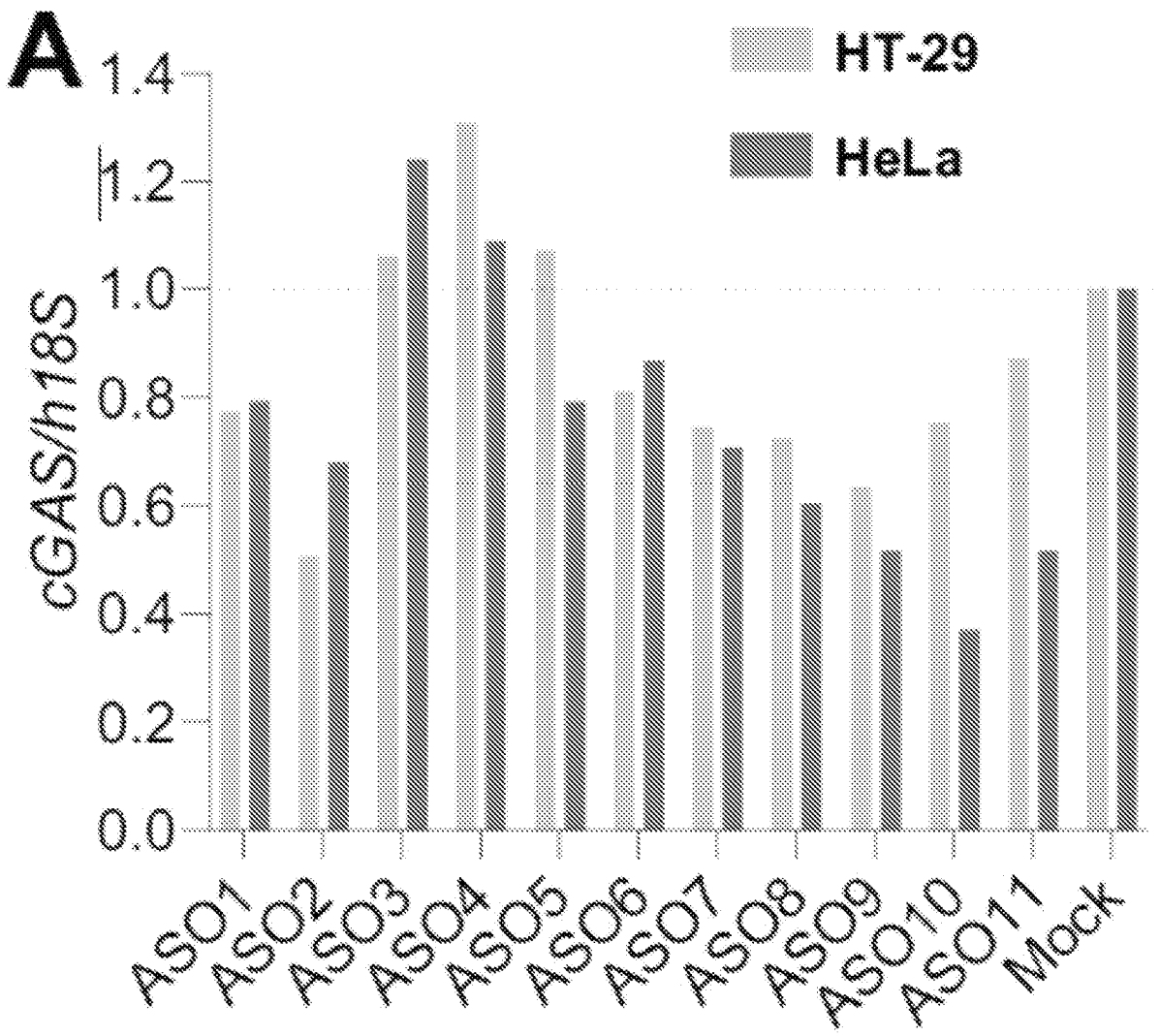

A
HT-29
HeLa
cGAS/h18S
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ASO1
ASO2
ASO3
ASO4
ASO5
ASO6
ASO7
ASO8
ASO9
ASO10
ASO11
Mock

FIGURE 1A

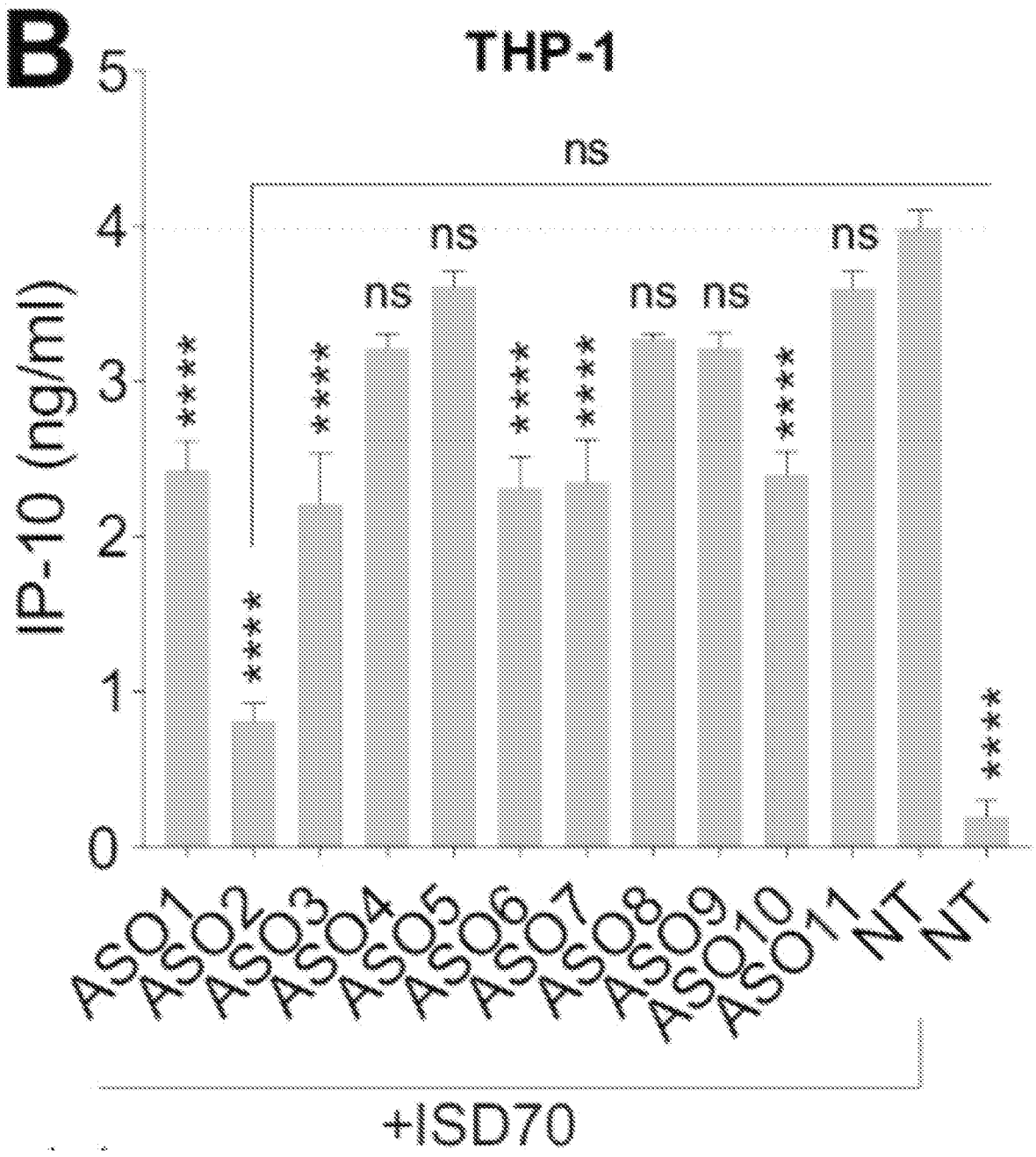

B
THP-1
IP-10 (ng/ml)
0
1
2
3
4
5
ns
ns
ns
ns
ns
ns
ns
****
ASO1
ASO2
ASO3
ASO4
ASO5
ASO6
ASO7
ASO8
ASO9
ASO10
ASO11
NT
NT
+ISD70

FIGURE 1B

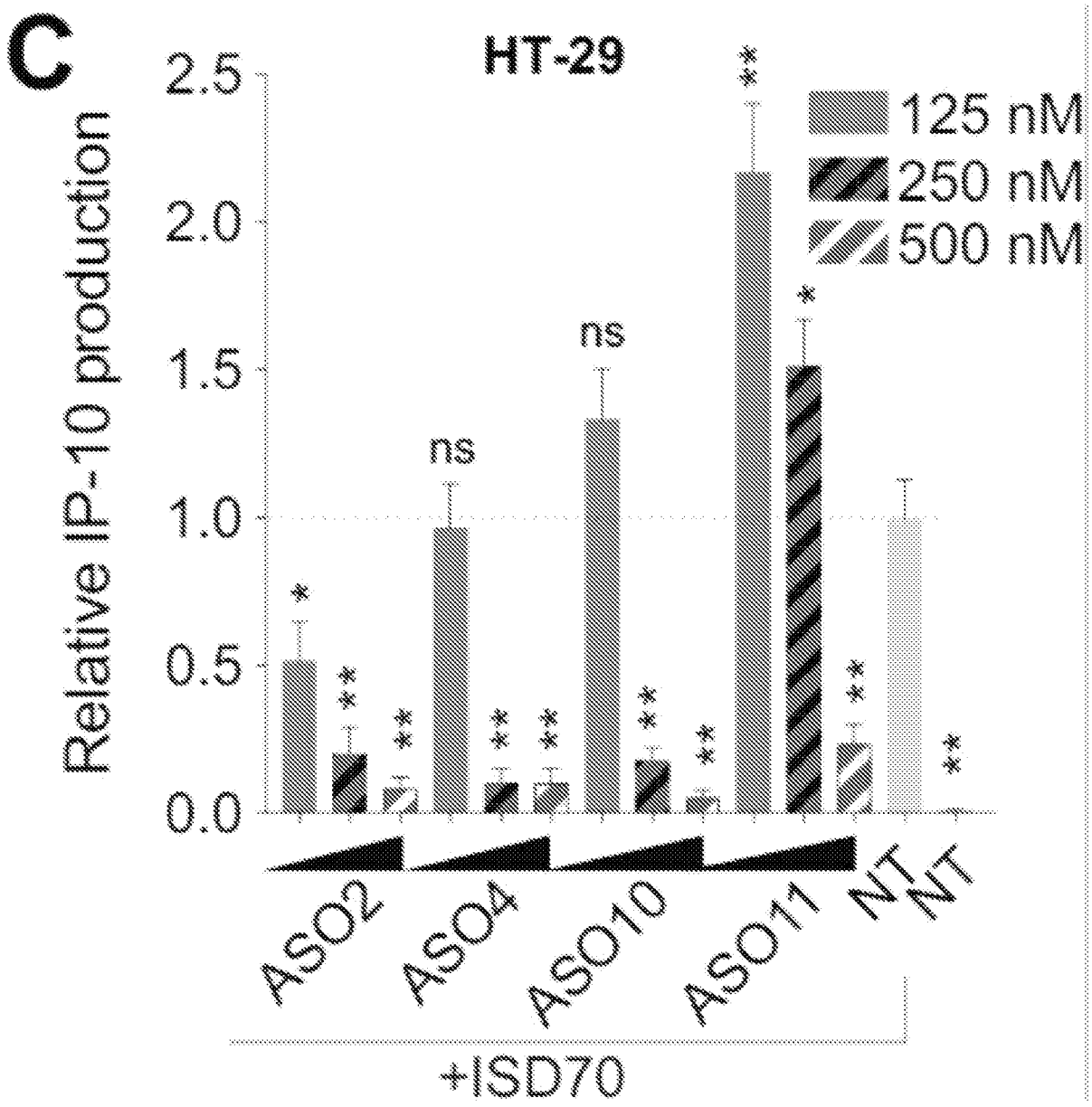

C
HT-29
Relative IP-10 production
2.5
2.0
1.5
1.0
0.5
0.0
125 nM
250 nM
500 nM
ns
ns
*
**
***
NT
NT
ASO2
ASO4
ASO10
ASO11
+ISD70

FIGURE 1C

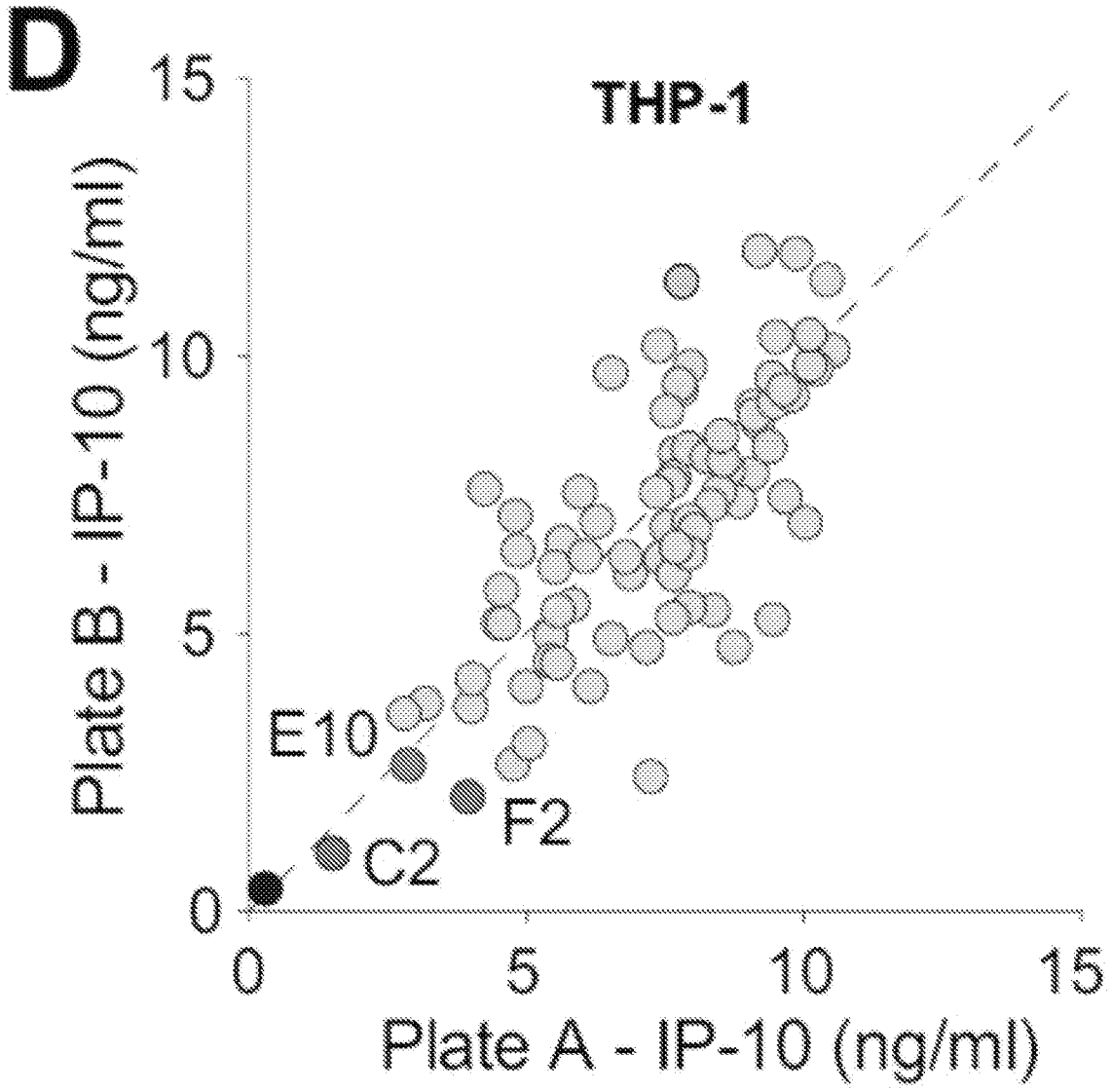


FIGURE 1D

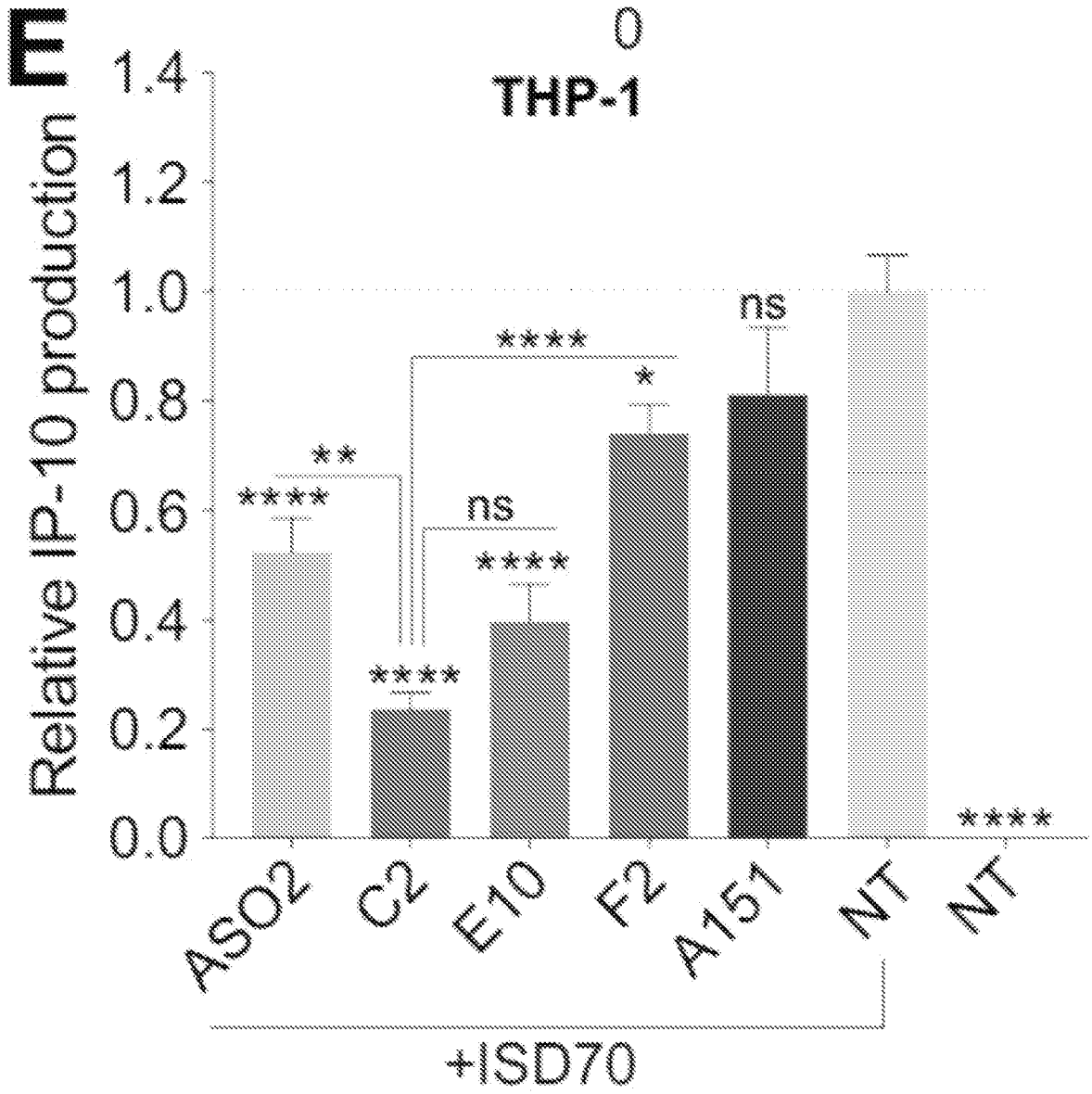

0
THP-1
Relative IP-10 production
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
****
**
****
ns
****
*
ns
****
ASO2
C2
E10
F2
A151
NT
NT
+ISD70

