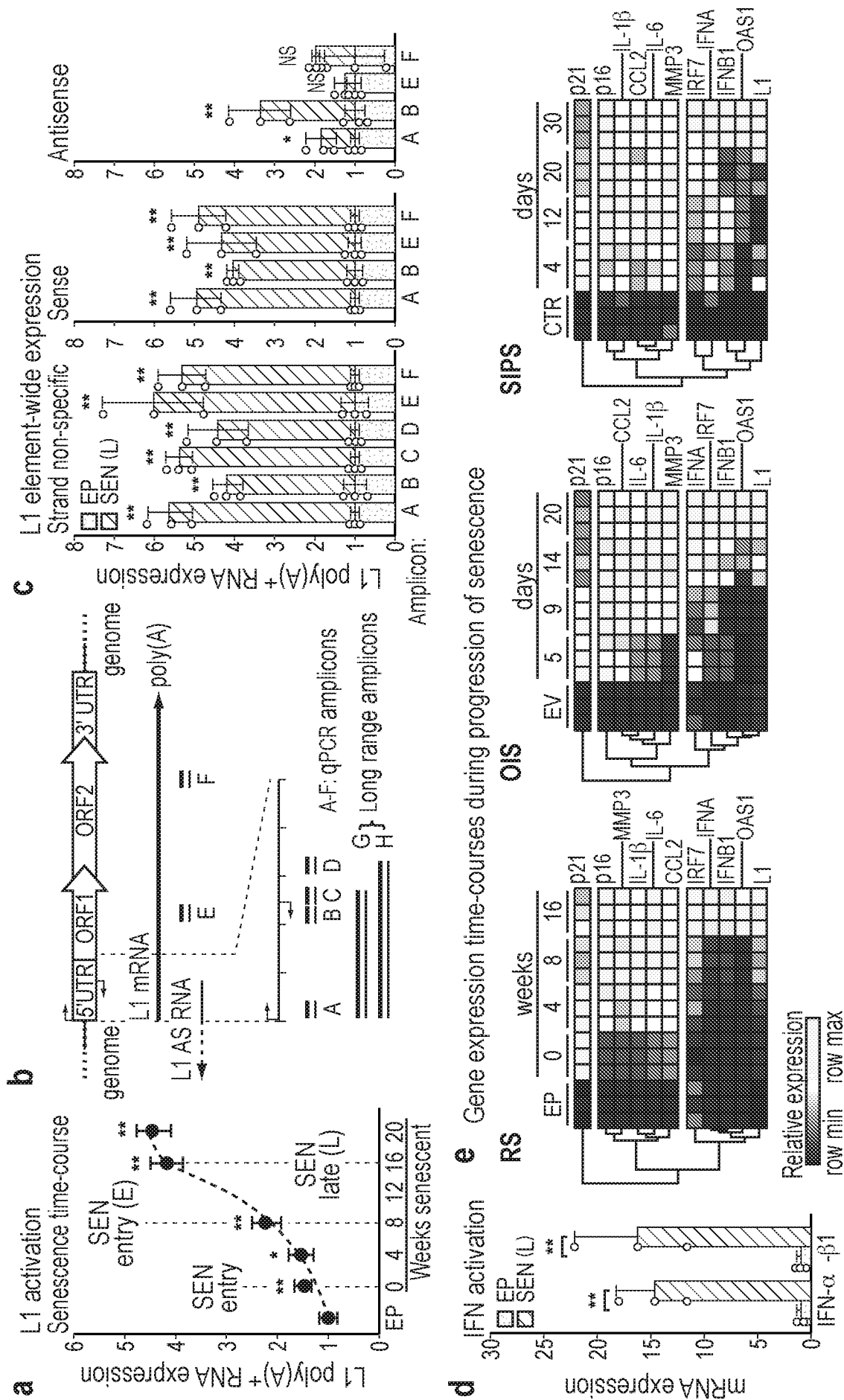






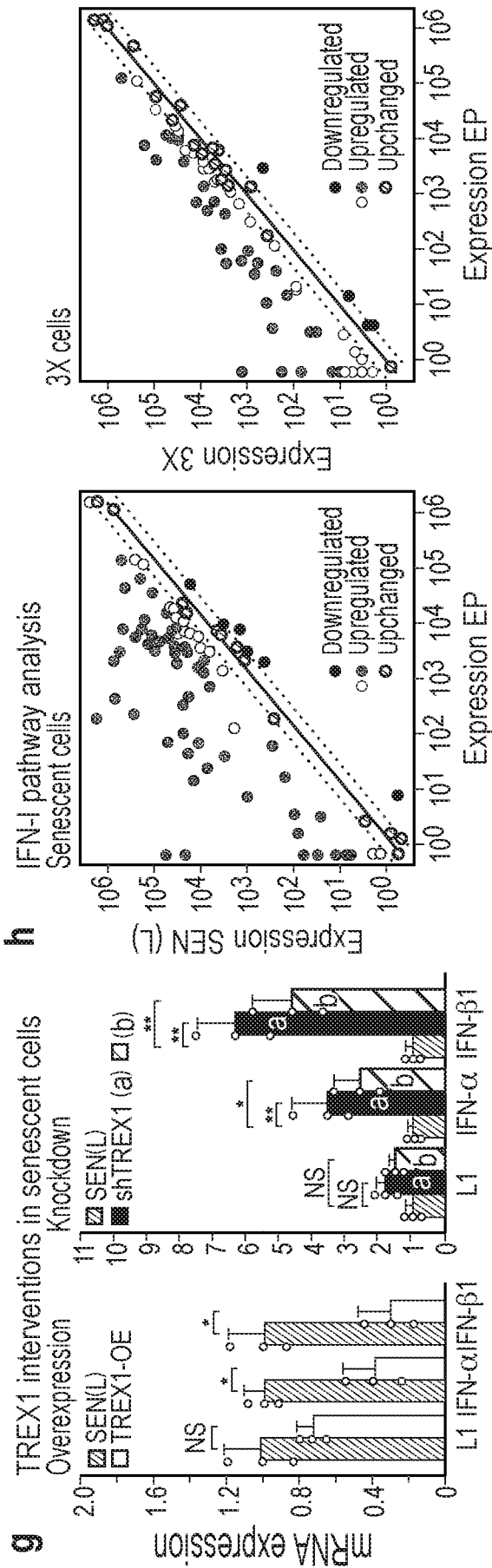


FIG. 2

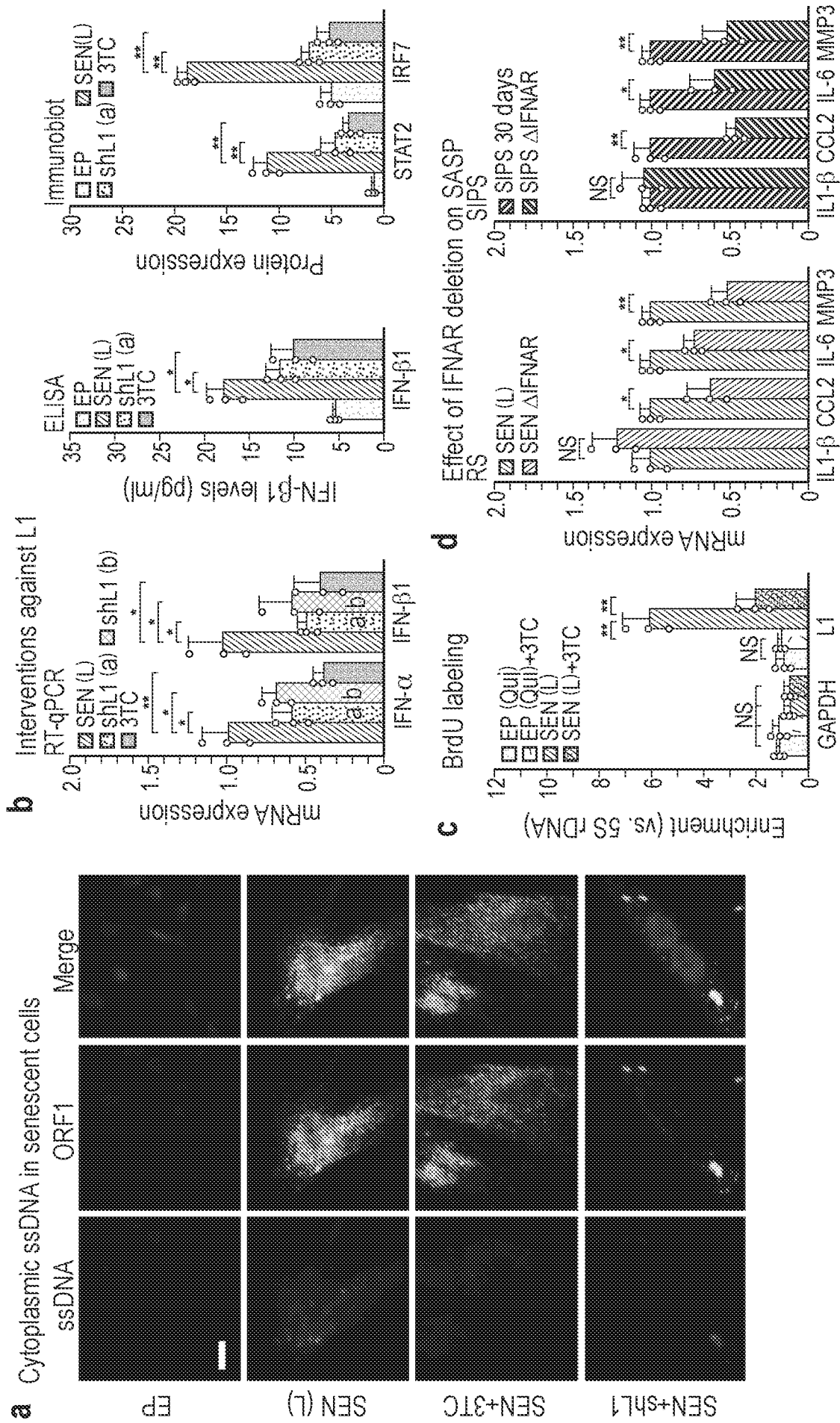
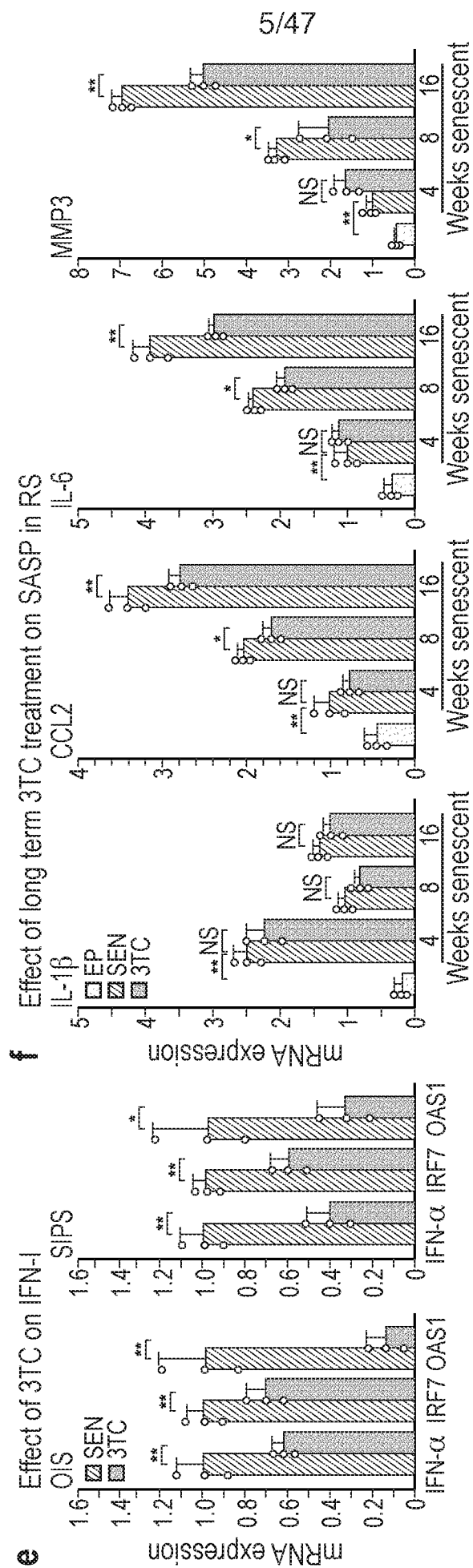
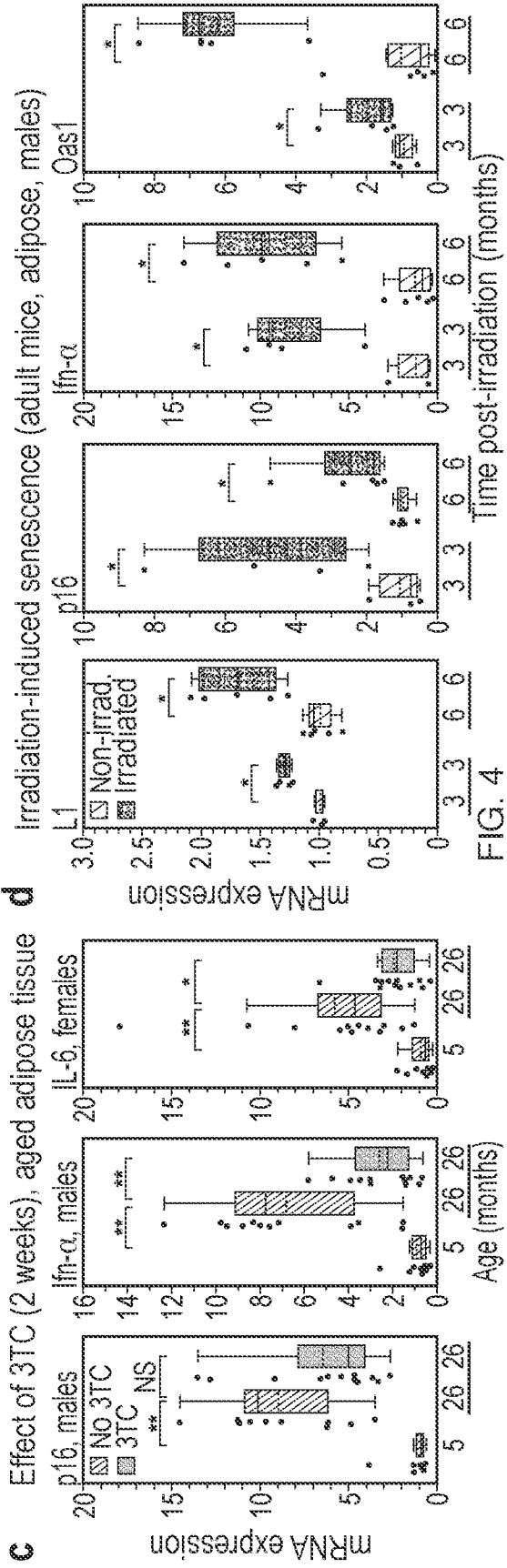
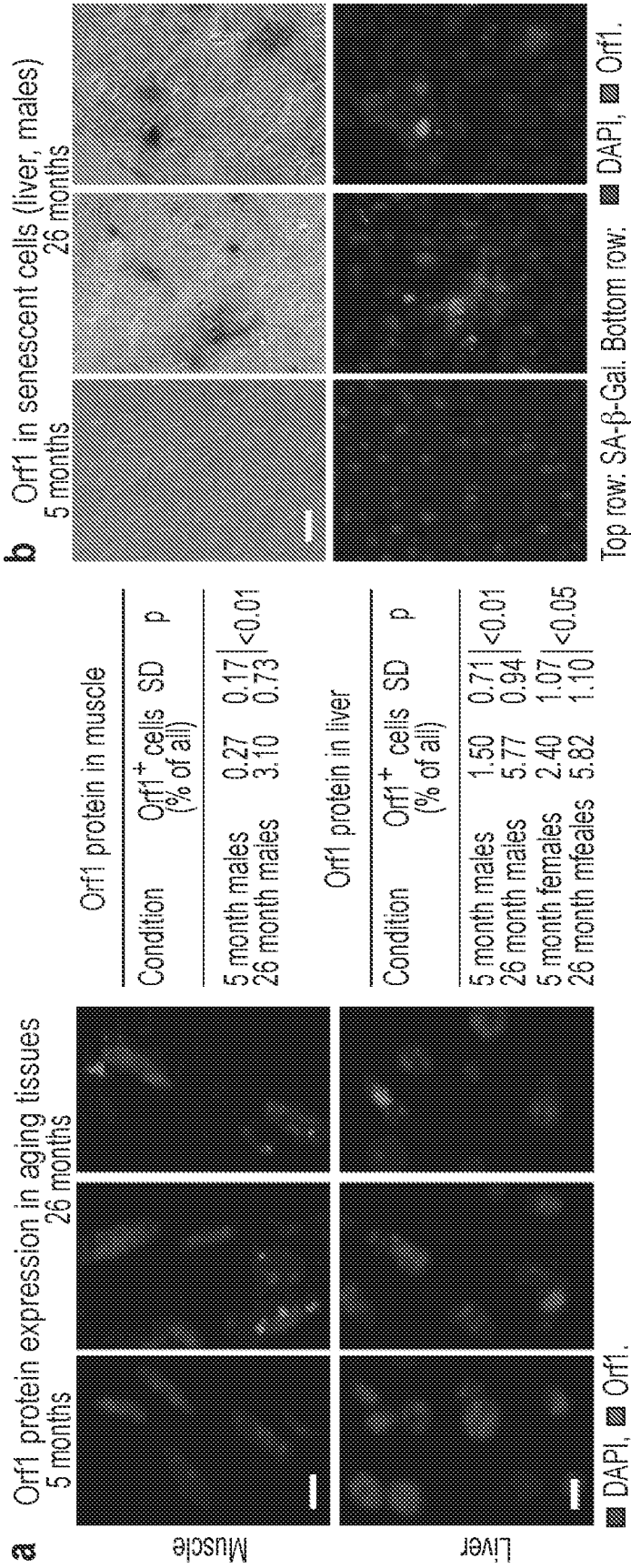


