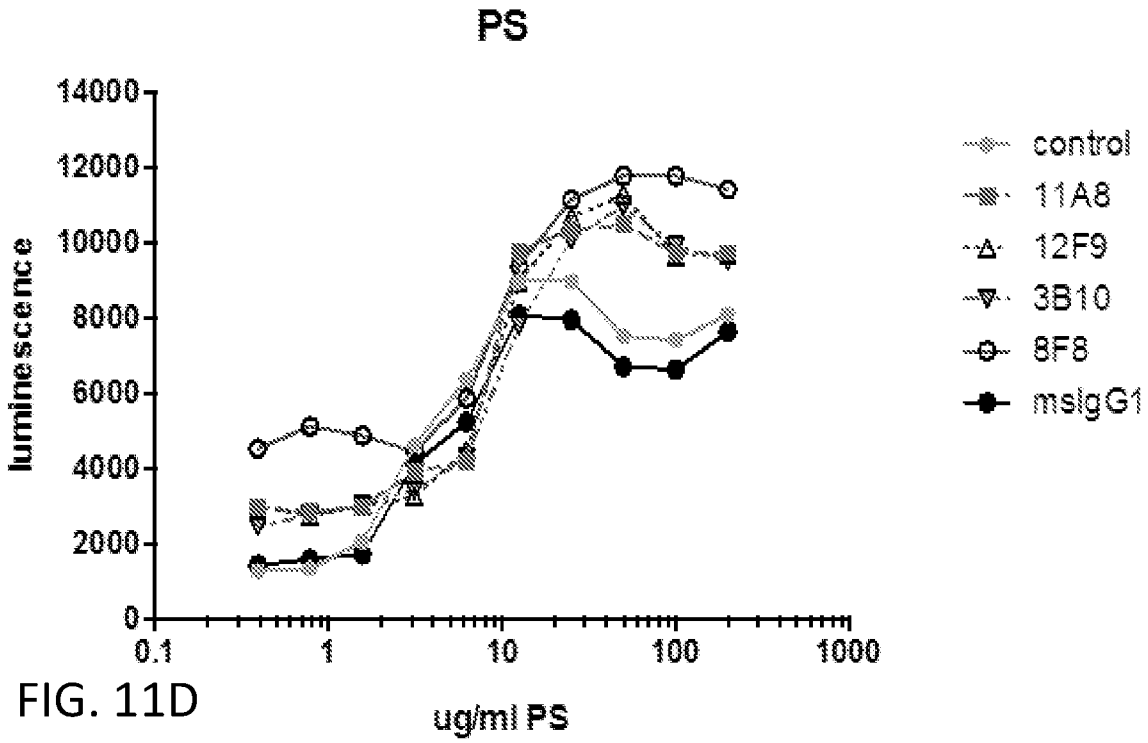


FIG. 11D

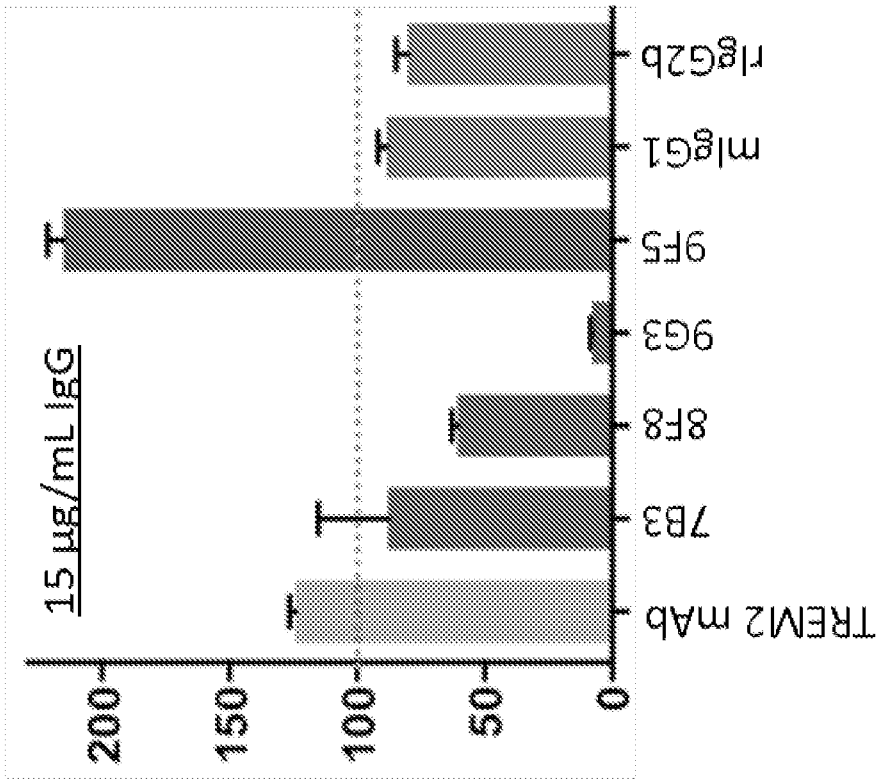


FIG. 11F

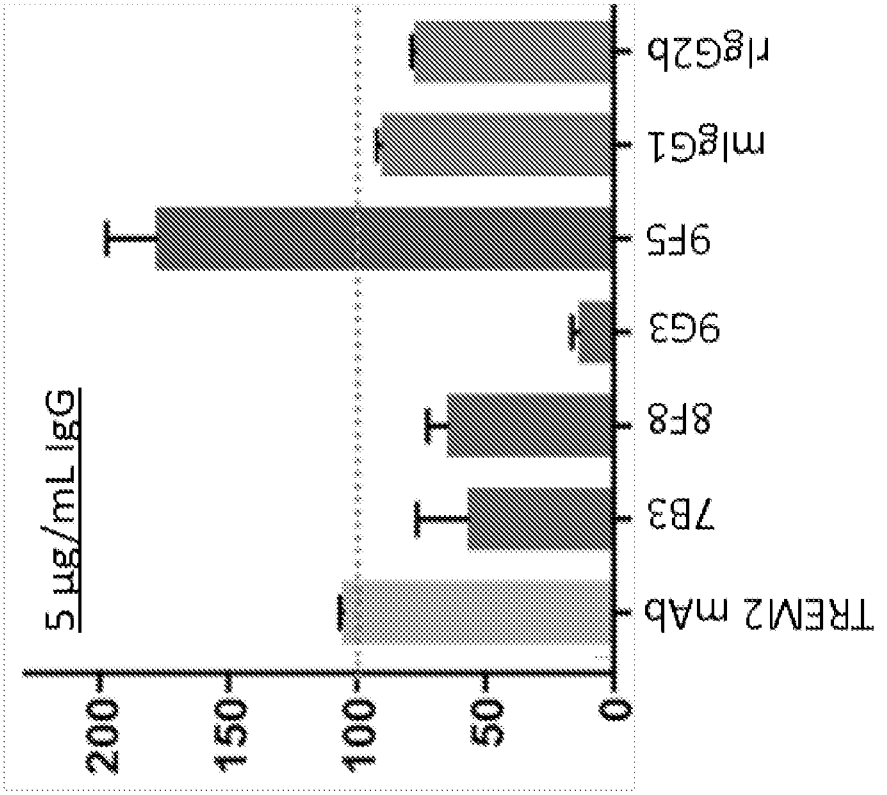


FIG. 11E

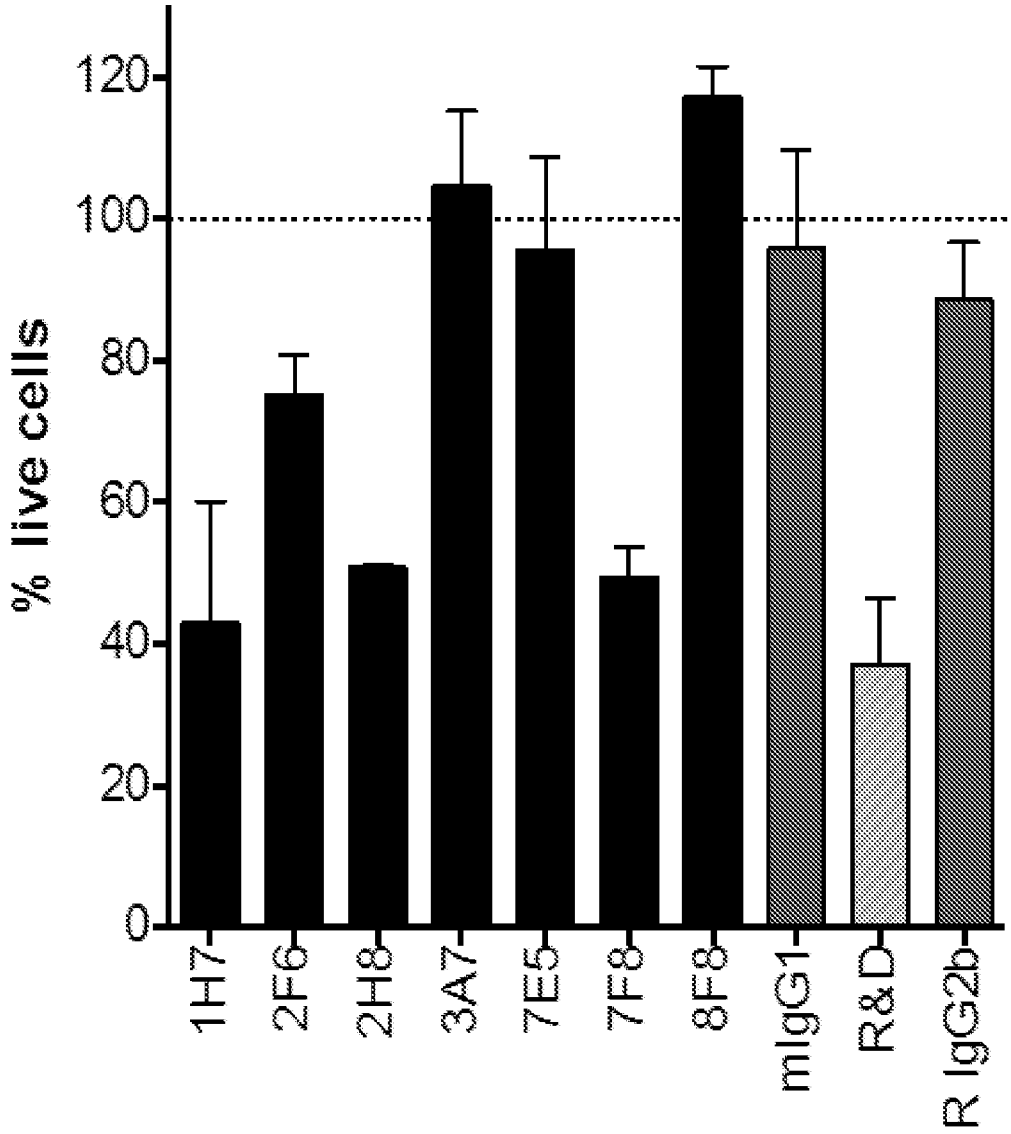

% live cells
120
100
80
60
40
20
0
1H7
2F6
2H8
3A7
7E5
7F8
8F8
mIgG1
R&D
R IgG2b

FIG. 12A

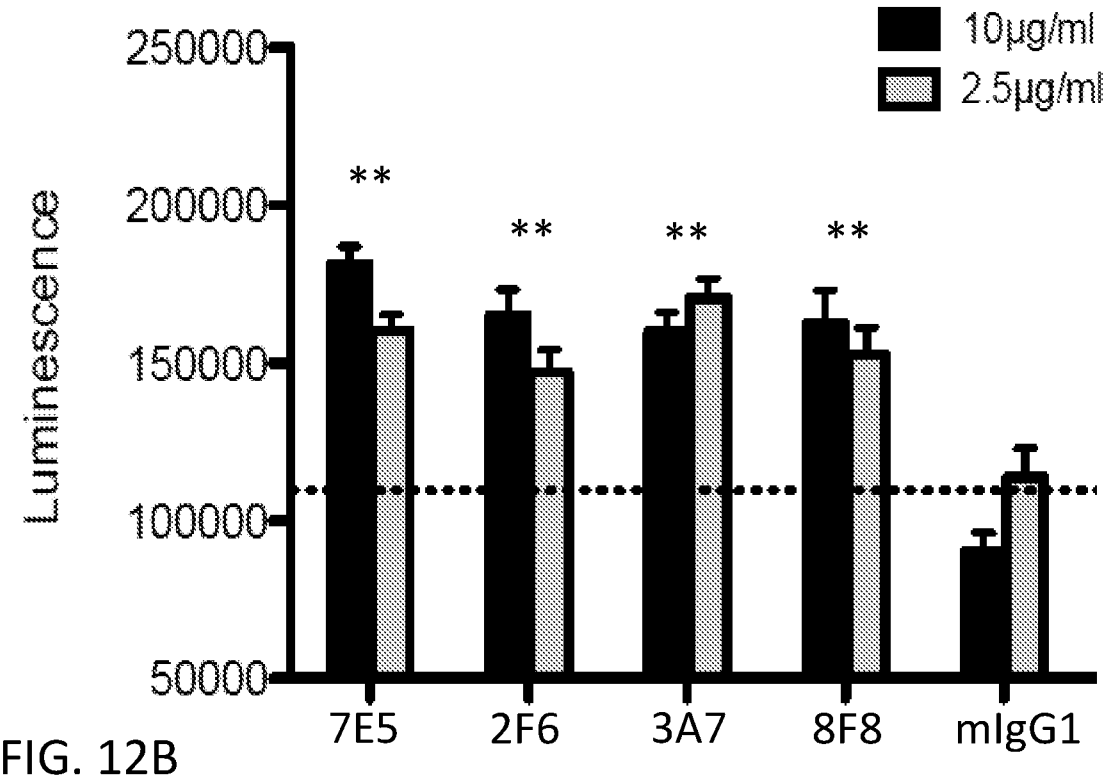


FIG. 12B

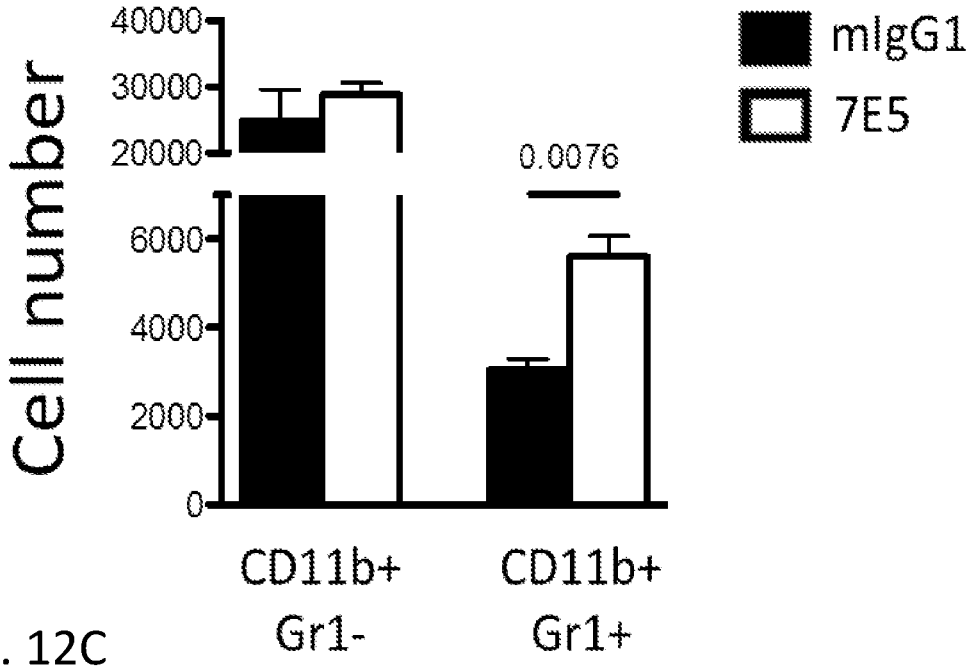


FIG. 12C

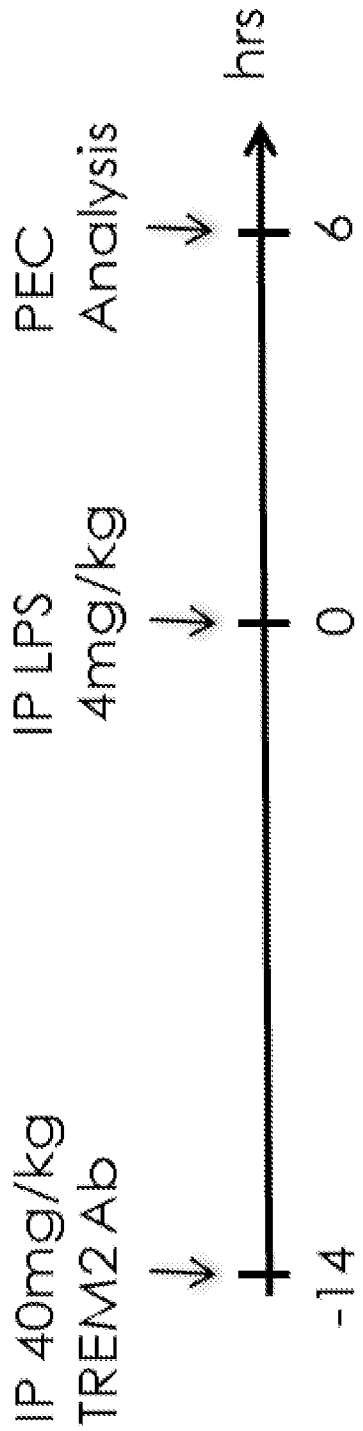


FIG. 13A

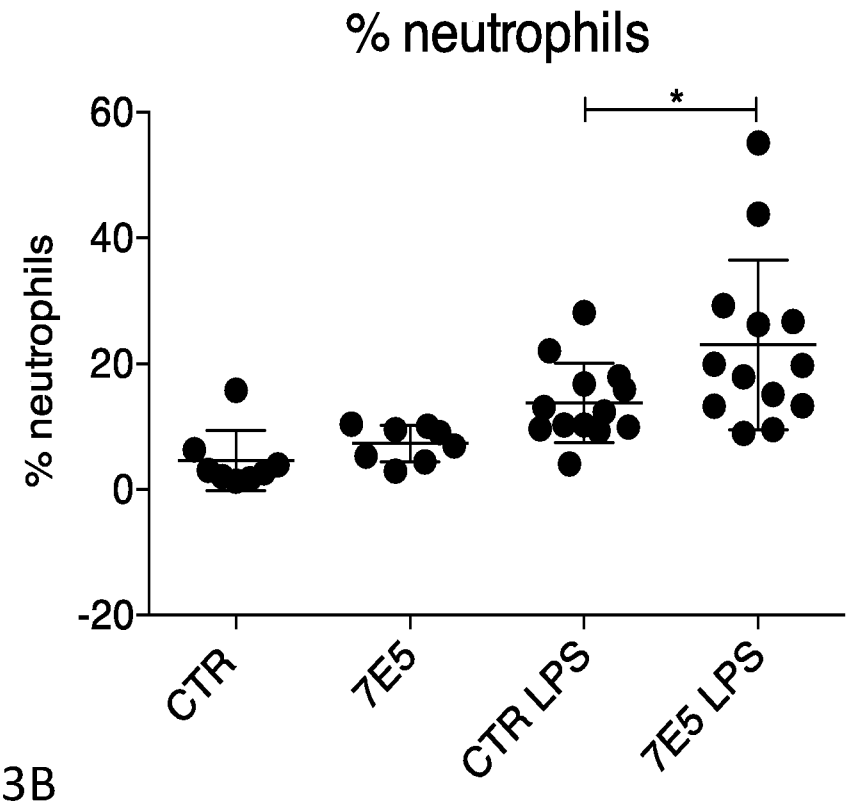