FIGURE 1E

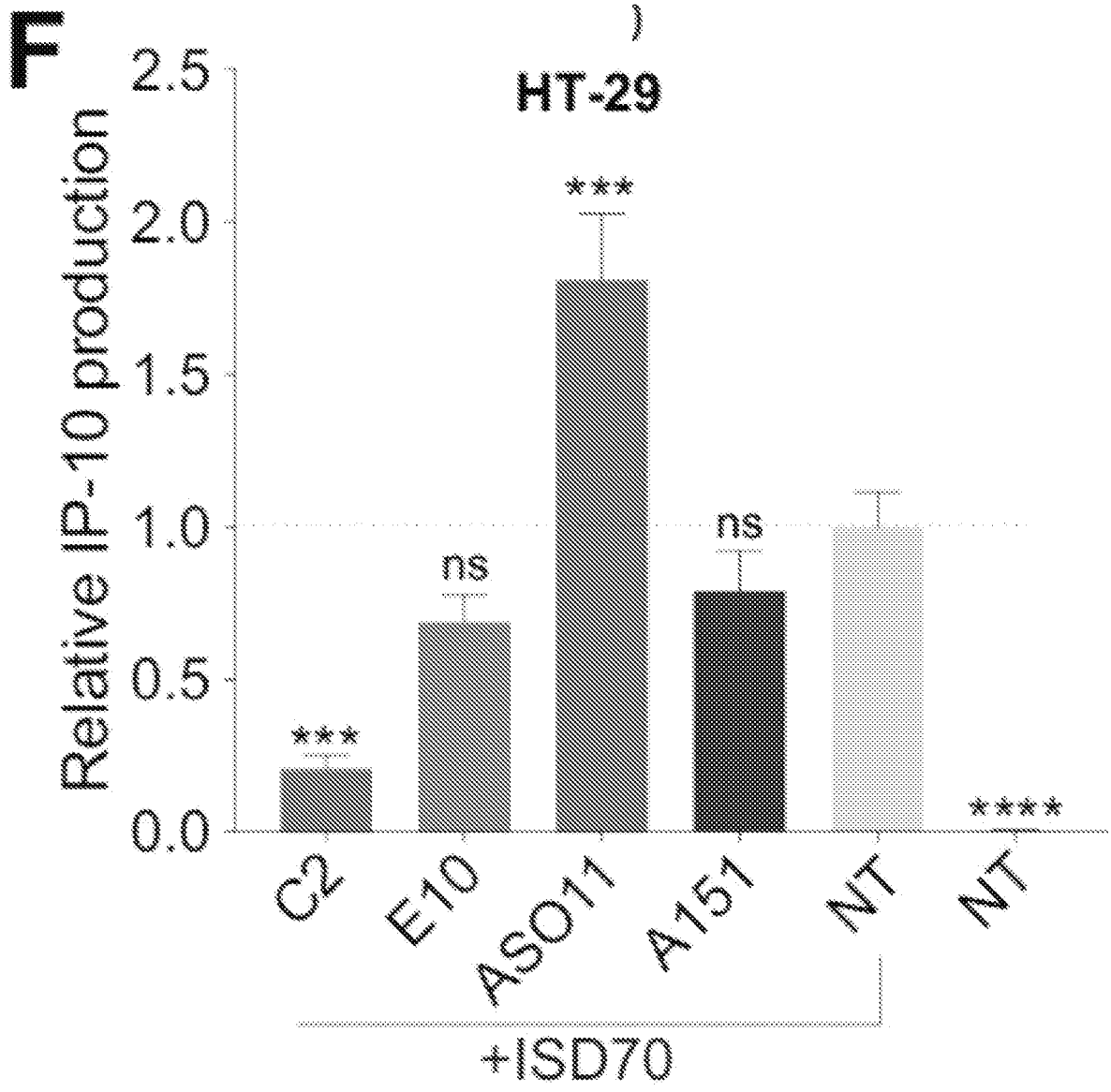

F
HT-29
Relative IP-10 production
2.5
2.0
1.5
1.0
0.5
0.0
***
ns
***
ns
****
C2
E10
ASO11
A151
NT
NT
+ISD70

FIGURE 1F

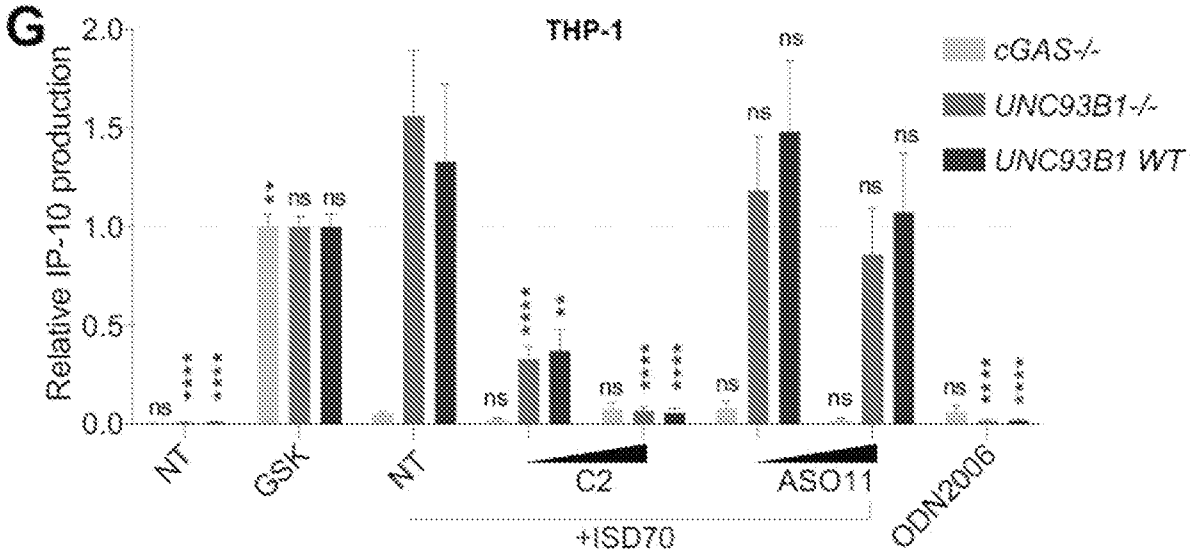
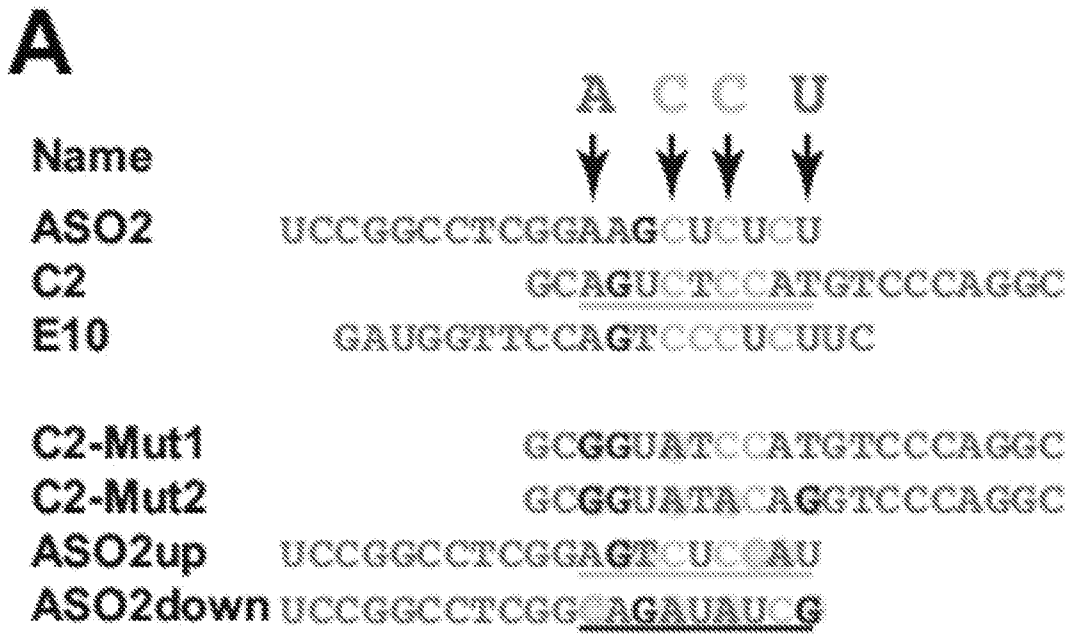
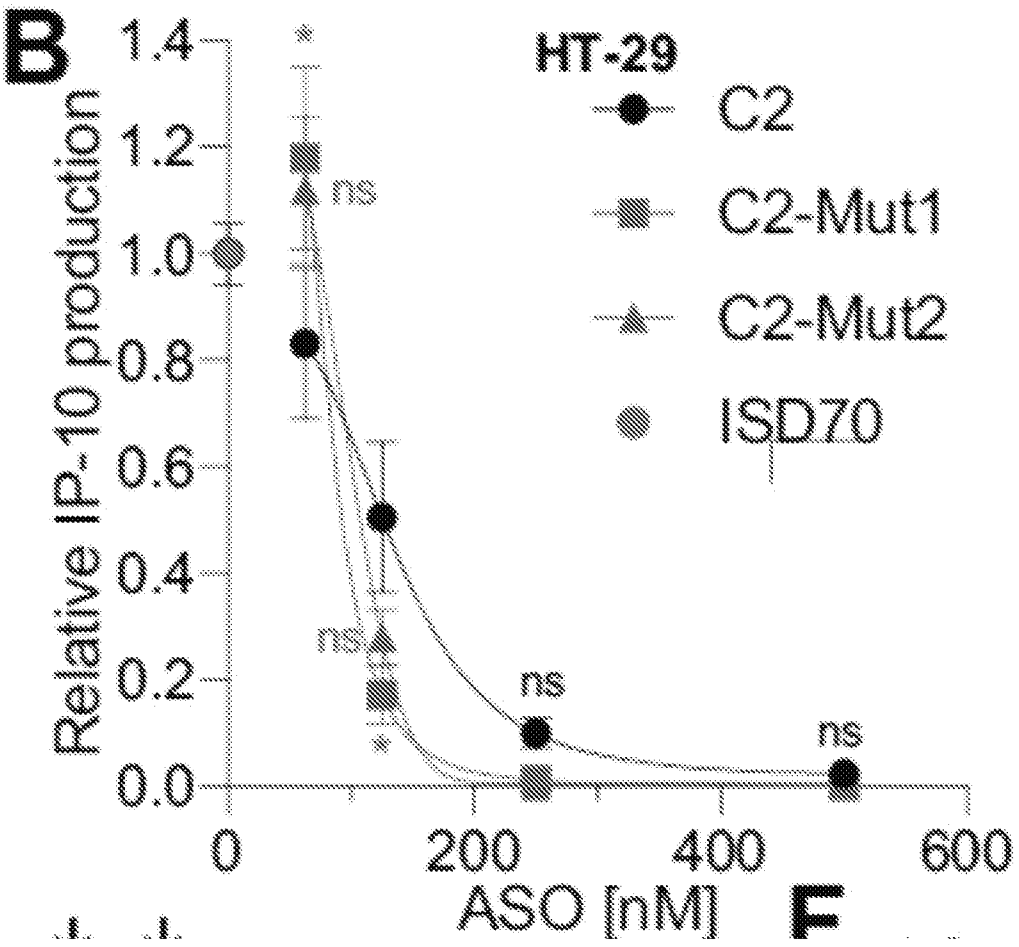

G
THP-1
Relative IP-10 production
2.0
1.5
1.0
0.5
0.0
cGAS-/-
UNC93B1-/-
UNC93B1 WT
NT
GSK
NT
C2
ASO11
ODN2006
+ISD70

FIGURE 1G





FIGURES 2A & 2B

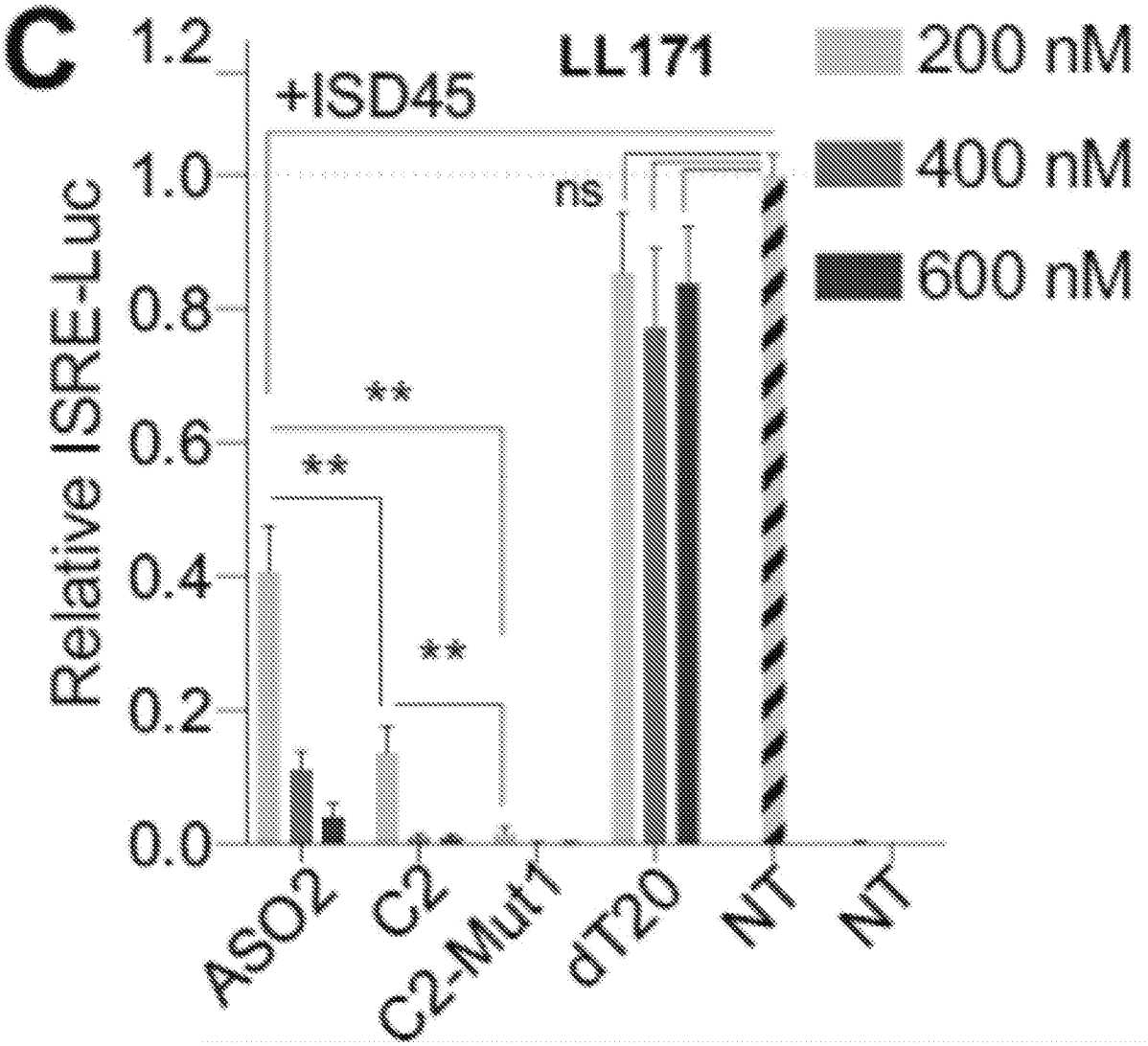

C
LL171
+ISD45
200 nM
400 nM
600 nM
Relative ISRE-Luc
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
**
**
**
ASO2
C2
C2-Mut1
dT20
NT
NT