FIG. 3





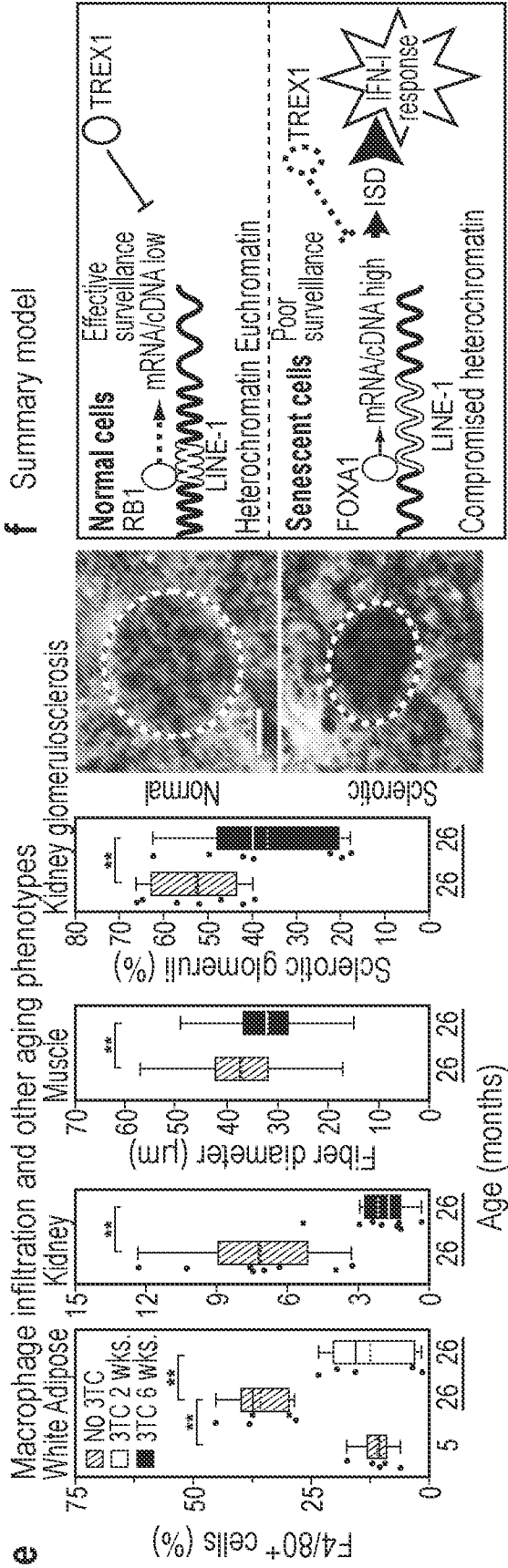


FIG. 4

ROLE OF CELLULAR SENESCENCE IN AGE-ASSOCIATED INFLAMMATION

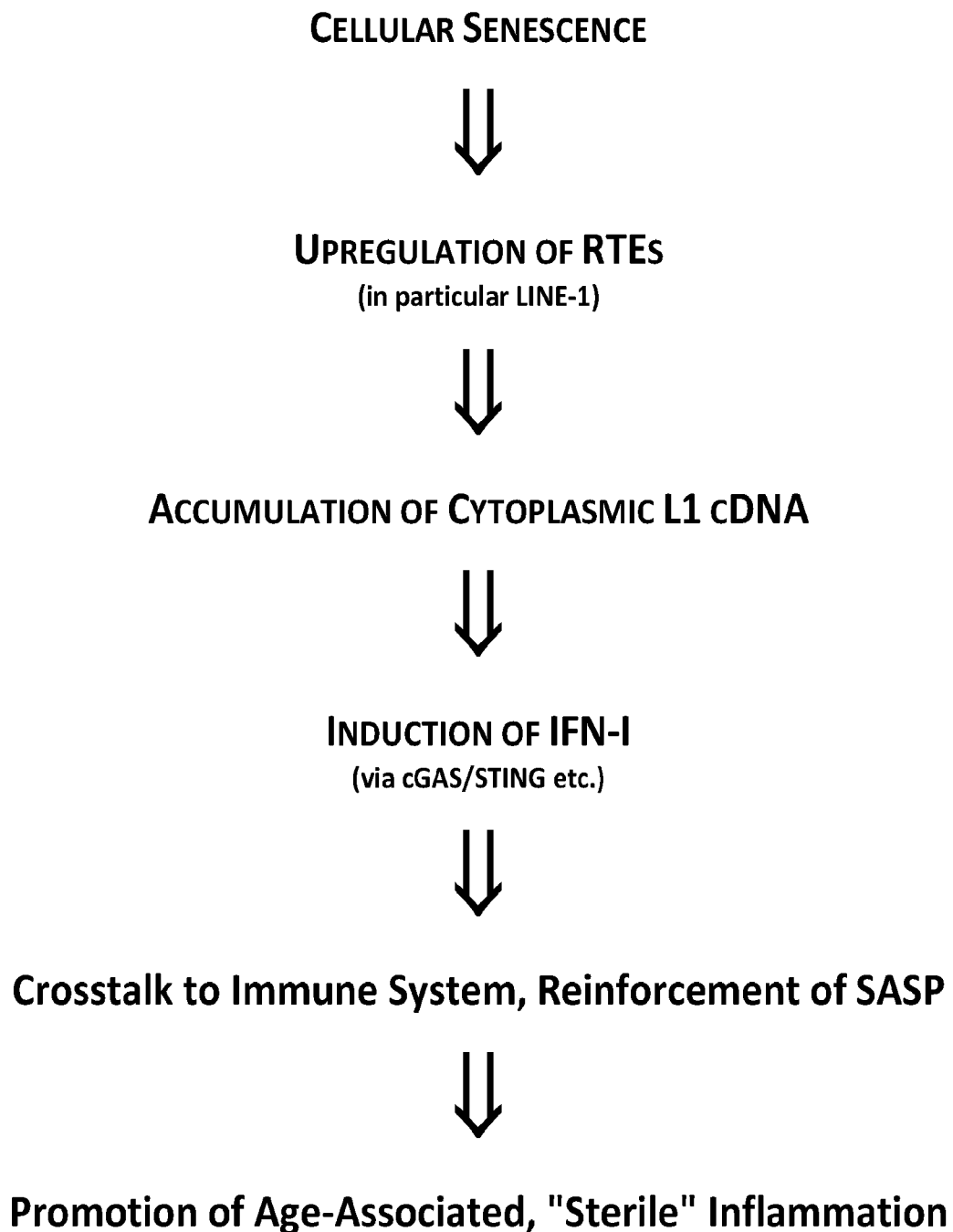


FIG. 5

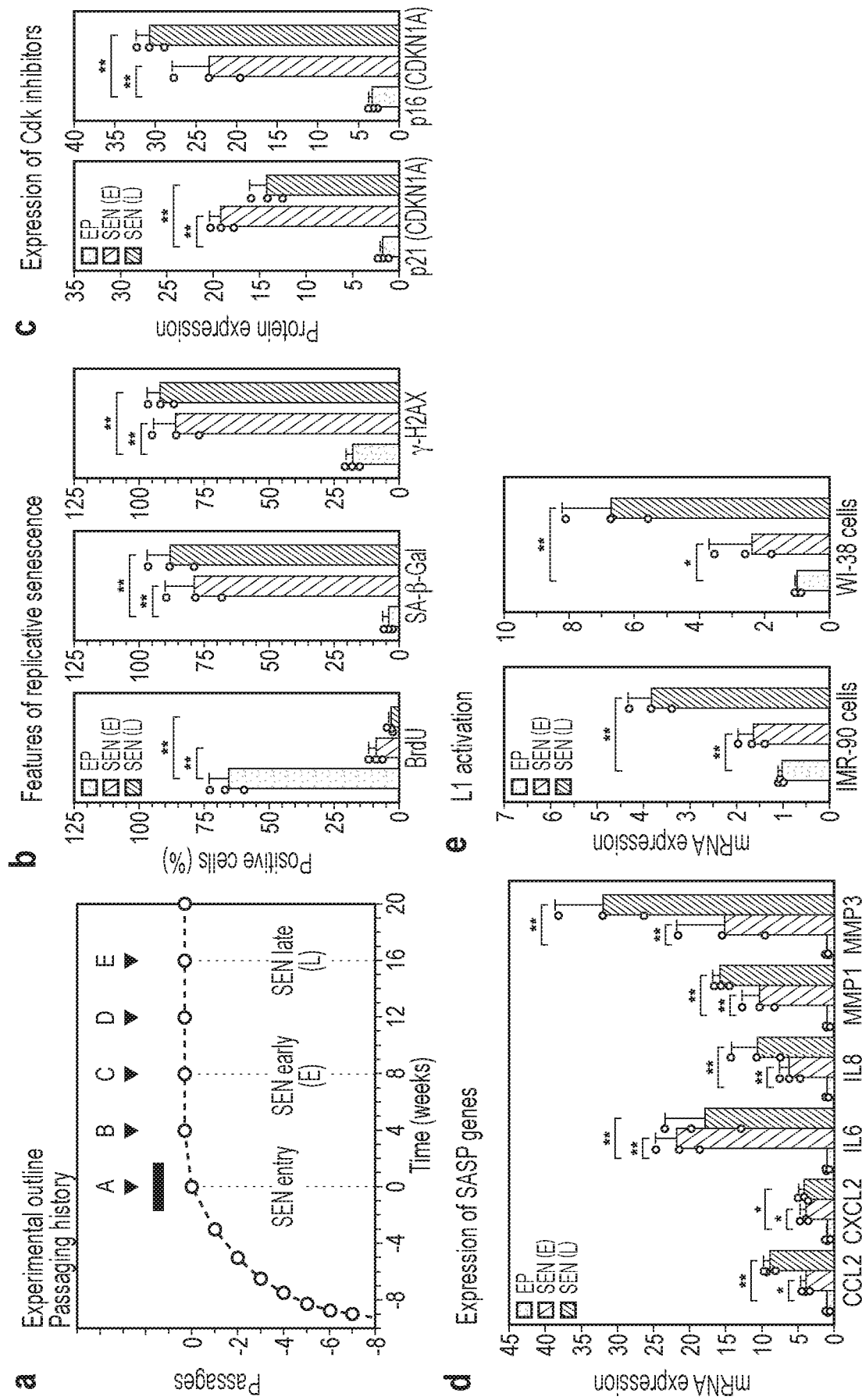


FIG. 6

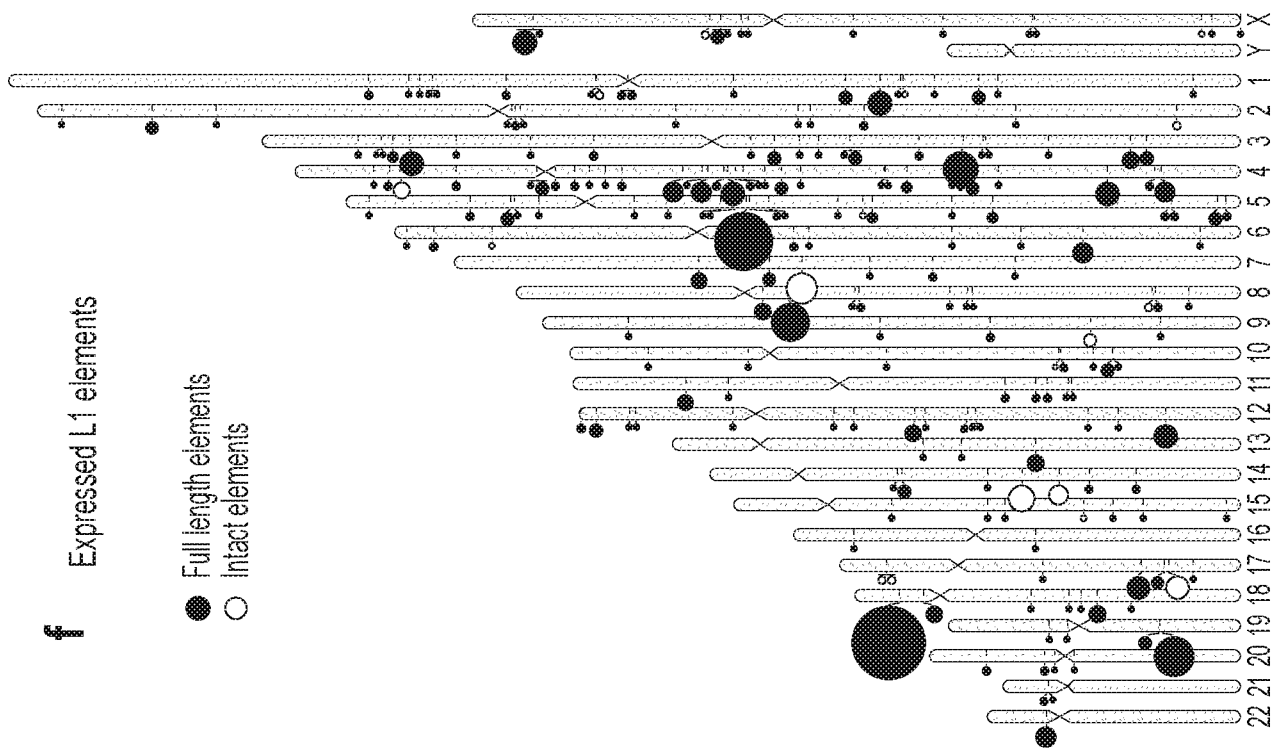
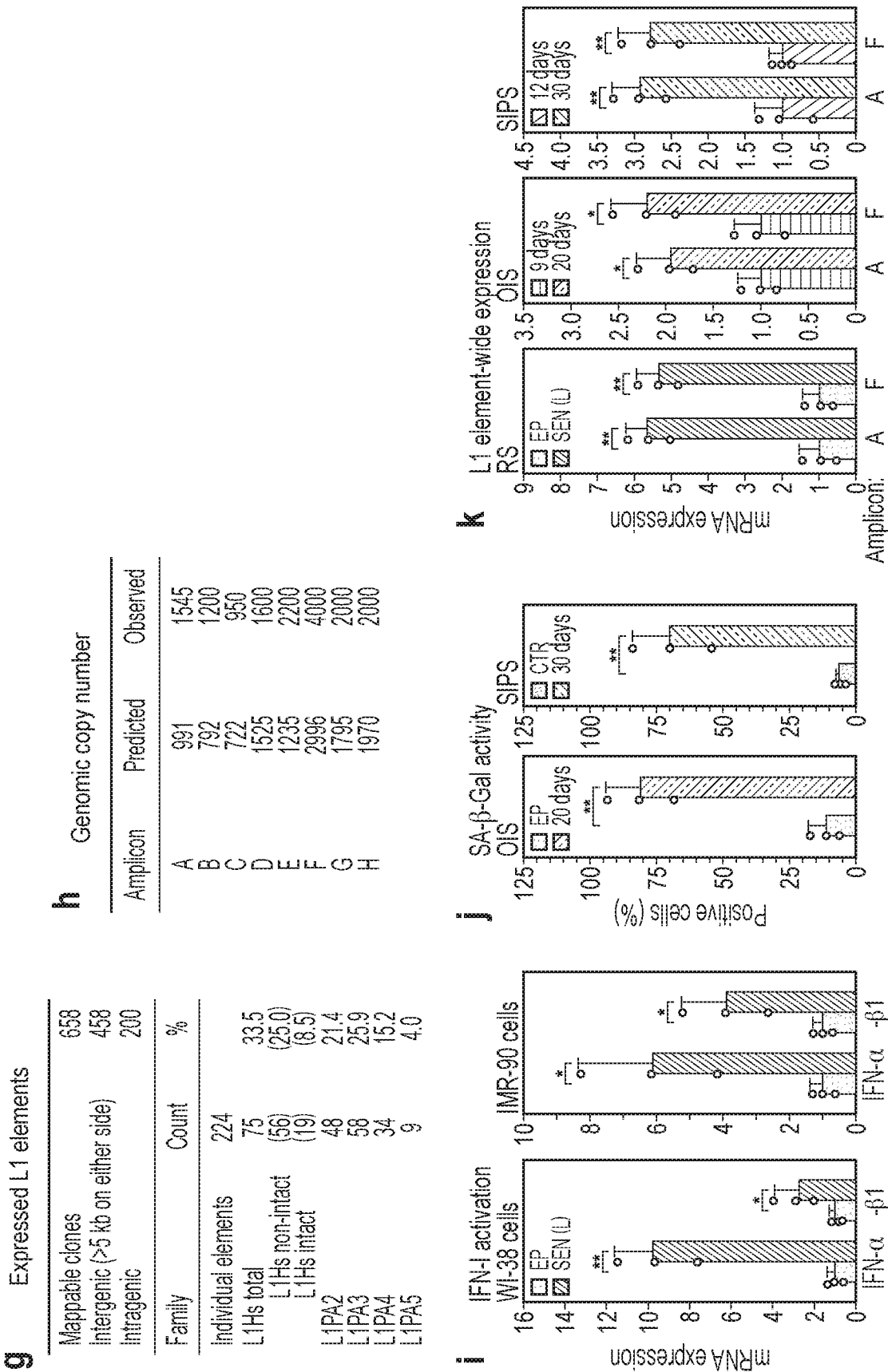