FIG. 13B

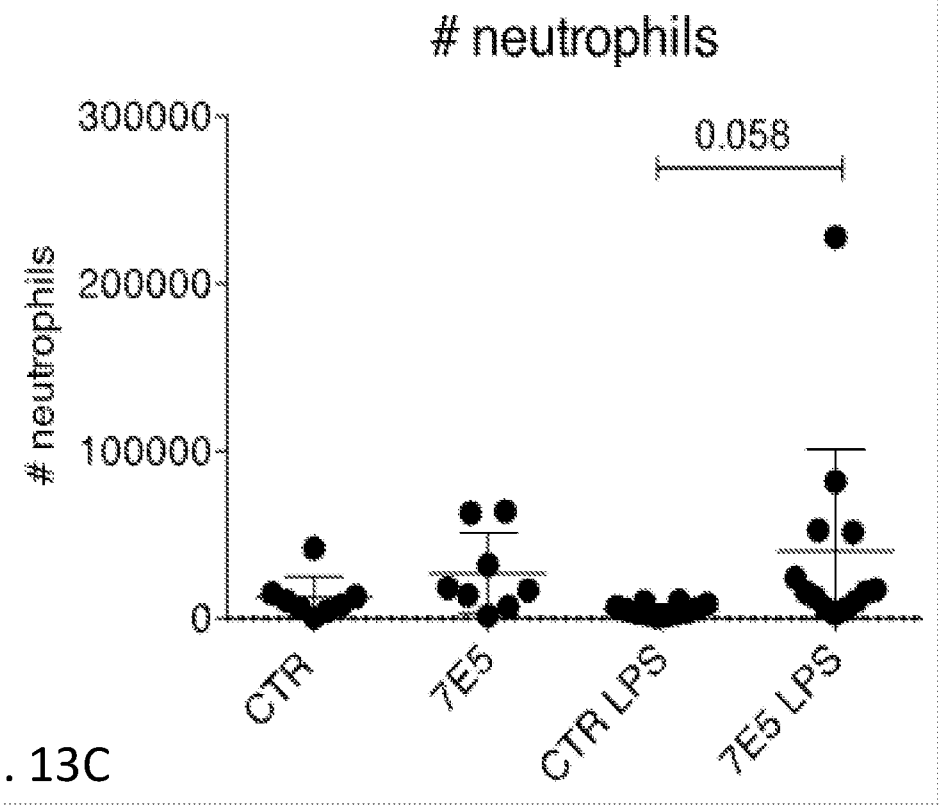


FIG. 13C

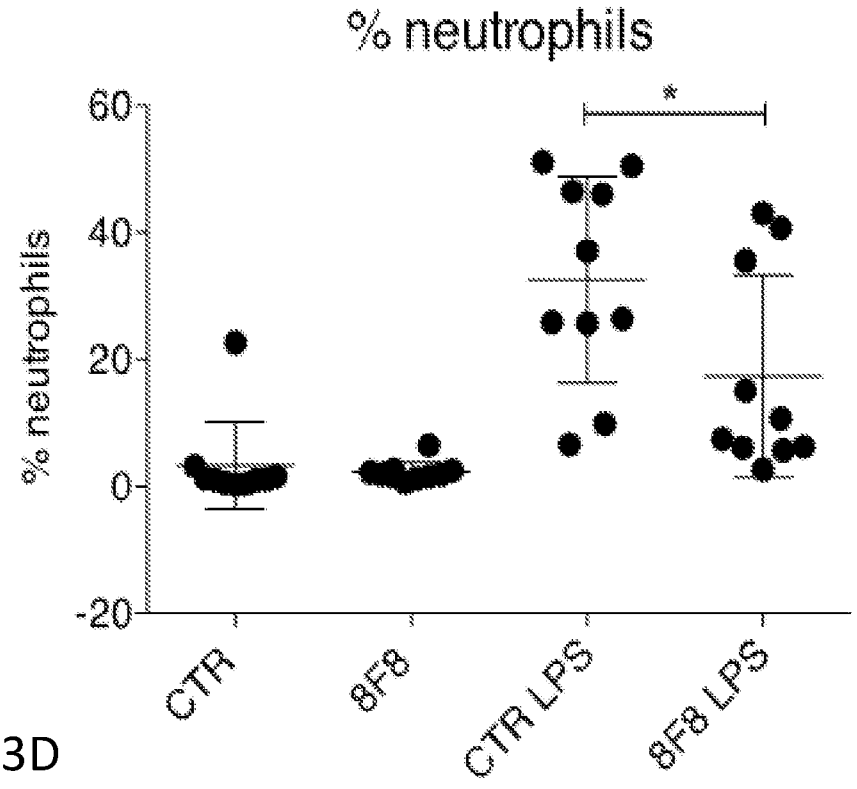


FIG. 13D

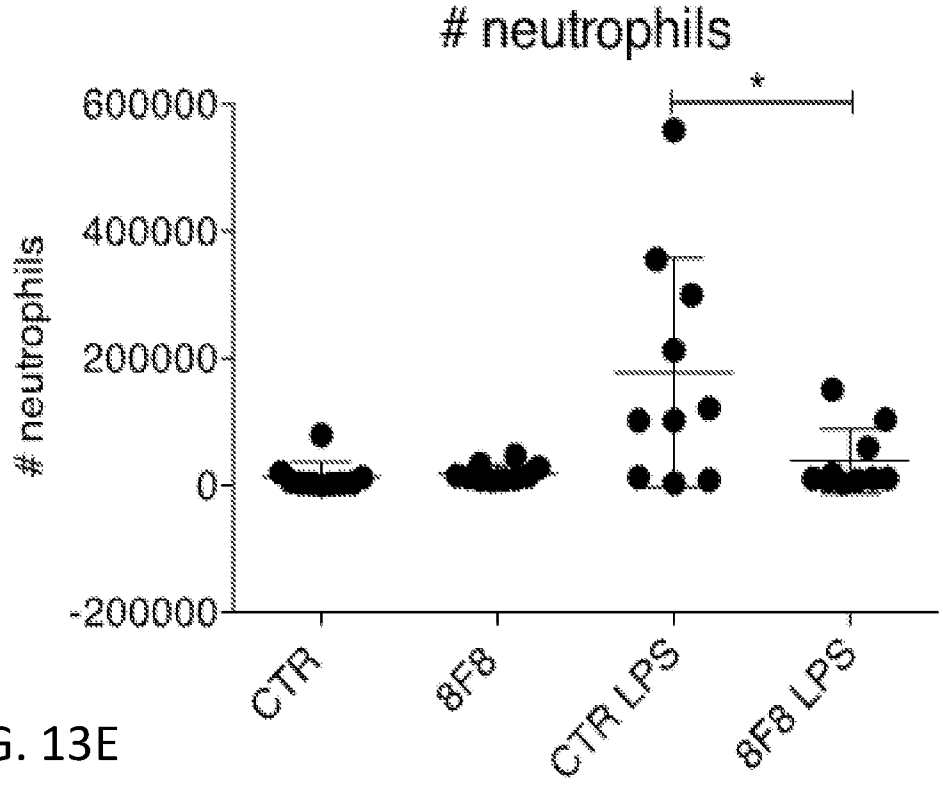


FIG. 13E

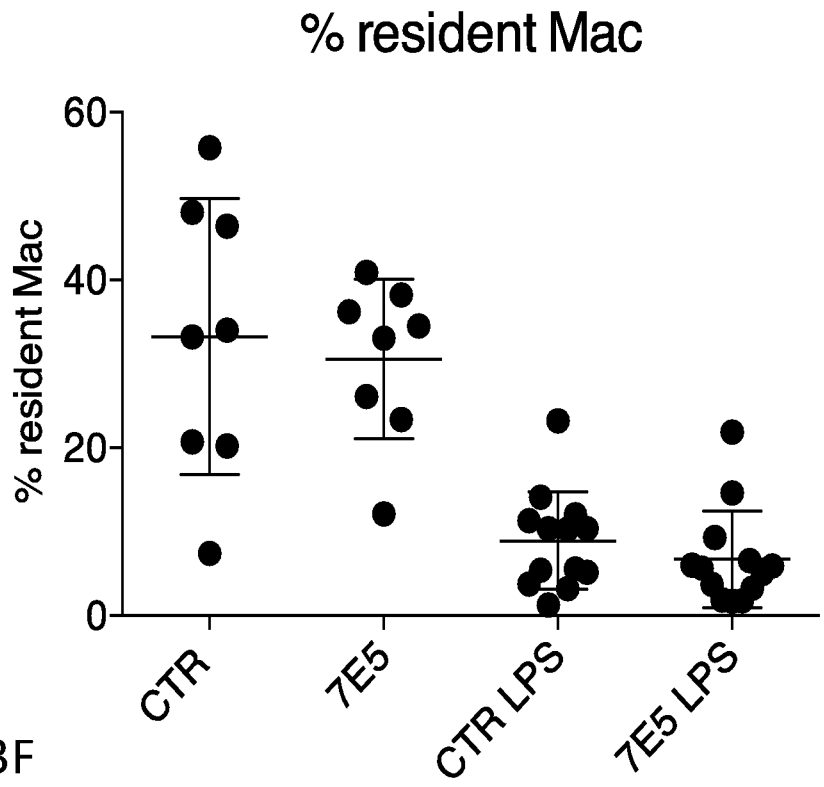


FIG. 13F

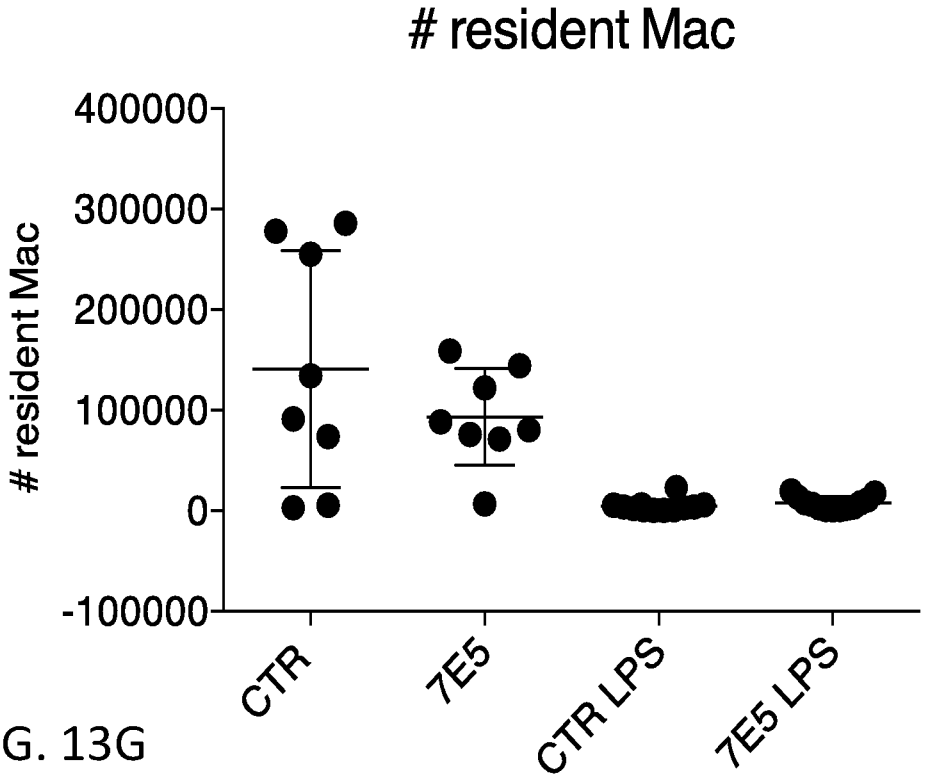


FIG. 13G

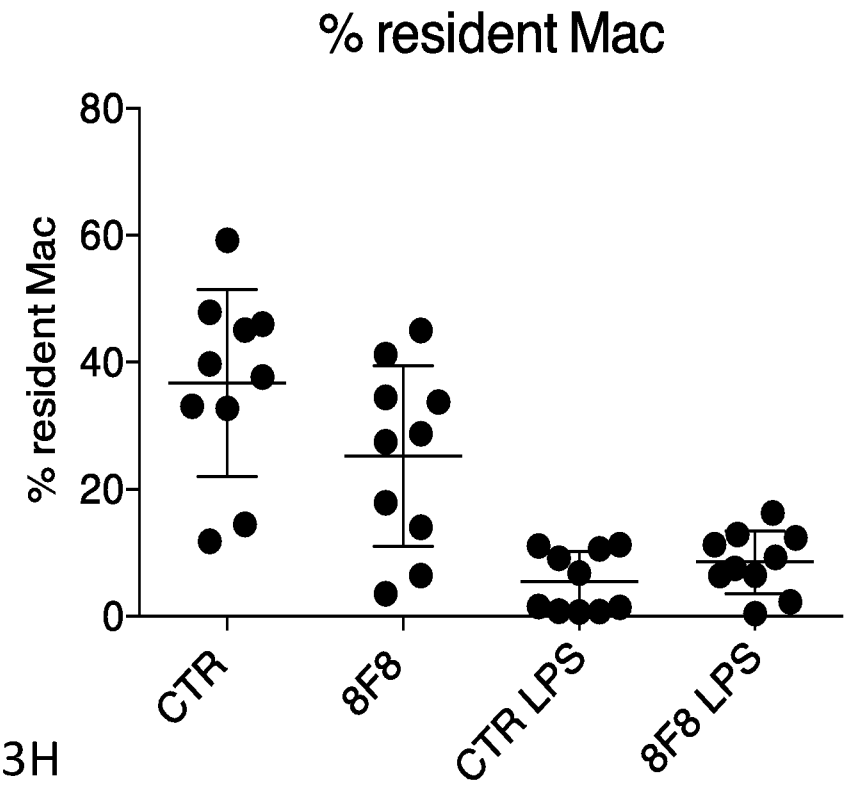


FIG. 13H

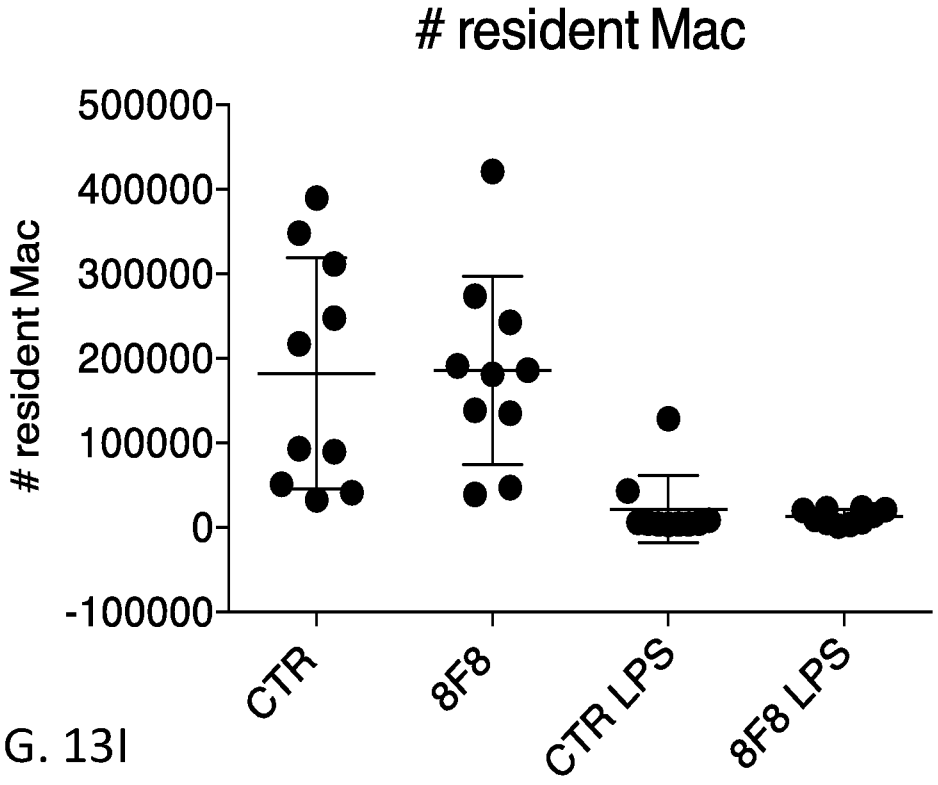


FIG. 13I

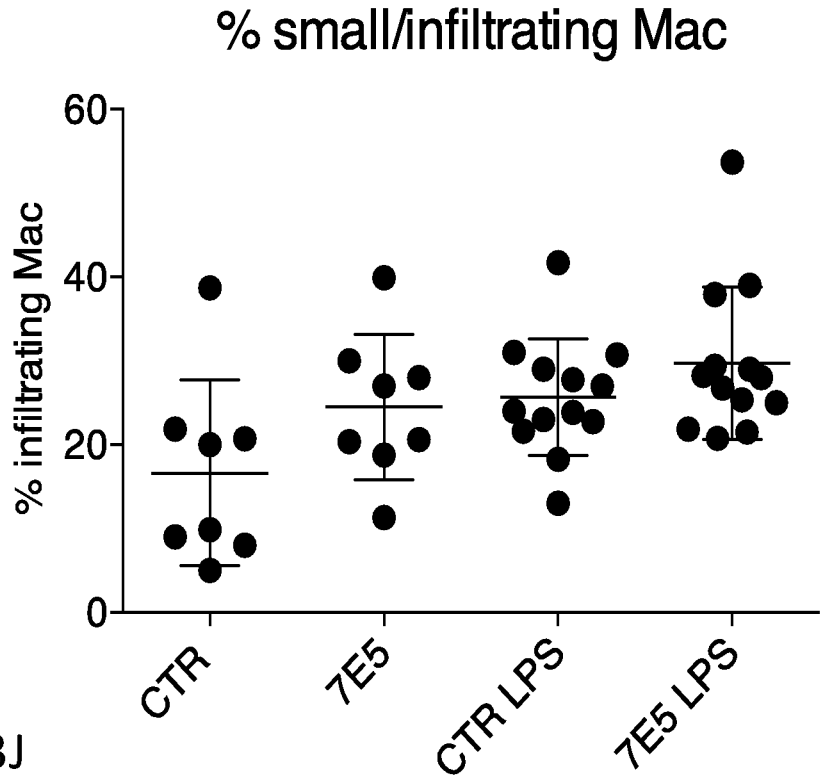


FIG. 13J

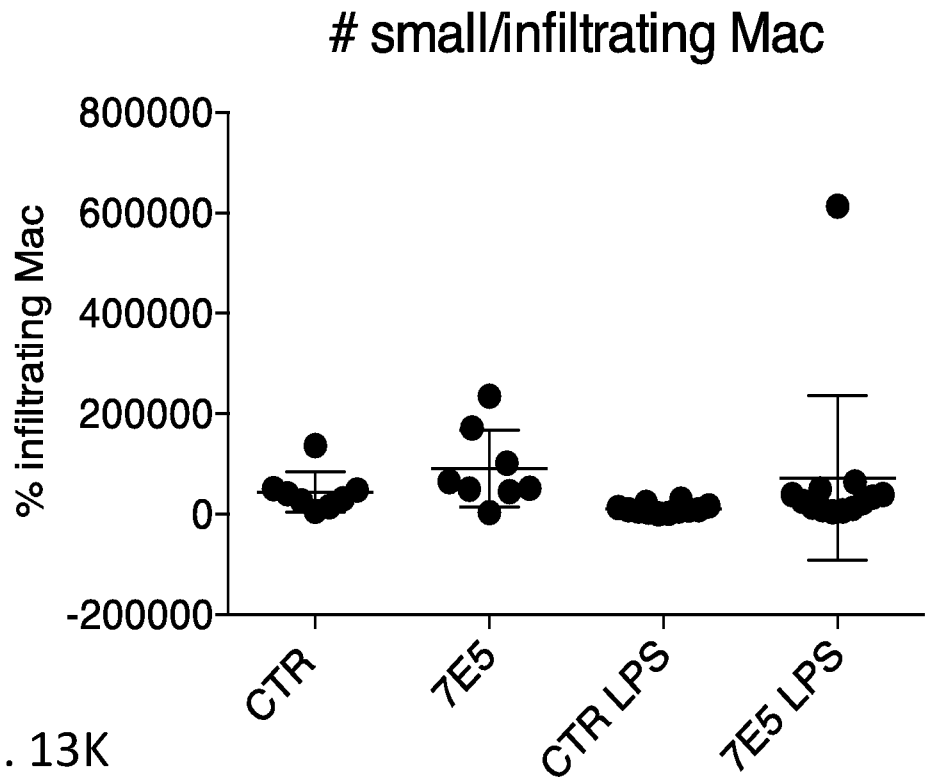