FIGURE 2C

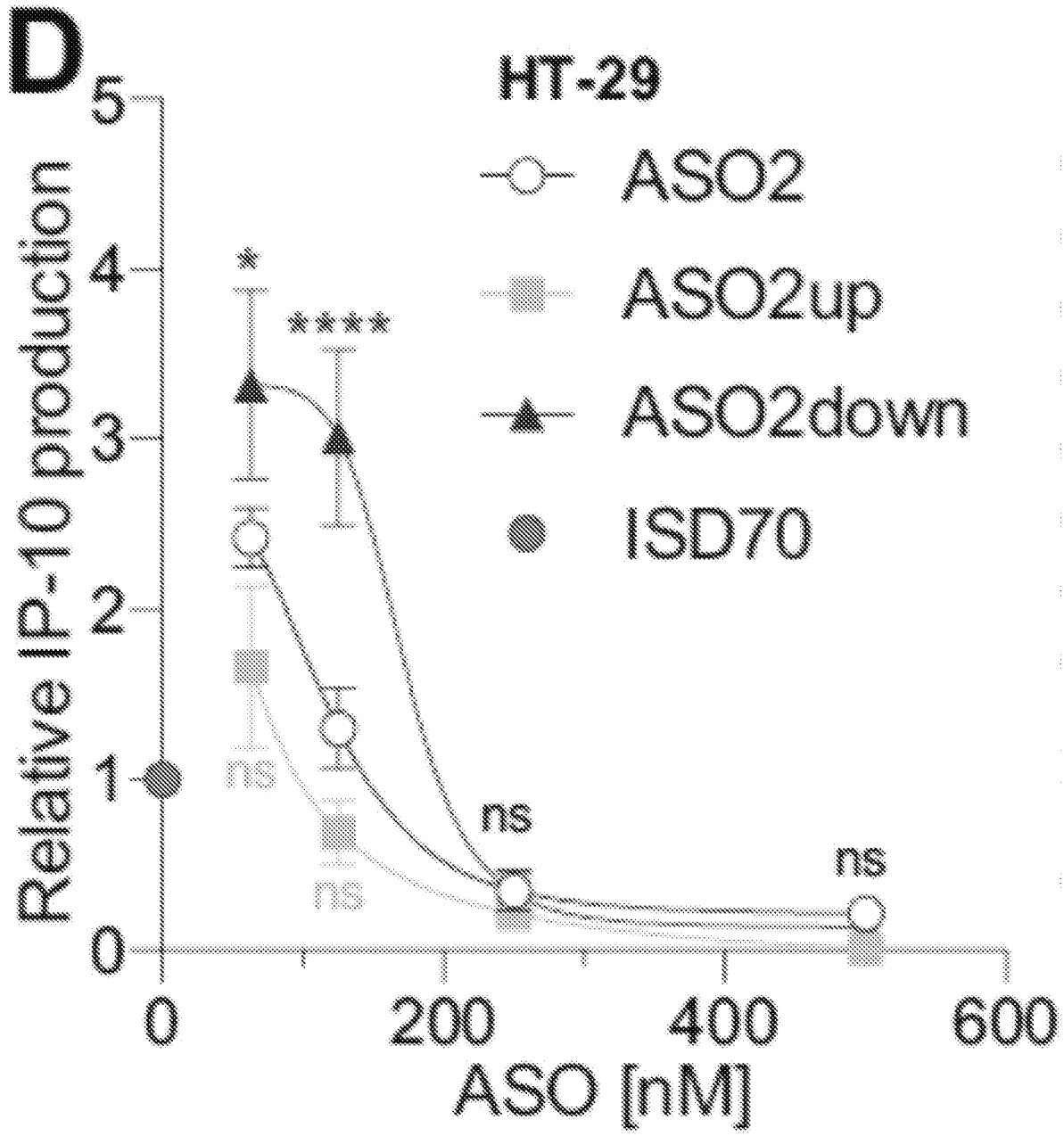

D
HT-29
ASO2
ASO2up
ASO2down
ISD70
Relative IP-10 production
5
4
3
2
1
0
*
****
ns
ns
ns
ns
0
200
400
600
ASO [nM]

FIGURE 2D

E

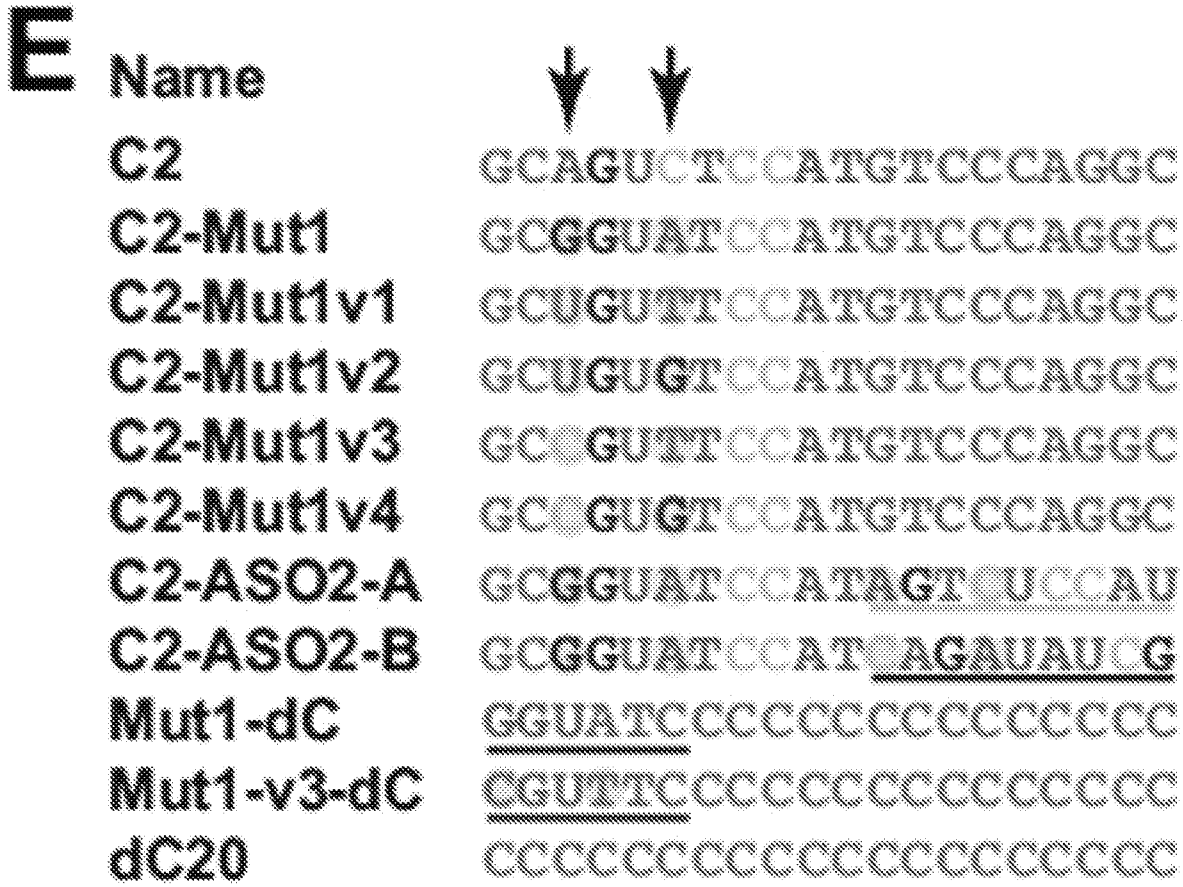

Name
C2
C2-Mut1
C2-Mut1v1
C2-Mut1v2
C2-Mut1v3
C2-Mut1v4
C2-ASO2-A
C2-ASO2-B
Mut1-dC
Mut1-v3-dC
dC20

FIGURE 2E

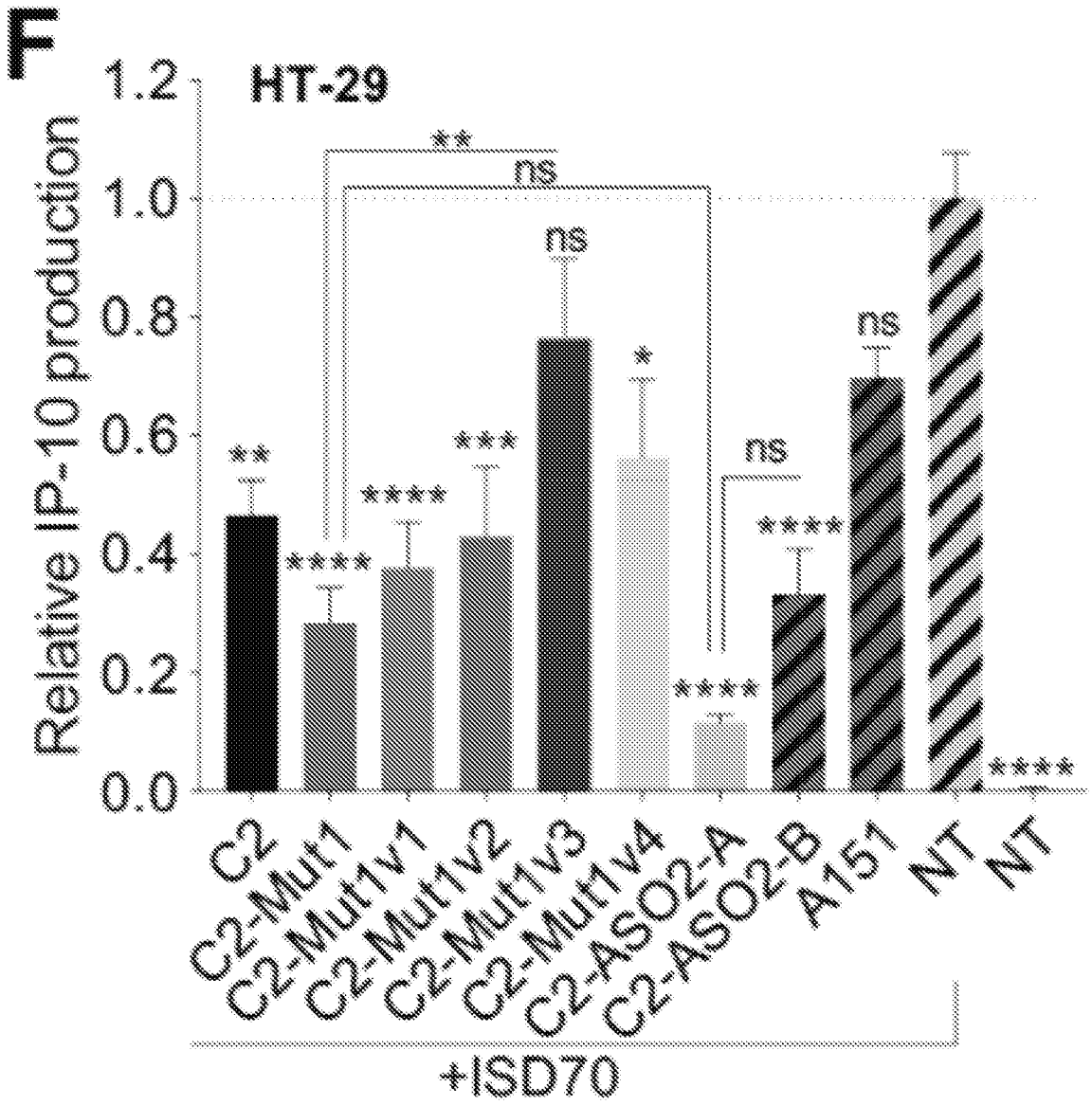

F
HT-29
Relative IP-10 production
1.2
1.0
0.8
0.6
0.4
0.2
0.0
**
ns
ns
**
****
***
*
ns
****
ns
****
****
C2
C2-Mut1
C2-Mut1v1
C2-Mut1v2
C2-Mut1v3
C2-Mut1v4
C2-ASO2-A
C2-ASO2-B
A151
NT
NT
+ISD70

FIGURE 2F

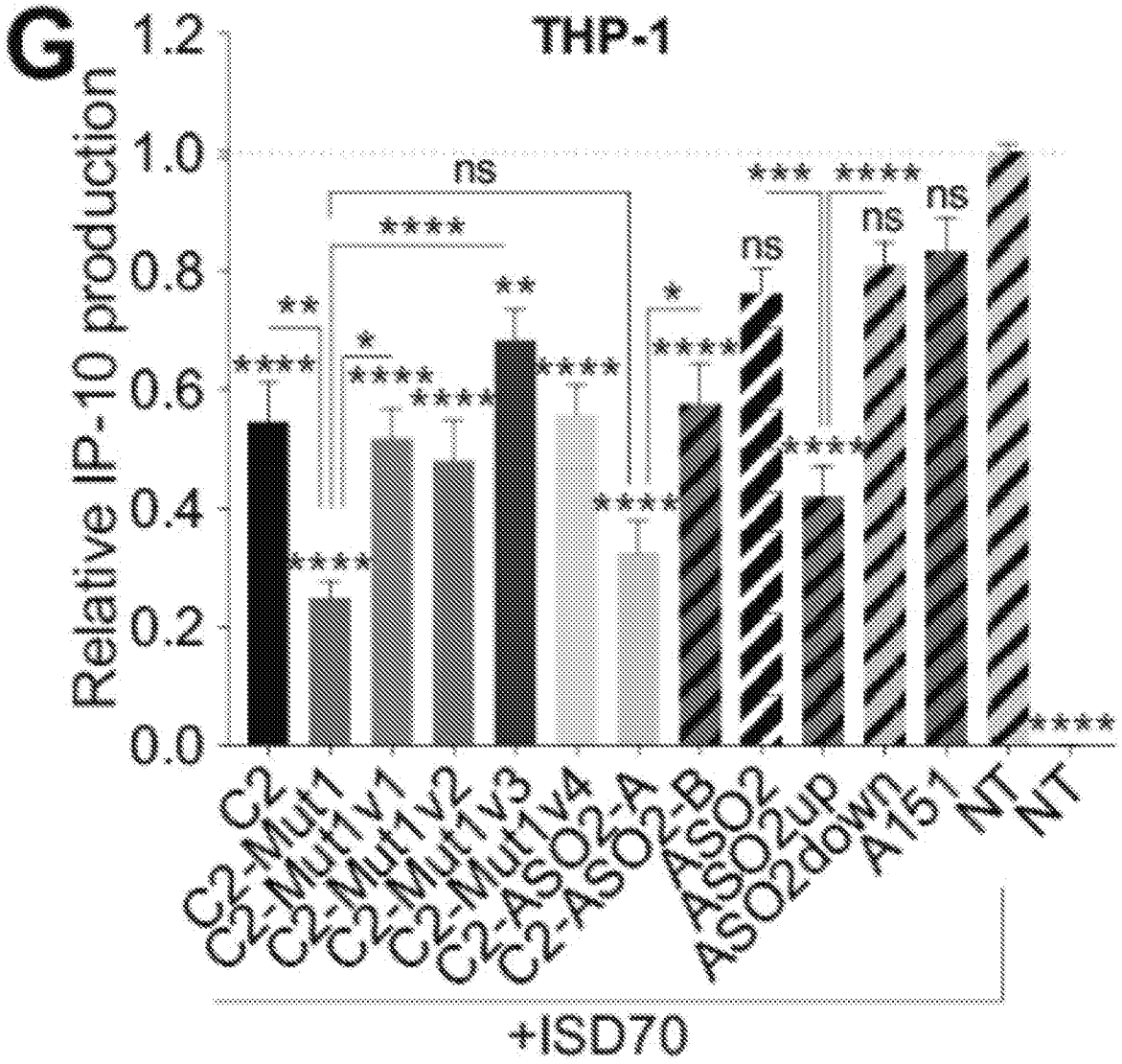
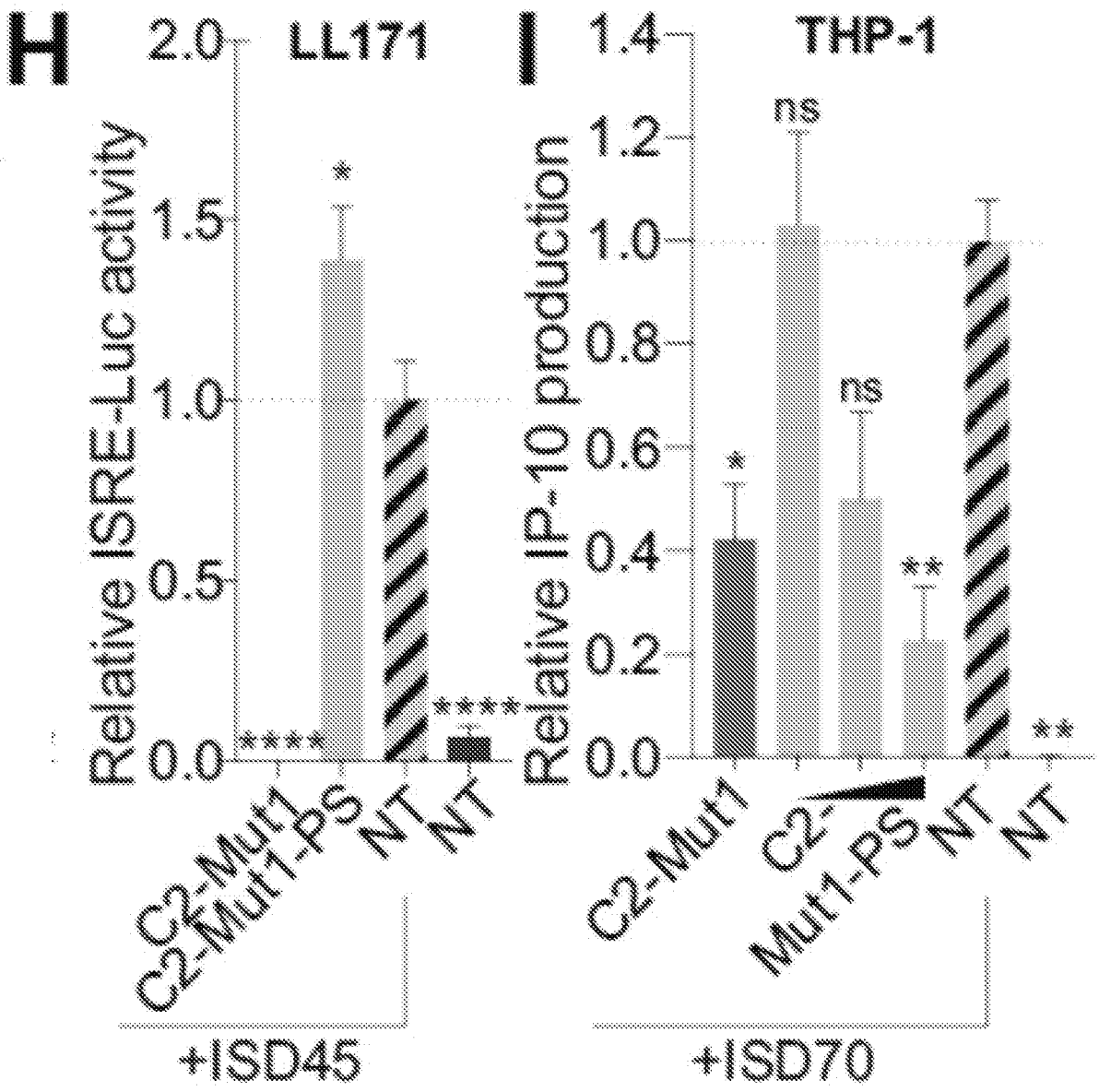