FIG. 6



a Sequence alignments of 5'RACE data

L1HS consensus start

-50 -40 -30 -20 -10 1 25 50 75 100

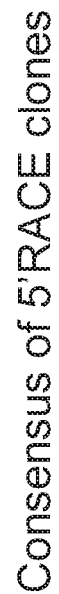
L1HS consensus

```
K01.IT.26N1-342 ..... ggacacaacccccacacgcggggagagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
G05.IT.26N1-179 ..... ggaggggggccacaaga tgg .. ccgaalaggccacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C01.IT.26N1-342 ..... ggagagcccg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
A01.IT.26N1-179 ..... agtagcgggcgcacagcgcac .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
M07.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C09.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
E01.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
A07.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
H01.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
E07.IT.26N1-179 ..... gtaa .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
M05.IT.26N1-342 ..... ggtaa .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
K01.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
K03.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
K07.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
I09.IT.26N1-342 ..... gtttctcaggagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
M09.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
A07.IT.26N1-342 ..... aaacgtgtaaaalaggagagagcc tggcagcagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
A09.IT.26N1-179 ..... ccaaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C03.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C05.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
E03.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
I07.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C01.IT.26N1-342 ..... tttlaagagagattt-ccagaalal taa .. aaalaa ggagagagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C05.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C03.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C07.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
M09.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
C03.IT.26N1-179 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
A05.IT.26N1-342 ..... ggagagagcacaaga tgg .. ccgaalagg .aacagctcc-ggctacagc tcccagag tggagcagcagaagagg gattcttgcga-ttccalc tggagttacc
```

FIG. 7

[illegible]

7
G
L

7
E
G

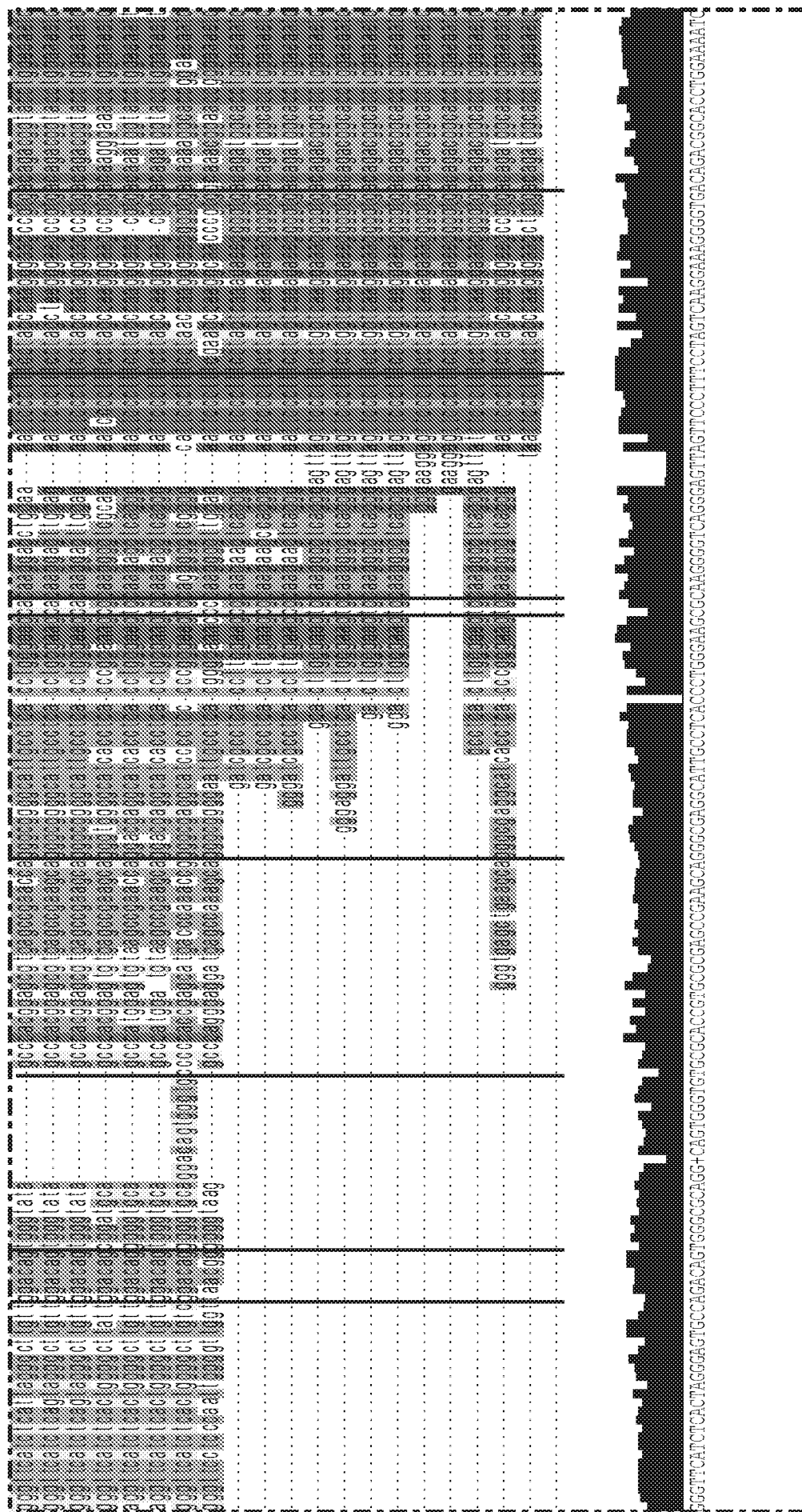
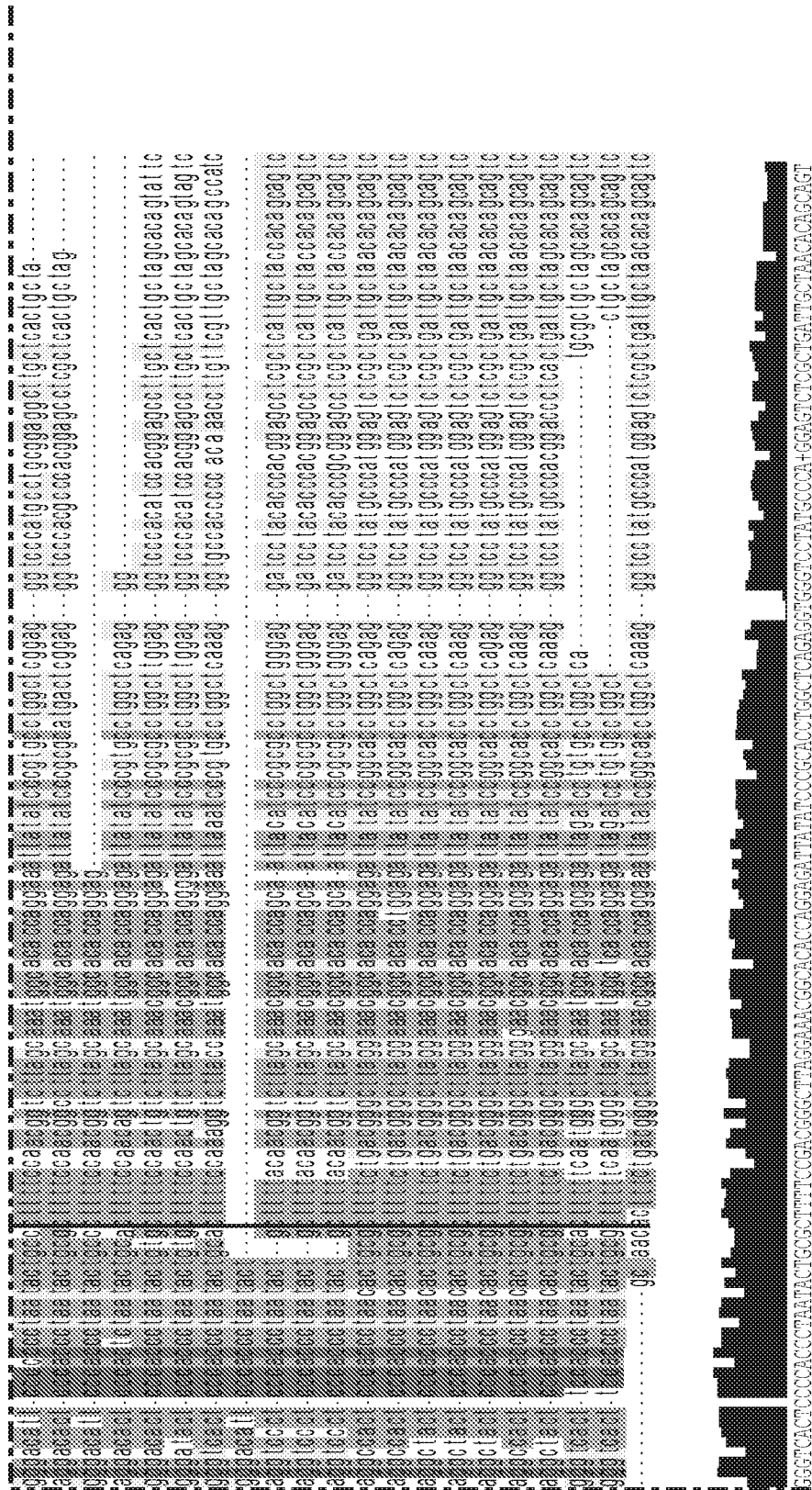


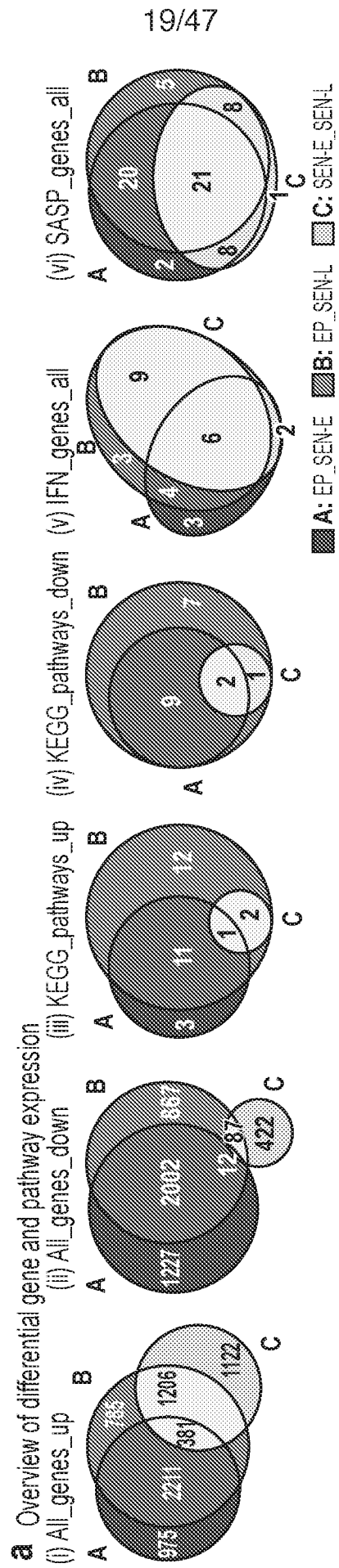
FIG. 7



b

Summary of 5'RACE data		
Sequenced clones		50
Start: < -40 bp		4
-25 bp to +25 bp		28
+25 bp to +180 bp		6
> +180 bp		12
Family	Count	%
L1HS	8	16
L1PA2	9	18
L1PA3	11	22
L1PA4	7	14
L1PA5	8	18
L1PA7	2	4
L1P1	5	10

FIG. 7



19/47

FIG. 8

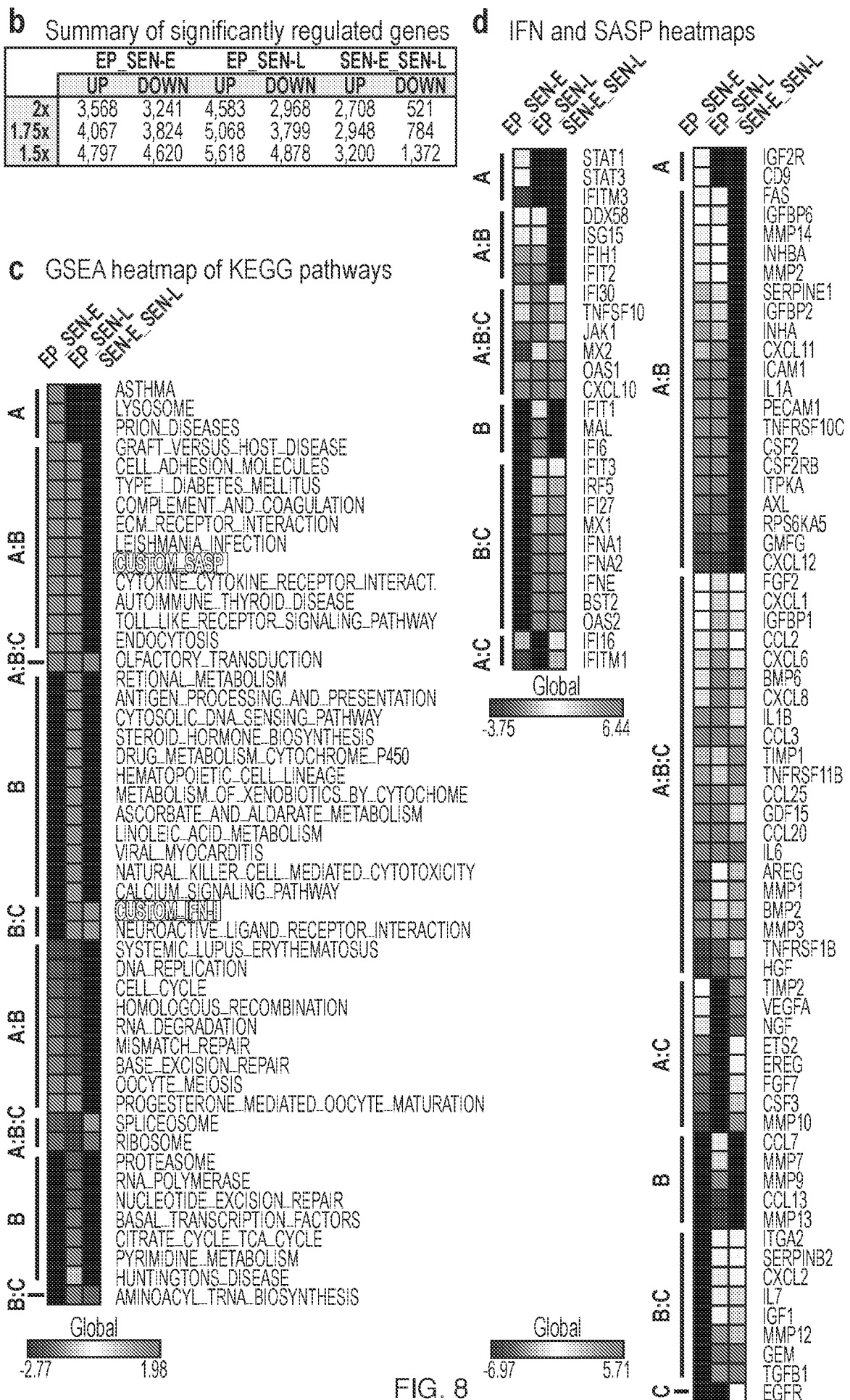


FIG. 8

e GSEA analysis of all KEGG pathways

Upregulated from early passage to early senescence (EP_SEN-E_UP)

Pathway name	Size	NES	NOM p-val	FDR p-val
ASTHMA	28	1.7864	<1.00E-03	<1.00E-02
GRAFT VERSUS HOST DISEASE	35	1.7654	<1.00E-03	<1.00E-02
CELL ADHESION MOLECULES CAMS	127	1.7538	<1.00E-03	<1.00E-02
OLFACTORY TRANSDUCTION	367	1.7468	<1.00E-03	<1.00E-02
TYPE I DIABETES MELLITUS	41	1.7140	<1.00E-03	<1.00E-02
LYSOSOME	119	1.6878	<1.00E-03	<1.00E-02
COMPLEMENT AND COAG. CASCADES	67	1.6854	<1.00E-03	<1.00E-02
ECM RECEPTOR INTERACTION	84	1.5487	<1.00E-03	<1.00E-02
LEISHMANIA INFECTION	68	1.6559	1.79E-03	<1.51E-02
CUSTOM SASP	85	1.6517	1.80E-03	<1.51E-02
PRION DISEASES	34	1.6397	1.84E-03	<1.51E-02
CYTOKINE CYTOKINE RECEPTOR INTERACT.	254	1.5705	1.62E-03	<1.51E-02
TOLL LIKE RECEPTOR SIGNALING PATHWAY	99	1.4920	1.73E-03	<1.51E-02
AUTOIMMUNE THYROID DISEASE	48	1.5336	3.77E-03	<2.66E-02
ENDOCYTOSIS	174	1.4427	5.21E-03	<3.49E-02

Upregulated from early passage to late senescence (EP_SEN-L_UP)

Pathway name	Size	NES	NOM p-val	FDR p-val
OLFACTORY TRANSDUCTION	367	1.9816	<1.00E-03	<5.00E-03
TYPE I DIABETES MELLITUS	41	1.7551	<1.00E-03	<5.00E-03
GRAFT VERSUS HOST DISEASE	35	1.7098	<1.00E-03	<5.00E-03
CELL ADHESION MOLECULES CAMS	127	1.6868	<1.00E-03	<5.00E-03
RETINOL METABOLISM	56	1.6689	<1.00E-03	<5.00E-03
CUSTOM SASP	85	1.6282	<1.00E-03	<5.00E-03
LEISHMANIA INFECTION	68	1.6260	<1.00E-03	<5.00E-03
CUSTOM IFN- γ	50	1.6248	<1.00E-03	<5.00E-03
COMPLEMENT AND COAG. CASCADES	67	1.6008	<1.00E-03	<5.00E-03
TOLL LIKE RECEPTOR SIGNALING PATHWAY	99	1.5759	<1.00E-03	<5.00E-03
NEUROACTIVE LIGAND RECEPTOR INTERACT.	270	1.5340	<1.00E-03	<5.00E-03
CYTOKINE CYTOKINE RECEPTOR INTERACT.	254	1.5008	<1.00E-03	<5.00E-03
HEMATOPOIETIC CELL LINEAGE	85	1.5269	1.07E-03	5.32E-03
DRUG METABOLISM CYTOCHROME P450	63	1.5343	1.12E-03	5.32E-03
ANTIGEN PROCESSING AND PRESENTATION	73	1.6286	1.08E-03	5.32E-03
XENOBIOTIC METAB. BY CYTOCHROME P450	62	1.5245	3.36E-03	1.51E-02
CYTOSOLIC DNA SENSING PATHWAY	52	1.5816	3.42E-03	1.51E-02
VIRAL MYOCARDITIS	68	1.4405	4.39E-03	1.96E-02
ASCORBATE AND ALDARATE METABOLISM	21	1.5205	6.20E-03	2.86E-02
NATURAL KILLER CELL MEDIATED CYTOTOX.	123	1.3730	7.22E-03	3.25E-02
STEROID HORMONE BIOSYNTHESIS	49	1.5533	7.94E-03	3.62E-02
CALCIUM SIGNALING PATHWAY	173	1.3406	9.14E-03	3.97E-02
LINOLEIC ACID METABOLISM	29	1.4904	1.00E-02	4.21E-02
AUTOIMMUNE THYROID DISEASE	48	1.5072	1.04E-02	4.21E-02
ECM RECEPTOR INTERACTION	84	1.4313	1.09E-02	4.53E-02