FIG. 13K

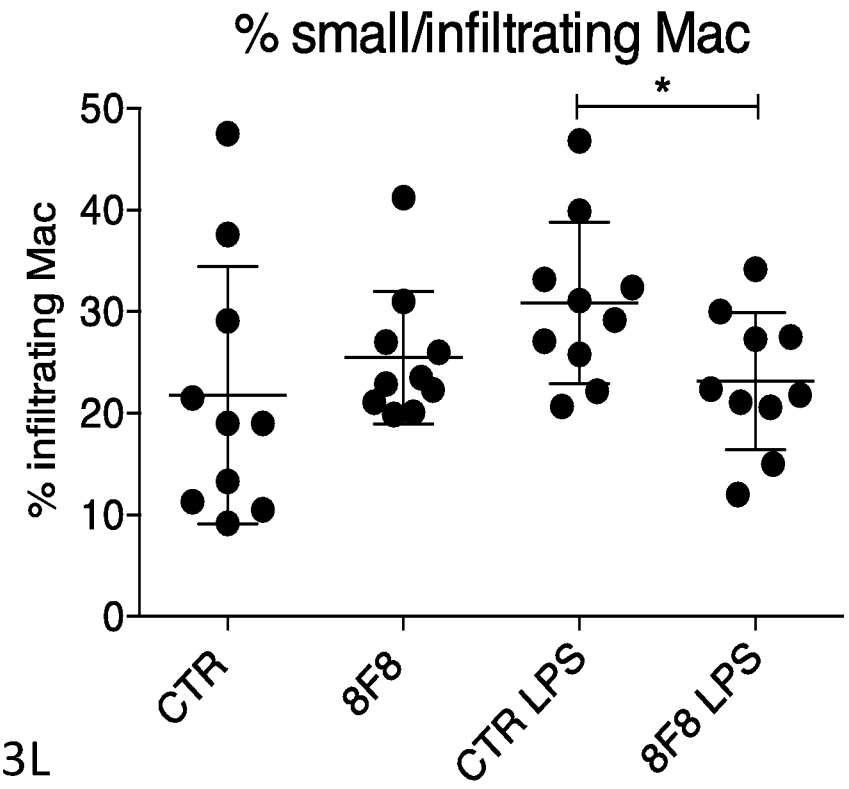


FIG. 13L

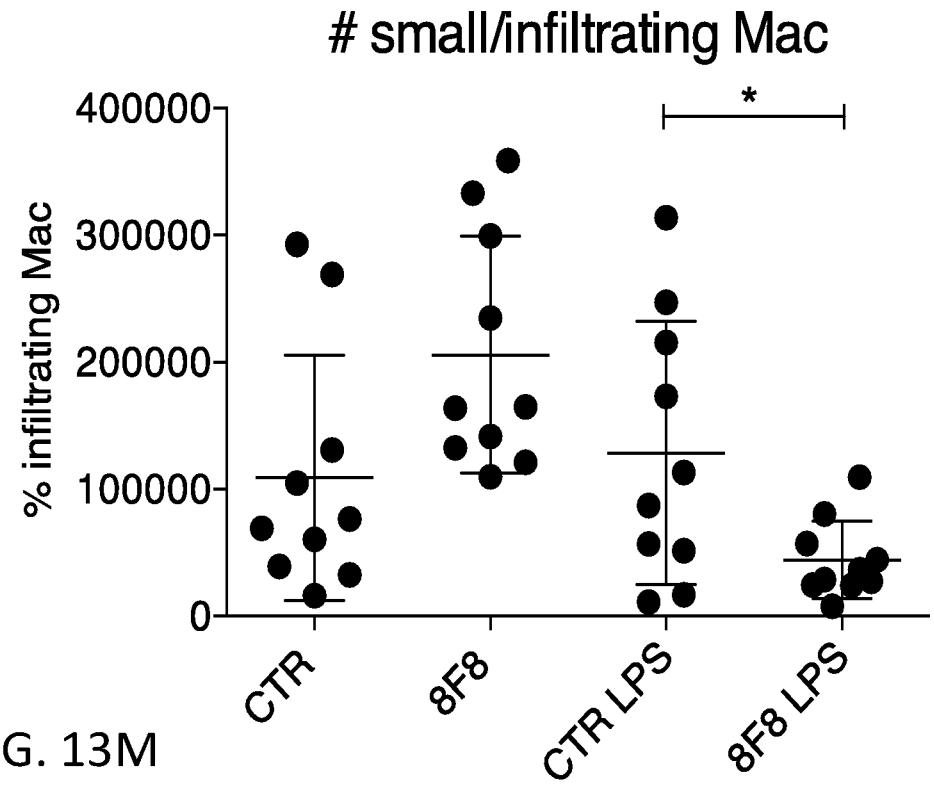


FIG. 13M

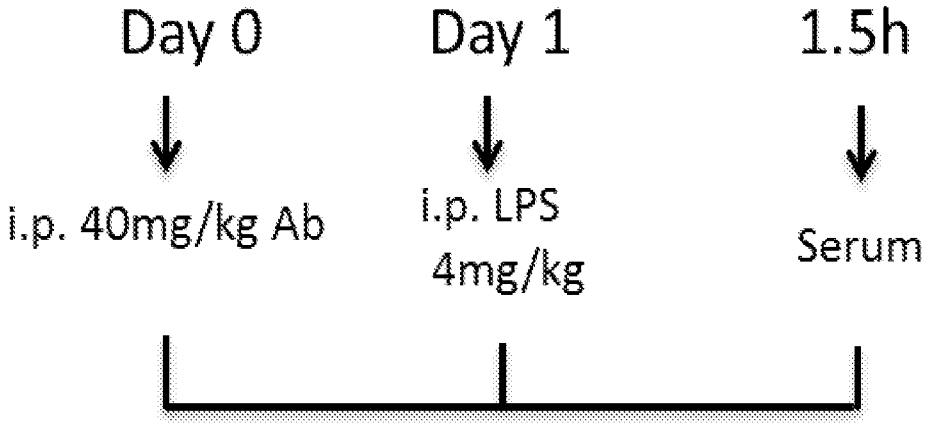


FIG. 13N

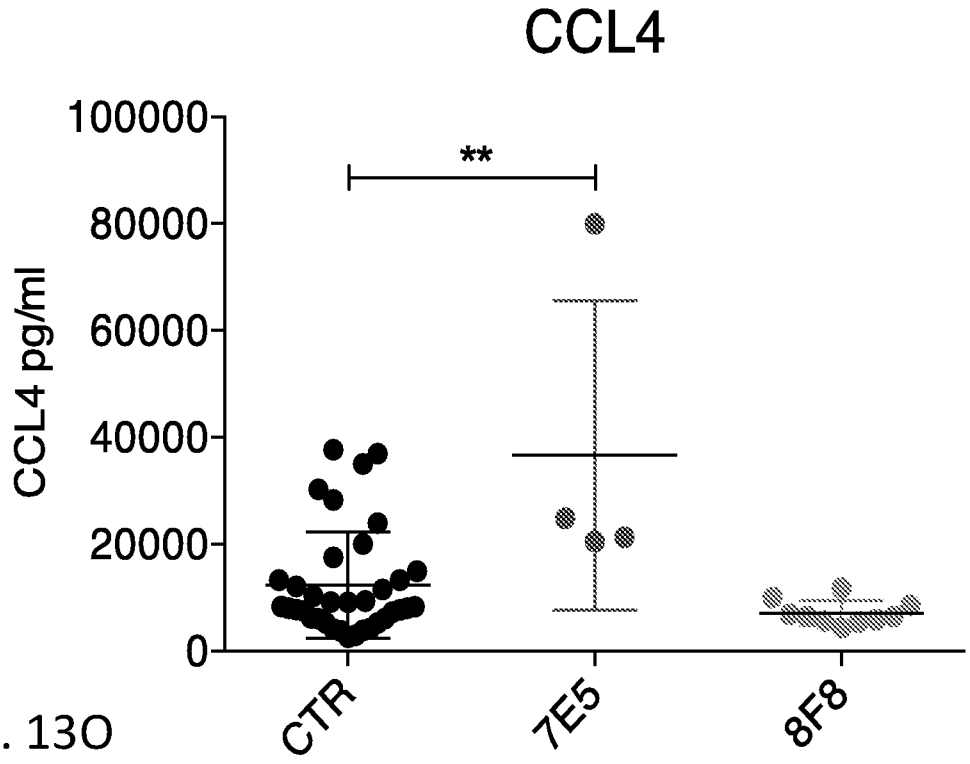


FIG. 13O

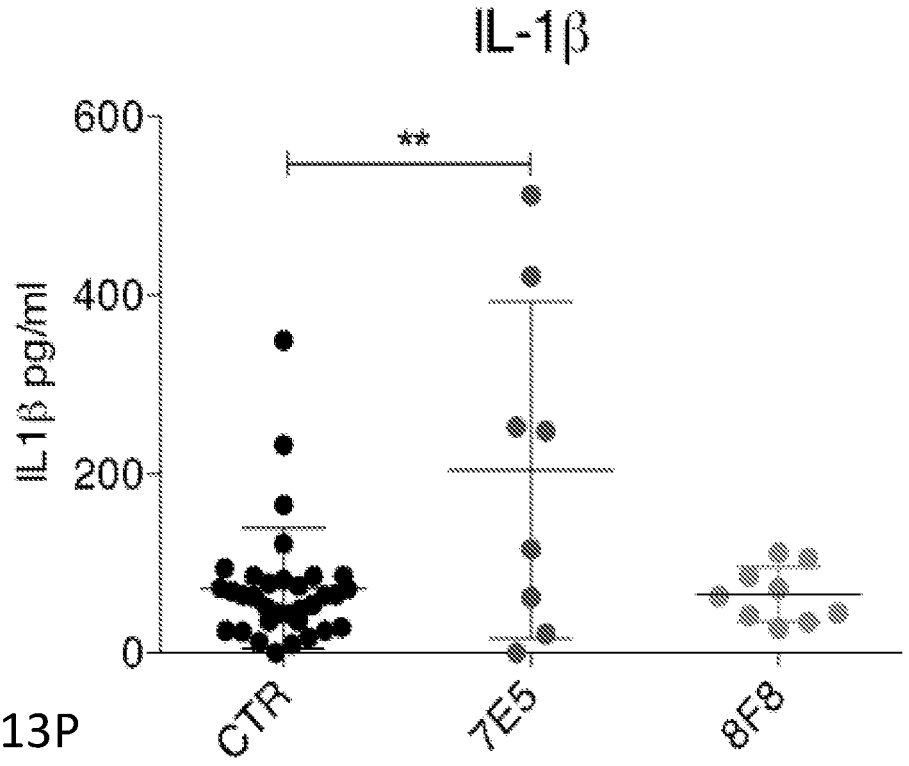


FIG. 13P

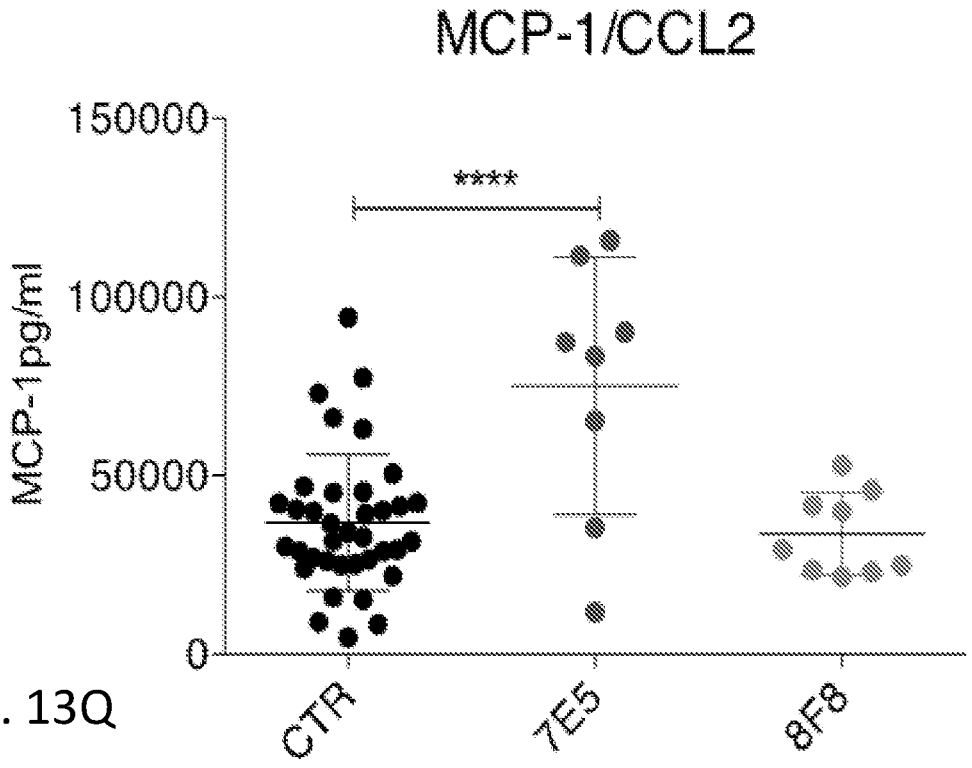


FIG. 13Q

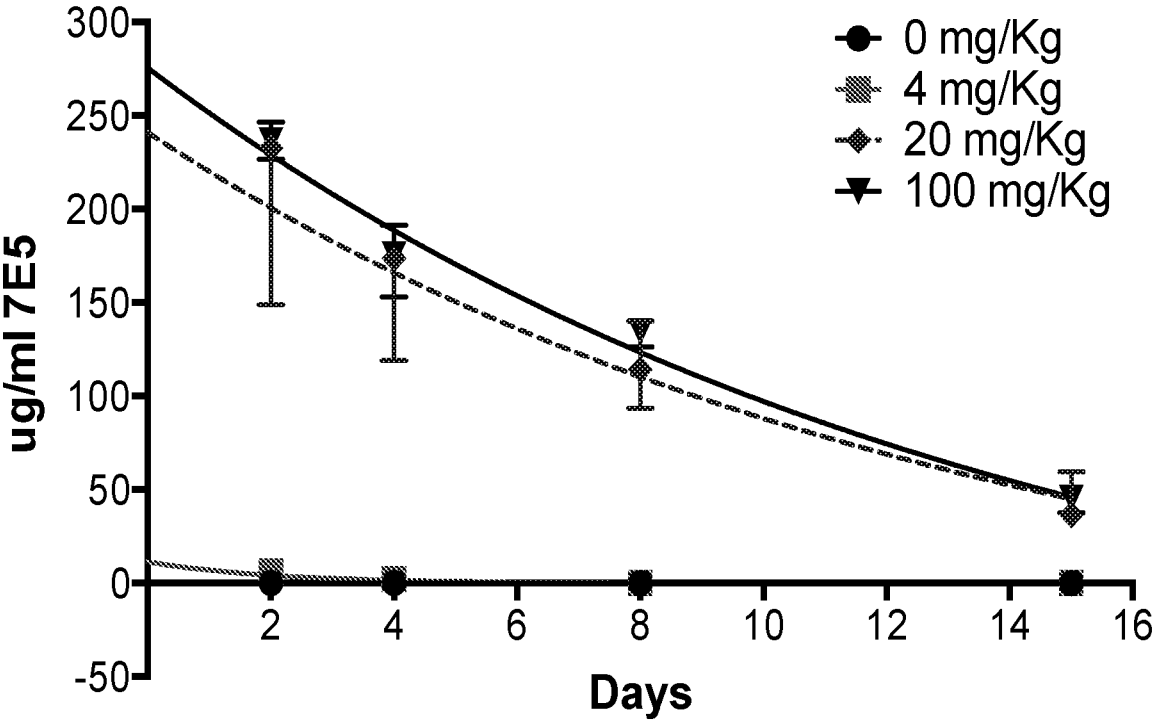

300
250
200
150
100
50
0
-50
ug/ml 7E5
2
4
6
8
10
12
14
16
Days
0 mg/Kg
4 mg/Kg
20 mg/Kg
100 mg/Kg