G
THP-1
Relative IP-10 production
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
****
**
*
***
C2
C2-Mut1
C2-Mut1v1
C2-Mut1v2
C2-Mut1v3
C2-Mut1v4
C2-ASO2-A
C2-ASO2-B
ASO2
ASO2up
ASO2down
A151
NT
NT
+ISD70

FIGURE 2G



FIGURES 2H & 2I

J

ASO101	UCCCATCCCTTCTGCUGCCA
ASO102	GUCCCATCCCTTCTGCUGCC
ASO103	GGUCCCATCCCTTCTGCUGC
ASO106	UCUGGTCCCATCCCTUCUGC
ASO108	UCUCUGGTCCCATCCCUUCU
ASO109	CUCUCTGGTCCCATCCCUUC
ASO110	UCUCUCTGGTCCCATCCCUU
ASO111	UUCUCTCTGGTCCCAUCCCU
ASO112	CUUCUCTCTGGTCCCAUCCC
ASO113	CCUUCTCTCTGGTCCCAUCC
ASO114	CCCUUCTCTCTGGTCCCAUC
ASO115	ACCCUTCTCTCTGGTCCCAU
ASO116	CACCCTTCTCTCTGGUCCCA

FIGURE 2J

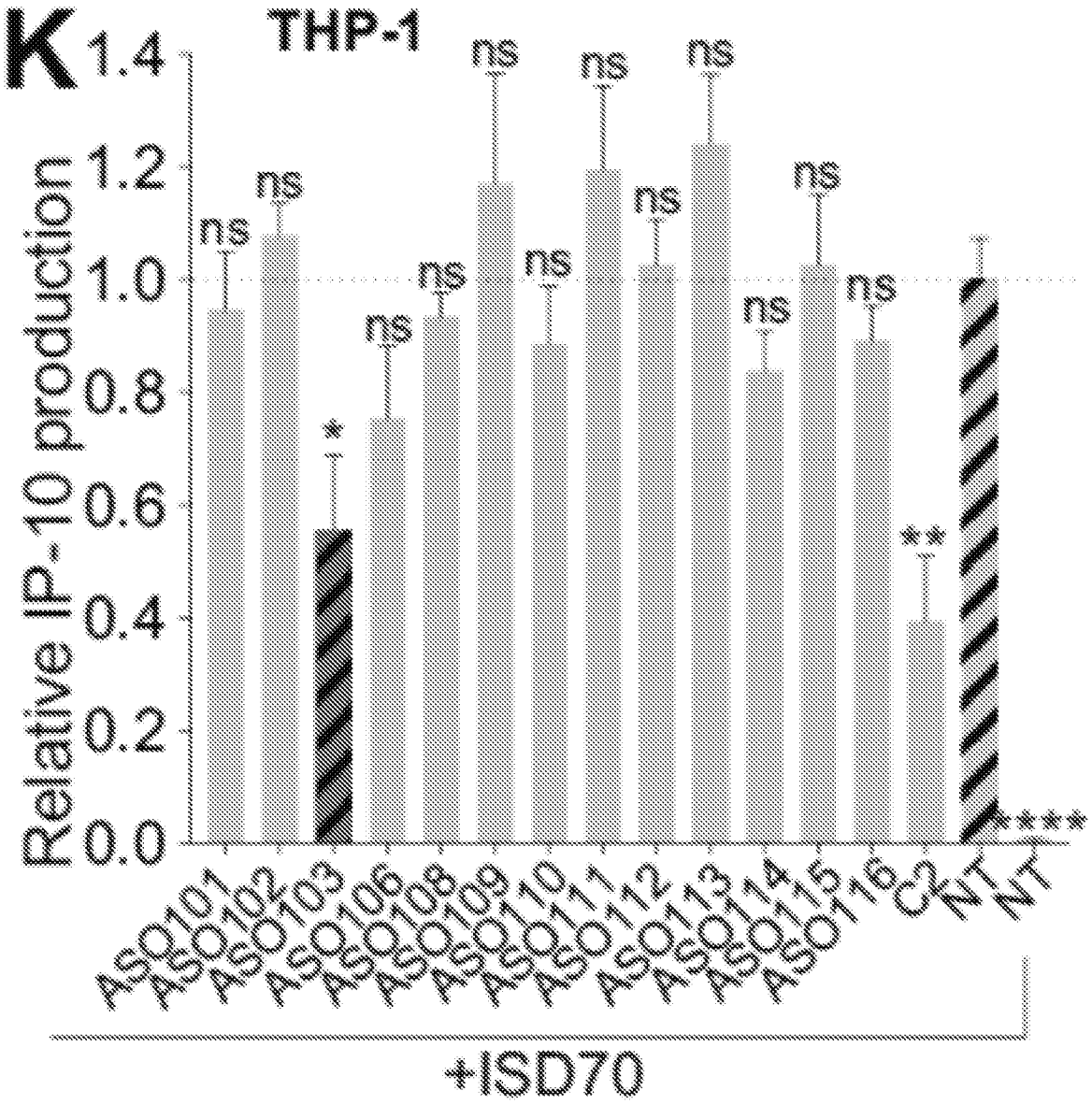

K
THP-1
Relative IP-10 production
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
*
**
****
ASO101
ASO102
ASO103
ASO106
ASO108
ASO109
ASO110
ASO111
ASO112
ASO113
ASO114
ASO115
ASO116
C2
NT
NT
+ISD70

FIGURE 2K

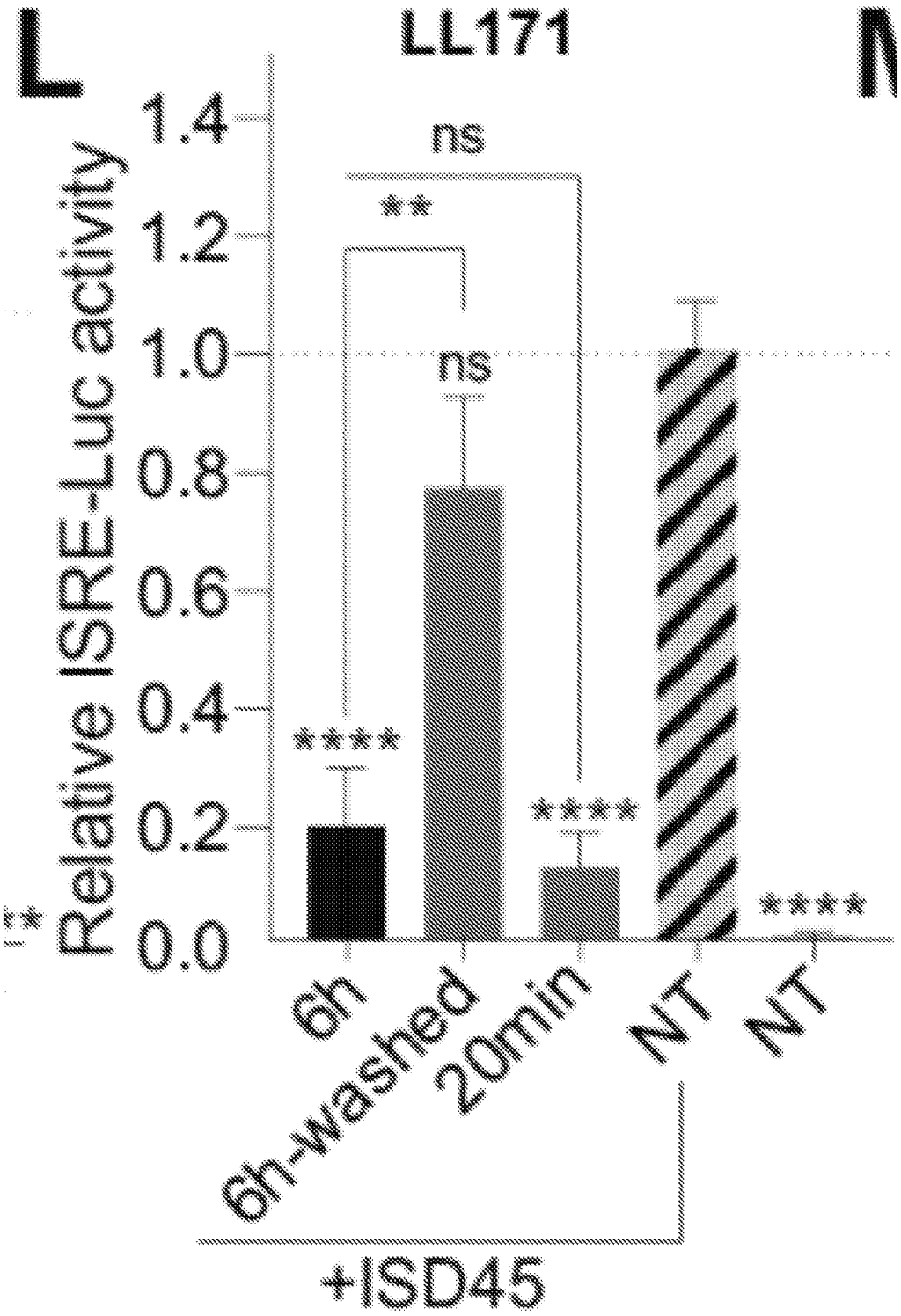

L
LL171
N
Relative ISRE-Luc activity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
**
ns
****
****
****
6h
6h-washed
20min
NT
NT
+ISD45

FIGURE 2L

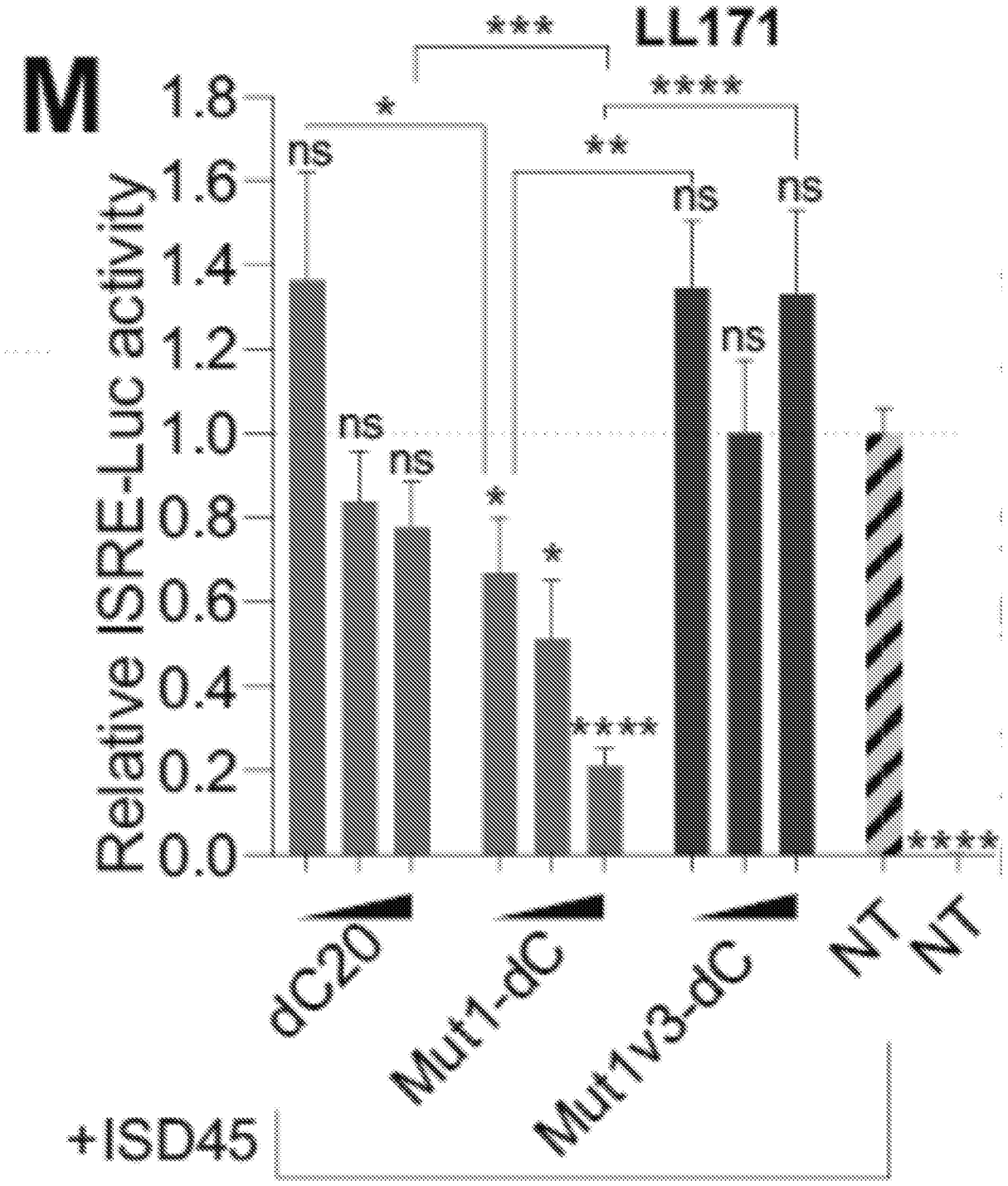

M
LL171
***
****
**
*
ns
Relative ISRE-Luc activity
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
dC20
Mut1-dC
Mut1v3-dC
NT
NT
+ISD45

FIGURE 2M

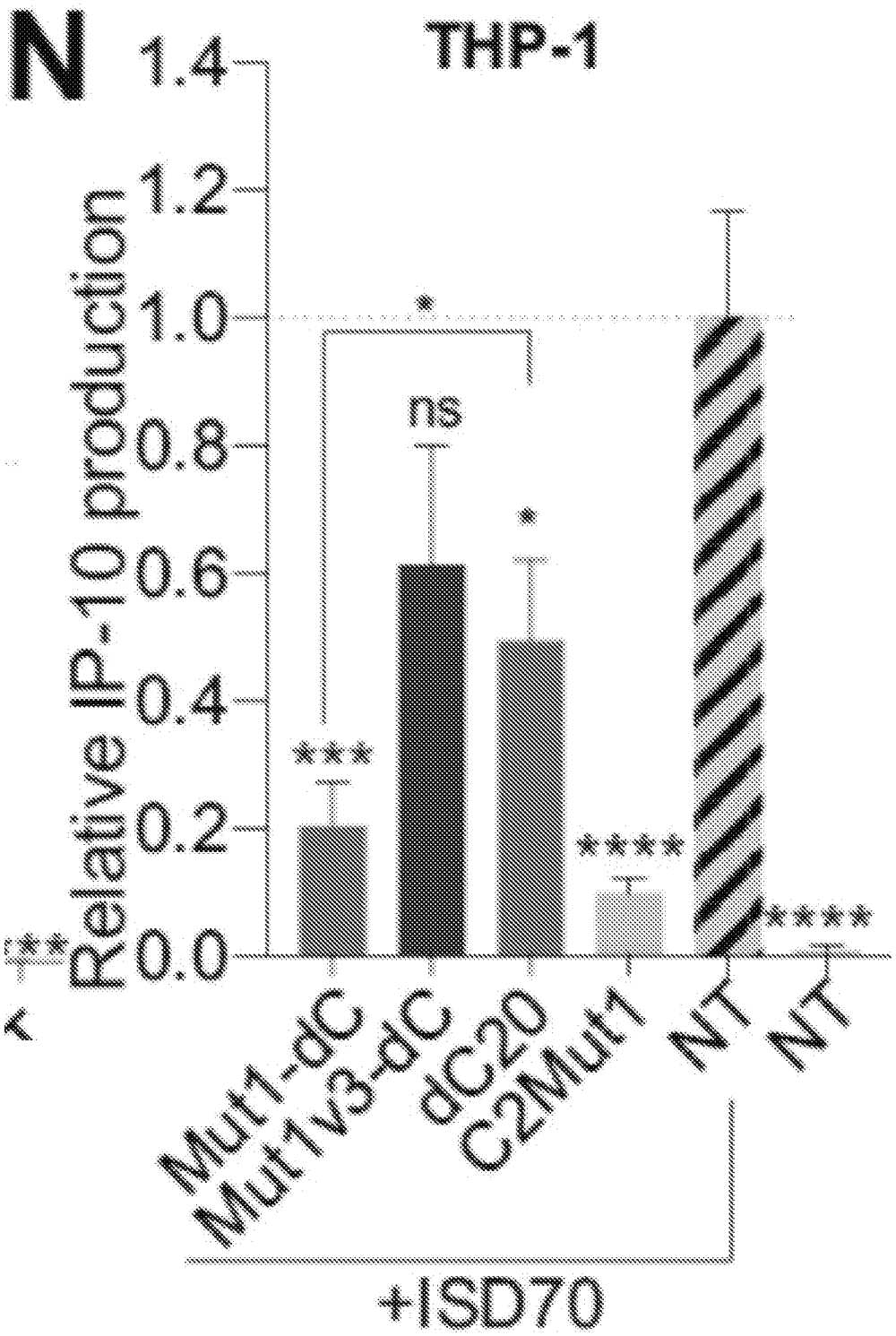

N
THP-1
Relative IP-10 production
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
ns
*
***
****
****
Mut1-dC
Mut1v3-dC
dC20
C2Mut1
NT
NT
+ISD70