Upregulated from early senescence to late senescence (SEN-E_SEN-L_UP)

Pathway name	Size	NES	NOM p-val	FDR p-val
OLFACTORY TRANSDUCTION	367	1.6009	<1.00E-03	<5.00E-02
CUSTOM IFN- γ	50	1.4722	<1.00E-03	<5.00E-02
NEUROACTIVE LIGAND RECEPTOR INTERACT.	270	1.3253	<1.00E-03	<5.00E-02

FIG. 8

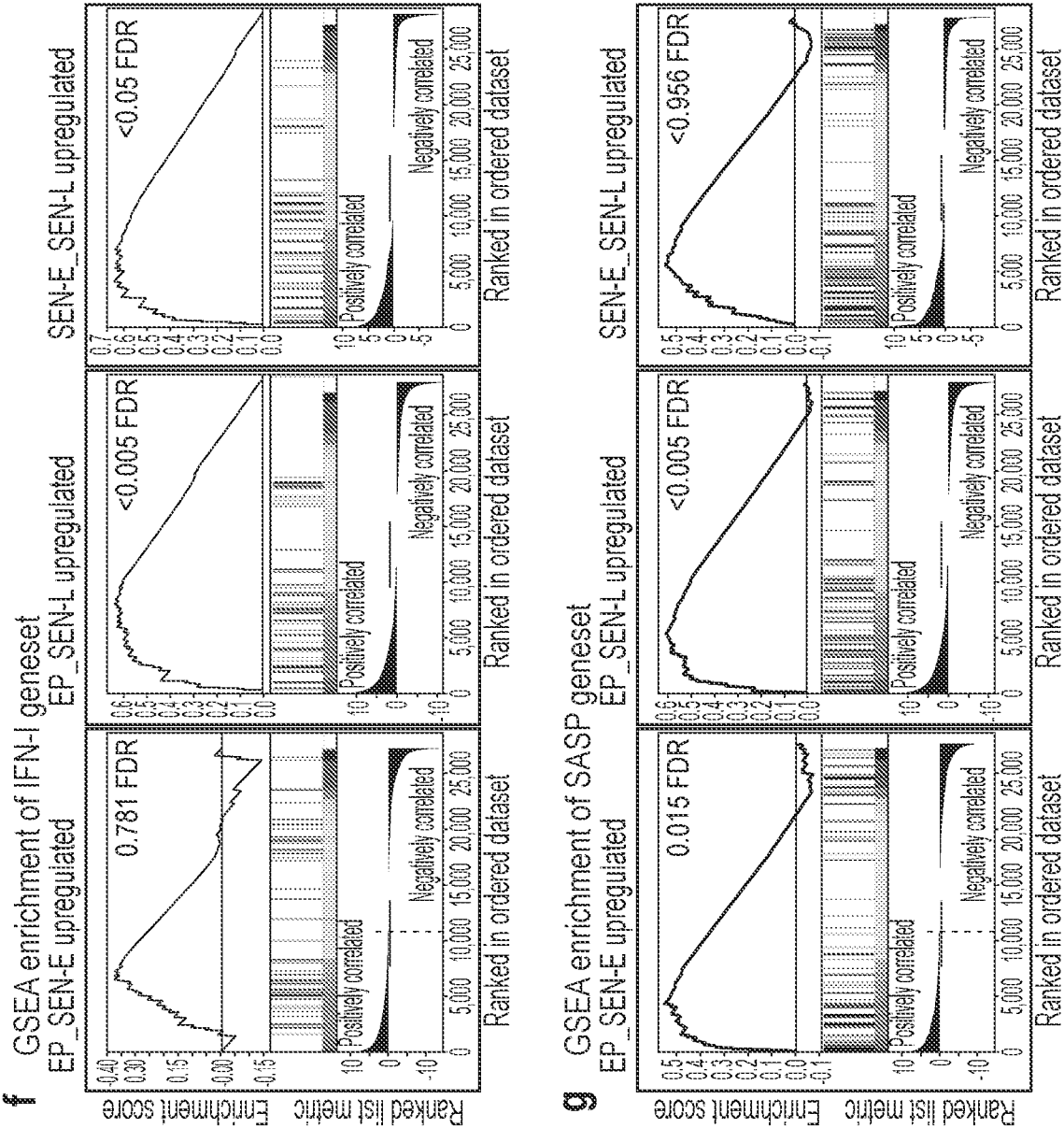


FIG. 8



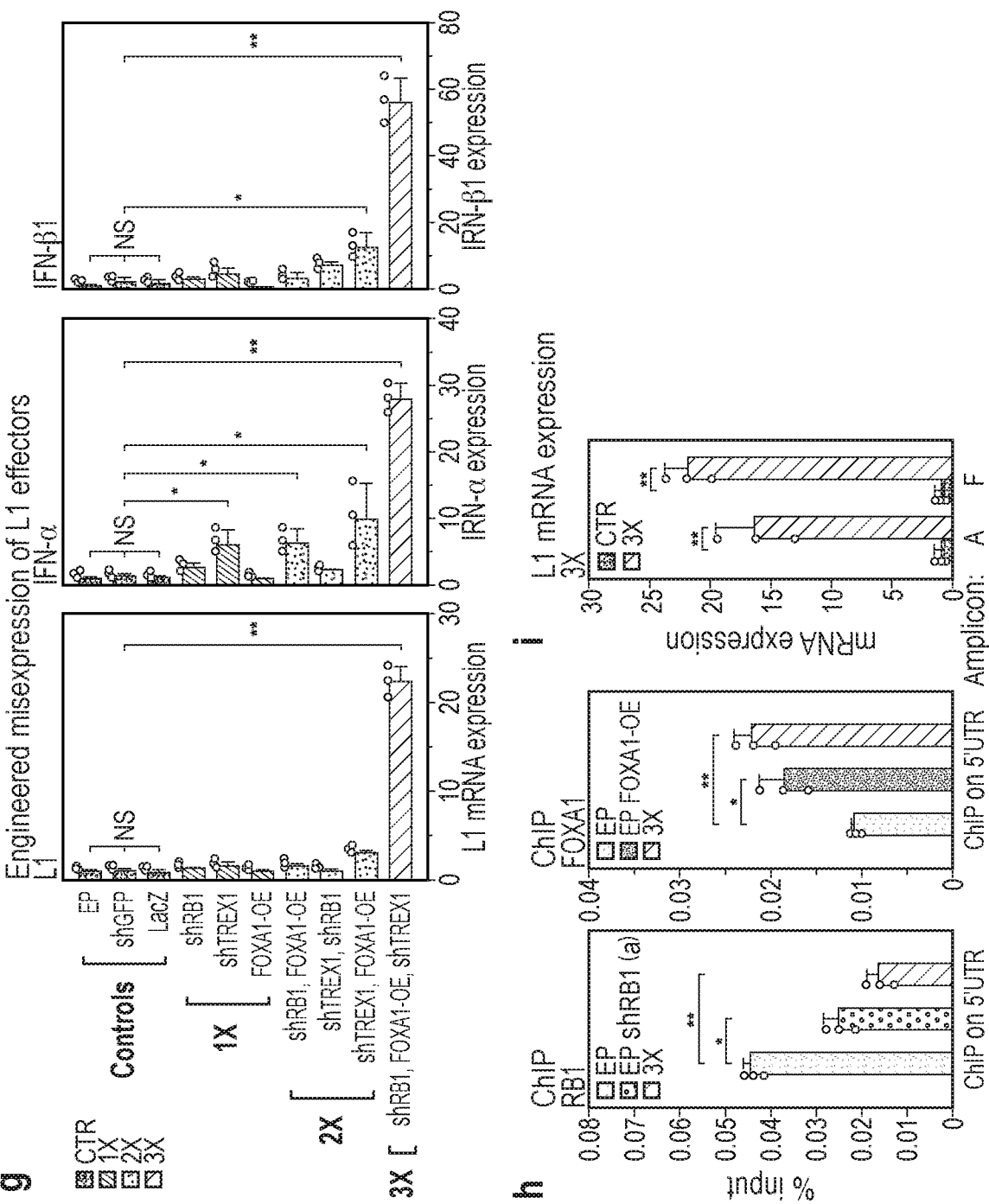


FIG. 9

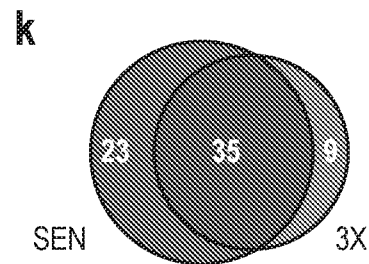
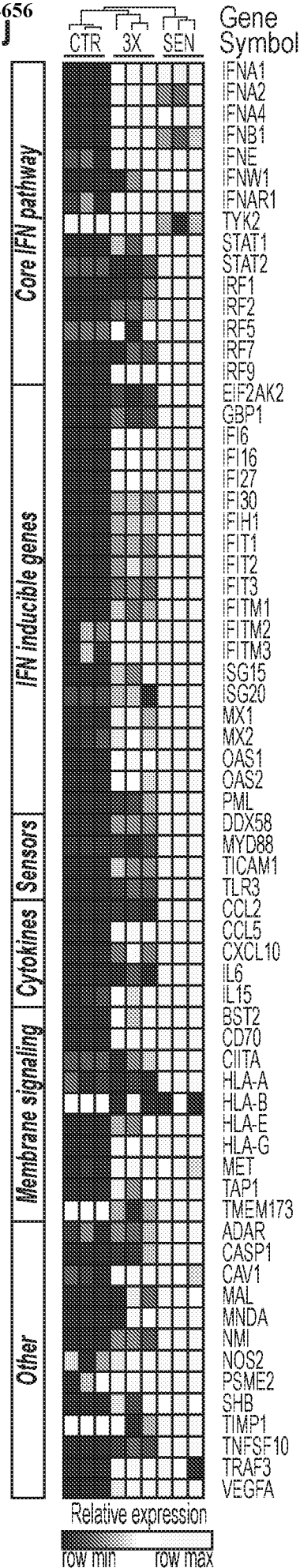


FIG. 9

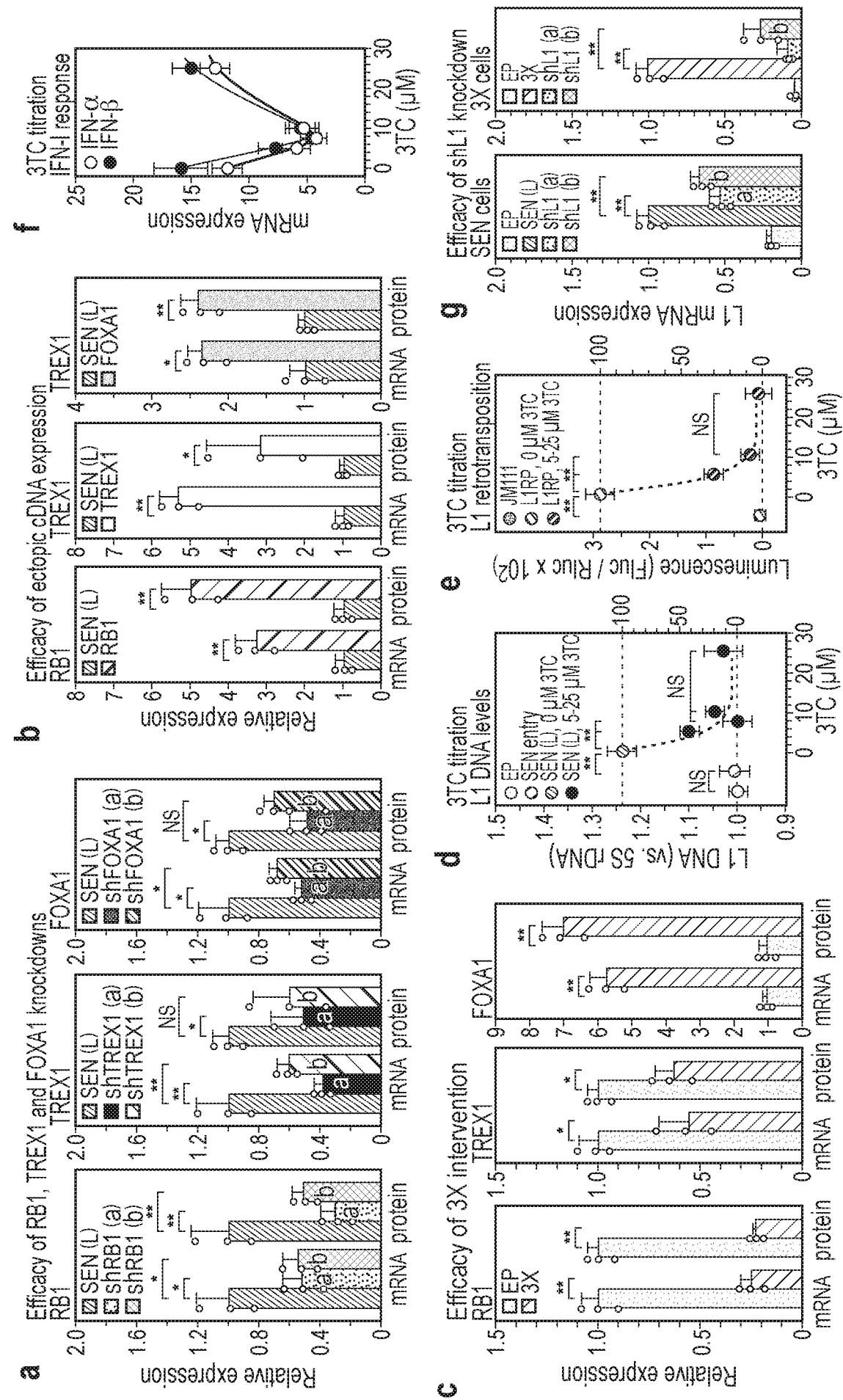
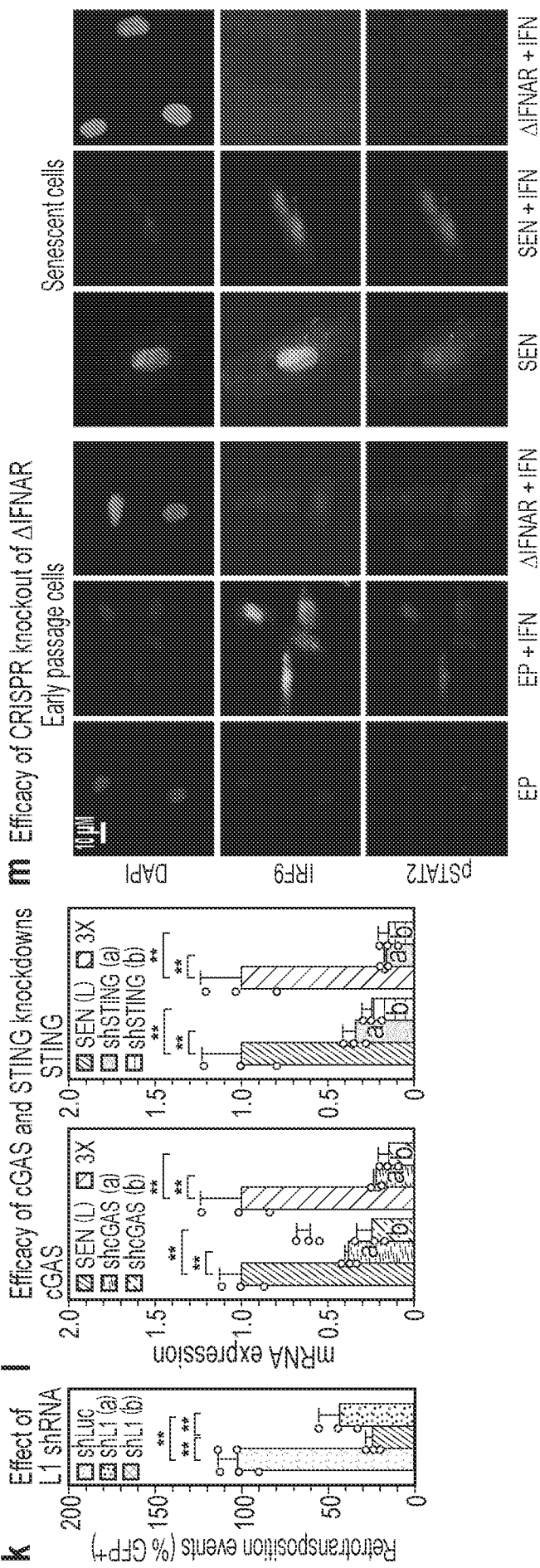
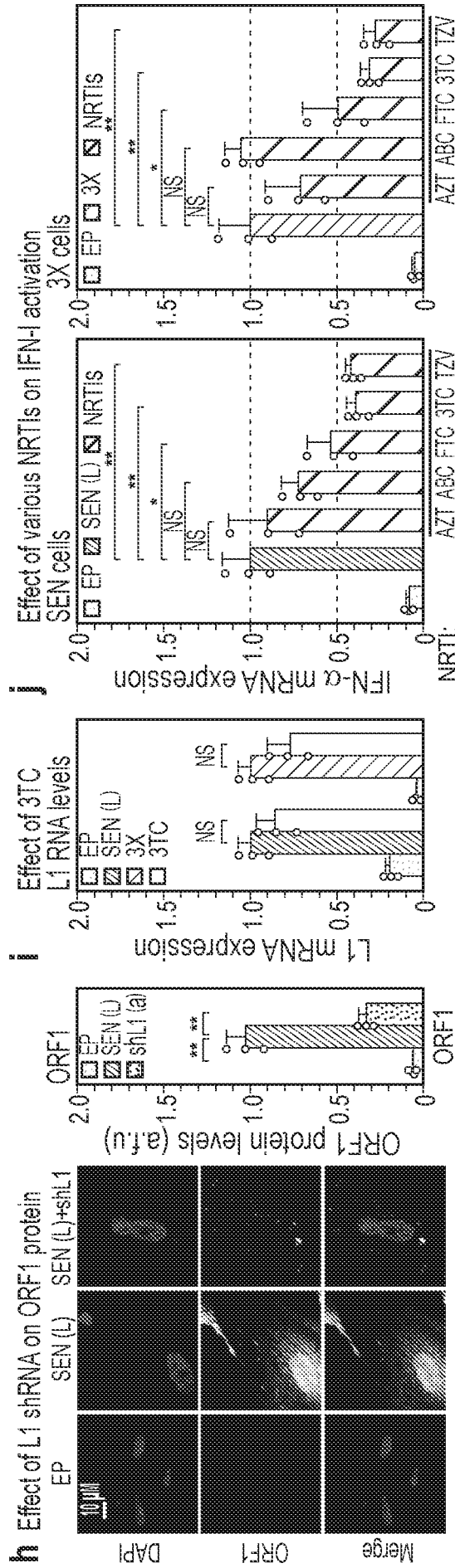