FIG. 14

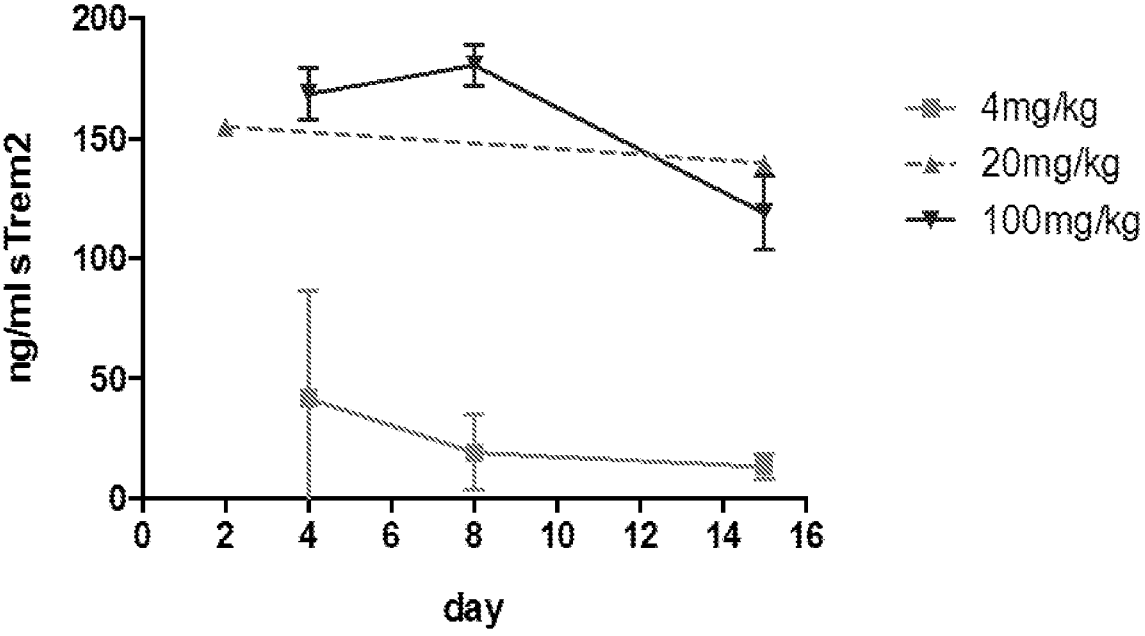

200
150
100
50
0
ng/ml sTrem2
0
2
4
6
8
10
12
14
16
day
4mg/kg
20mg/kg
100mg/kg

FIG. 15

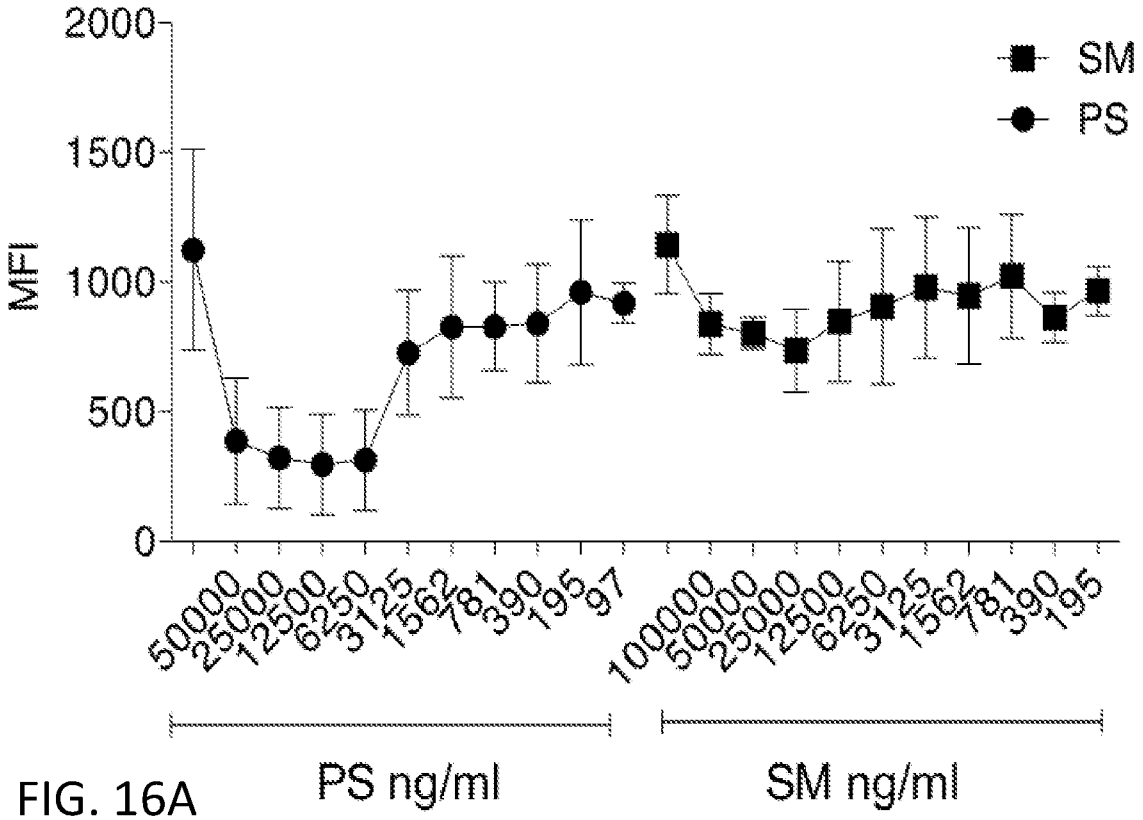


FIG. 16A

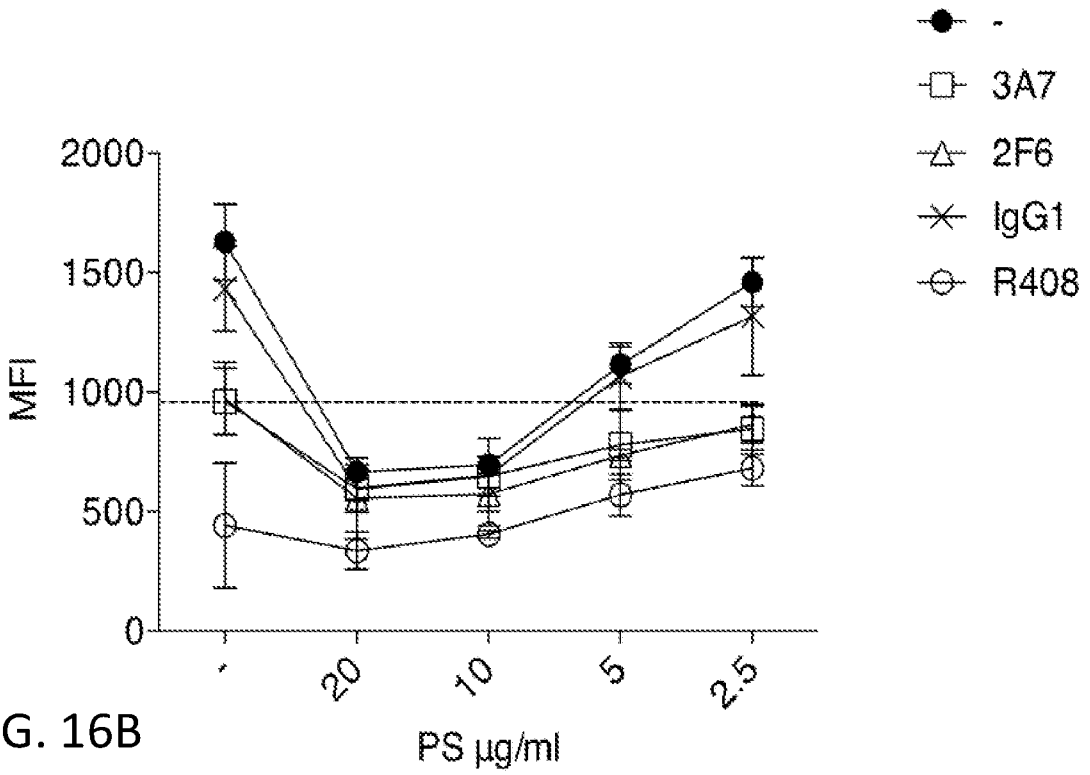


FIG. 16B

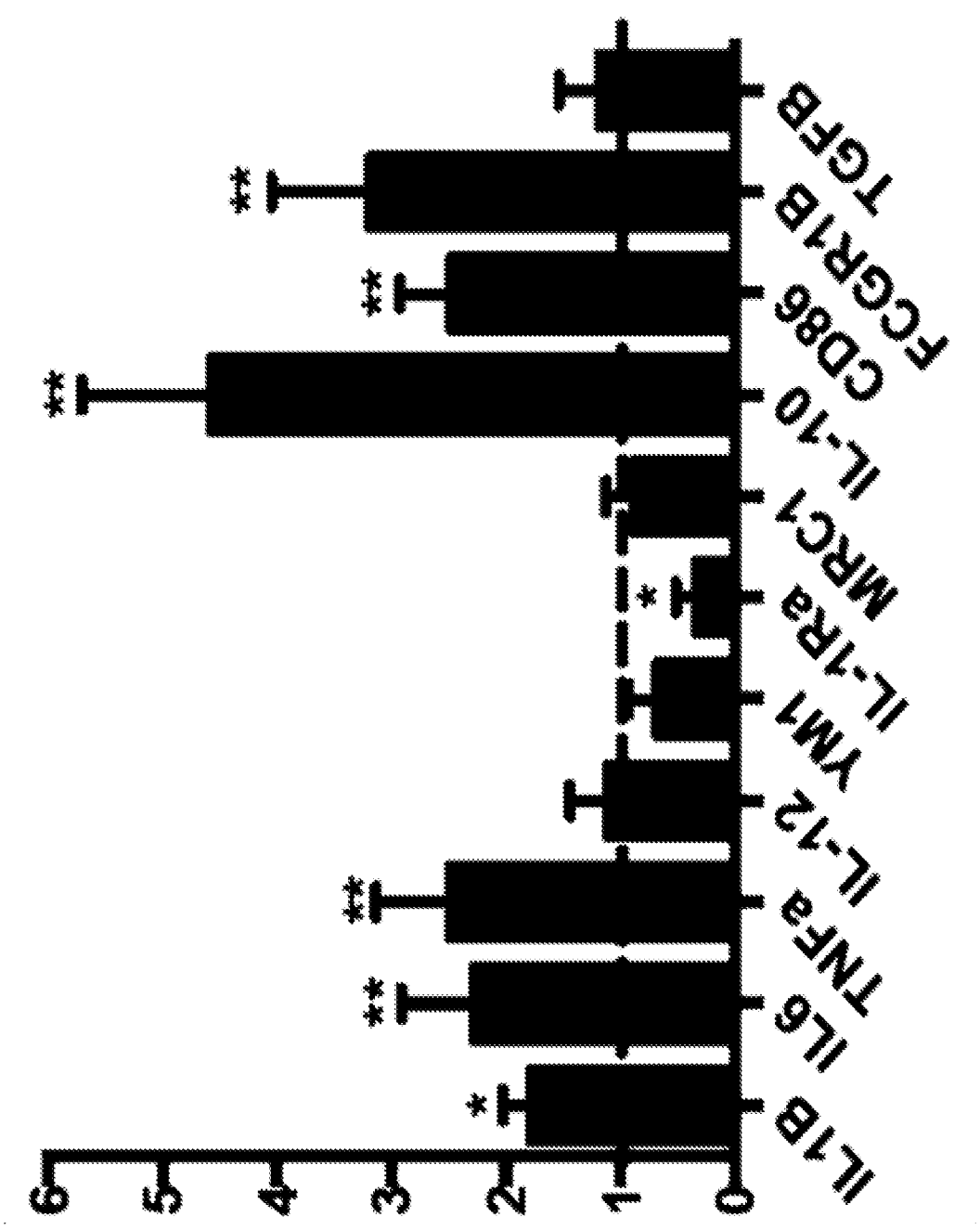

Fold change relative to control mouse
0
1
2
3
4
5
6
IL-1B
IL6
TNFa
IL-12
YM1
IL-1Ra
MRC1
IL-10
CD86
FCGR1B
TGFB
*
**
**
**
**

FIG. 17A

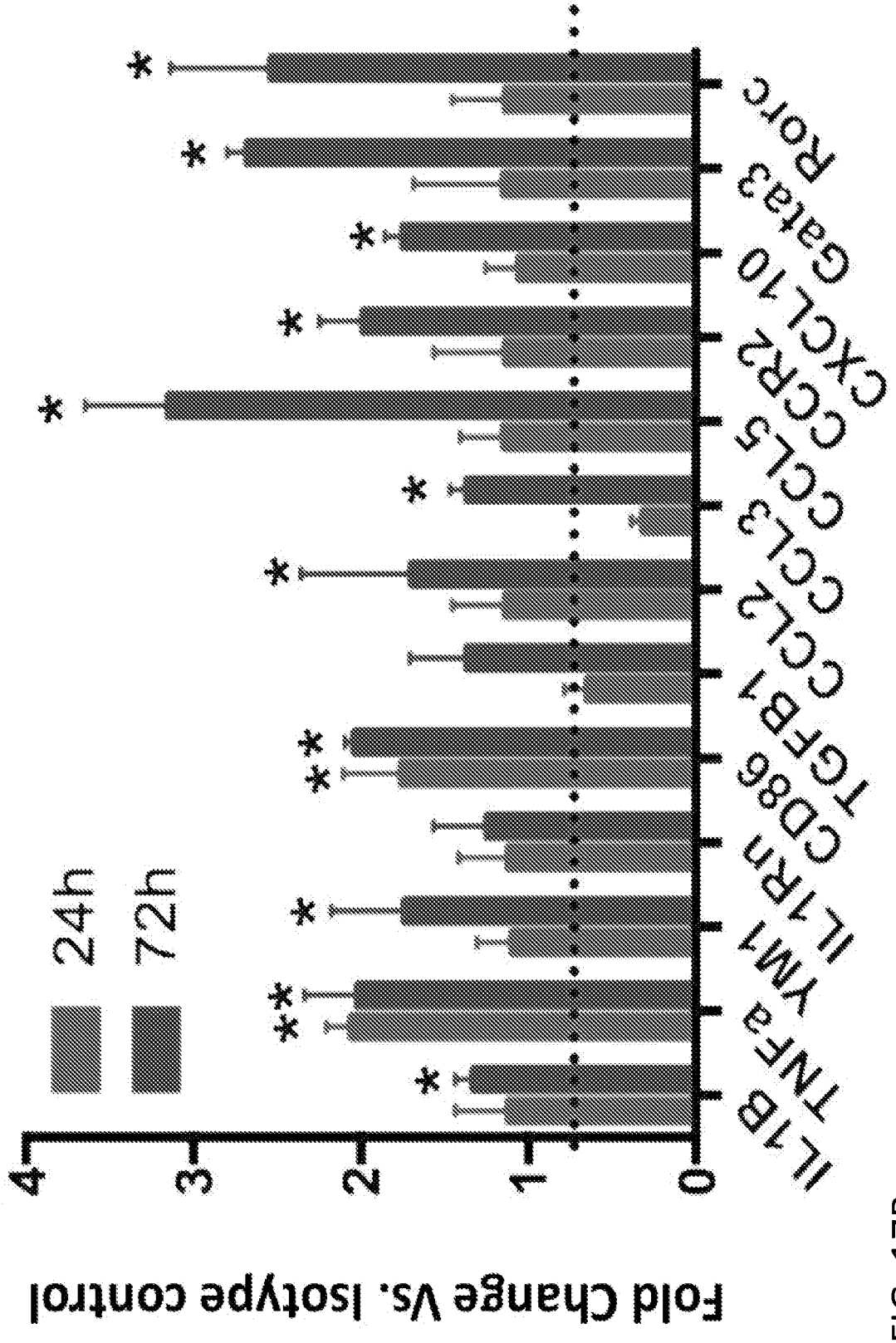

Fold Change Vs. Isotype control
0
1
2
3
4
24h
72h
IL1B
TNFa
YM1
IL4RA
CD86
TGFB1
CCL2
CCL3
CCL5
CCR2
CXCL10
Gata3
Rorc