FIGURE 2N

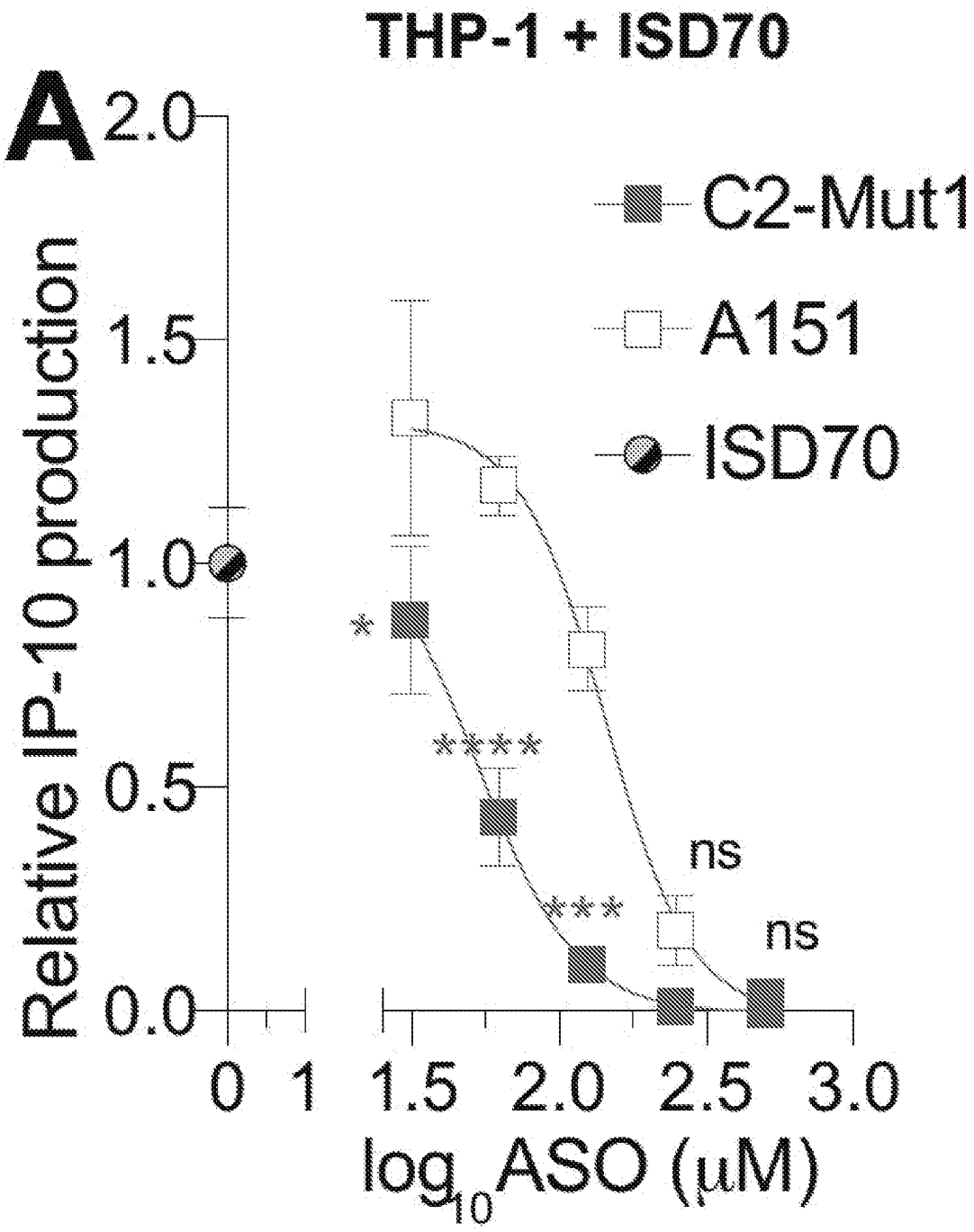

THP-1 + ISD70
A
2.0
1.5
1.0
0.5
0.0
Relative IP-10 production
C2-Mut1
A151
ISD70
*
****
***
ns
ns
0
1
1.5
2.0
2.5
3.0
log10ASO (μM)

FIGURE 3A

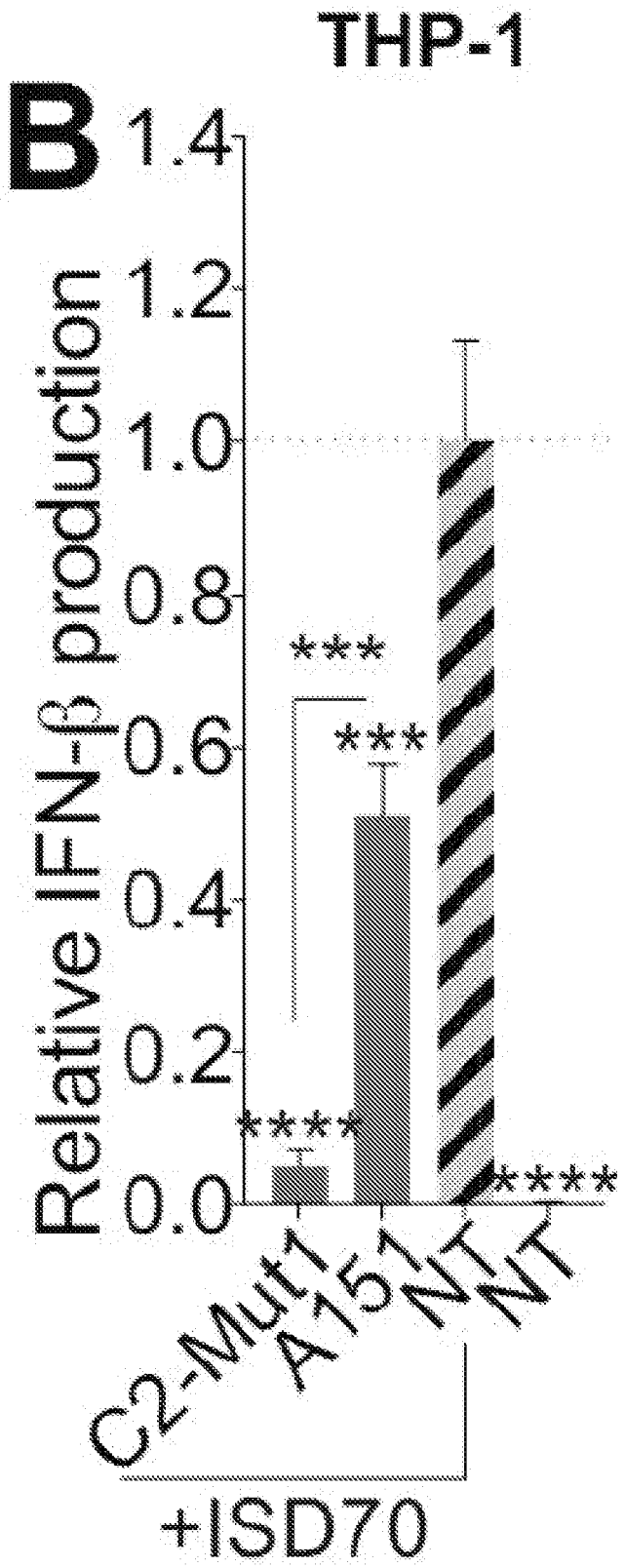

THP-1
B
Relative IFN-β production
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
***
***
****
****
C2-Mut1
A151
NT
NT
+ISD70

FIGURE 3B

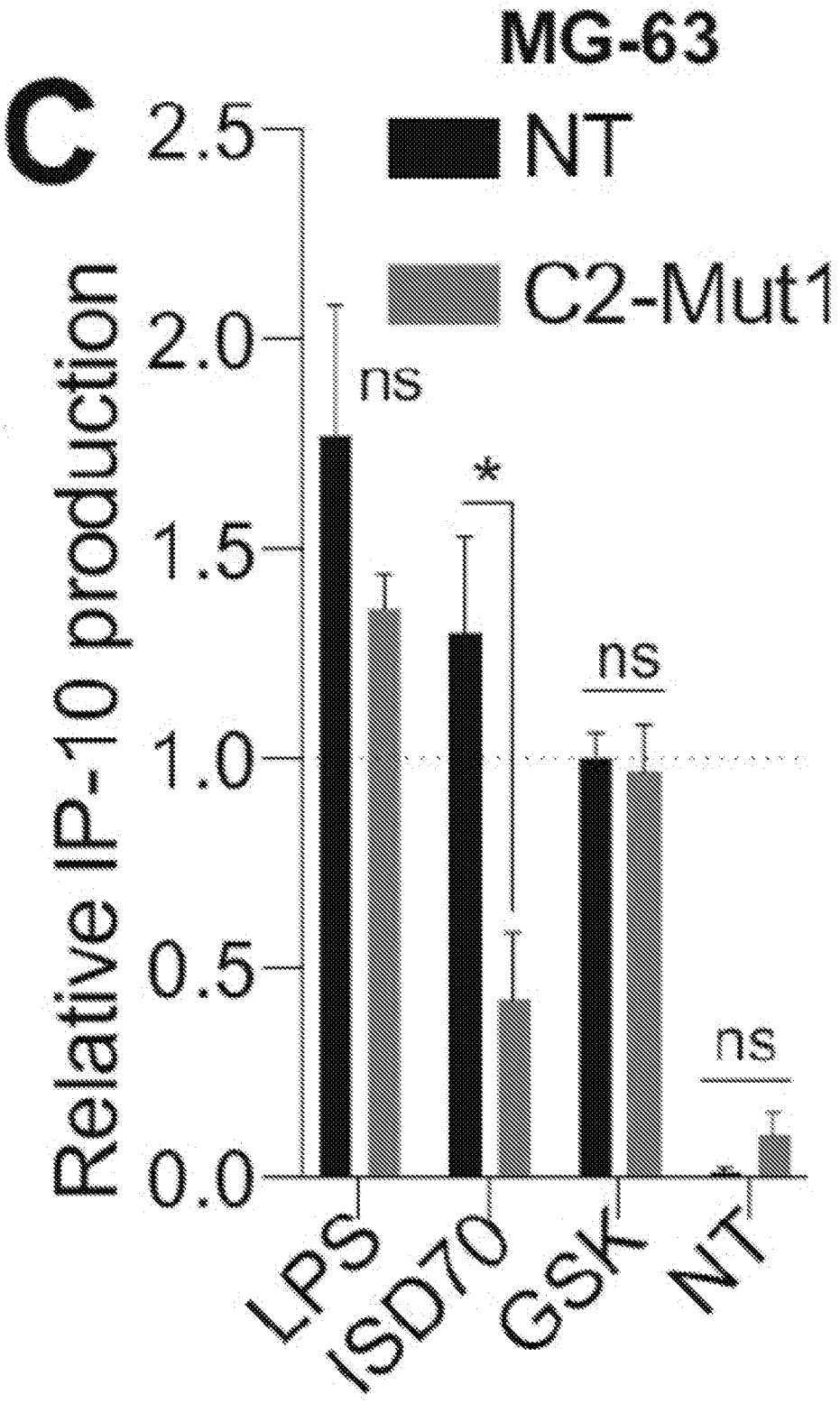

C
MG-63
NT
C2-Mut1
Relative IP-10 production
2.5
2.0
1.5
1.0
0.5
0.0
ns
*
ns
ns
LPS
ISD70
GSK
NT

FIGURE 3C

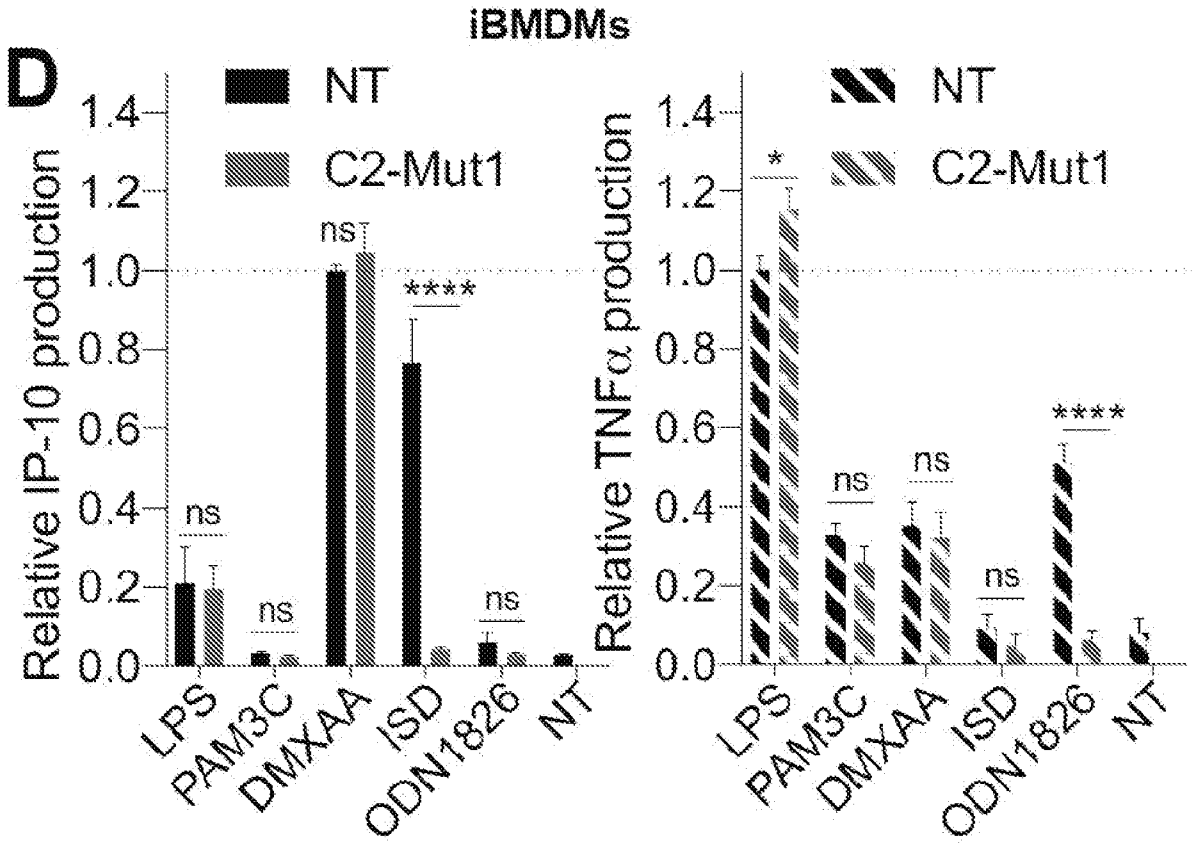

D
iBMDMs
NT
C2-Mut1
Relative IP-10 production
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
ns
ns
****
ns
LPS
PAM3C
DMXAA
ISD
ODN1826
NT
NT
C2-Mut1
Relative TNFα production
*
ns
ns
ns
****
LPS
PAM3C
DMXAA
ISD
ODN1826
NT