FIG. 10



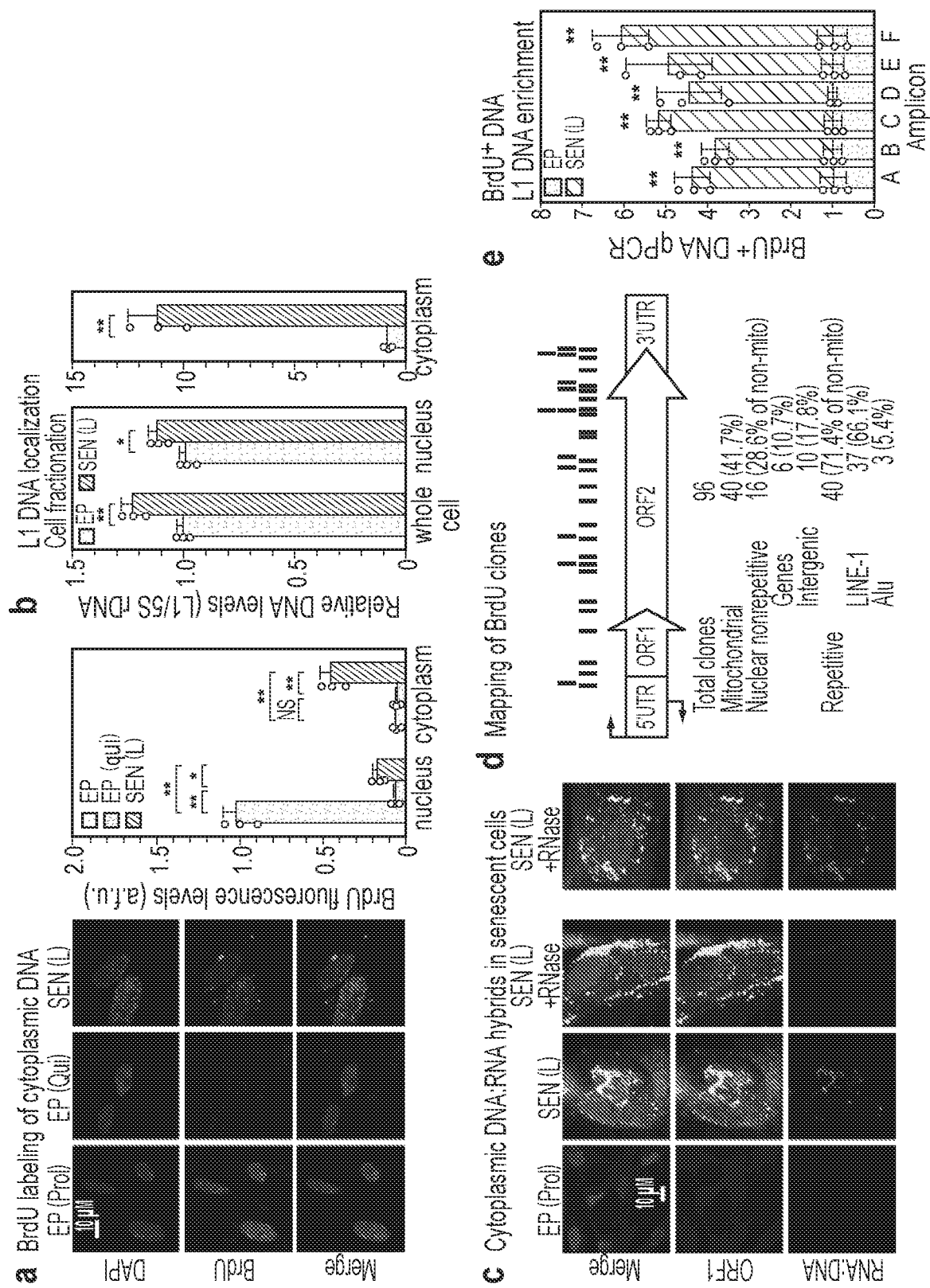


FIG. 11

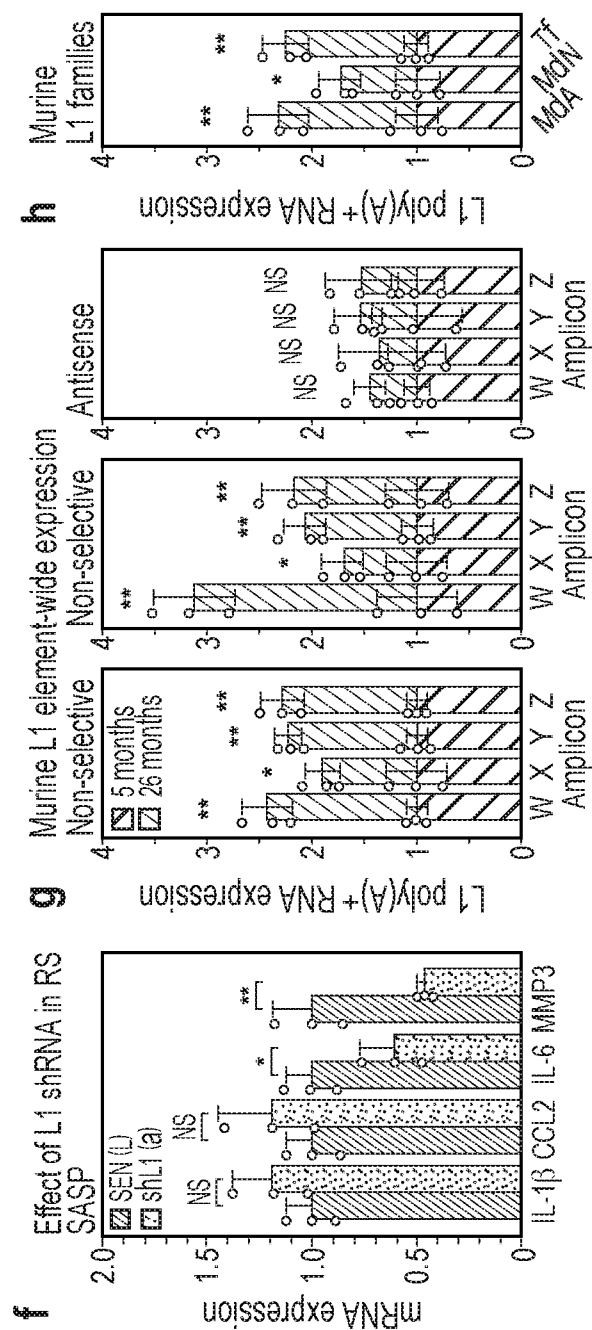
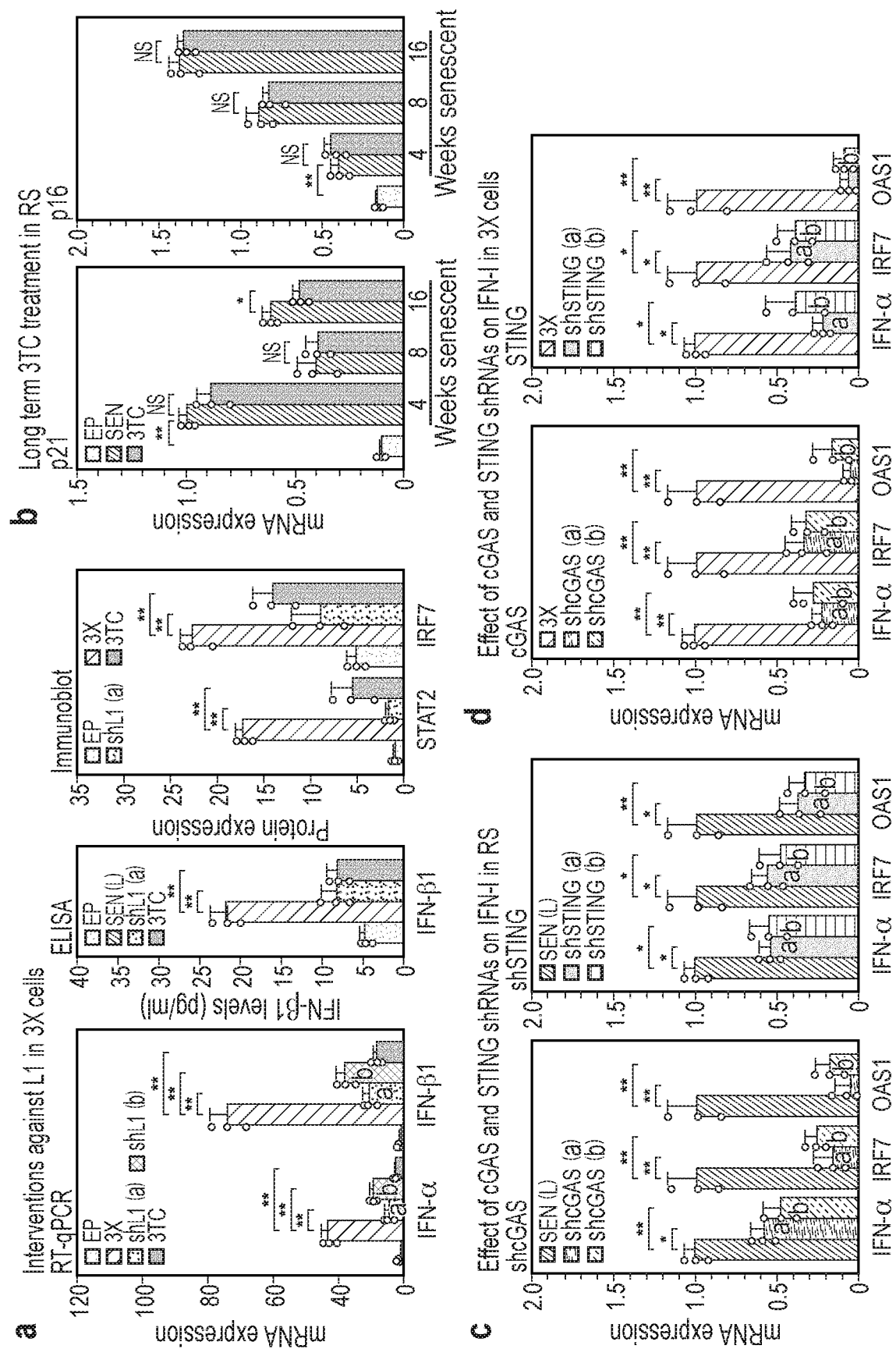