FIG. 17B

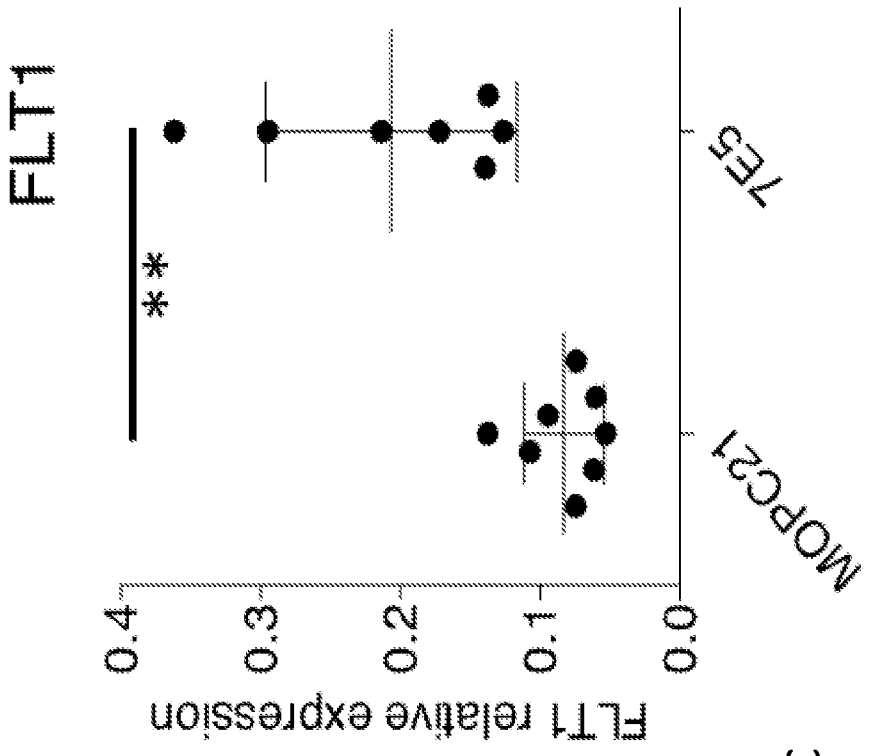


FIG. 17C

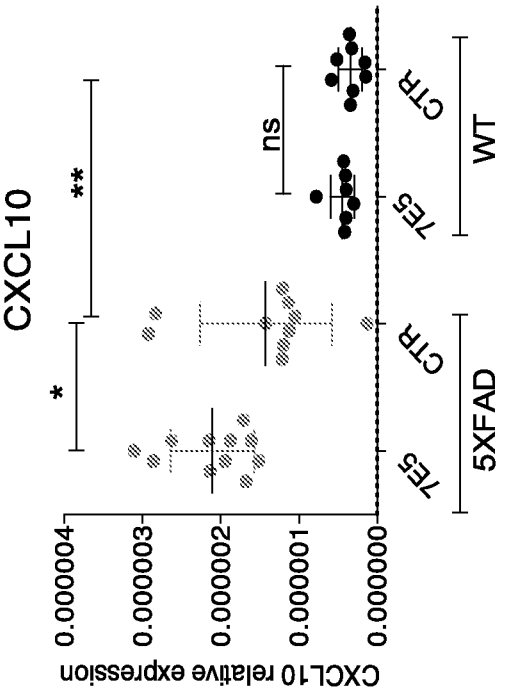


FIG. 17E

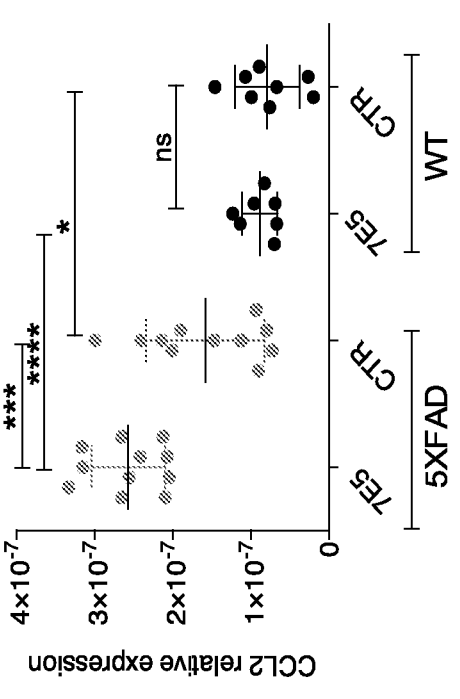


FIG. 17D

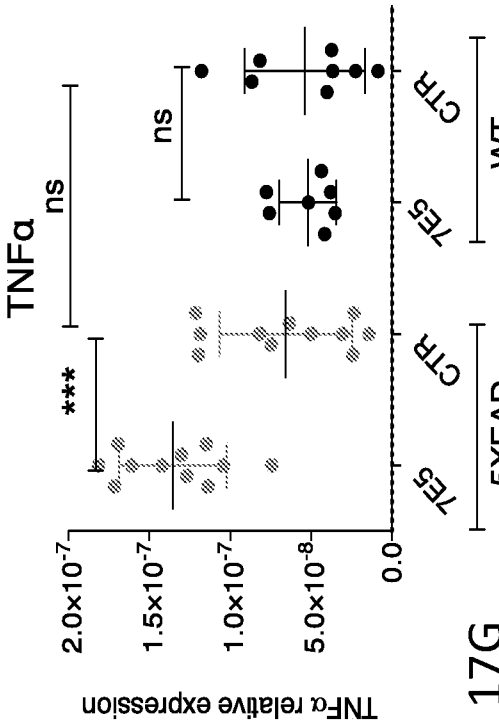


FIG. 17G

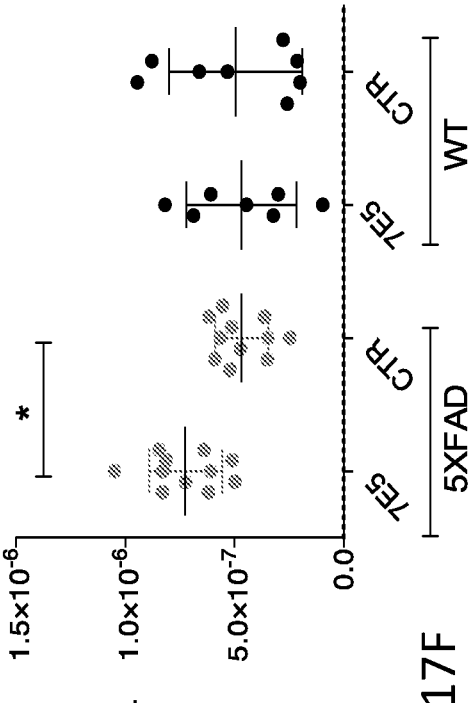


FIG. 17F

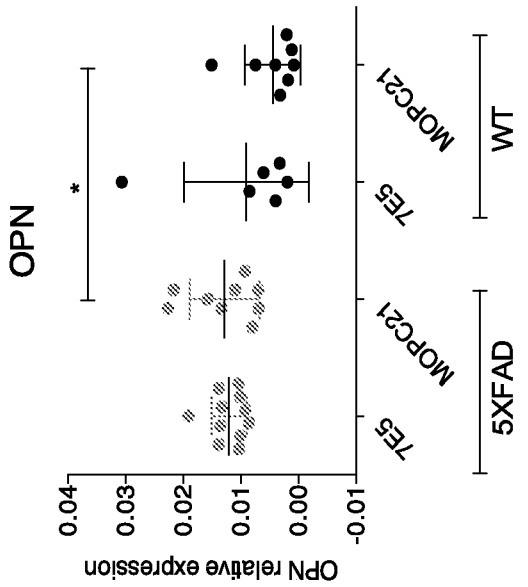


FIG. 17I

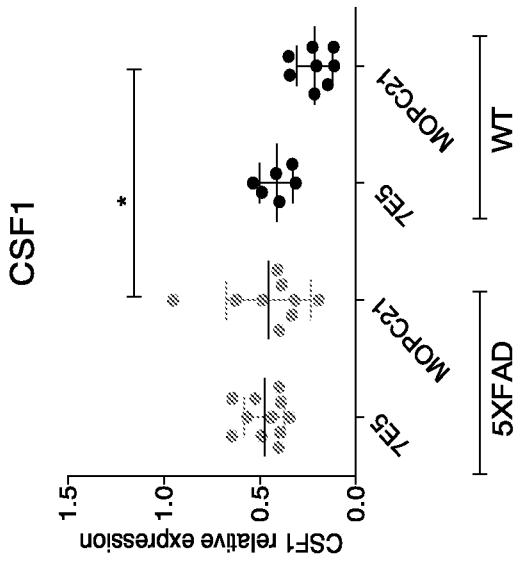


FIG. 17H

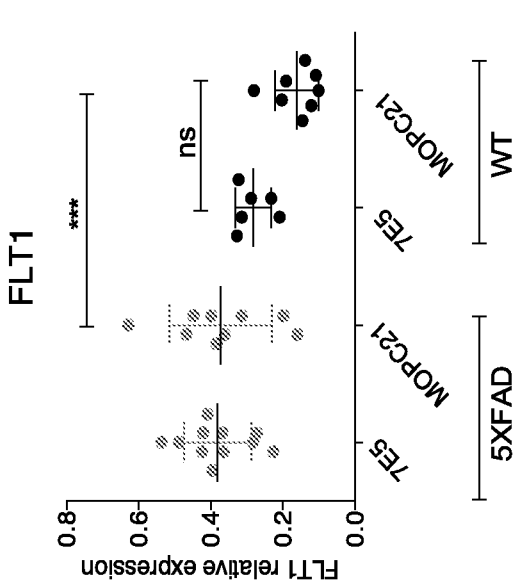


FIG. 17K

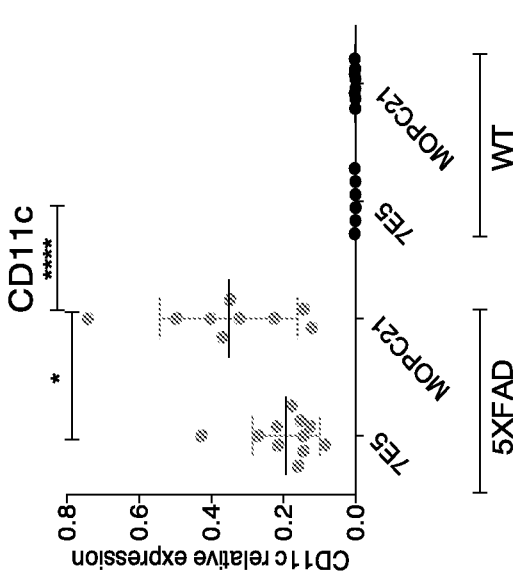


FIG. 17J

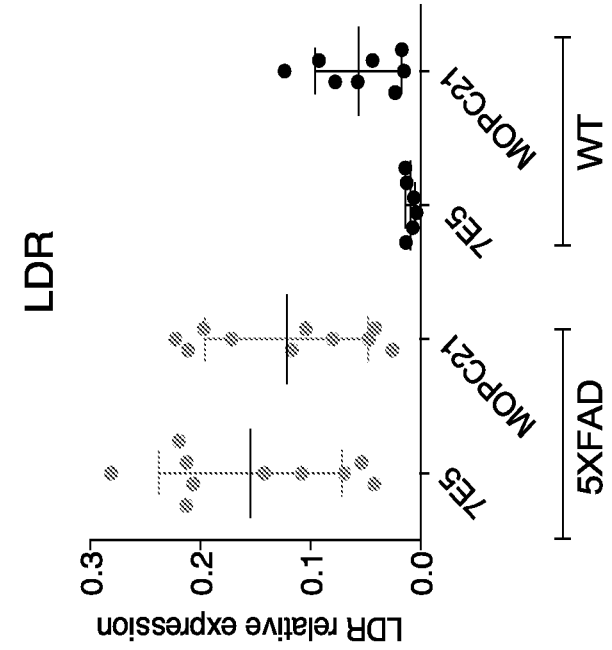


FIG. 17M

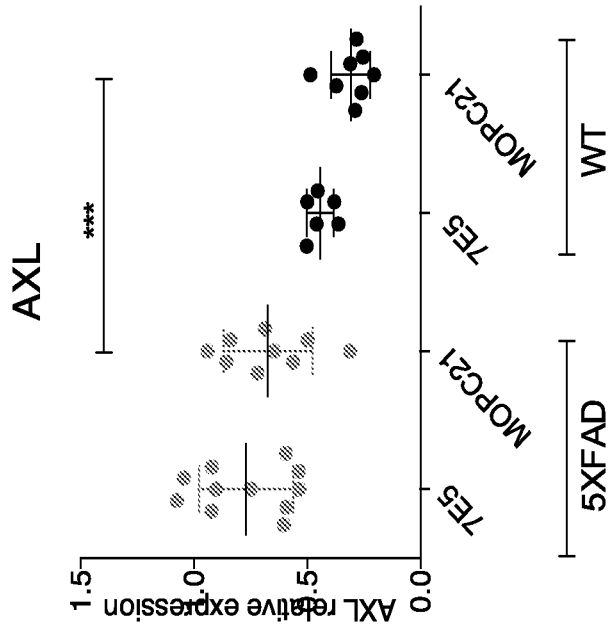


FIG. 17L

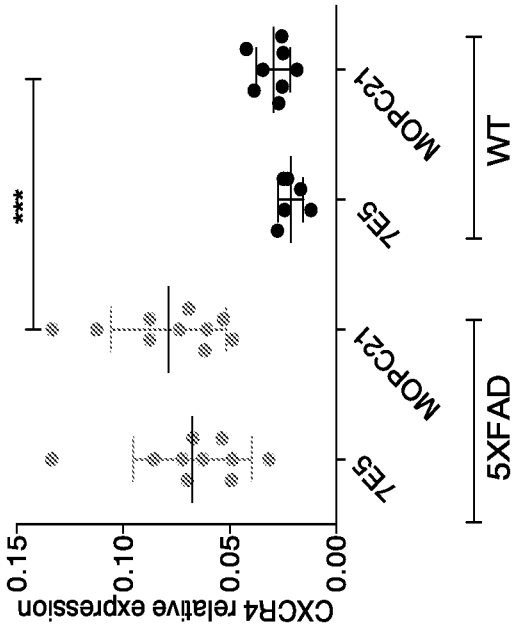


FIG. 17N

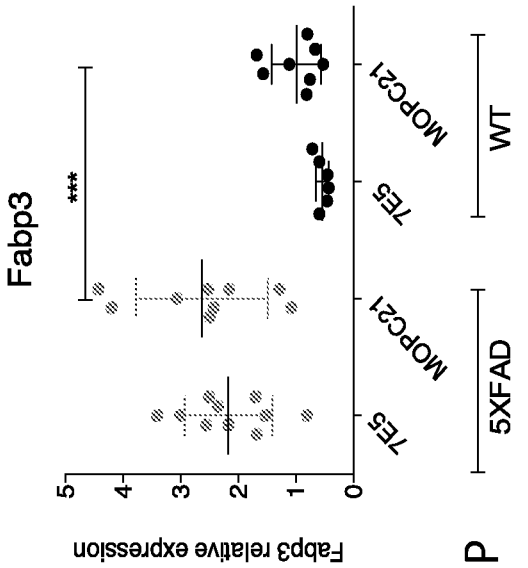


FIG. 17P

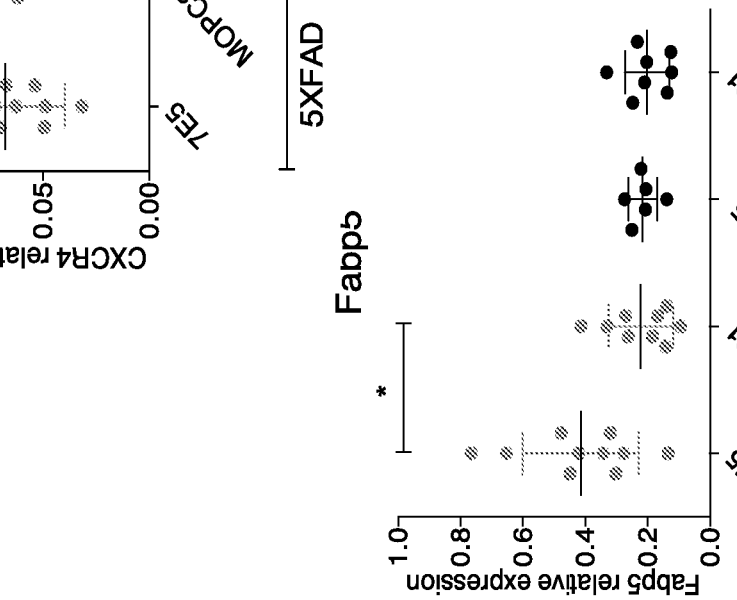


FIG. 17O

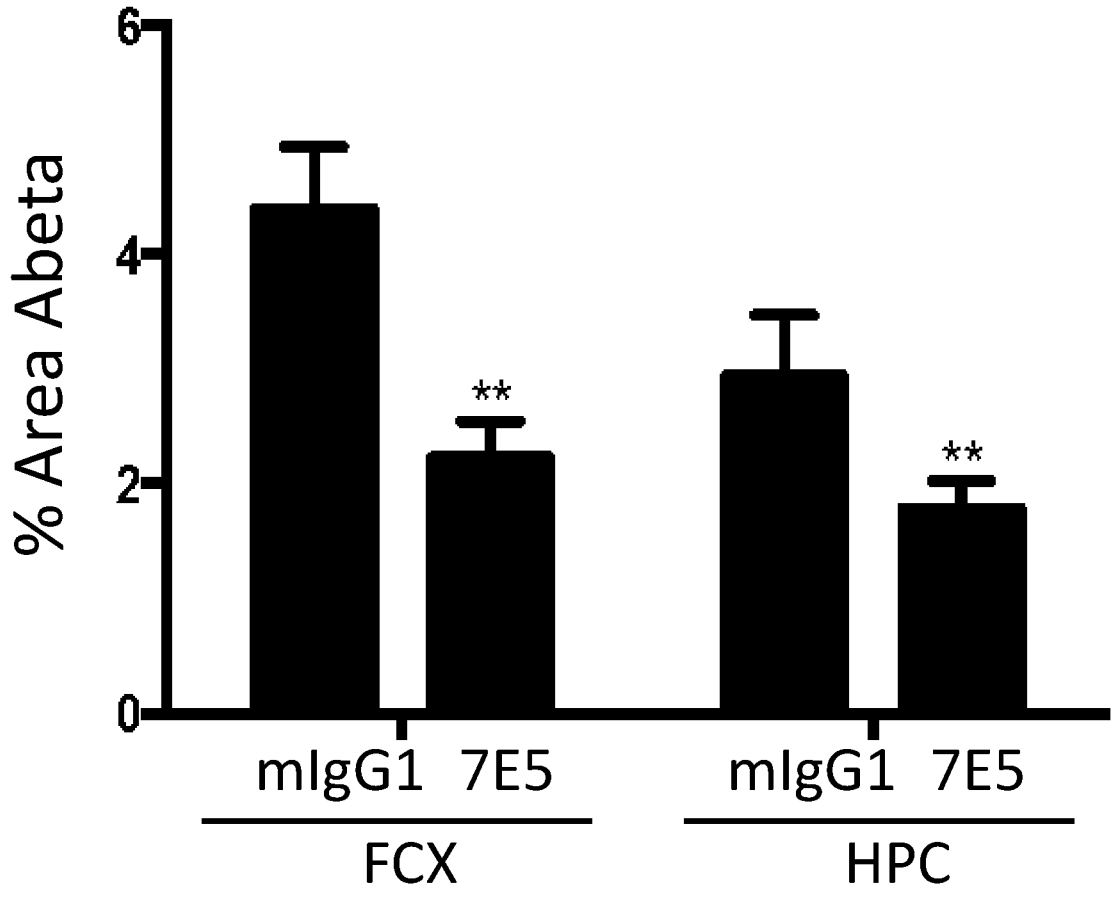


FIG. 17Q

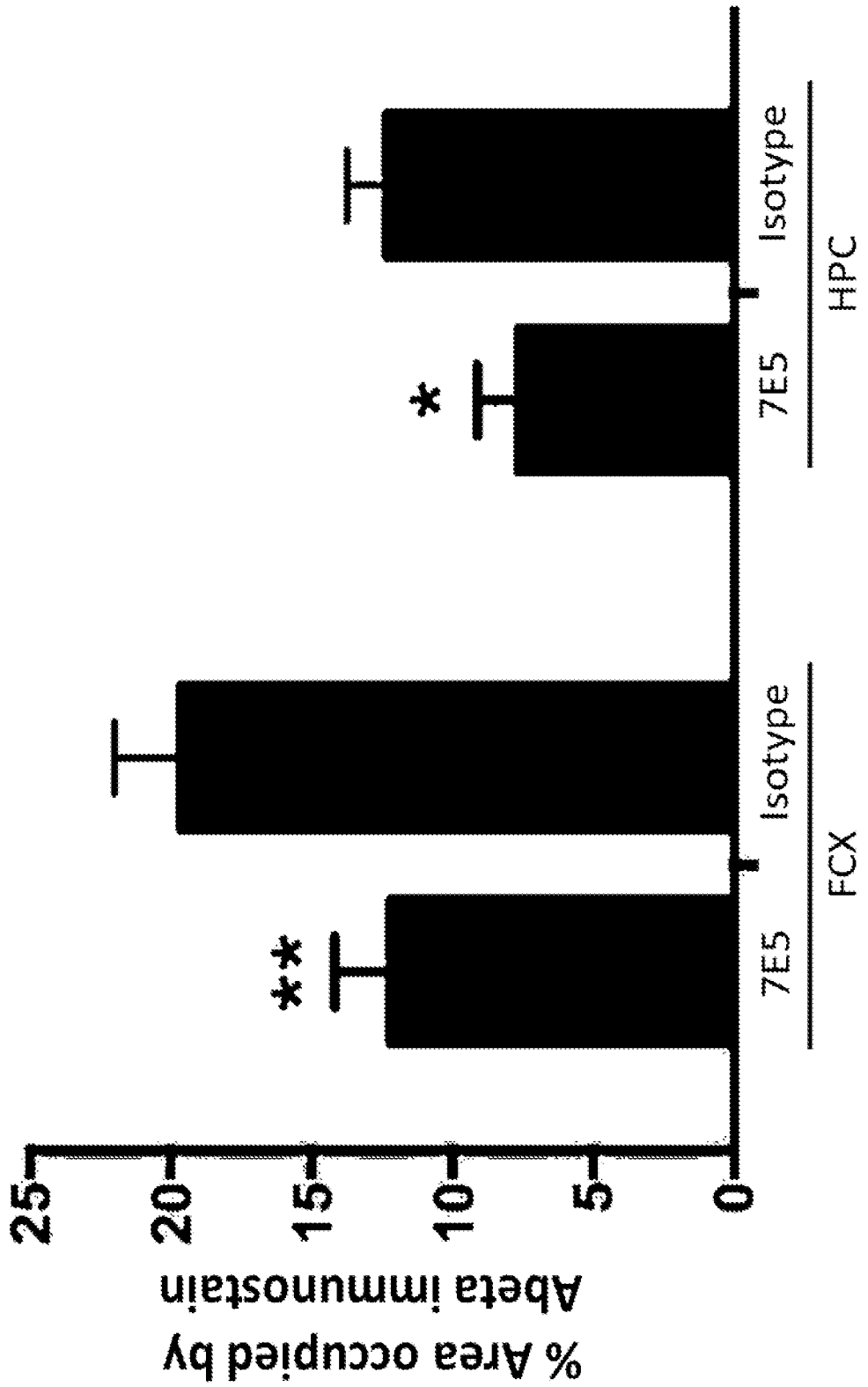

% Area occupied by
Abeta immunostain
25
20
15
10
5
0
**
*
7E5
Isotype
FCX
7E5
Isotype
HPC

FIG. 17R

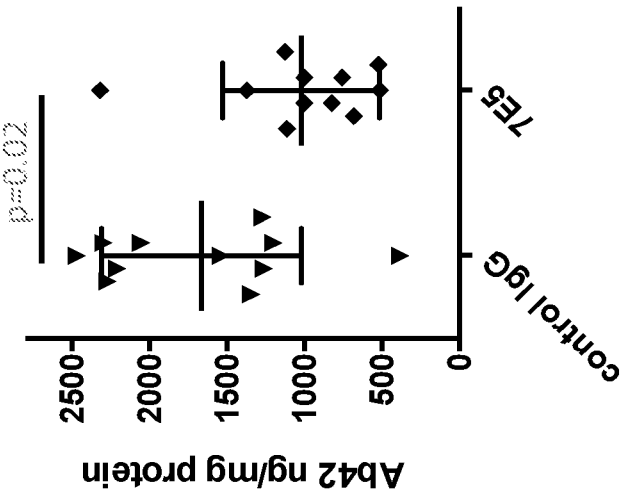


FIG. 17U

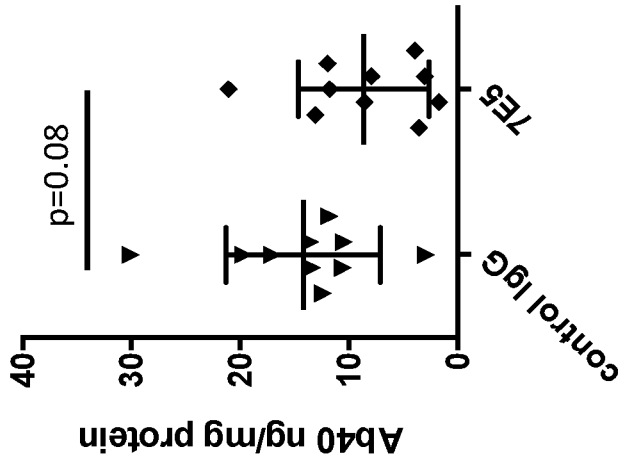


FIG. 17T

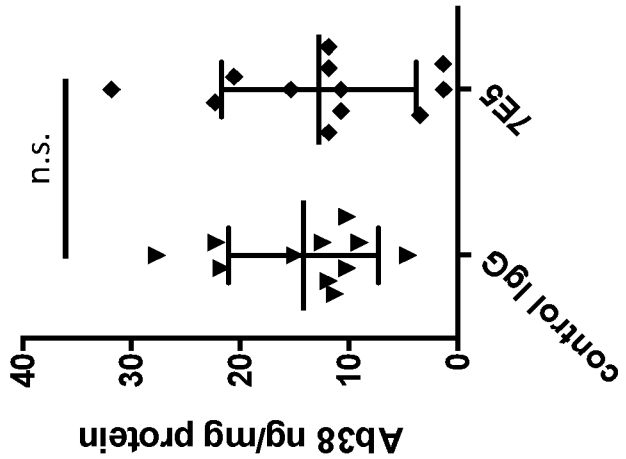


FIG. 17S

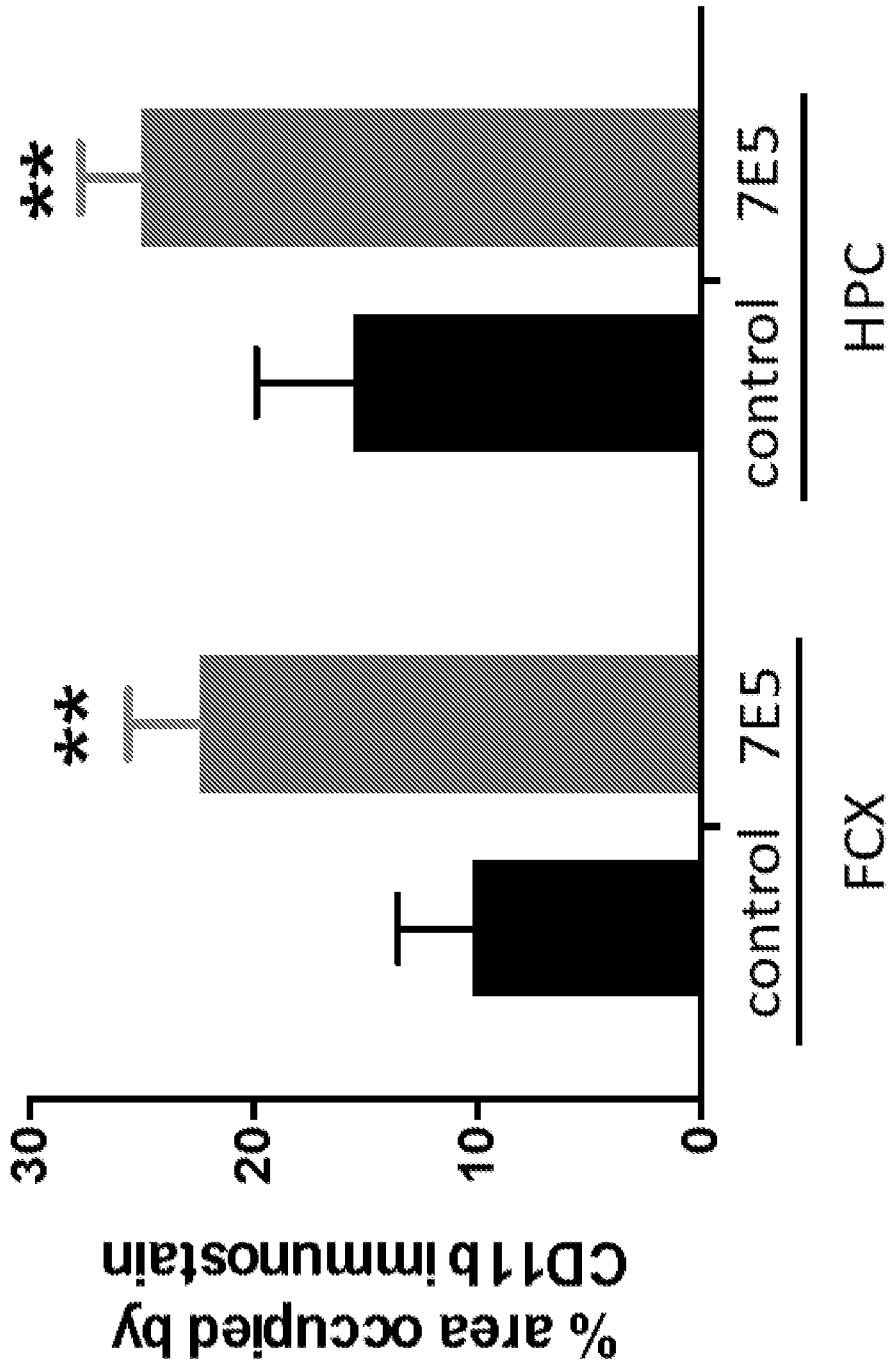

% area occupied by
CD11b immunostain
30
20
10
0
**
**
control
7E5
control
7E5
FCX
HPC