FIGURE 3D

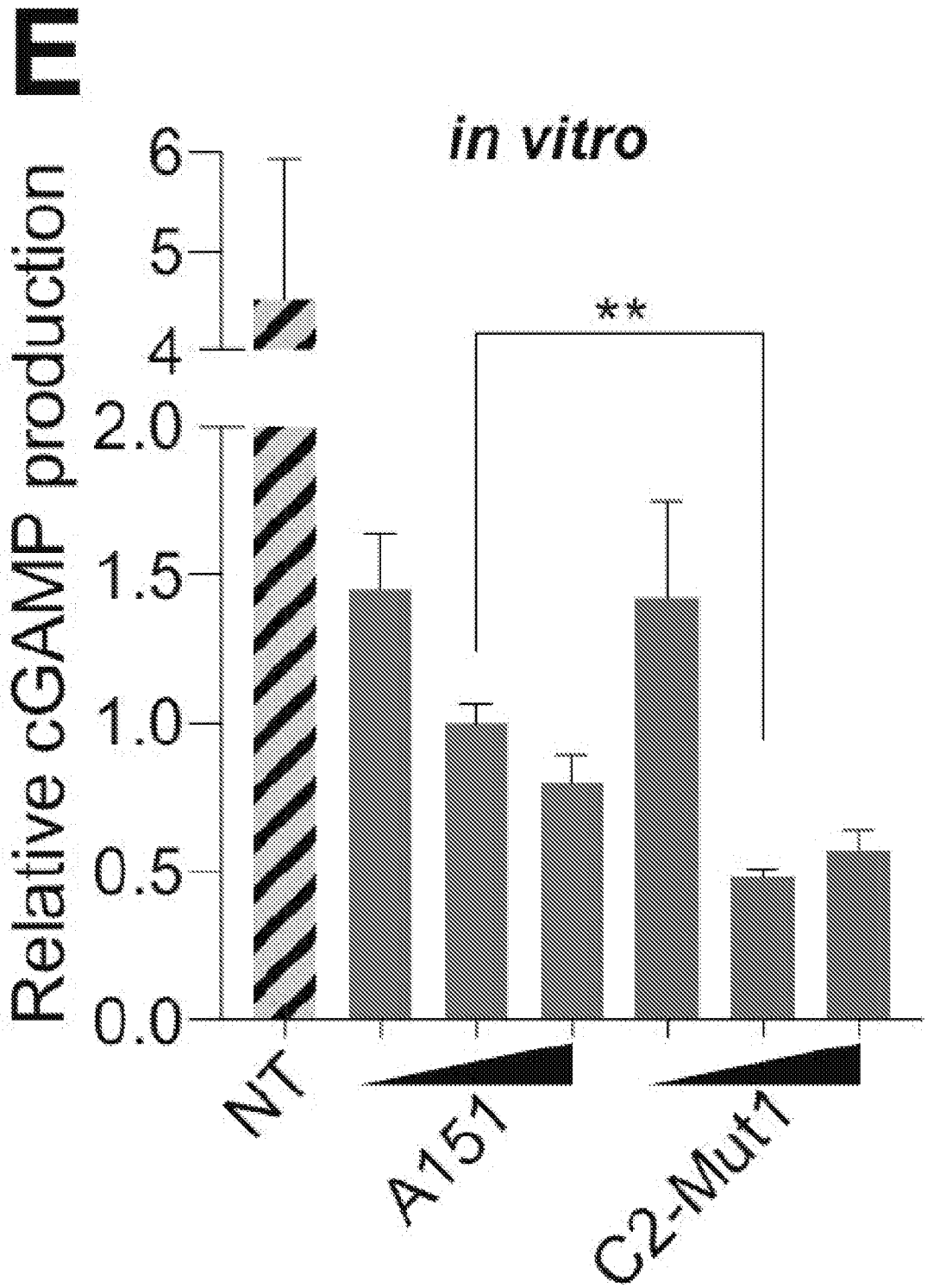

in vitro
Relative cGAMP production
6
5
4
2.0
1.5
1.0
0.5
0.0
**
NT
A151
C2-Mut1

FIGURE 3E

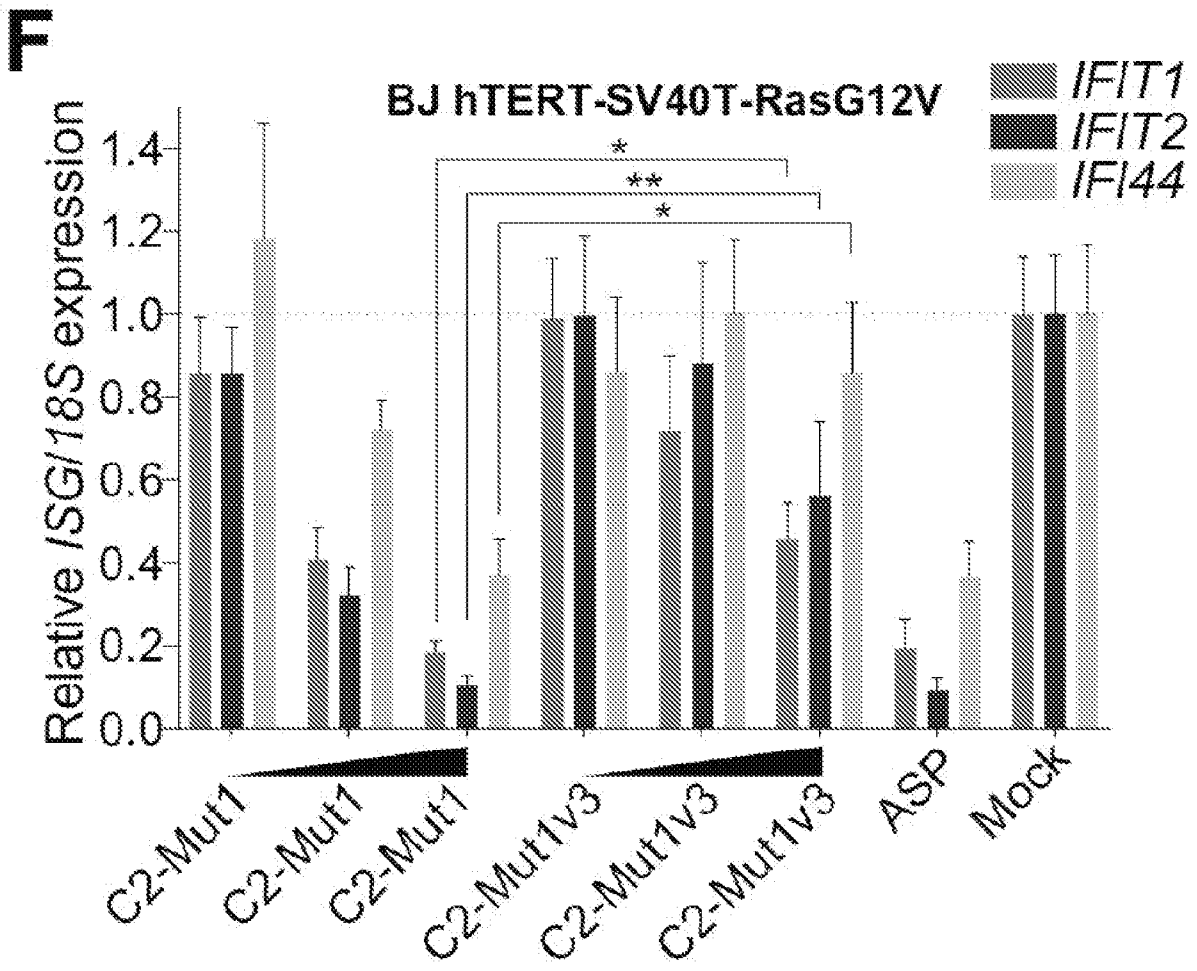

F
BJ hTERT-SV40T-RasG12V
IFIT1
IFIT2
IFI44
Relative ISG/18S expression
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
**
*
C2-Mut1
C2-Mut1
C2-Mut1
C2-Mut1v3
C2-Mut1v3
C2-Mut1v3
ASP
Mock

FIGURE 3F

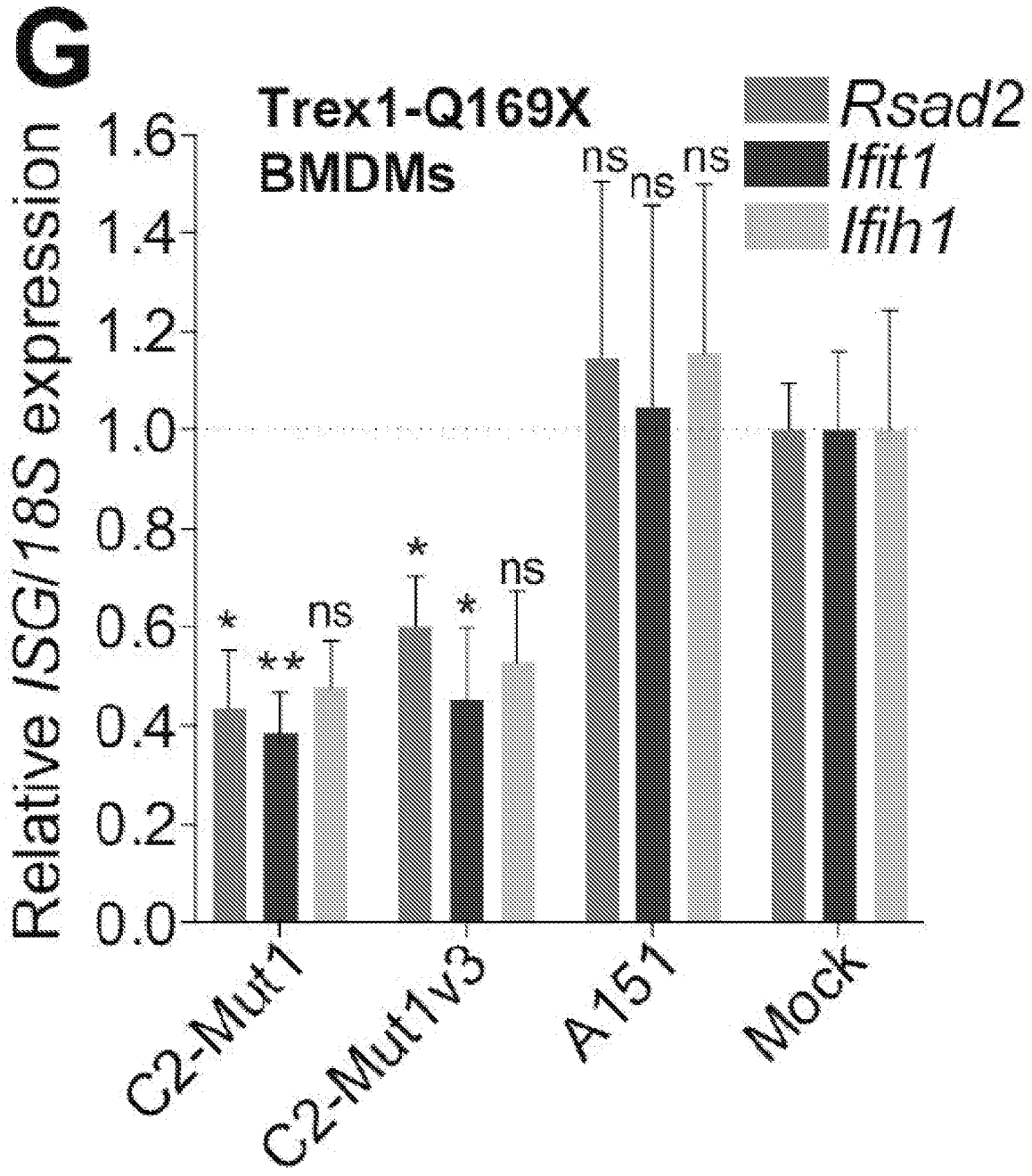
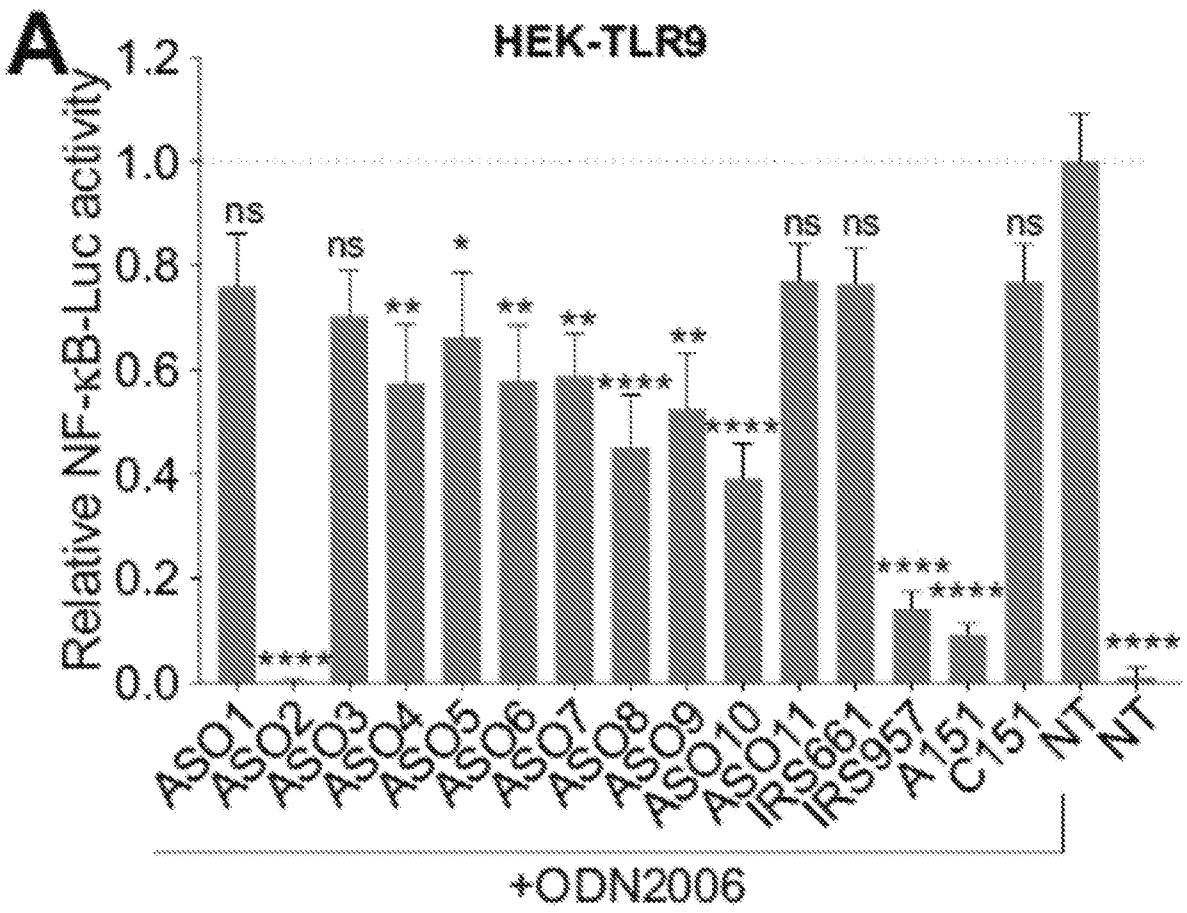

G
Trex1-Q169X
BMDMs
Rsad2
Ifit1
Ifih1
Relative ISG/18S expression
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
*
**
ns
*
*
ns
ns
ns
ns
C2-Mut1
C2-Mut1v3
A151
Mock

FIGURE 3G





ASO2	UCCGGCCTCGGAAGCUCUCU
ASO2up	UCCGGCCTCGGAGTCUCCAU
ASO2down	UCCGGCCTCGGCAGAUAUCG
ASO11	CUUUAGTCGTAGTTGCUUCC
ASO11Mut1	CUUUAGTCGTAGTTGUCUCU
ASO11Mut2	UCCGGGTCGTAGTTGCUUCC

FIGURES 4A & 4B

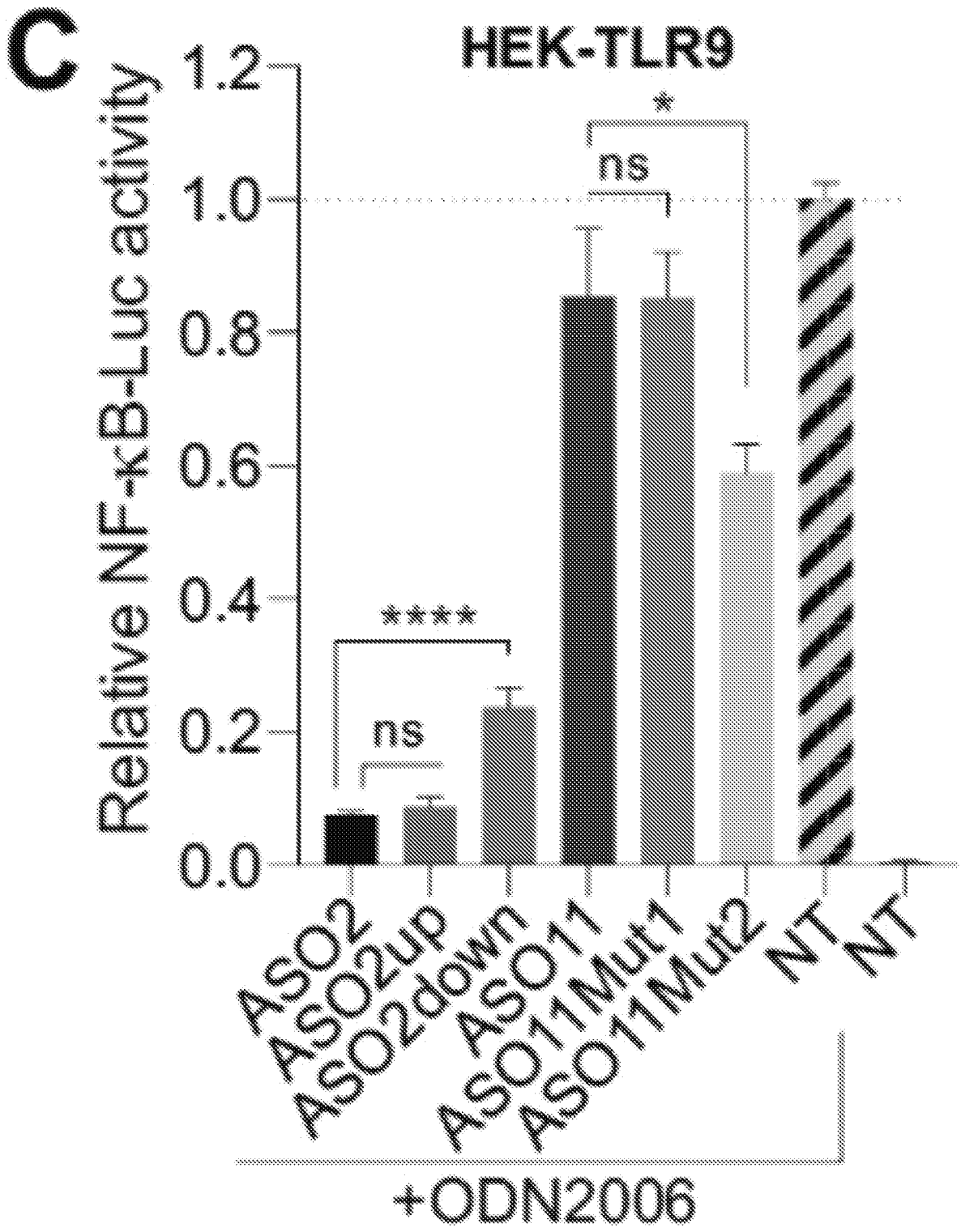

C
HEK-TLR9
Relative NF-κB-Luc activity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
****
ns
*
ns
ASO2
ASO2up
ASO2down
ASO11
ASO11Mut1
ASO11Mut2
NT
NT
+ODN2006