FIG. 11



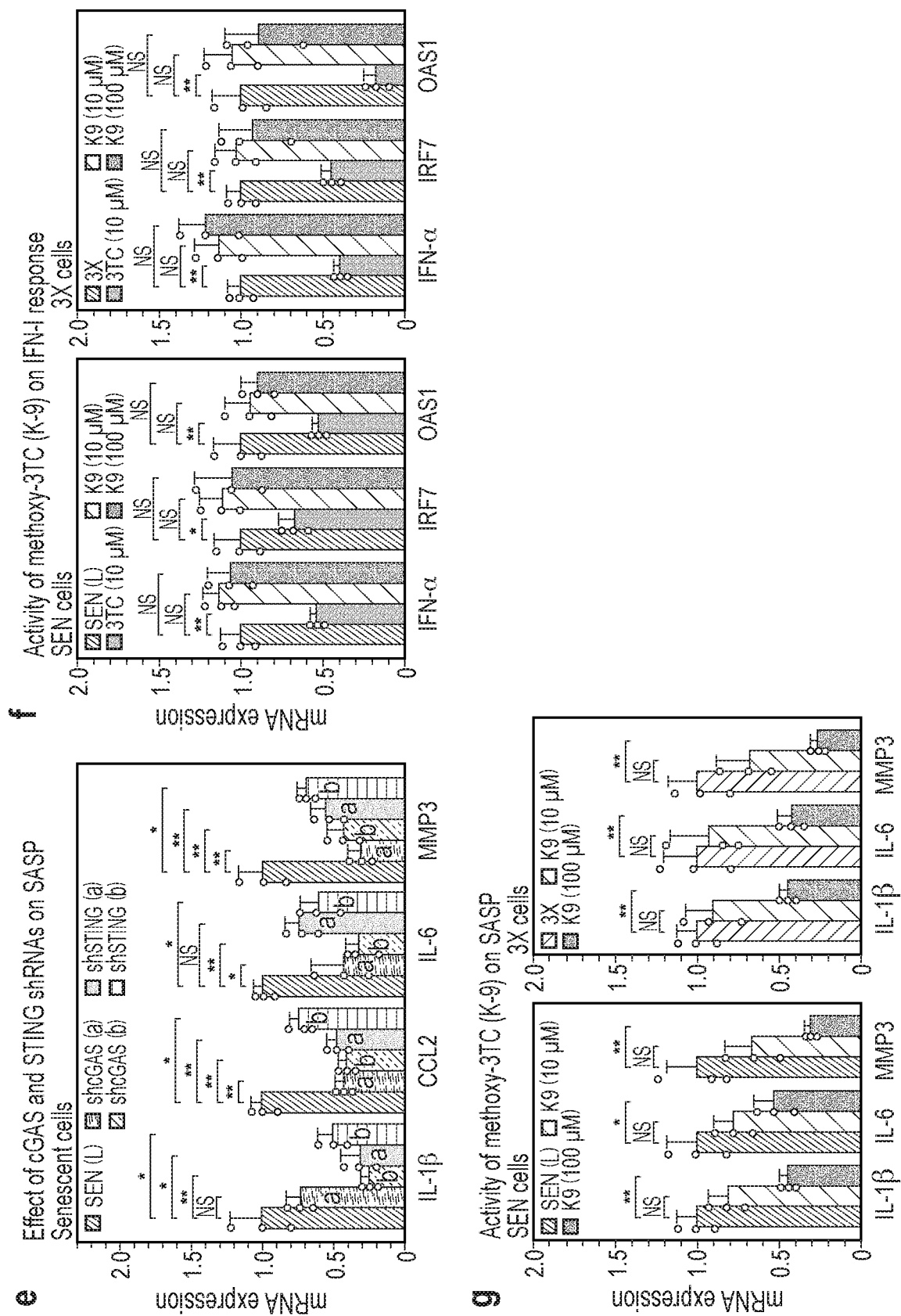


FIG. 12

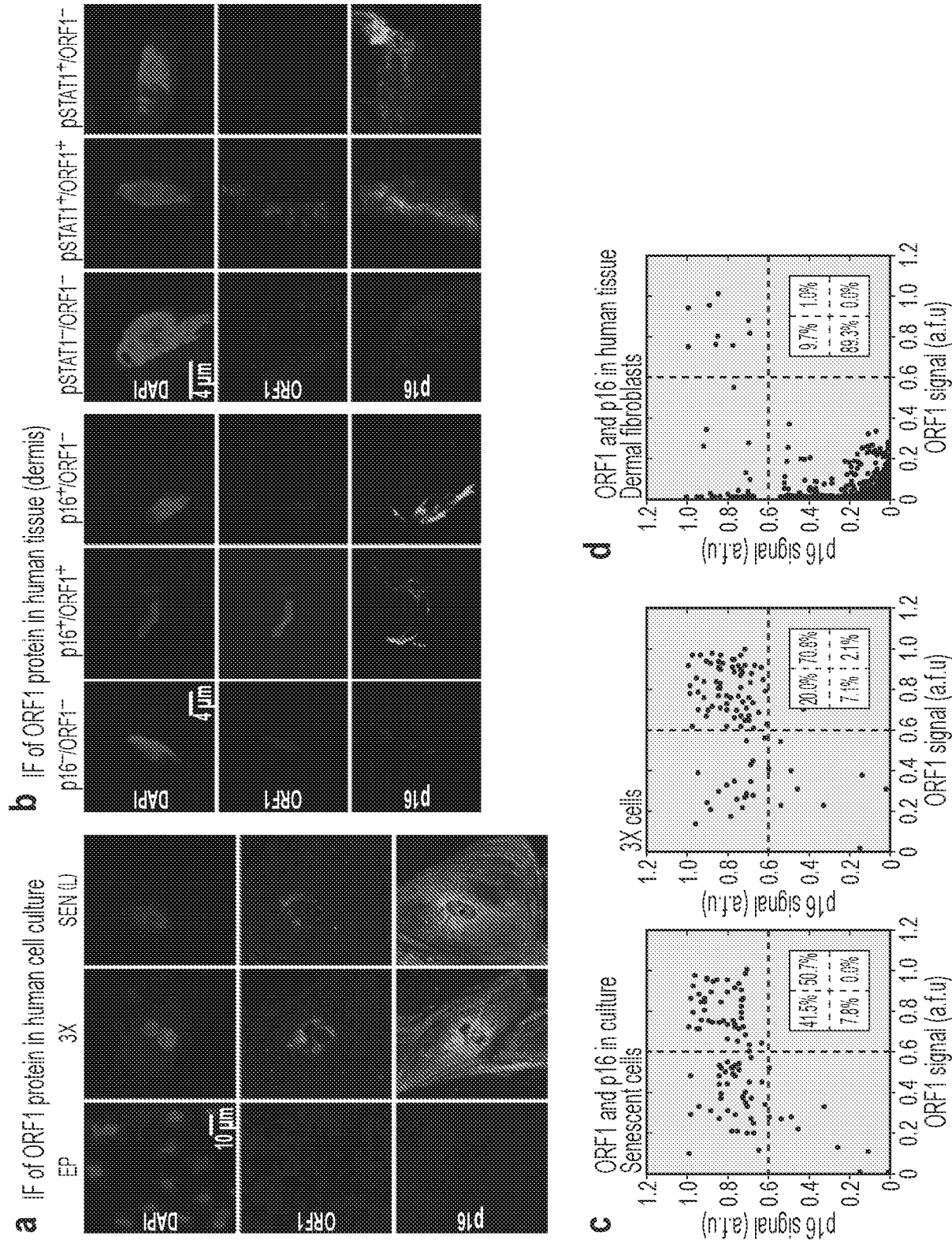


FIG. 13

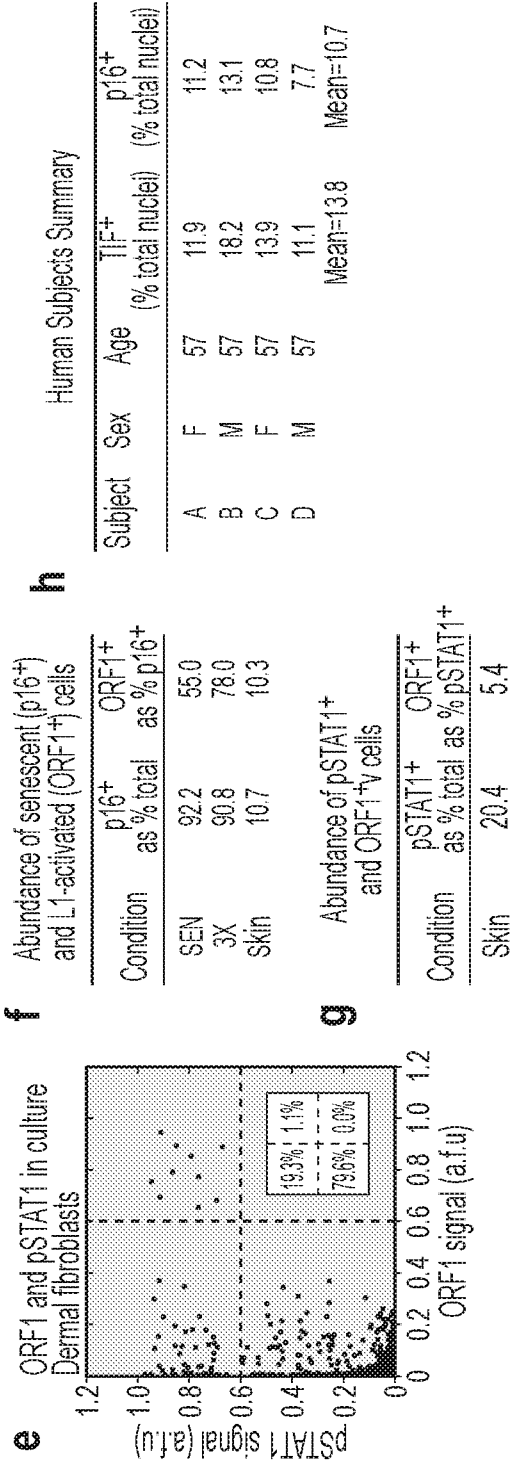


FIG. 13

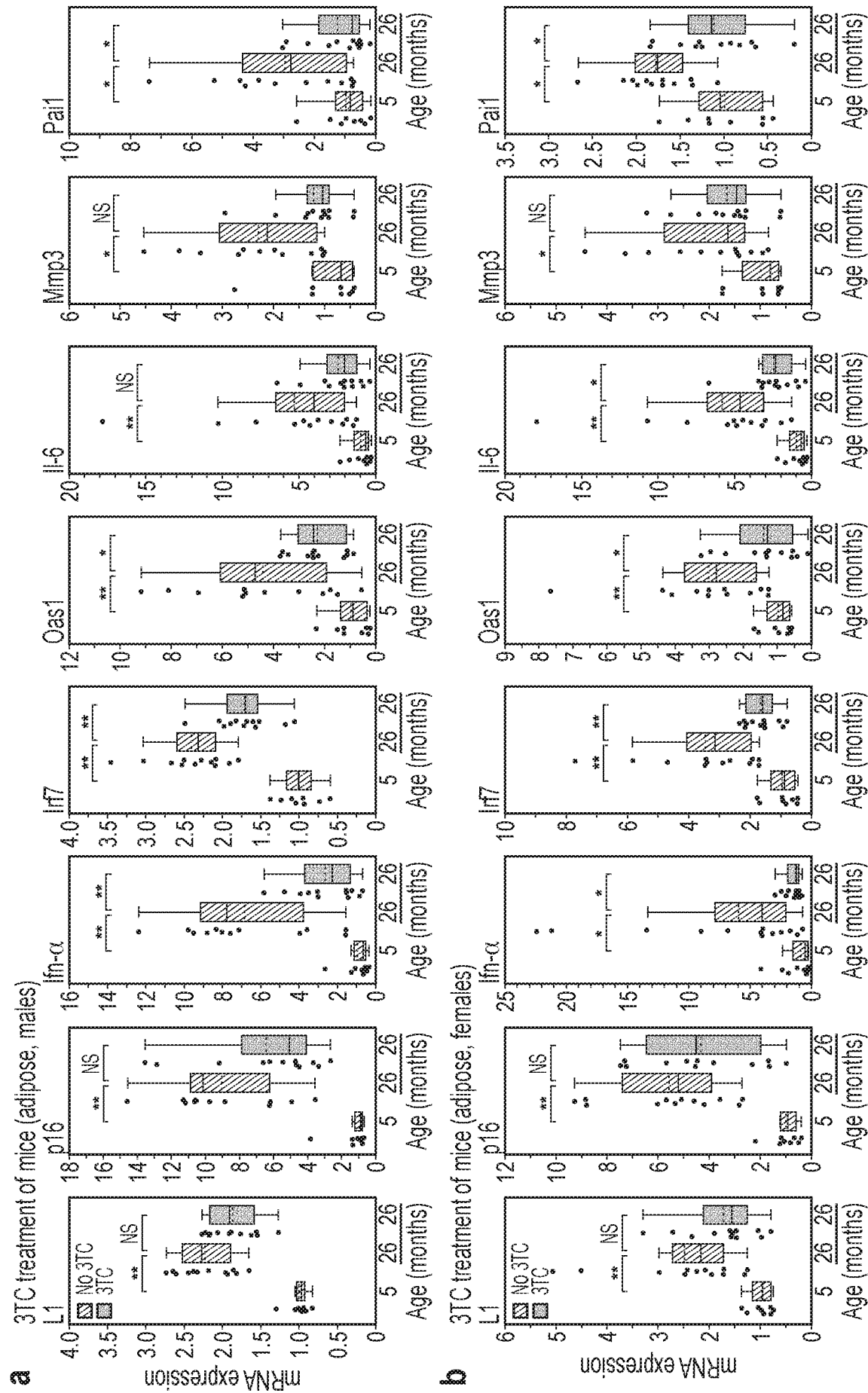


FIG. 14

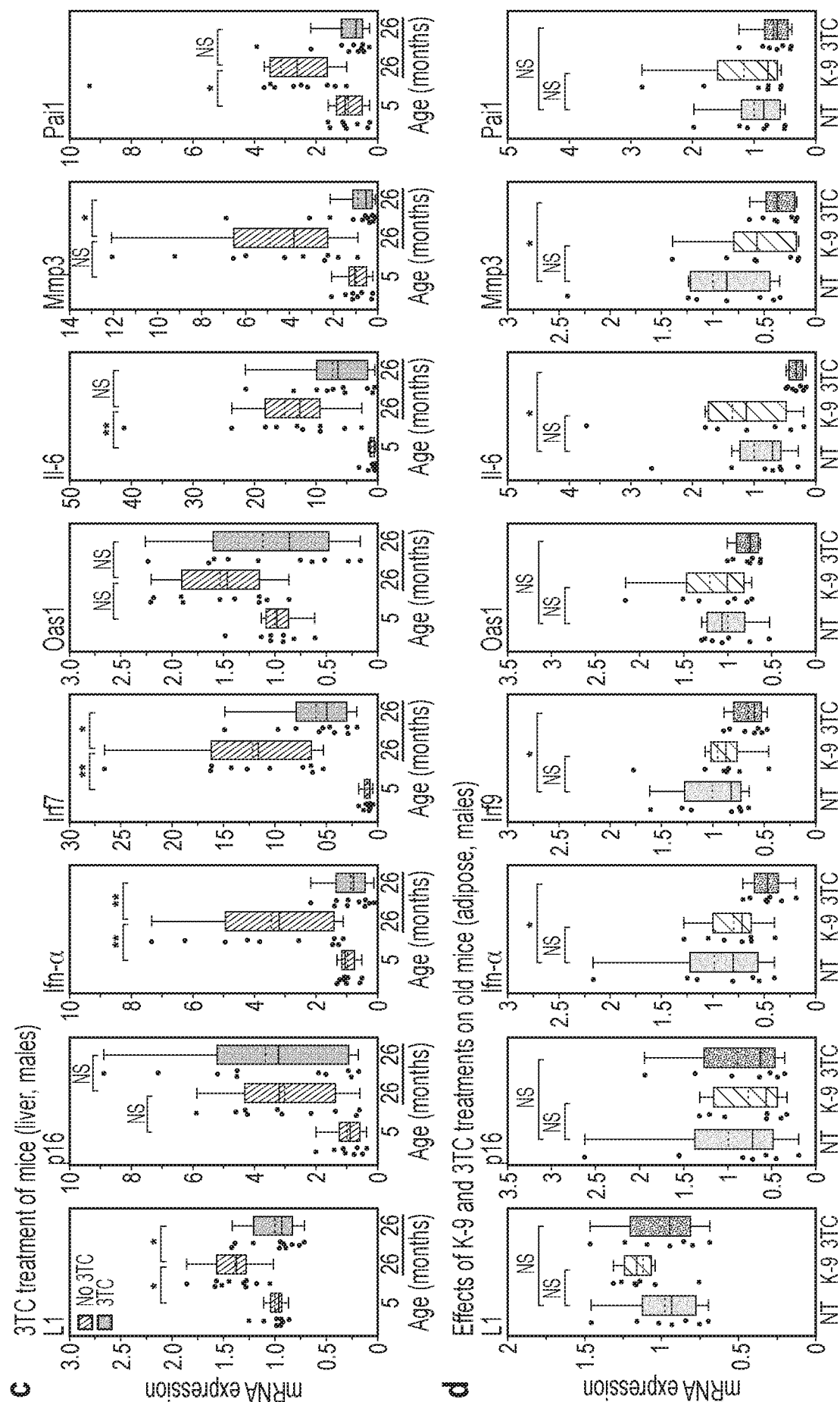


FIG. 14

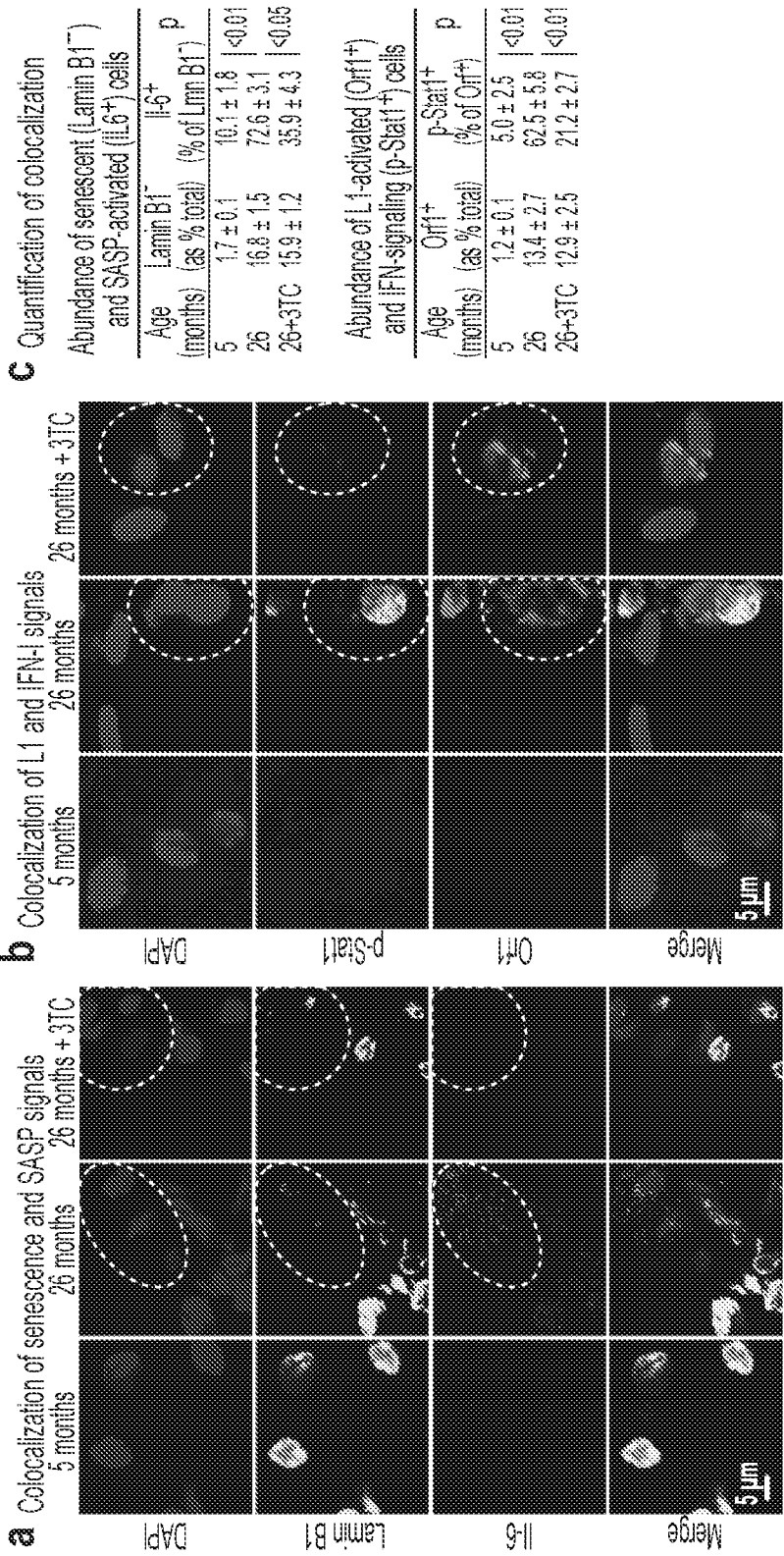


FIG. 15

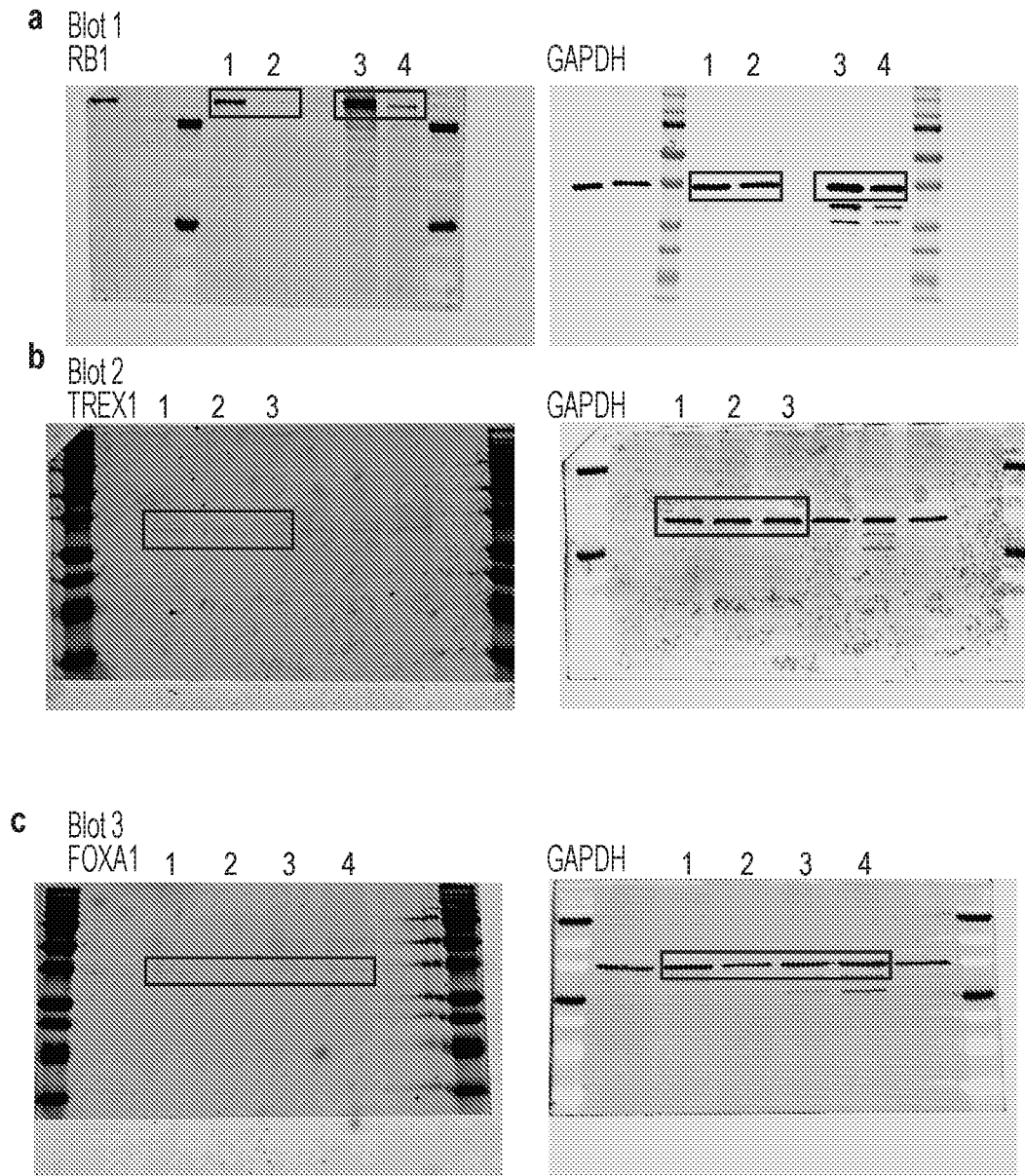


FIG. 16A

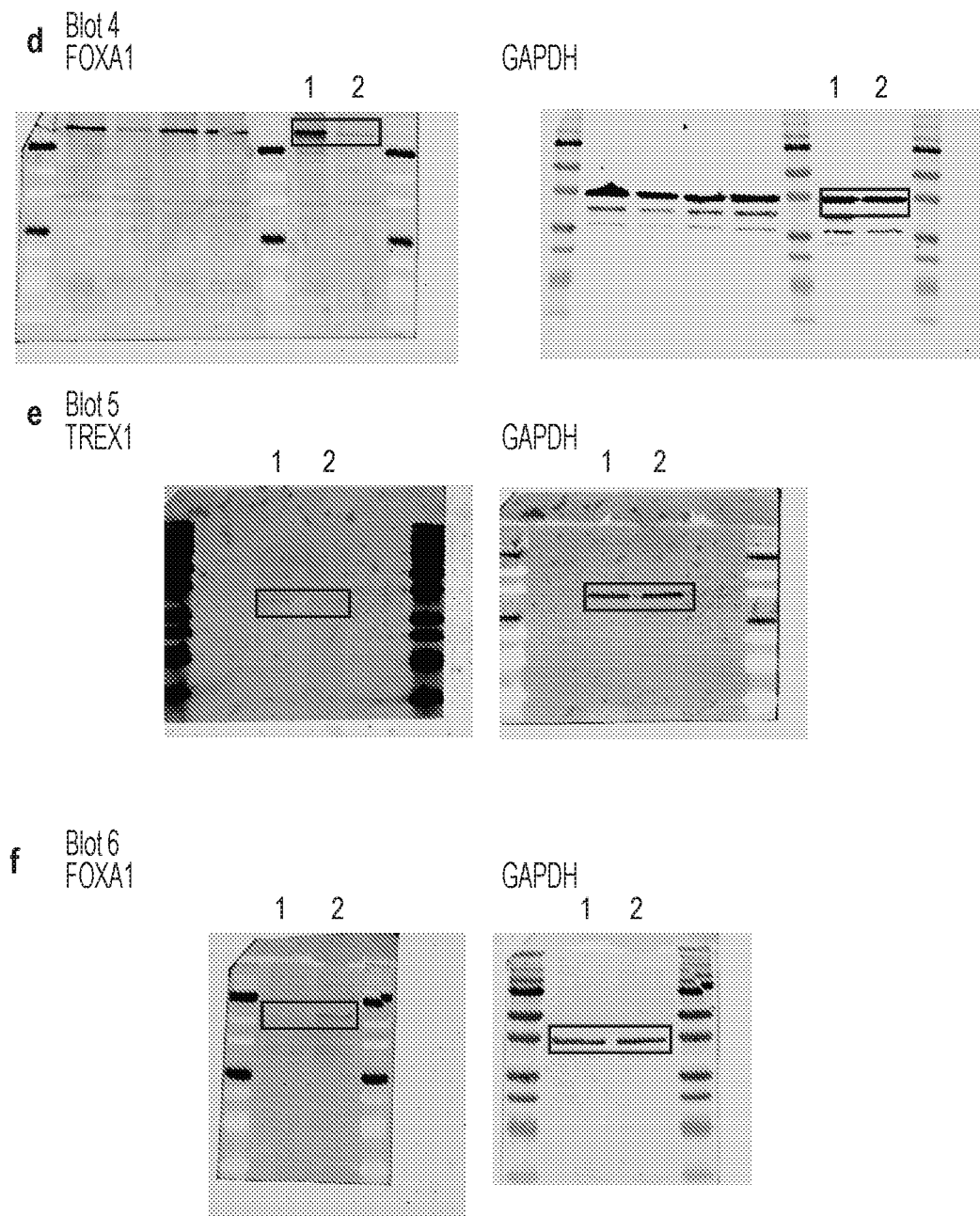


FIG. 16B

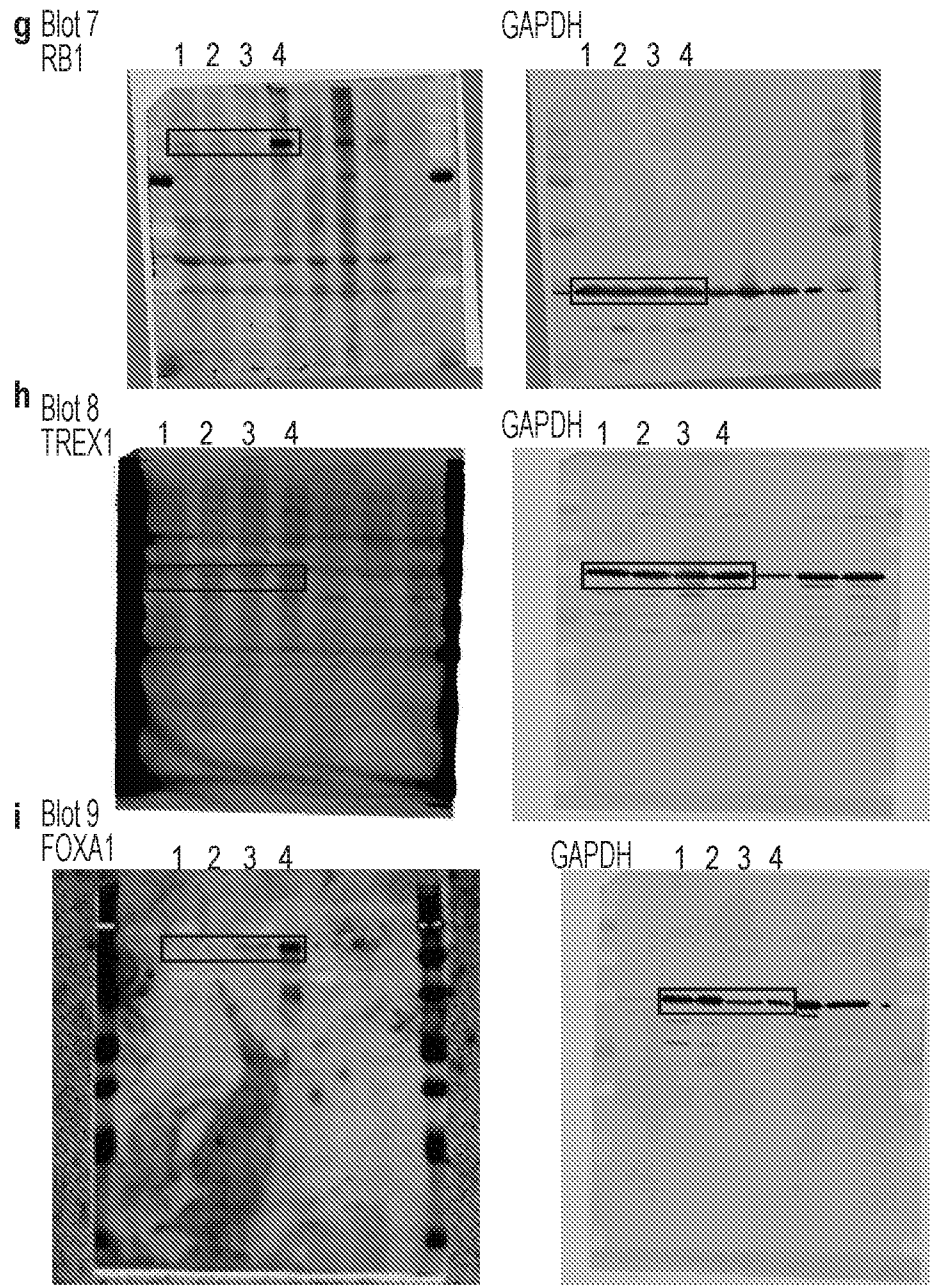


FIG. 16C

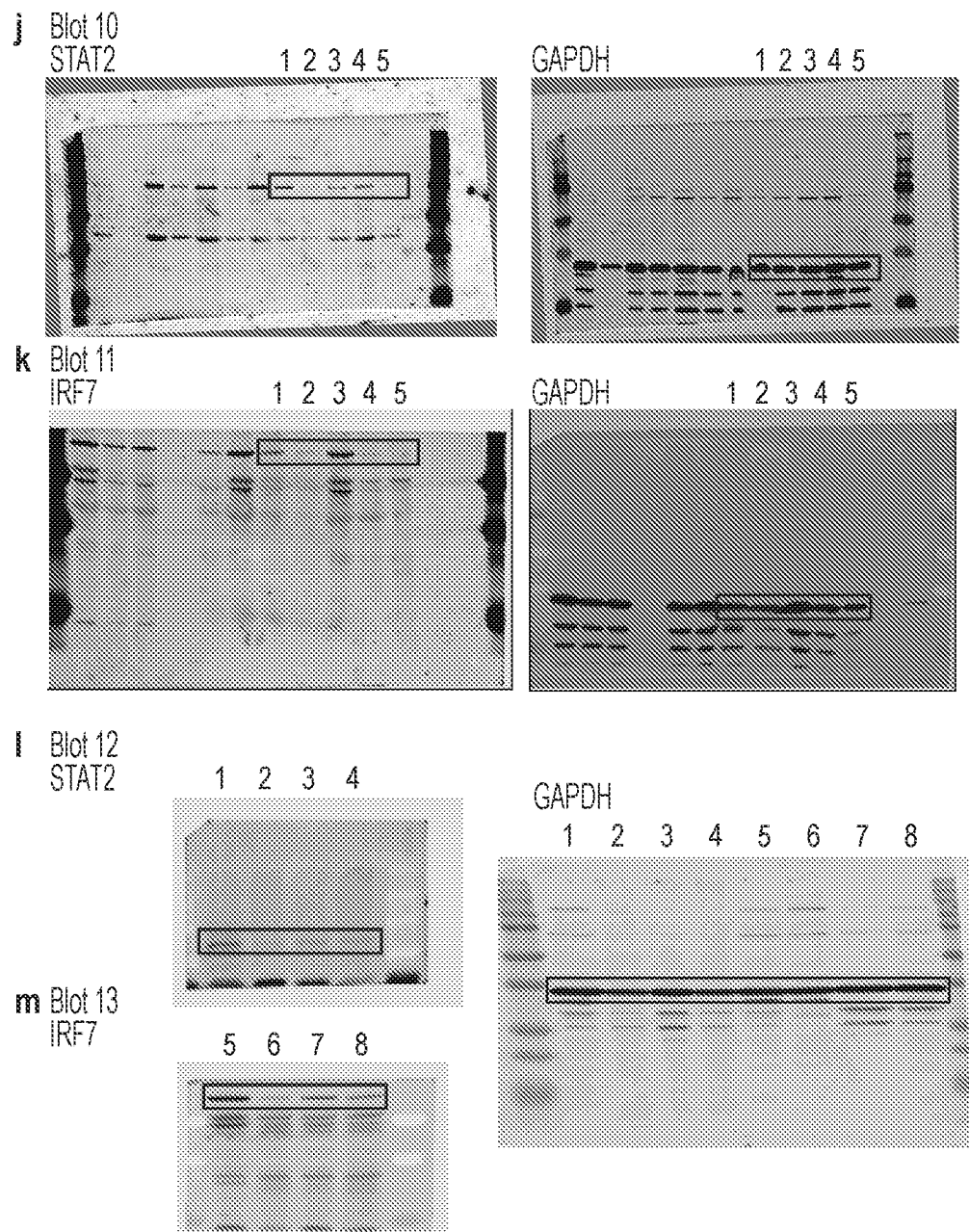
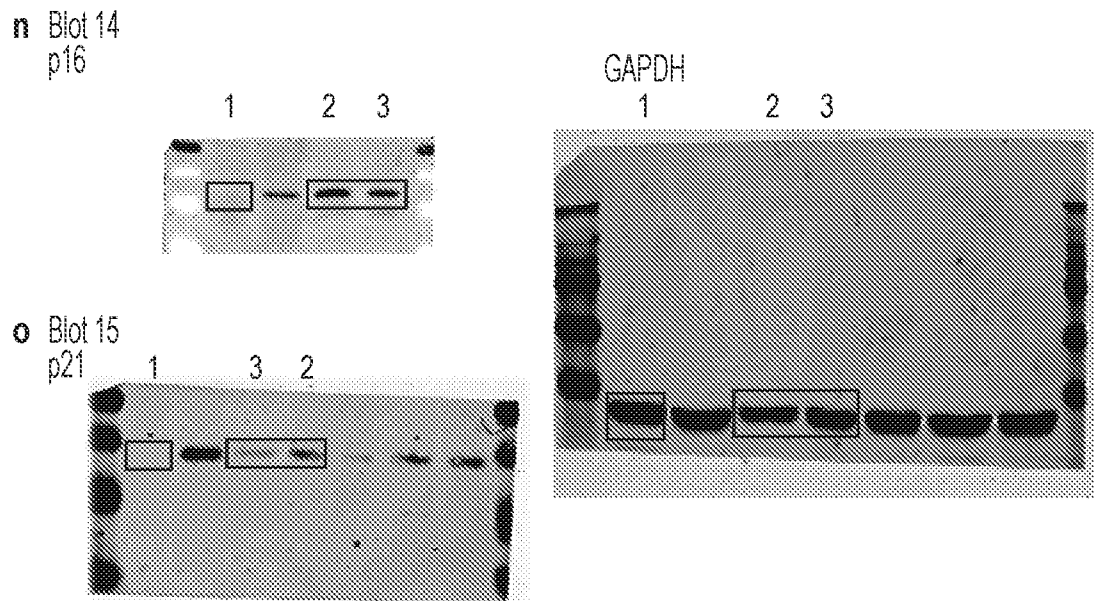


FIG. 16D



- a, Blot 1 - RB1: 1. EP; 2. SEN (L); 3. OE - SEN; 4. SEN (E)
b, Blot 2 - TREX1: 1. EP; 2. SEN (E); 3. SEN (L)