FIG. 17V

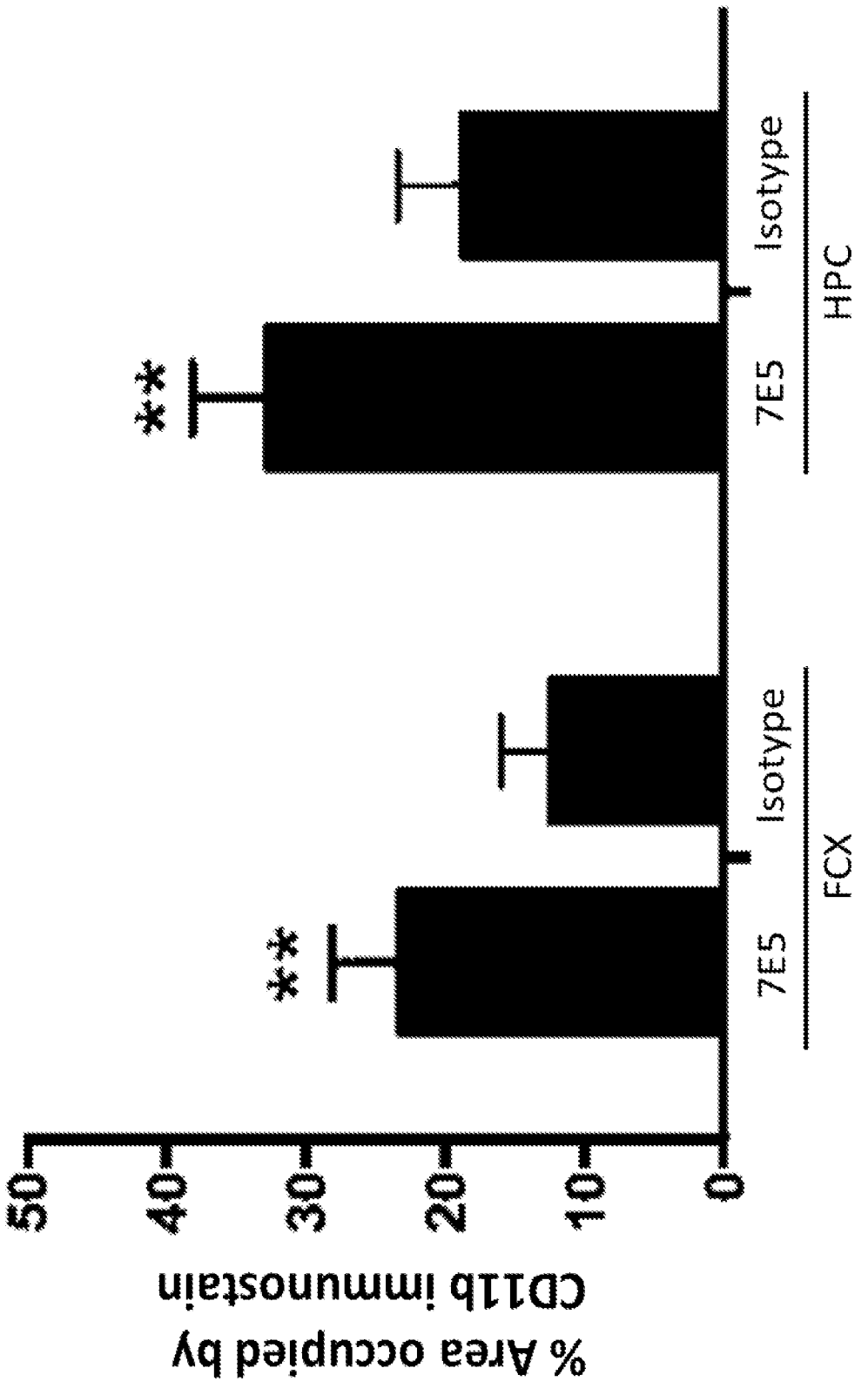

% Area occupied by
CD11b immunostain
50
40
30
20
10
0
**
**
7E5
Isotype
FCX
7E5
Isotype
HPC

FIG. 17W

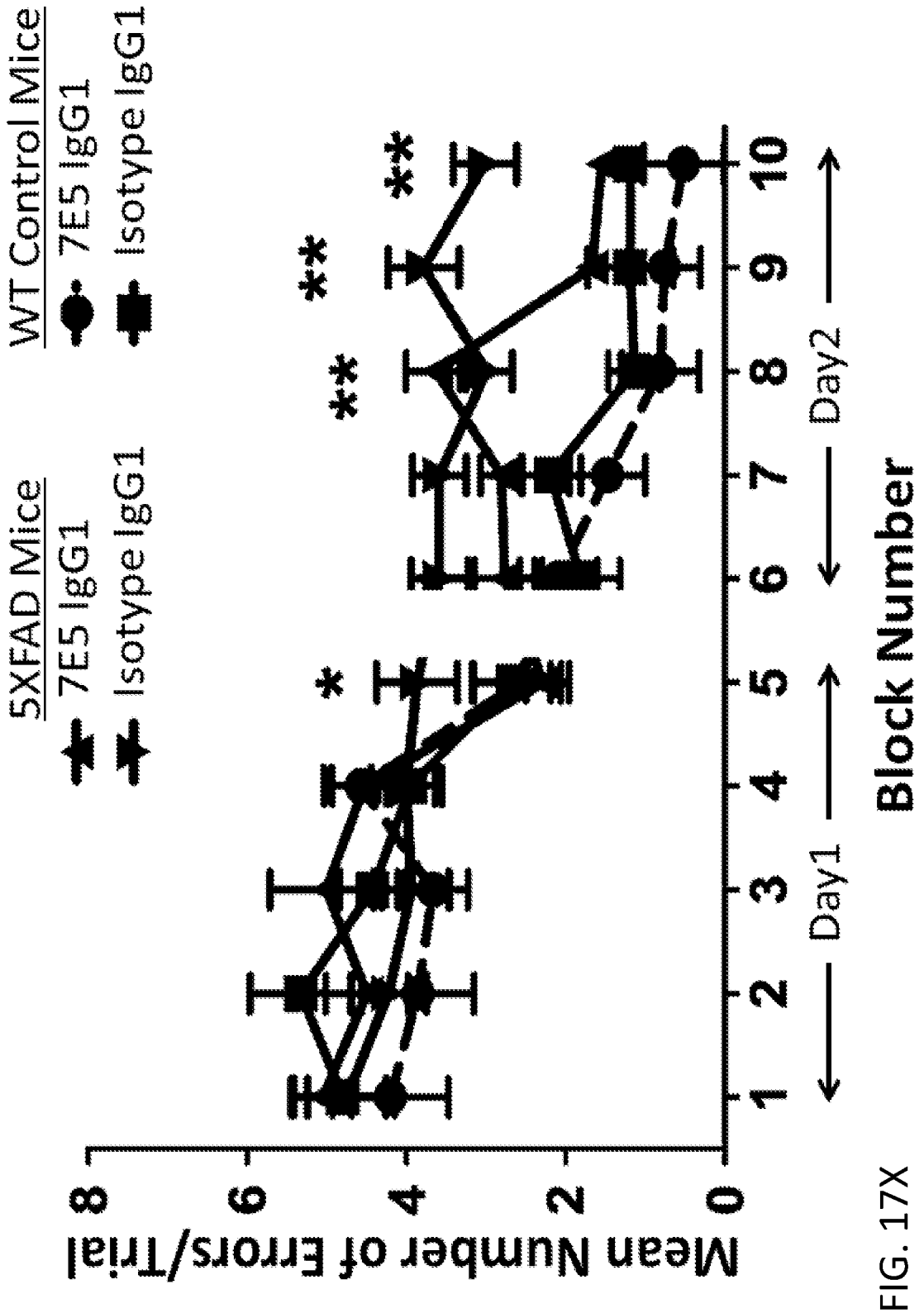

5XFAD Mice
7E5 IgG1
Isotype IgG1
WT Control Mice
7E5 IgG1
Isotype IgG1
Mean Number of Errors/Trial
0
2
4
6
8
1 2 3 4 5 6 7 8 9 10
Day1
Day2
Block Number
*
**
**
**

FIG. 17X

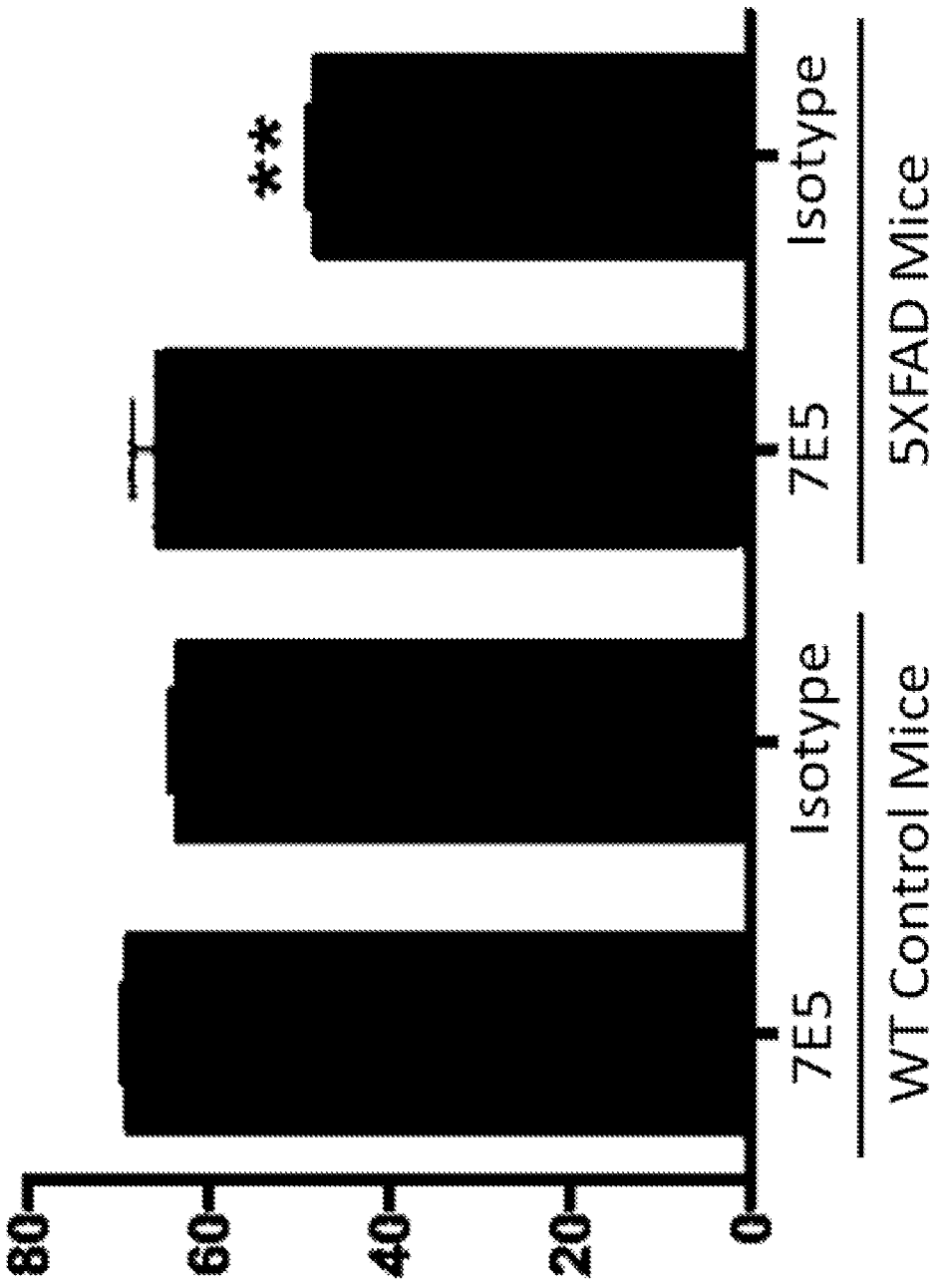

% Time with novel object
80
60
40
20
0
**
7E5
Isotype
7E5
Isotype
WT Control Mice
5XFAD Mice

FIG. 17Y

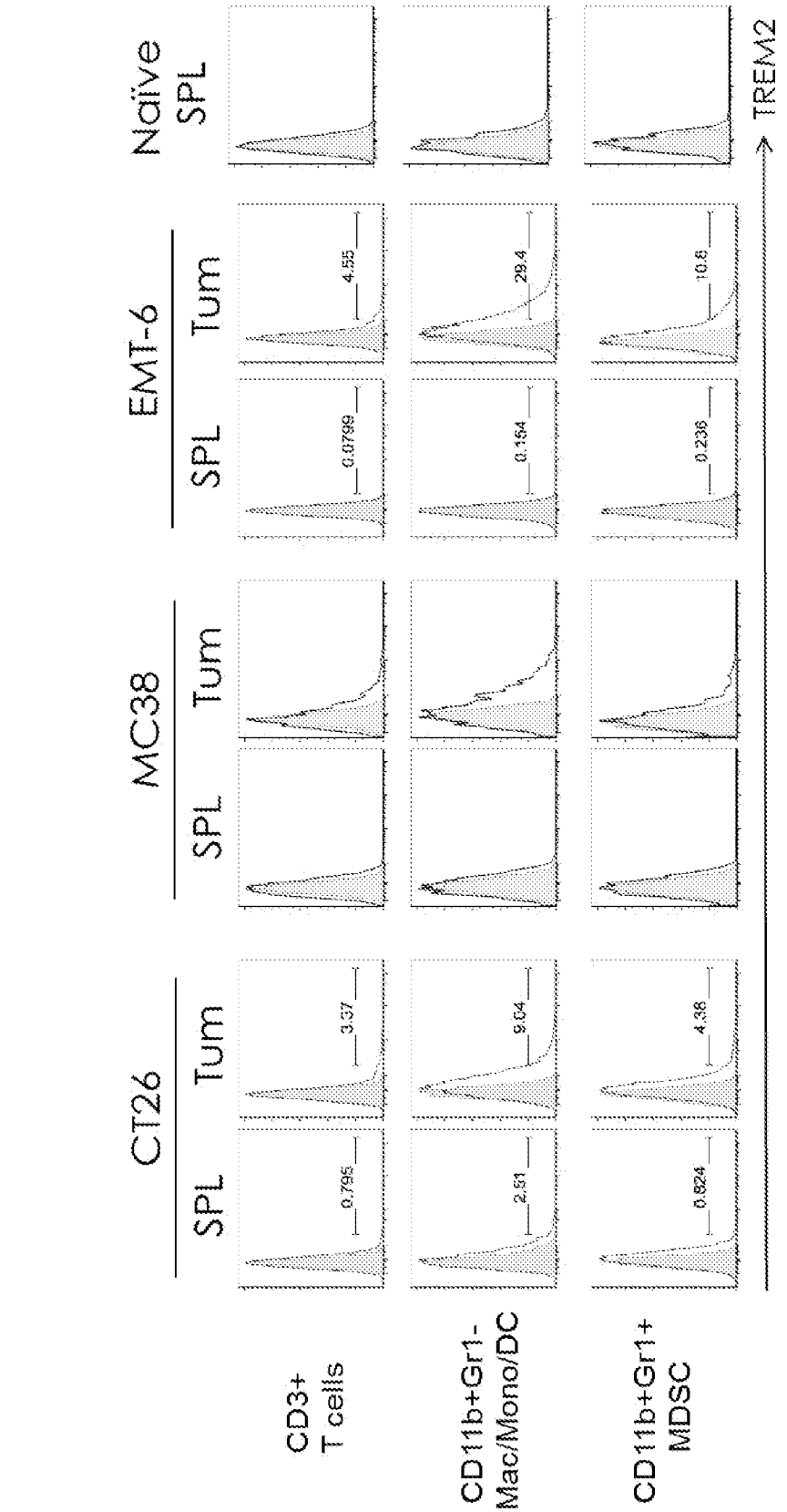

CT26
MC38
EMT-6
Naïve SPL
SPL
Tum
SPL
Tum
SPL
Tum
SPL
CD3+ T cells
CD11b+Gr1- Mac/Mono/DC
CD11b+Gr1+ MDSC
0.795
3.37
2.51
9.04
0.824
4.38
0.0799
4.55
0.164
29.4
0.236
10.8
TREM2