FIGURE 4C

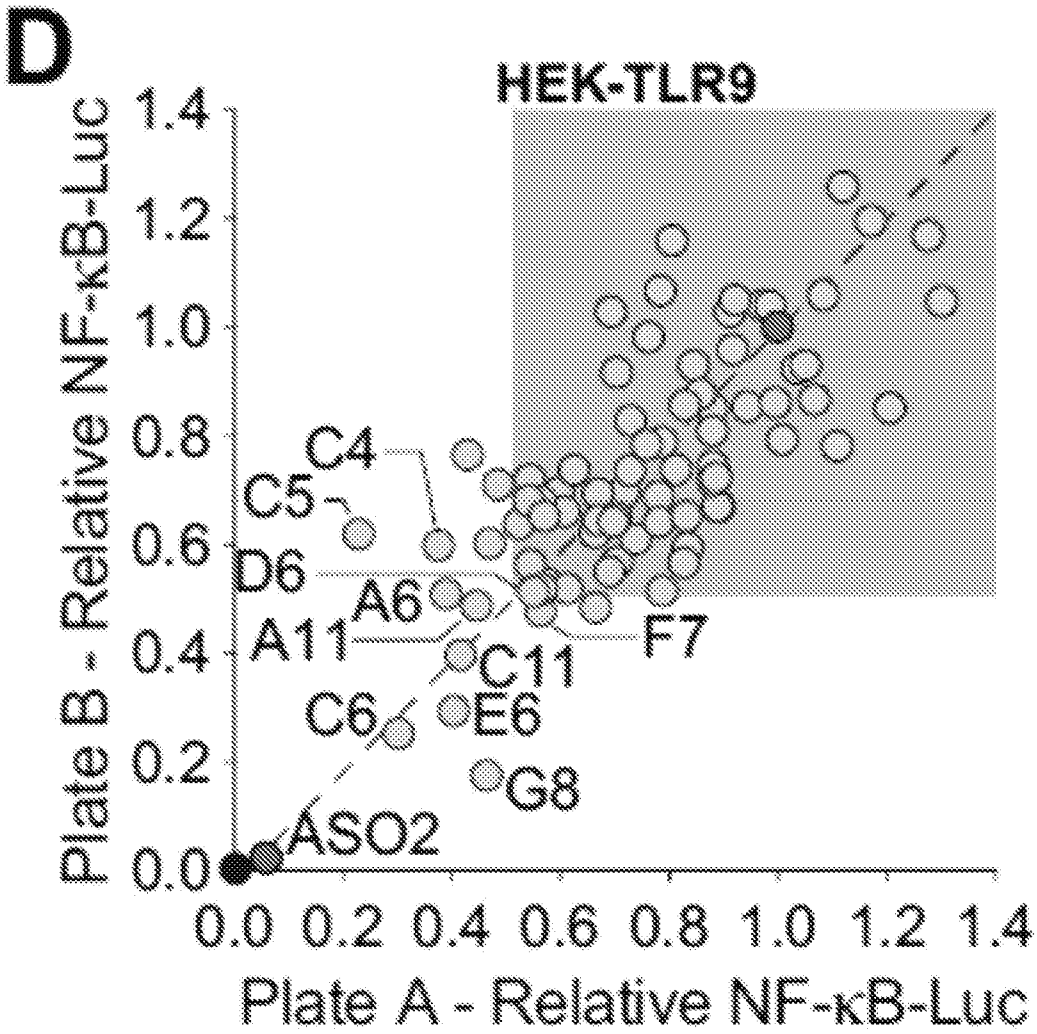
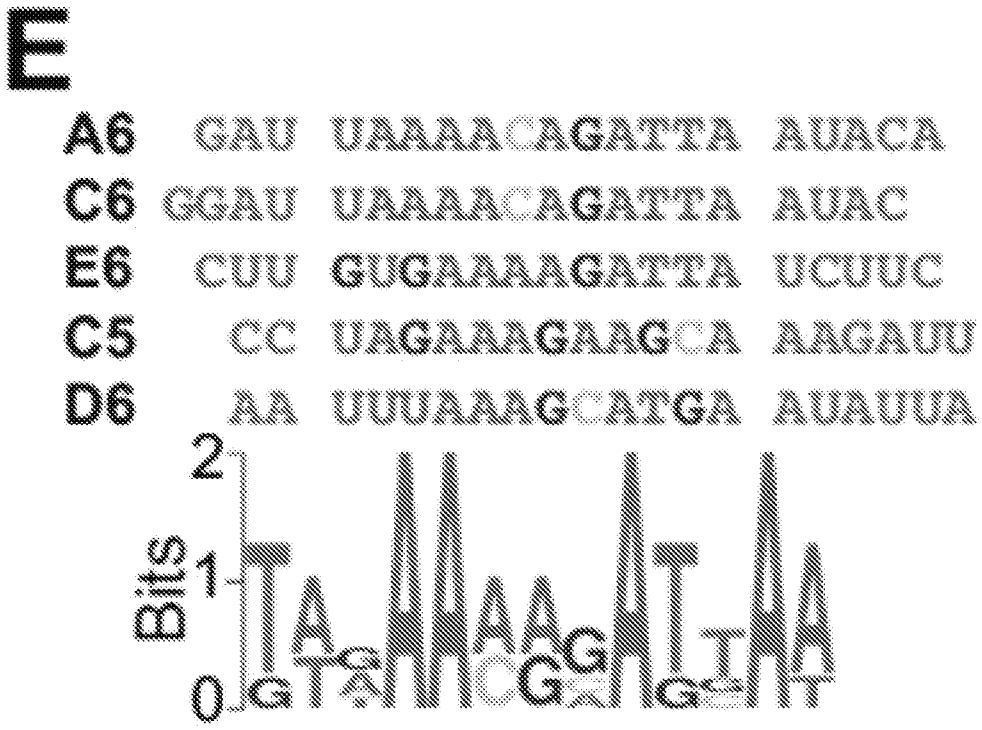

D
HEK-TLR9
Plate B - Relative NF-κB-Luc
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
C4
C5
D6
A6
A11
F7
C11
C6
E6
G8
ASO2
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
Plate A - Relative NF-κB-Luc

FIGURE 4D

E



F



FIGURES 4E & 4F

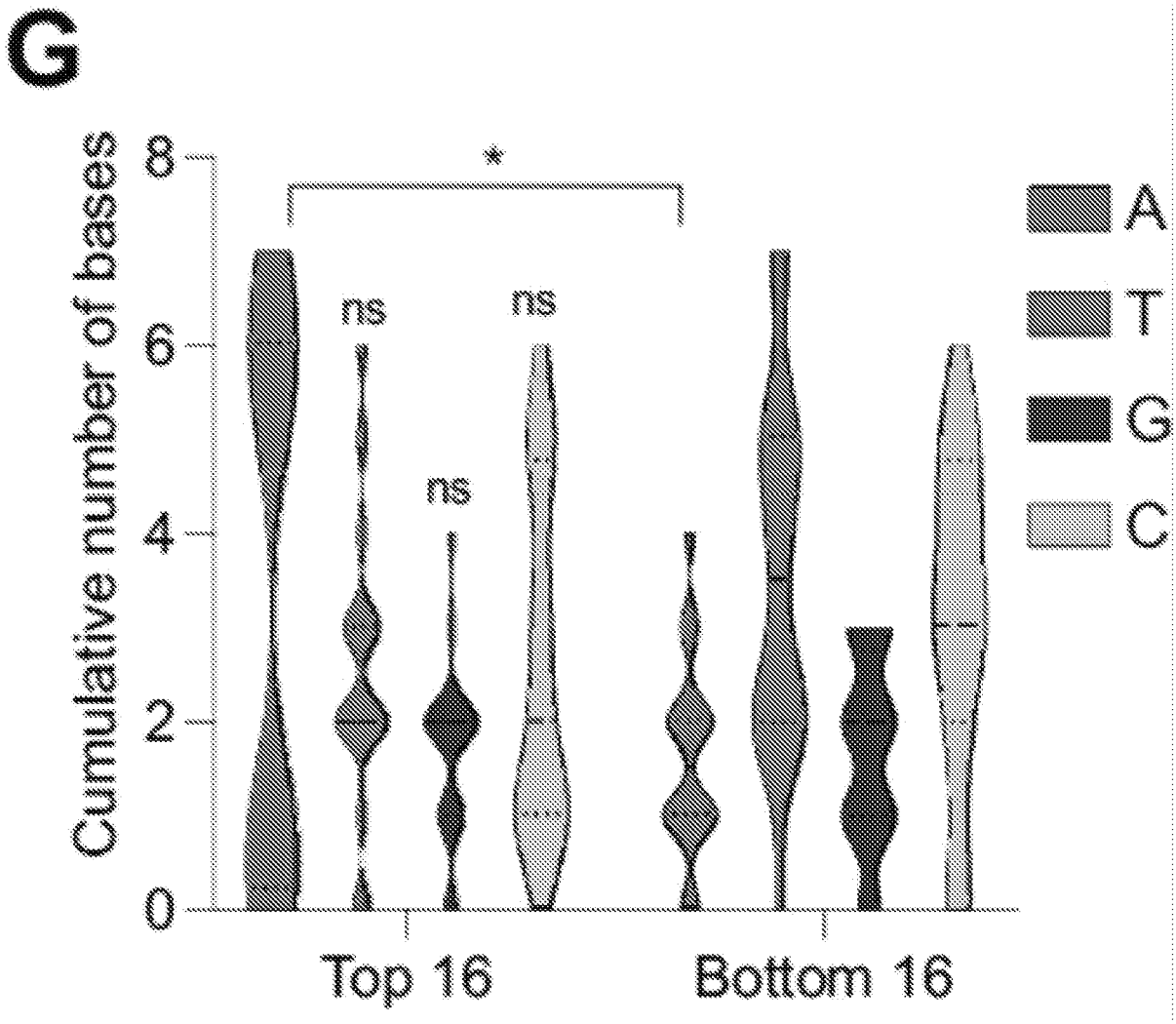

G
Cumulative number of bases
0
2
4
6
8
*
ns
ns
ns
A
T
G
C
Top 16
Bottom 16

FIGURE 4G

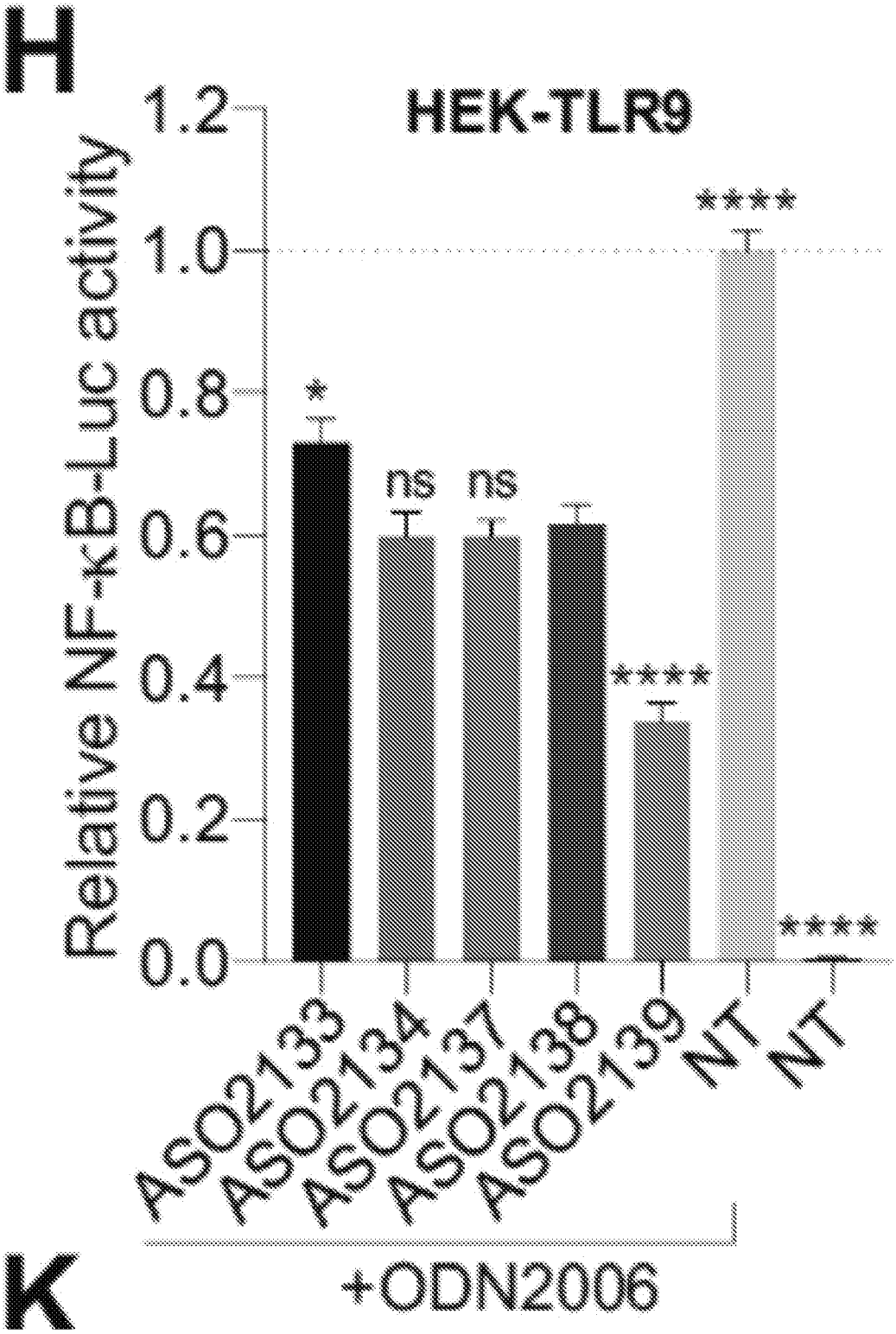

H
HEK-TLR9
Relative NF-κB-Luc activity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
****
*
ns
ns
****
****
ASO2133
ASO2134
ASO2137
ASO2138
ASO2139
NT
NT
K
+ODN2006