c, Blot 3 - FOXA1: 1. EP; 2. Arrest; 3. SEN (E); 4. SEN (L)
d, Blot 4 - RB1: 1. EP; 2. 3X
e, Blot 5 - TREX1: 1. EP; 2. 3X
f, Blot 6 - FOXA1: 1. EP; 2. 3X
g, Blot 7 - RB1: 1. SEN (L); 2. shRB1(b); 3. shRB1(a); 4. OE-RB1
h, Blot 8 - TREX1: 1. SEN (L); 2. shTREX1 (b); 3. shTREX1 (a); 4. OE-TREX1
i, Blot 9 - FOXA1: 1. shFOXA1 (a); 2. shFOXA1 (b); 3. SEN (L); 4. OE-FOXA1
j, Blot 10 - STAT2: 1. 3X; 2. shL1; 3. NRTI; 4. ΔIFNAR; 5. EP
k, Blot 11 - IRF7: 1. EP; 2. shL1; 3. 3X; 4. shL1; 5. ΔIFNAR
l, Blot 12 - STAT2: 1. SEN (L); 2. ΔIFNAR; 3. shL1; 4. NRTI
m, Blot 13 - IRF7: 5. SEN (L); 6. ΔIFNAR; 7. shL1; 8. NRTI
n, Blot 14 - p16 (CDKN2A): 1. EP; 2. SEN (E); 3. SEN (L)
o, Blot 15 - p21 (CDKN1A): 1. EP; 2. SEN (E); 3. SEN (L)