FIG. 18

FIG. 19A

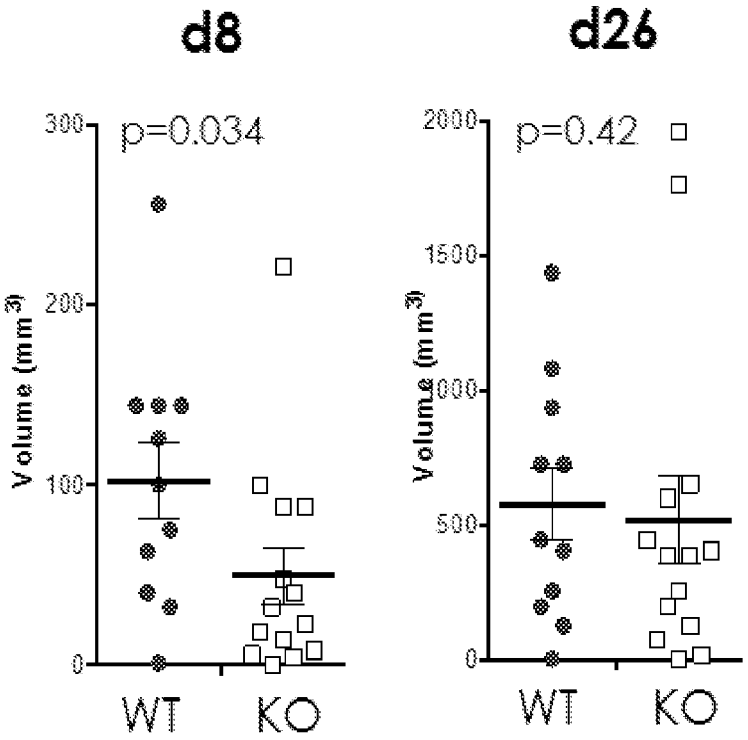
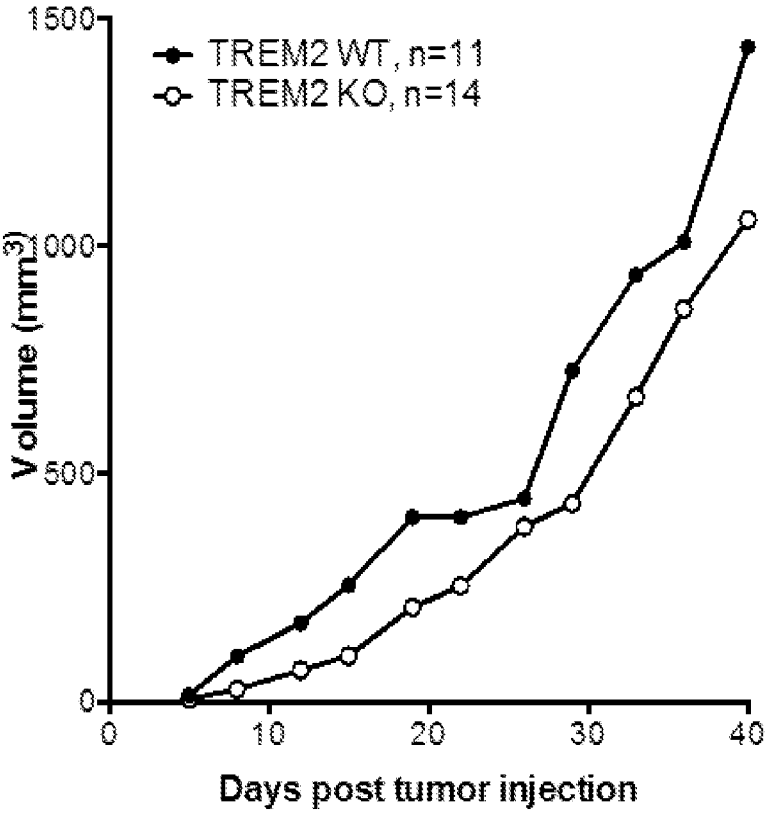


FIG. 19B



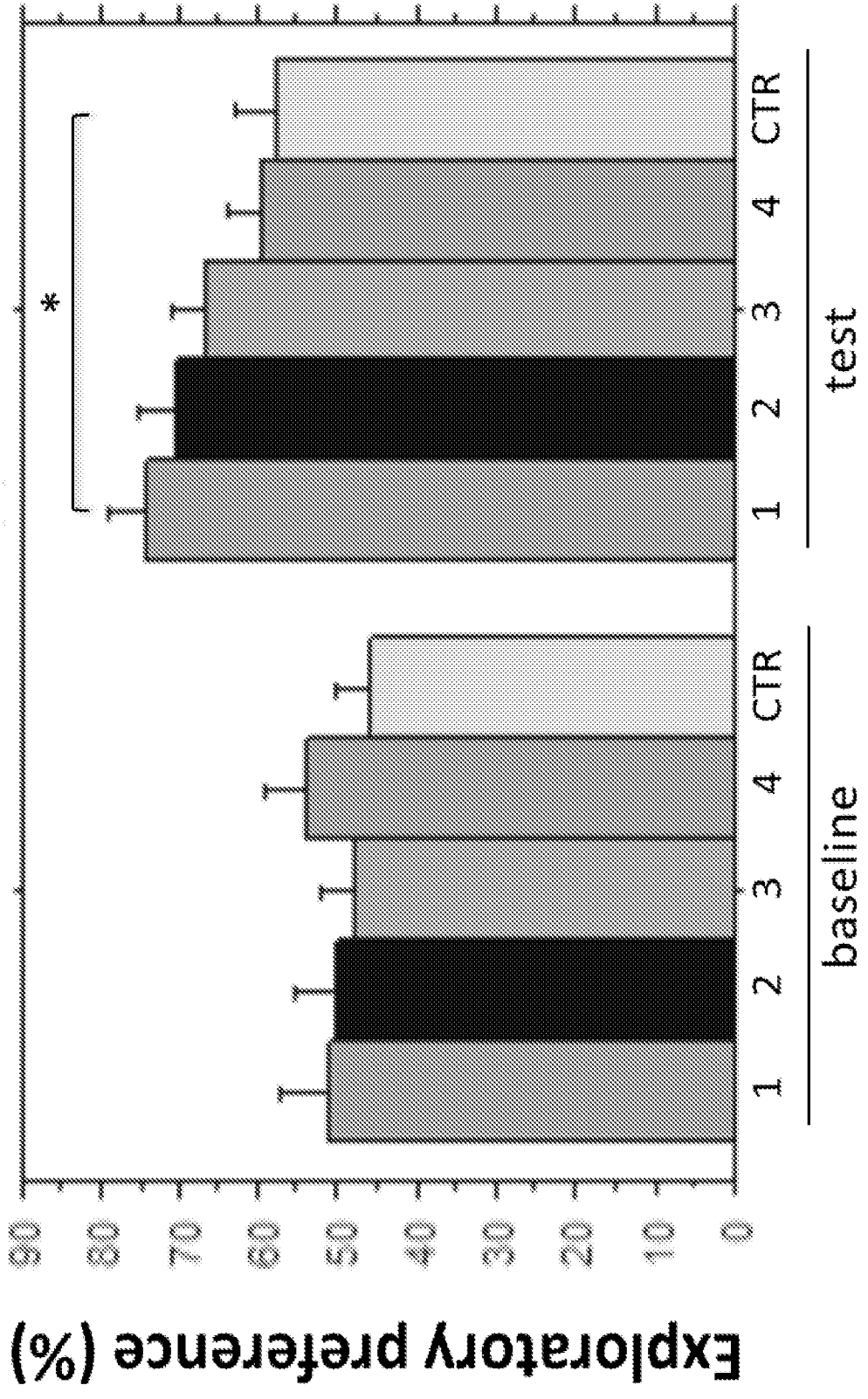

Exploratory preference (%)
0
10
20
30
40
50
60
70
80
90
baseline
test
1
2
3
4
CTR
1
2
3
4
CTR
*

FIG. 20

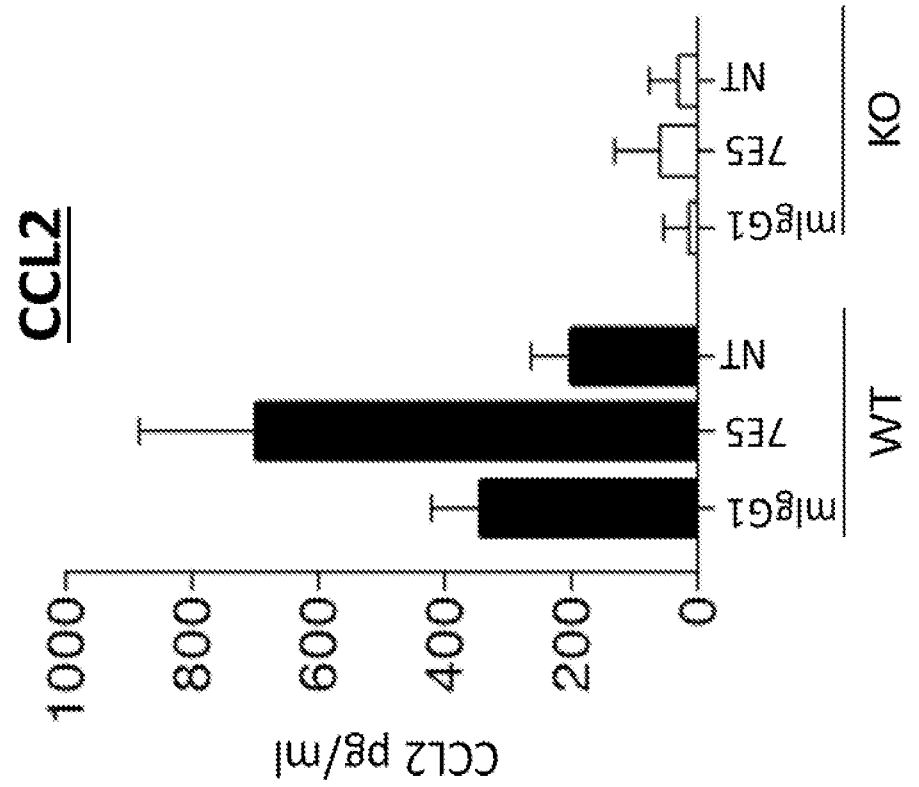


FIG. 21B

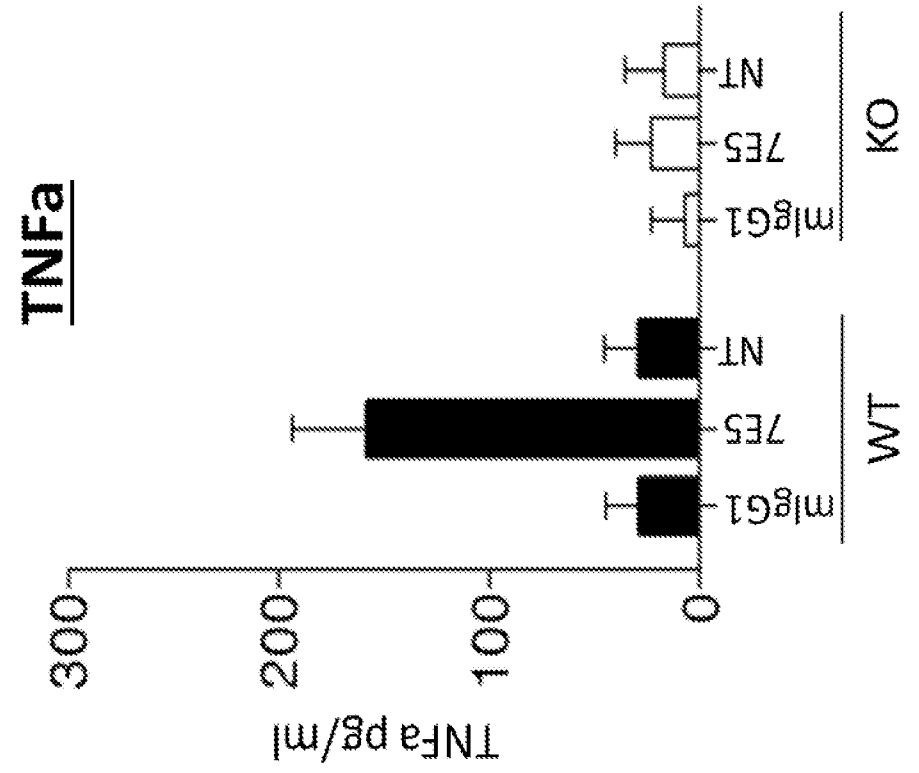


FIG. 21A

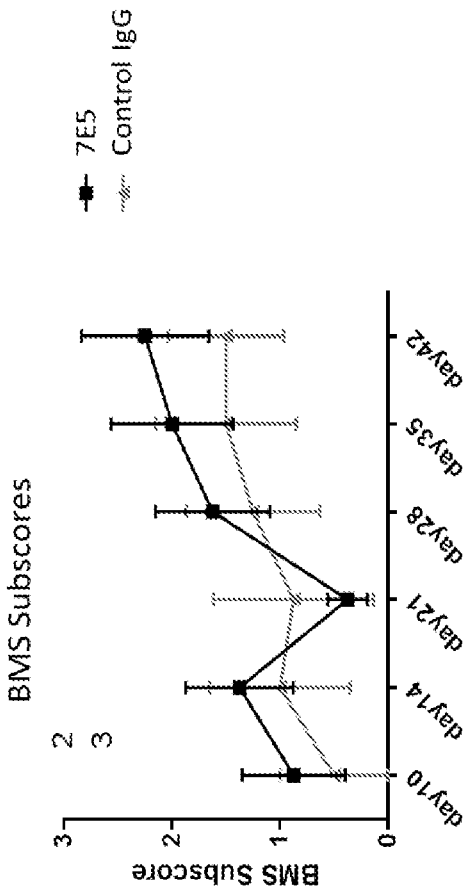


FIG. 22B

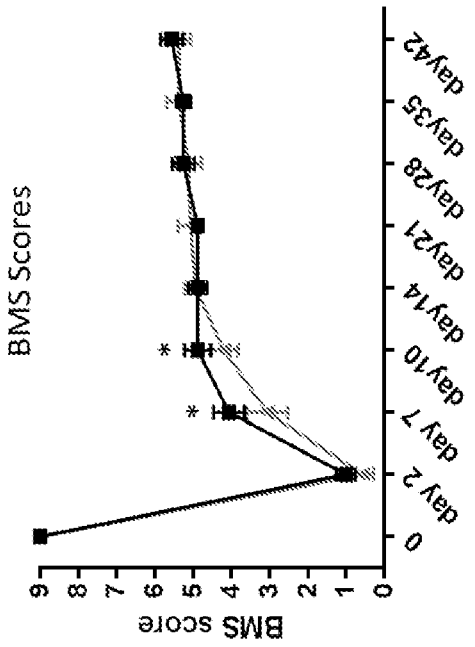


FIG. 22A

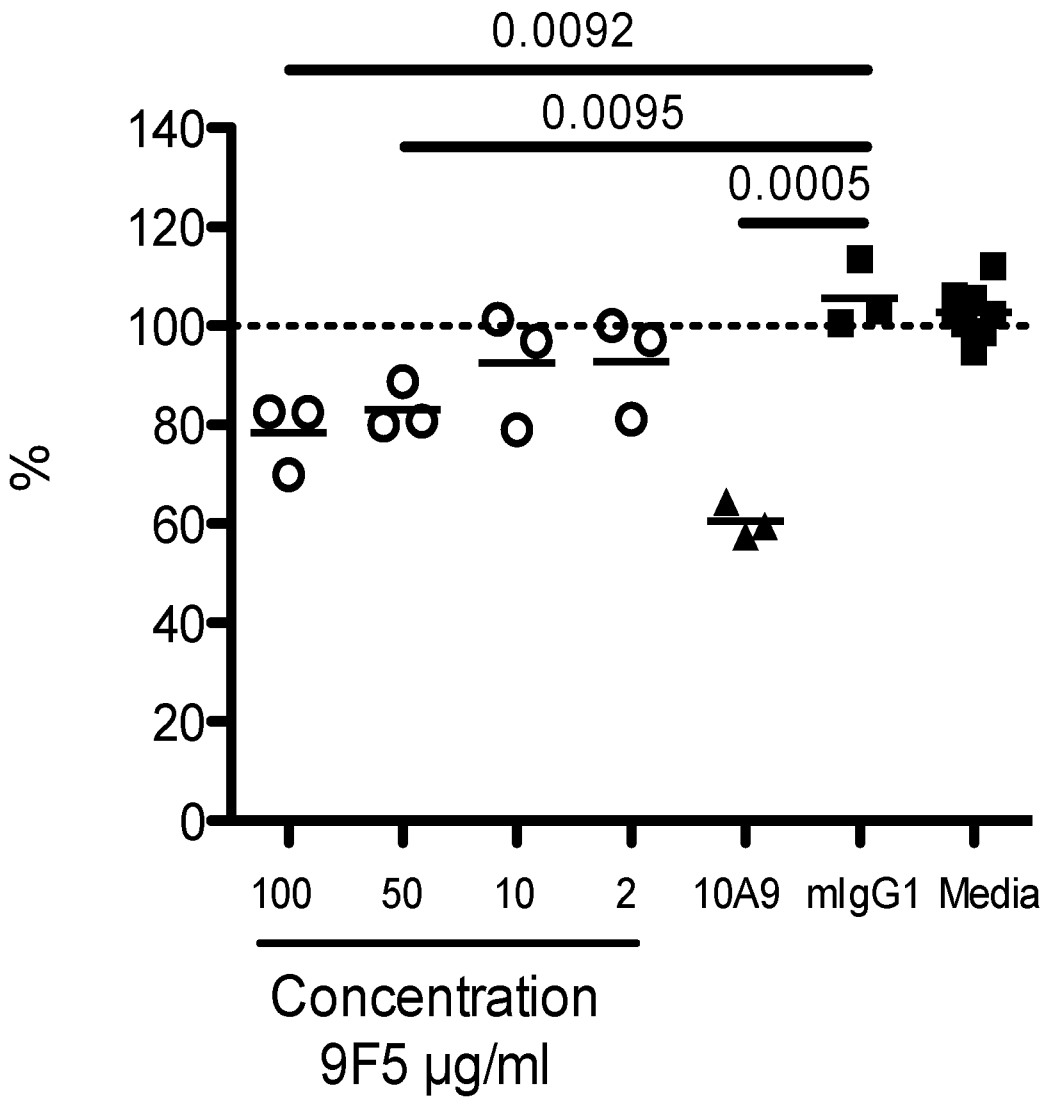

0.0092
0.0095
0.0005
140
120
100
80
60
40
20
0
%
100
50
10
2
10A9
mIgG1
Media
Concentration
9F5 µg/ml