FIG. 16E

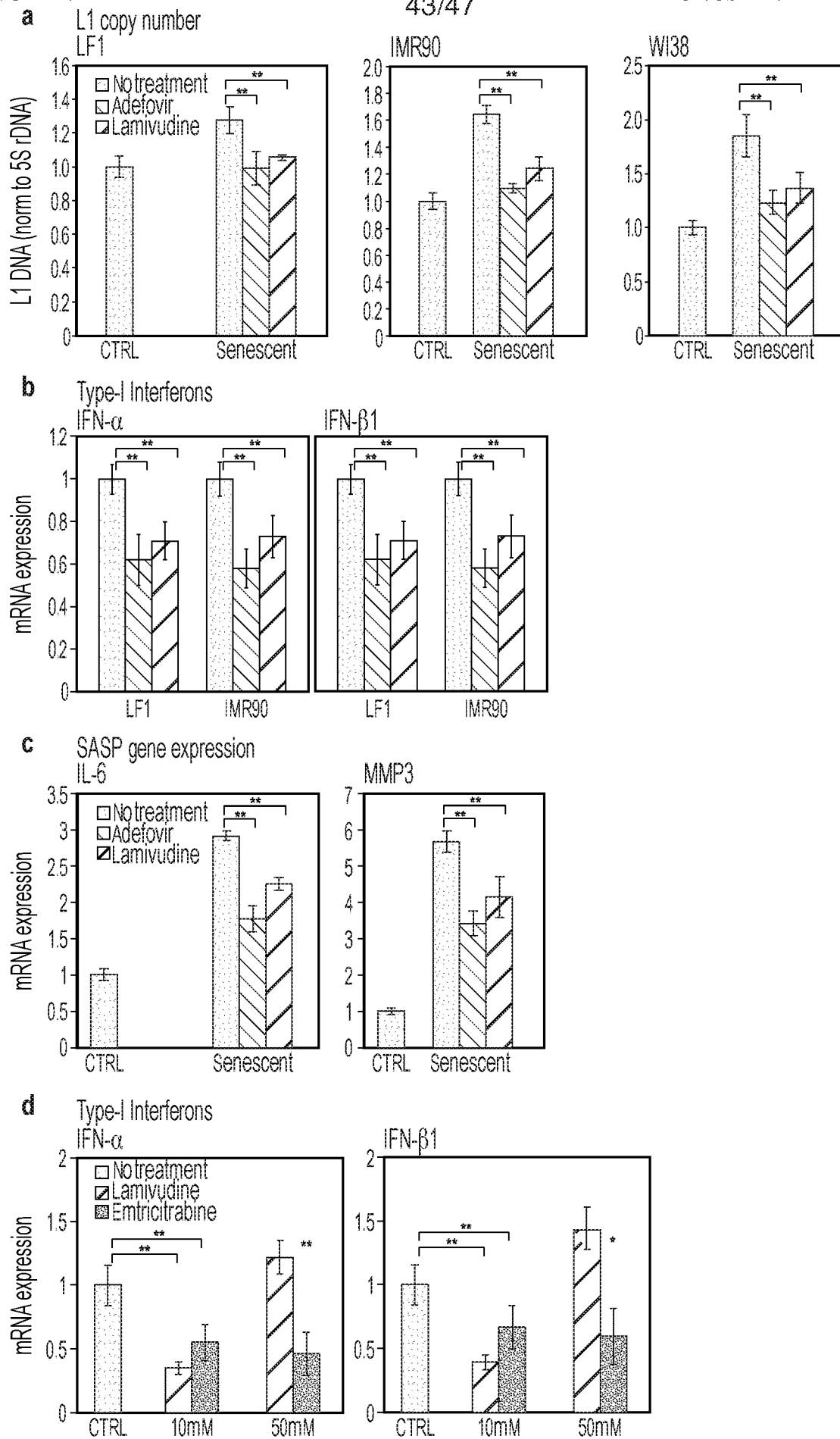


FIG. 17

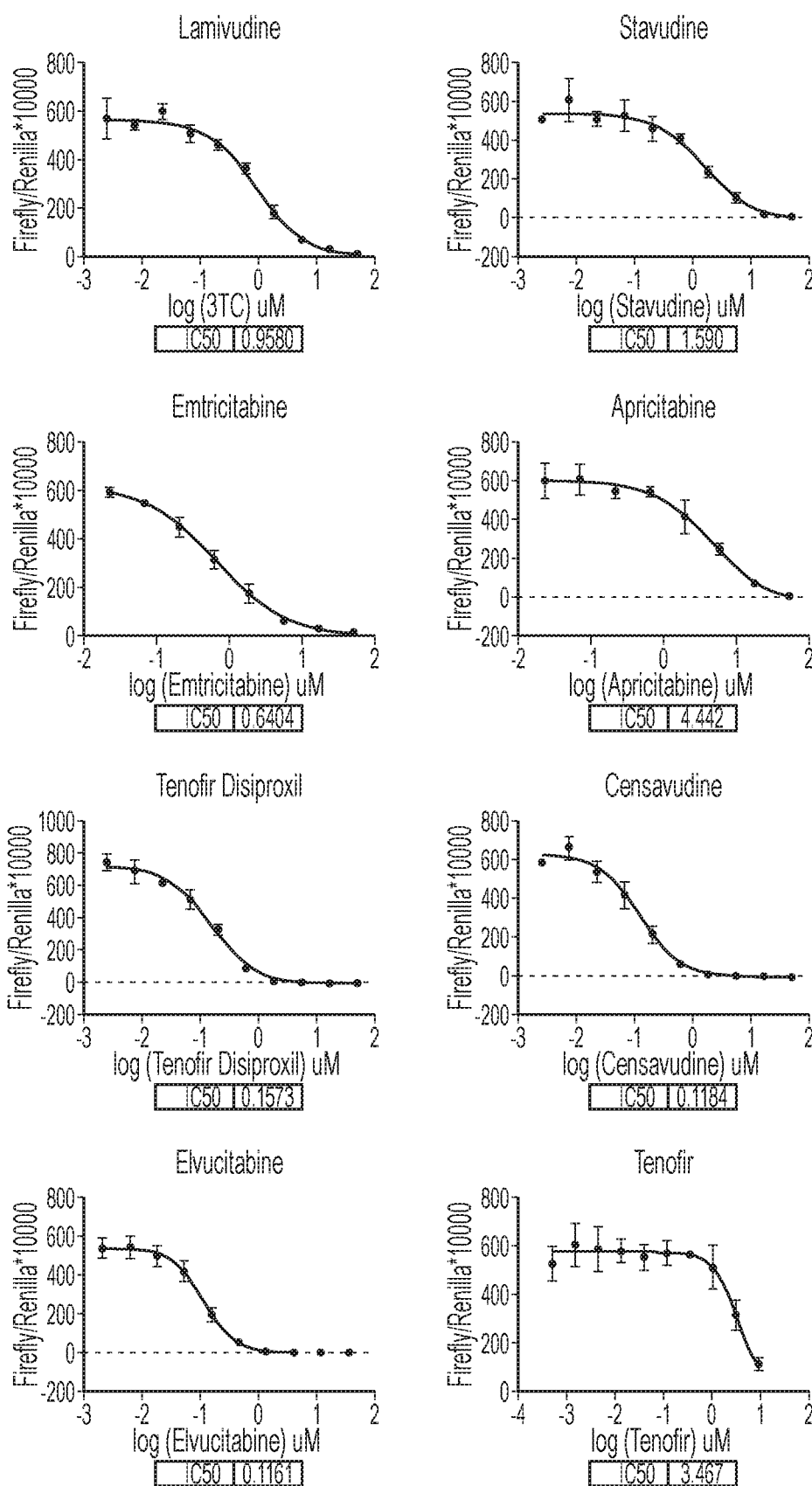


FIG. 18A

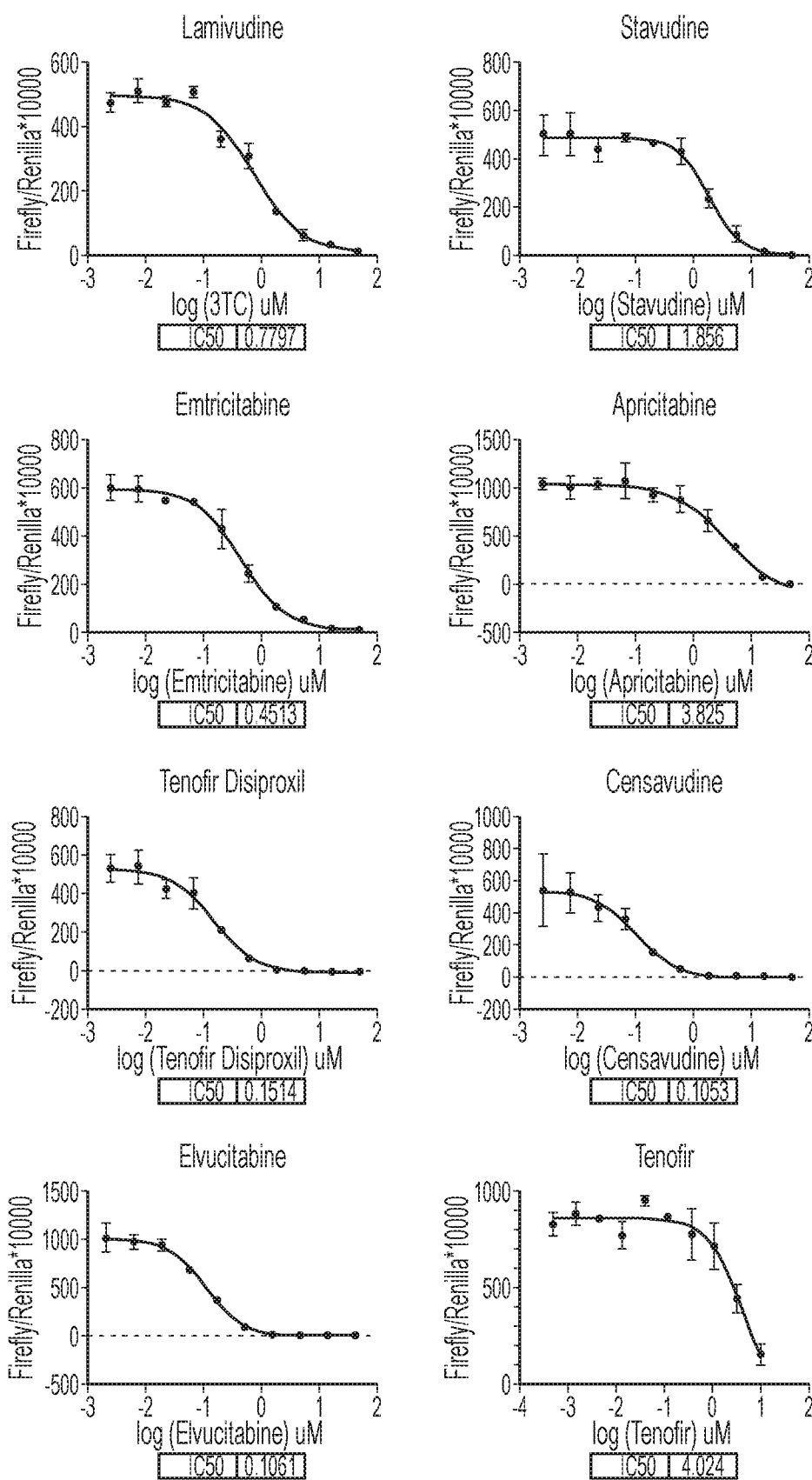


FIG. 18B

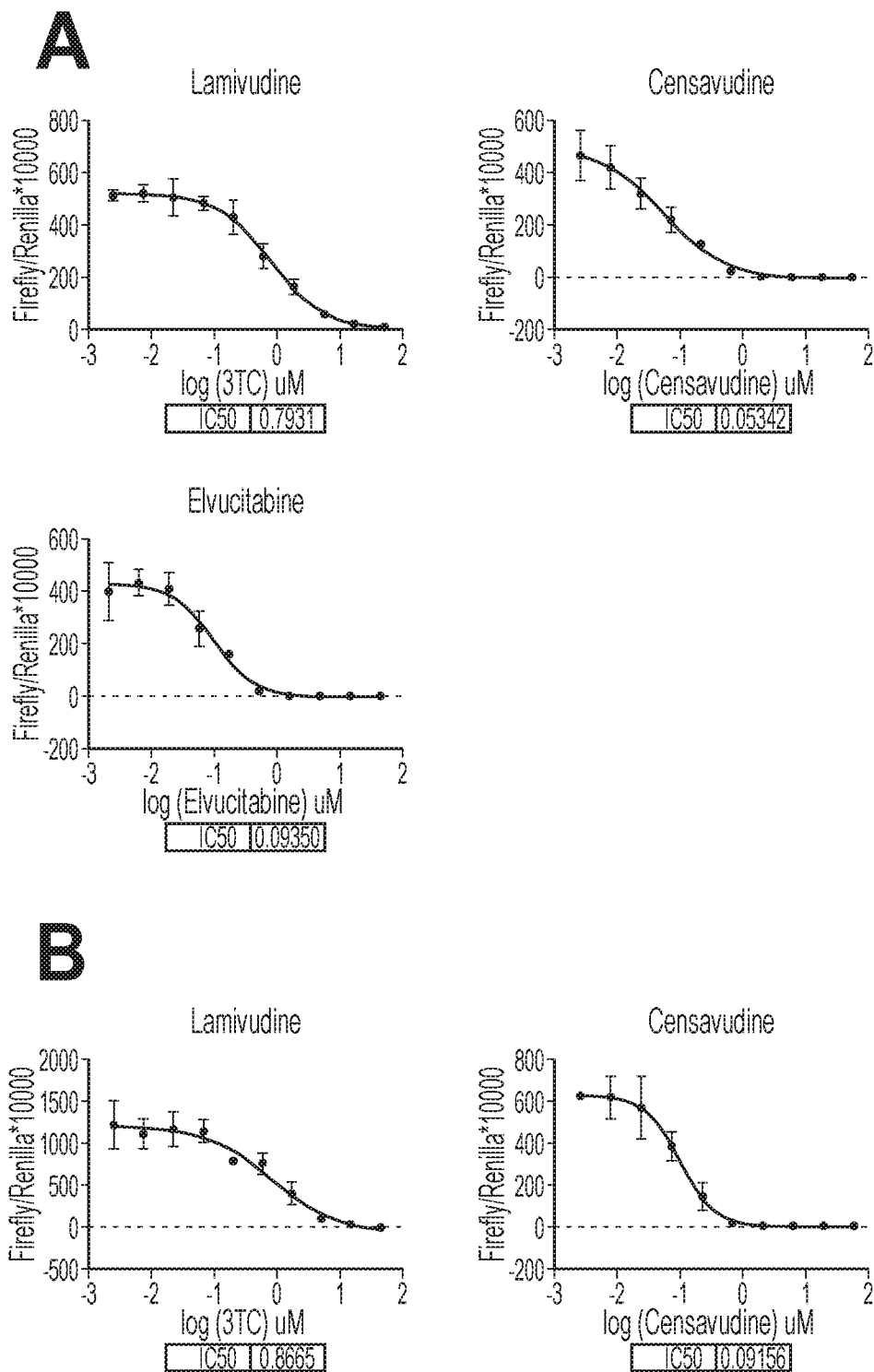


FIG. 19

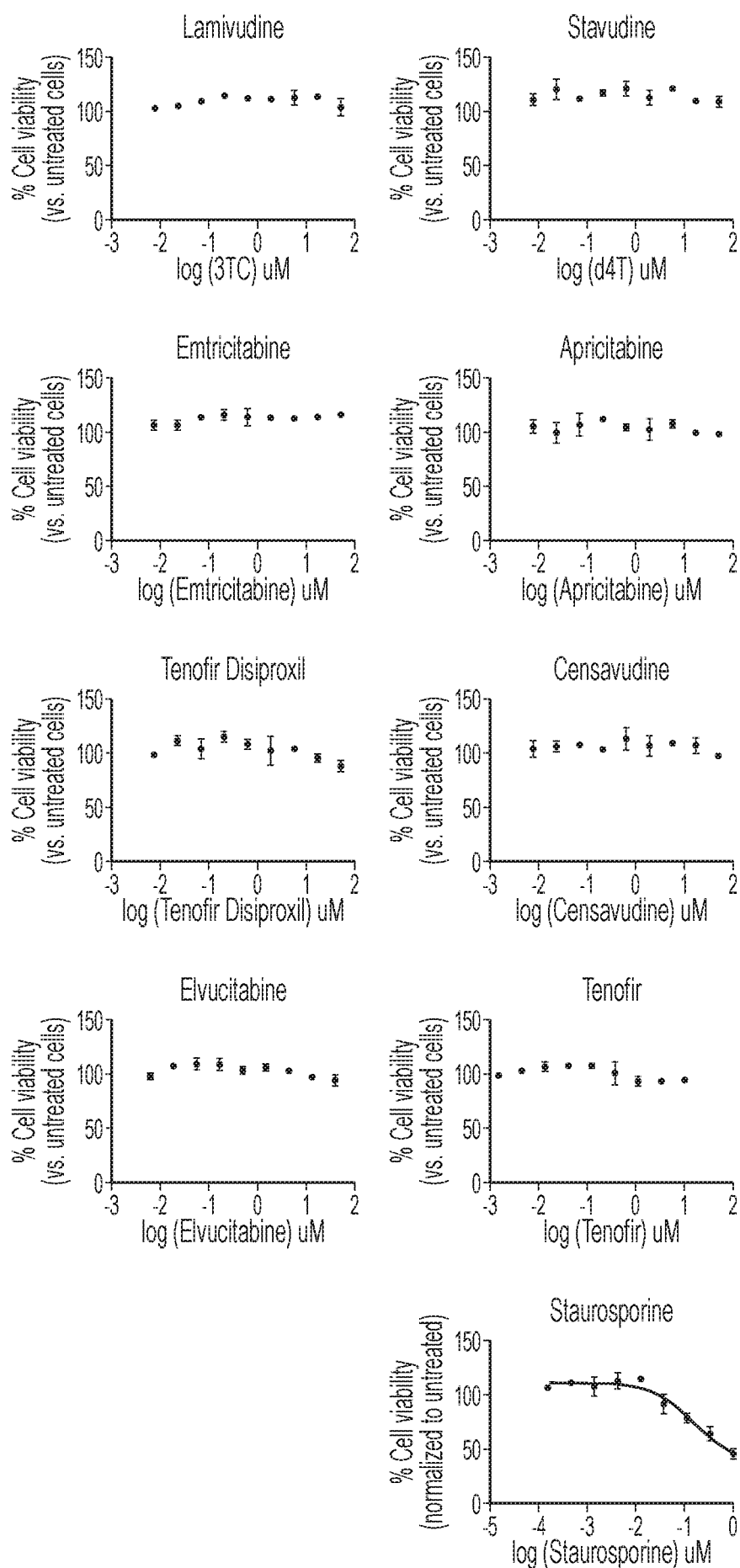


FIG. 20