FIG. 23

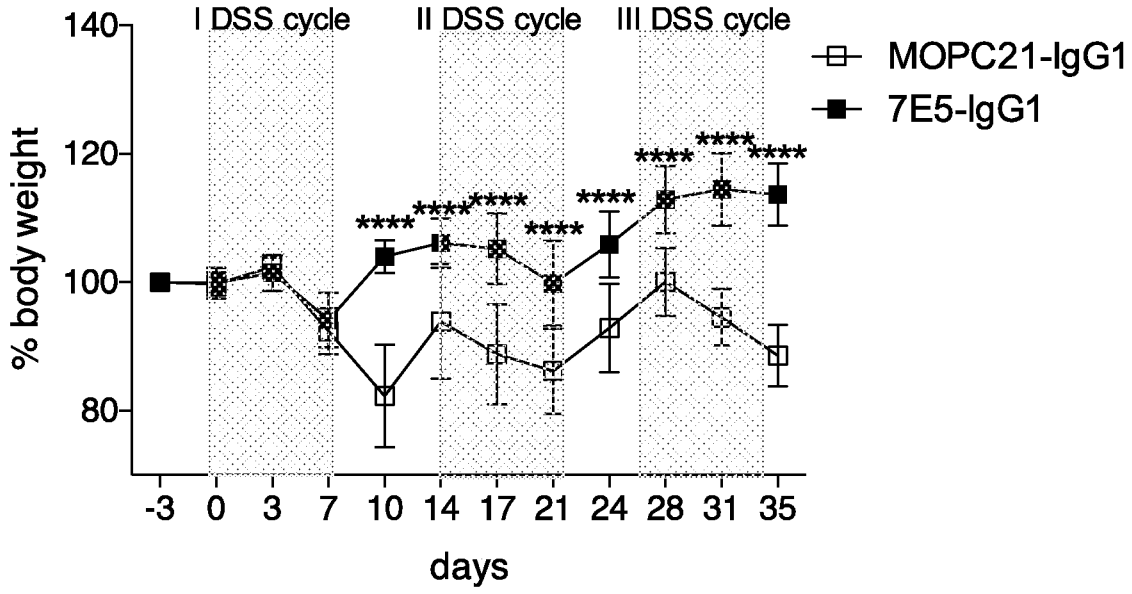


FIG. 24A

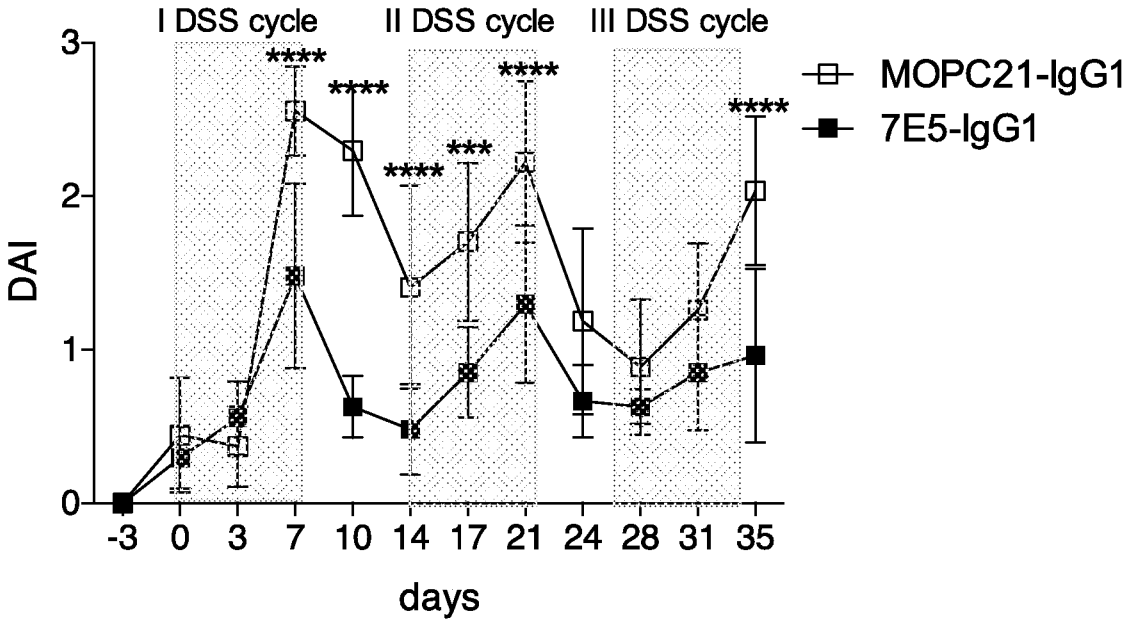


FIG. 24B

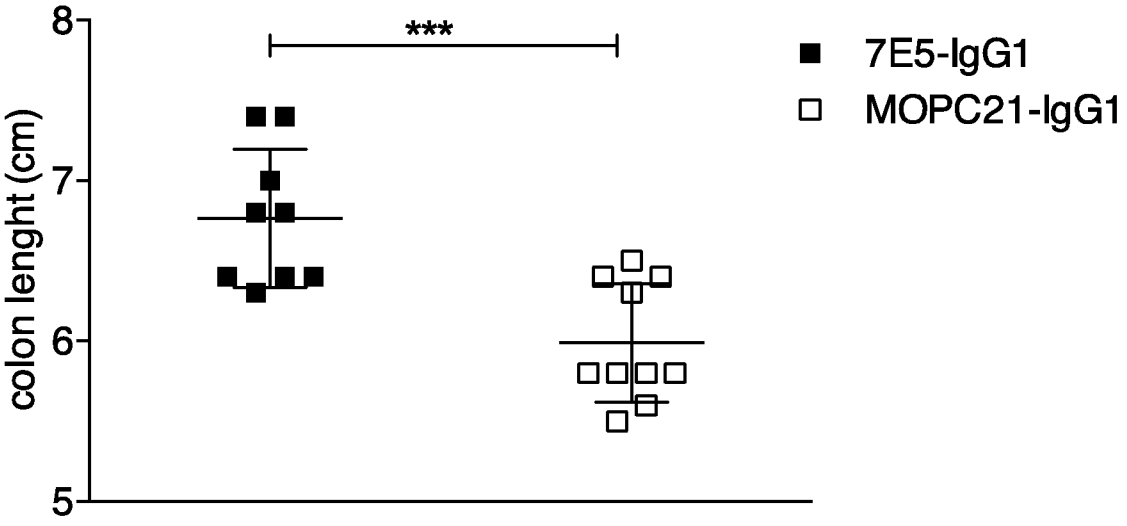


FIG. 24C

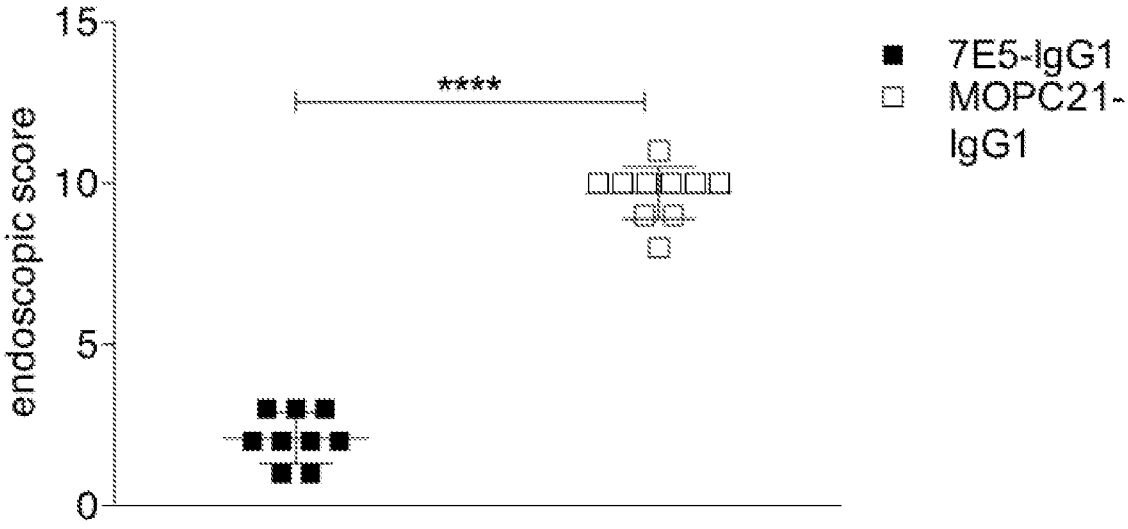


FIG. 24D

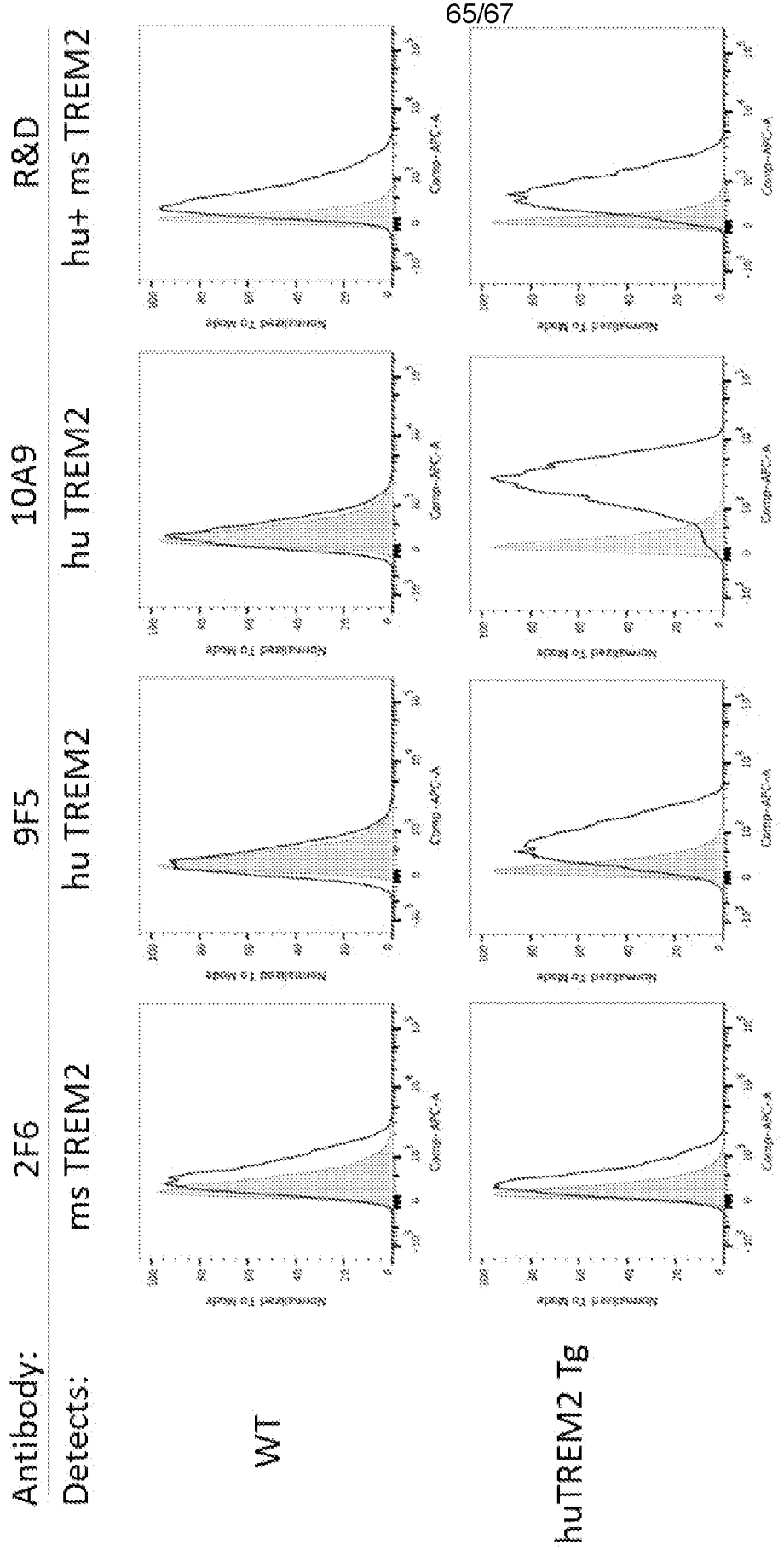

Antibody:
2F6
9F5
10A9
R&D
Detects:
ms TREM2
hu TREM2
hu TREM2
hu+ ms TREM2
WT
huTREM2 Tg

FIG. 25A

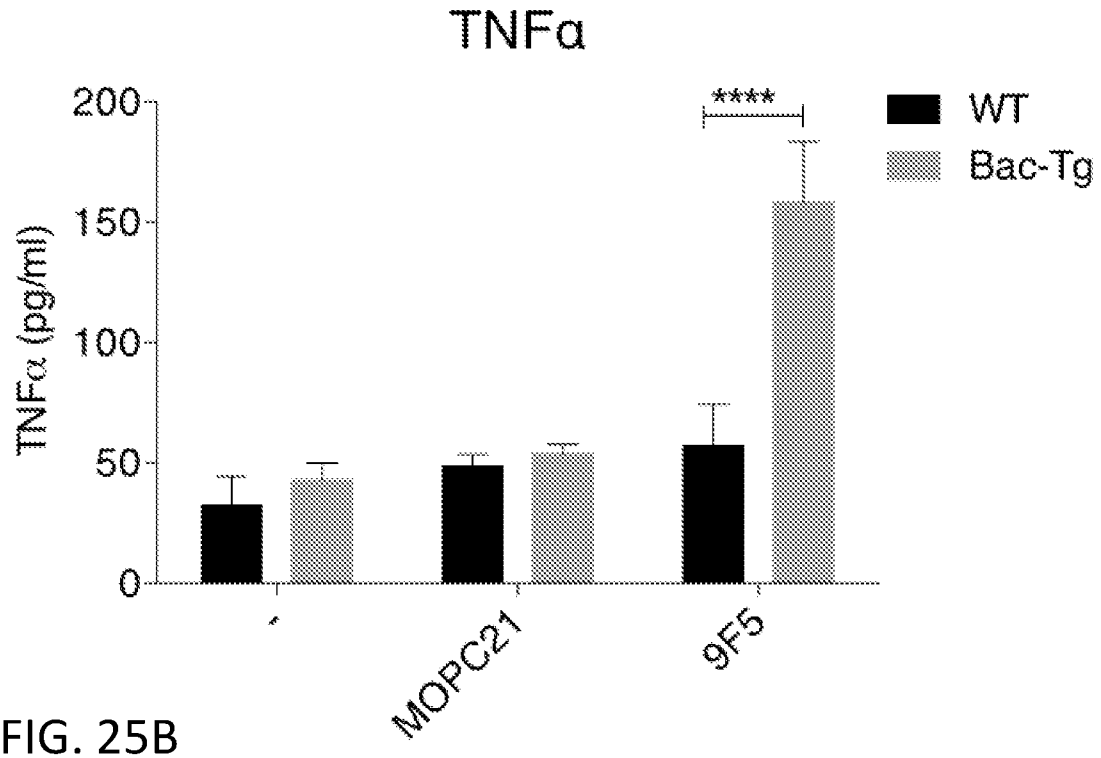


FIG. 25B

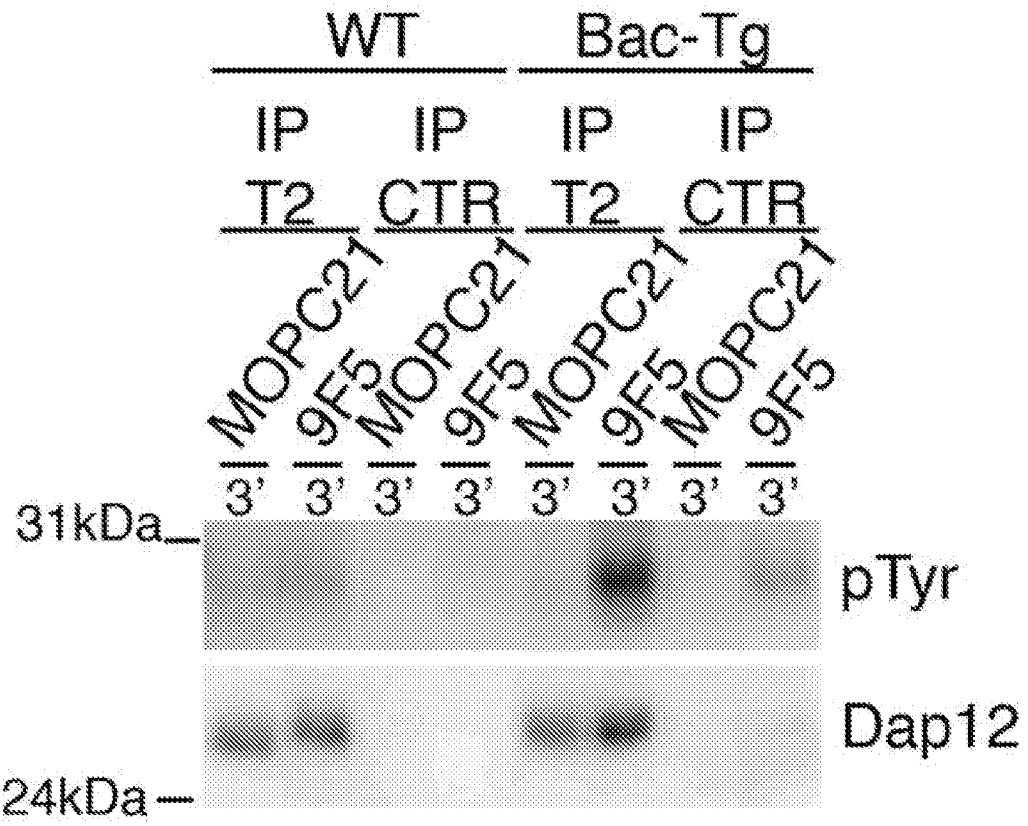


FIG. 25C

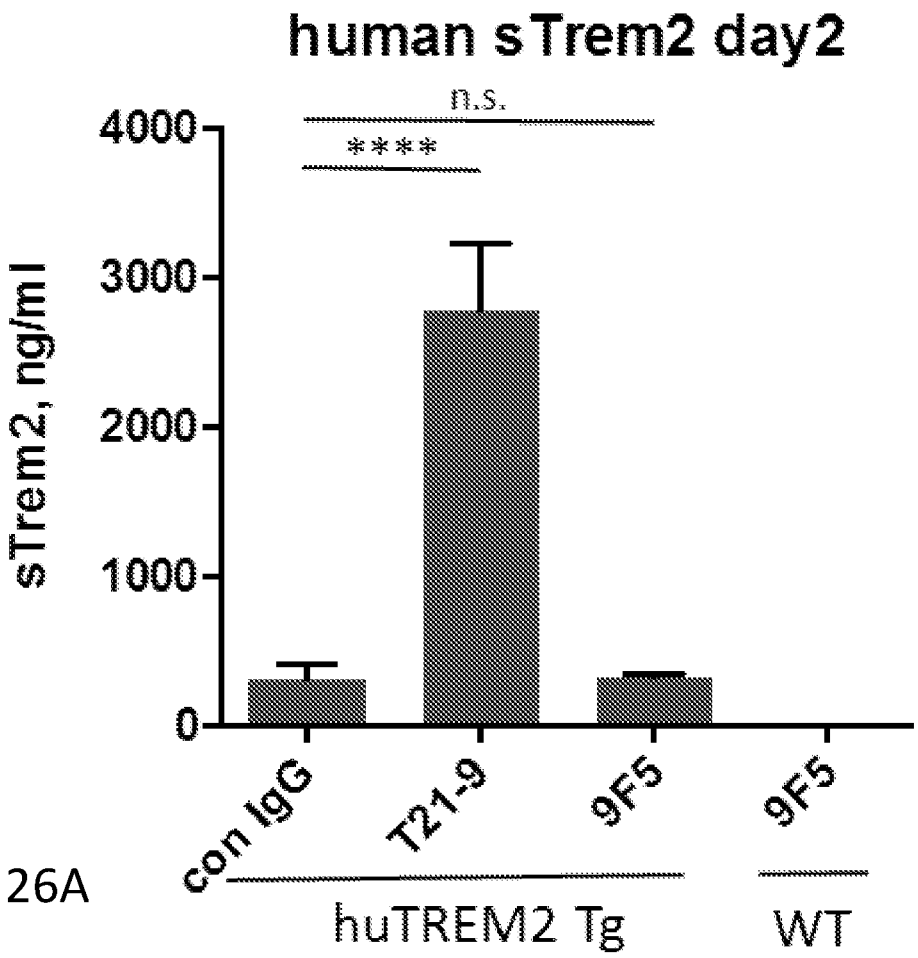


FIG. 26A

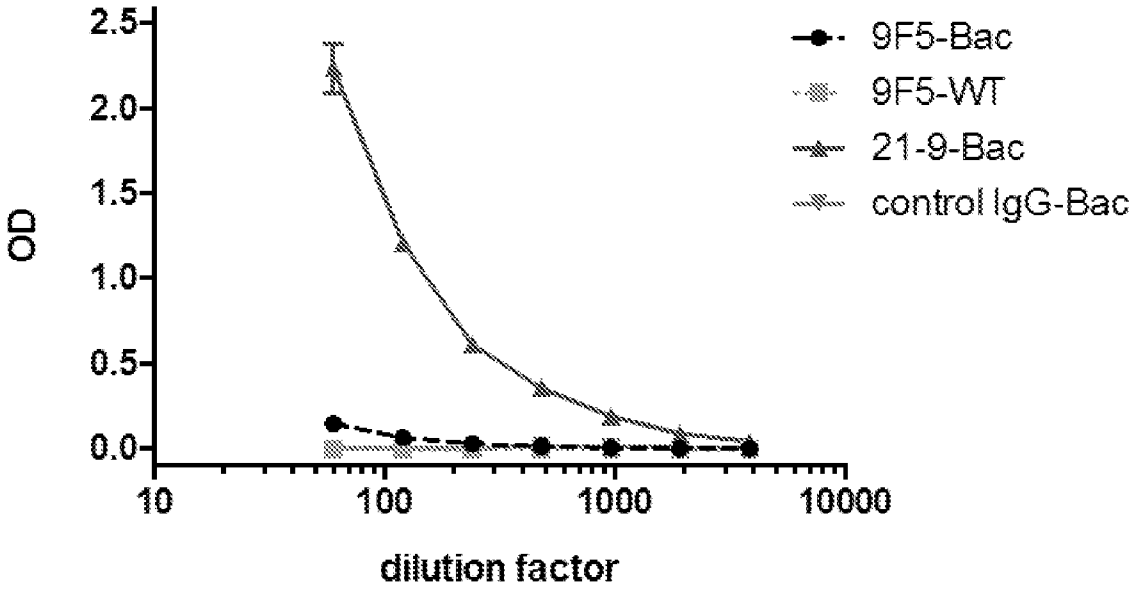


FIG. 26B