FIGURE 4H

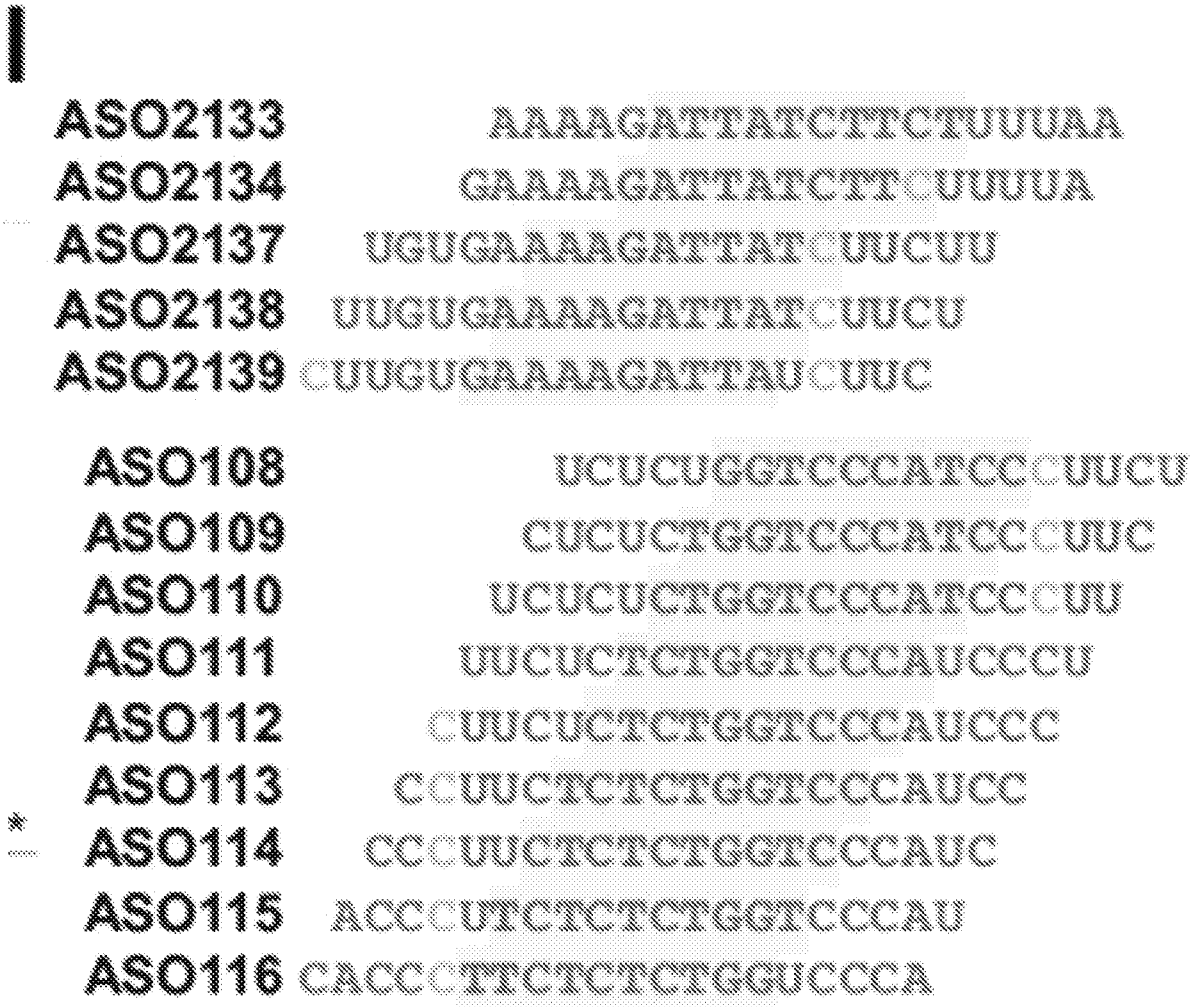
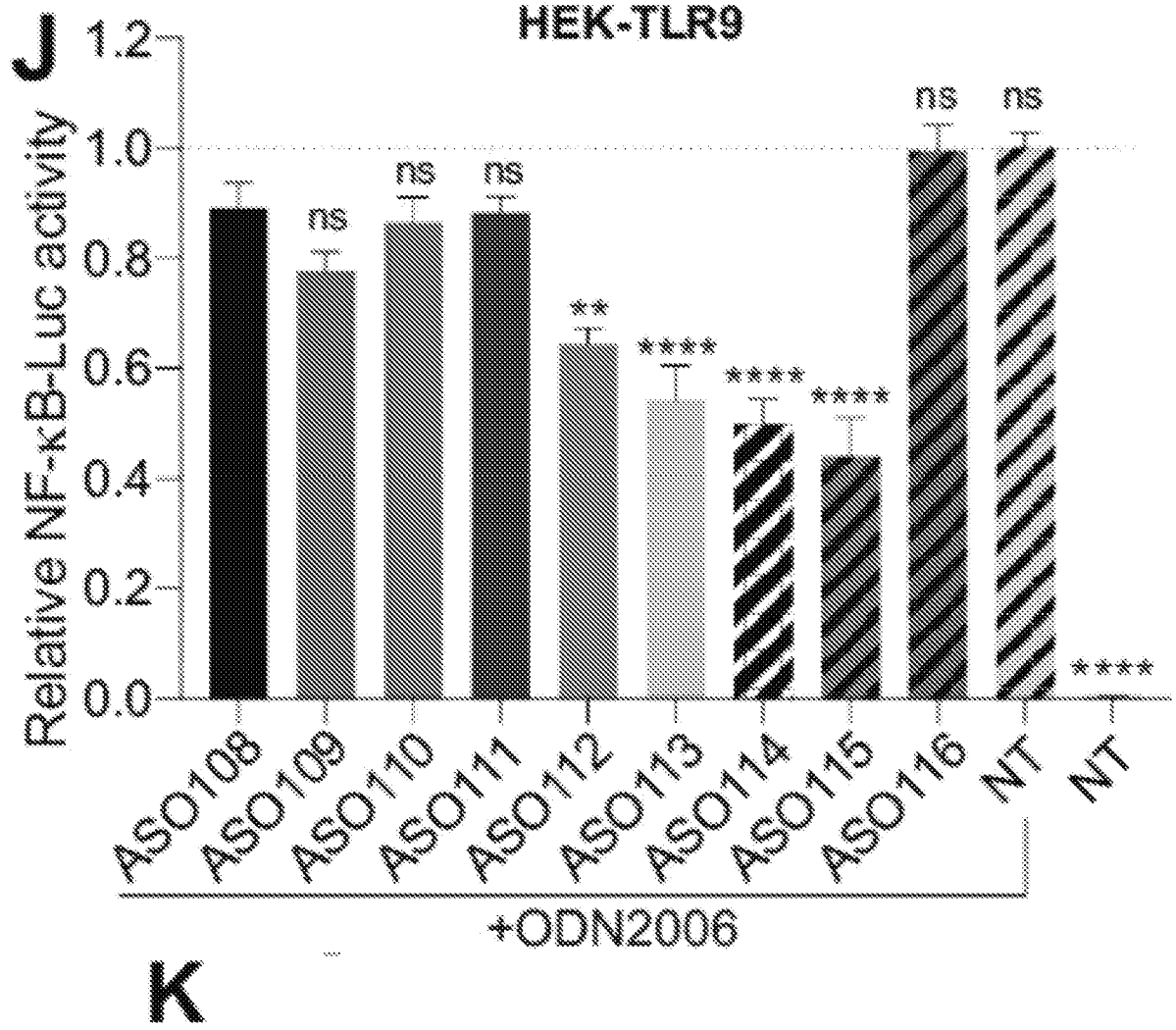

ASO2133 AAAAGATTATCTTCTUUUAA
ASO2134 GAAAAGATTATCTTCUUUUA
ASO2137 UGUGAAAAGATTATCUUCUU
ASO2138 UUGUGAAAAGATTATCUUCU
ASO2139 CUUGUGAAAAGATTAUCUUC
ASO108 UCUCUGGTCCCATCCCUUCU
ASO109 CUCUCTGGTCCCATCCCUUC
ASO110 UCUCUCTGGTCCCATCCCUU
ASO111 UUCUCTCTGGTCCCAUCCCU
ASO112 CUUCUCTCTGGTCCCAUCCC
ASO113 CCUUCTCTCTGGTCCCAUCC
ASO114 CCCUUCTCTCTGGTCCCAUC
ASO115 ACCCUTCTCTCTGGTCCCAU
ASO116 CACCCTTCTCTCTGGUCCCA

FIGURE 4I



K

HPRT551	CUUCCACAATCAAGACAUUC
HPRT660	CUUCGTGGGGTCCTTUUCAC
HPRT661	ACUUCGTGGGGTCCTUUUCA
HPRT662	CACUUCGTGGGGTCCUUUUC
HPRT664	AACACTTCGTGGGGTCCUUU
HPRT665	CAACACTTCGTGGGGUCCUU
HPRT666	CCAACACTTCGTGGGGUCCU

FIGURES 4J & 4K

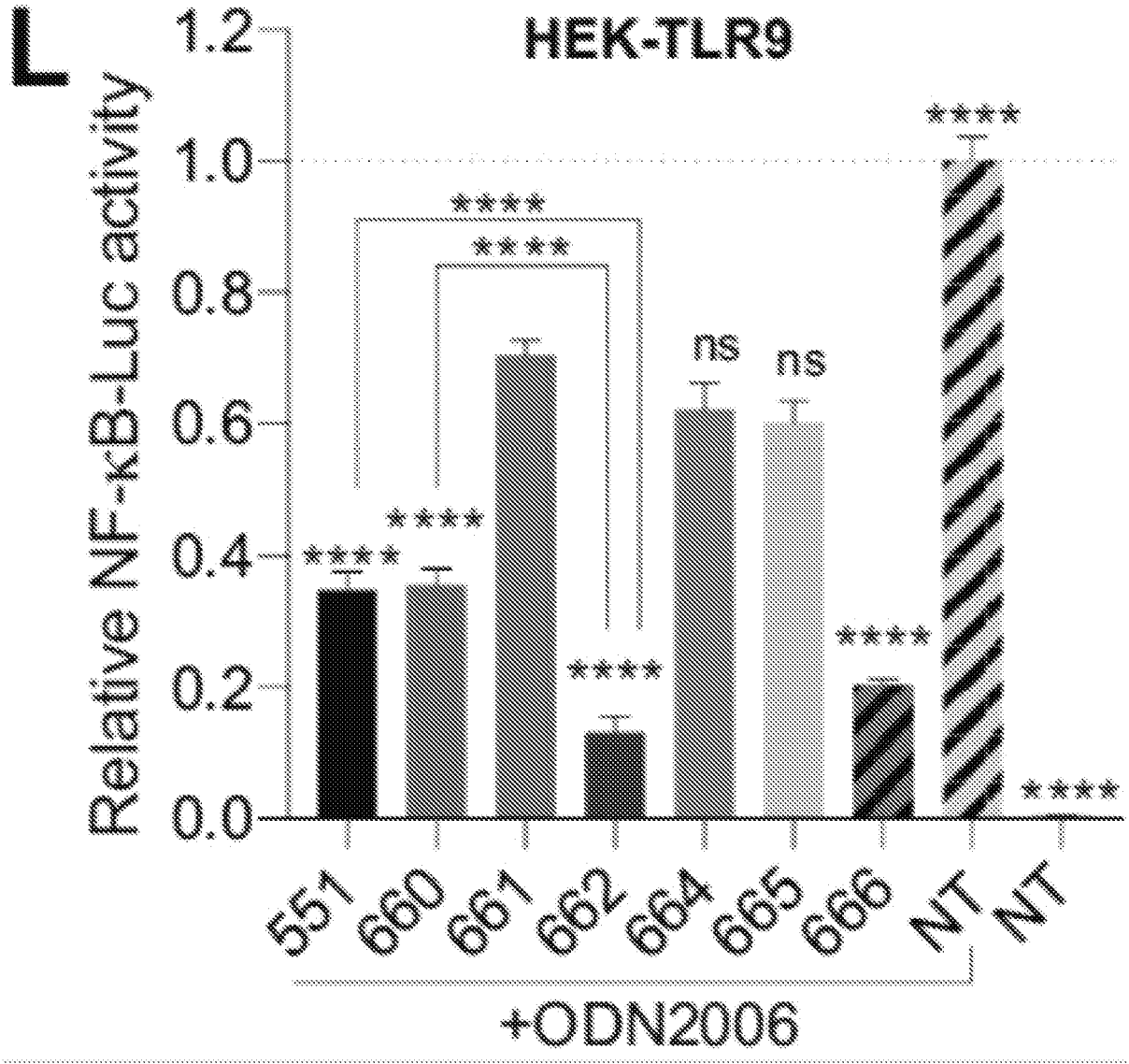

L
HEK-TLR9
Relative NF-κB-Luc activity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
****
****
****
****
****
ns
ns
****
****
****
551
660
661
662
664
665
666
NT
NT
+ODN2006

FIGURE 4L

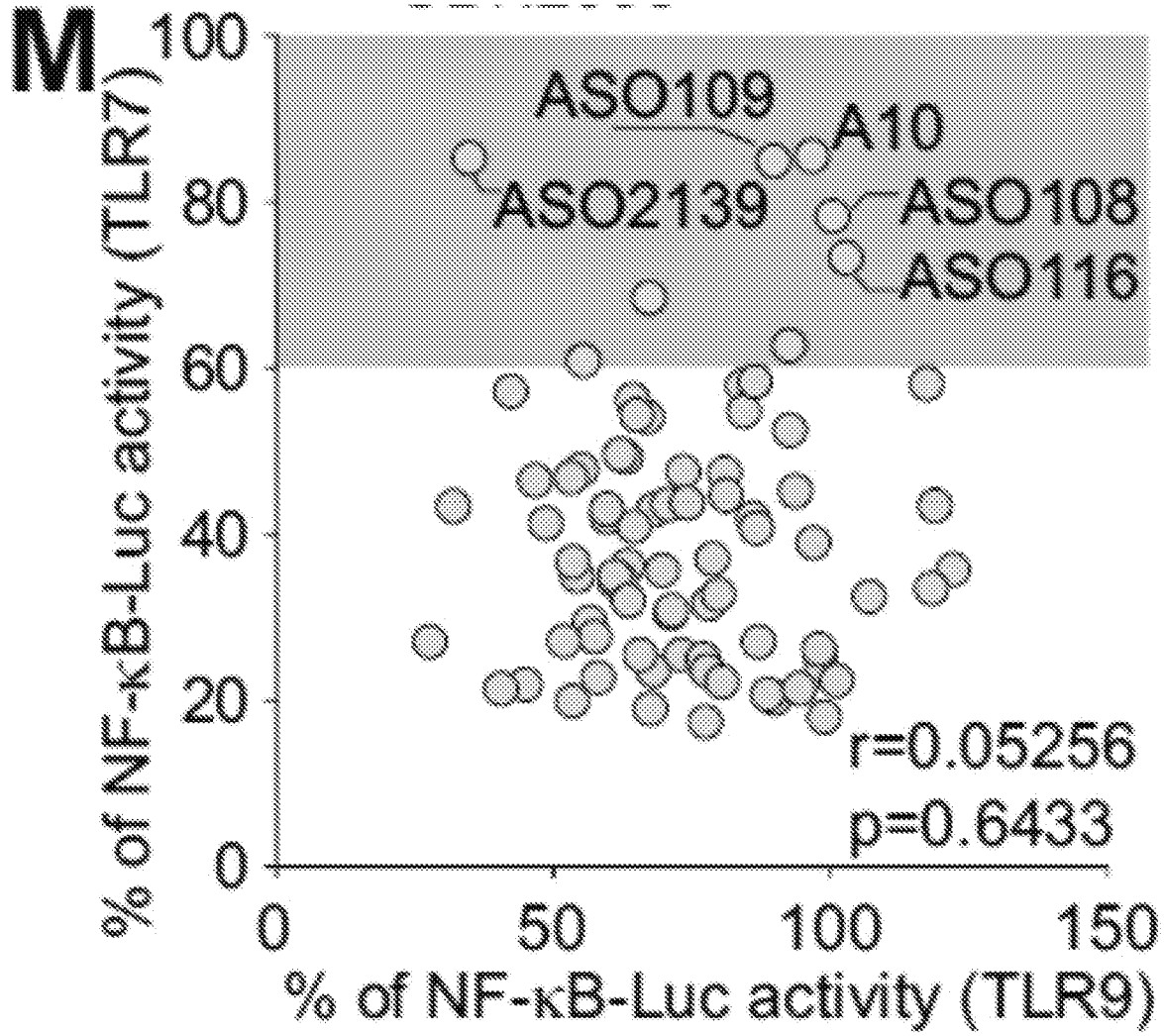

M
100
80
60
40
20
0
% of NF-κB-Luc activity (TLR7)
ASO109
A10
ASO2139
ASO108
ASO116
r=0.05256
p=0.6433
0
50
100
150
% of NF-κB-Luc activity (TLR9)

FIGURE 4M

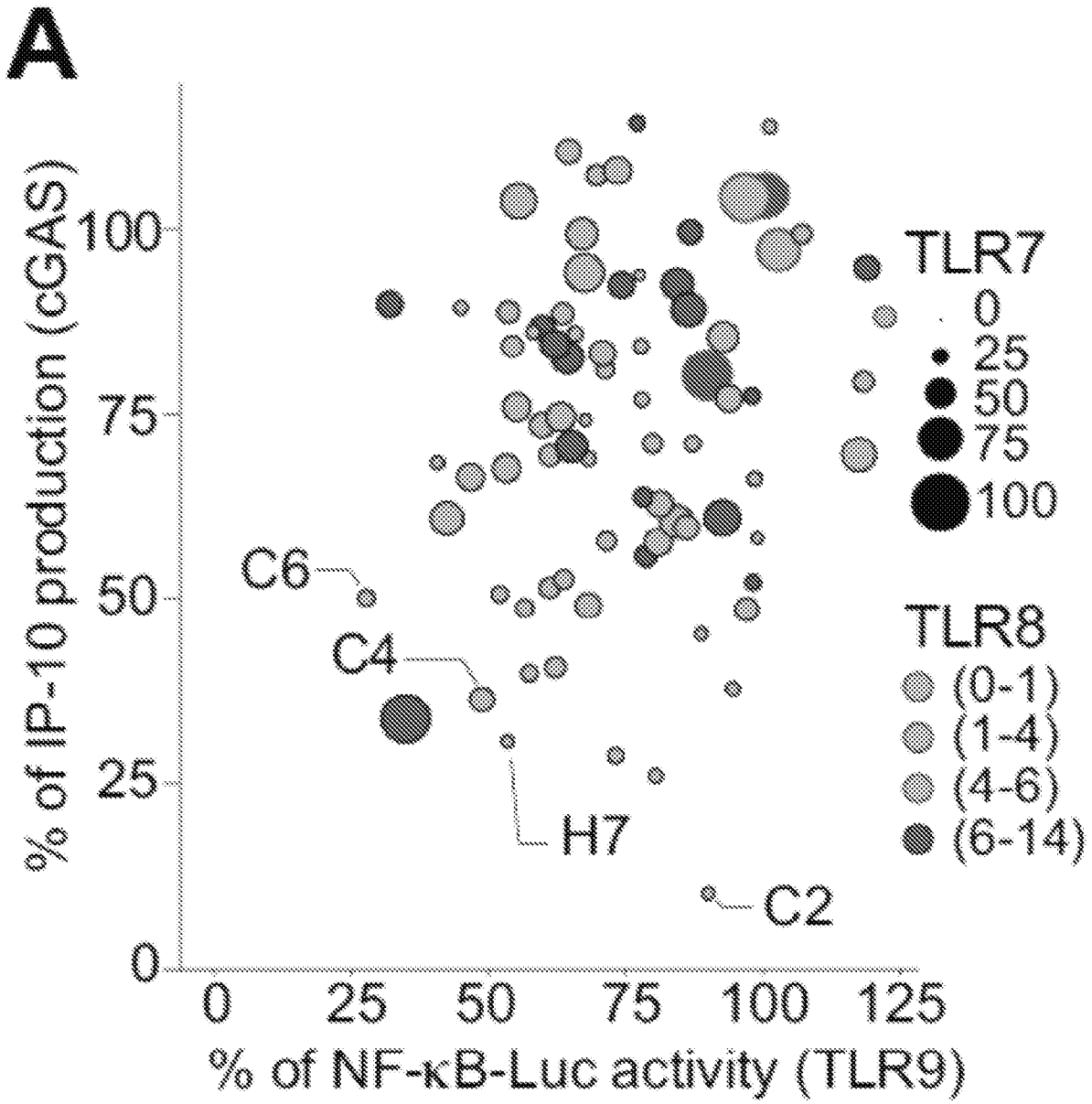

A
% of IP-10 production (cGAS)
100
75
50
25
0
0
25
50
75
100
125
% of NF-κB-Luc activity (TLR9)
C6
C4
H7
C2
TLR7
0
25
50
75
100
TLR8
(0-1)
(1-4)
(4-6)
(6-14)

FIGURE 5A

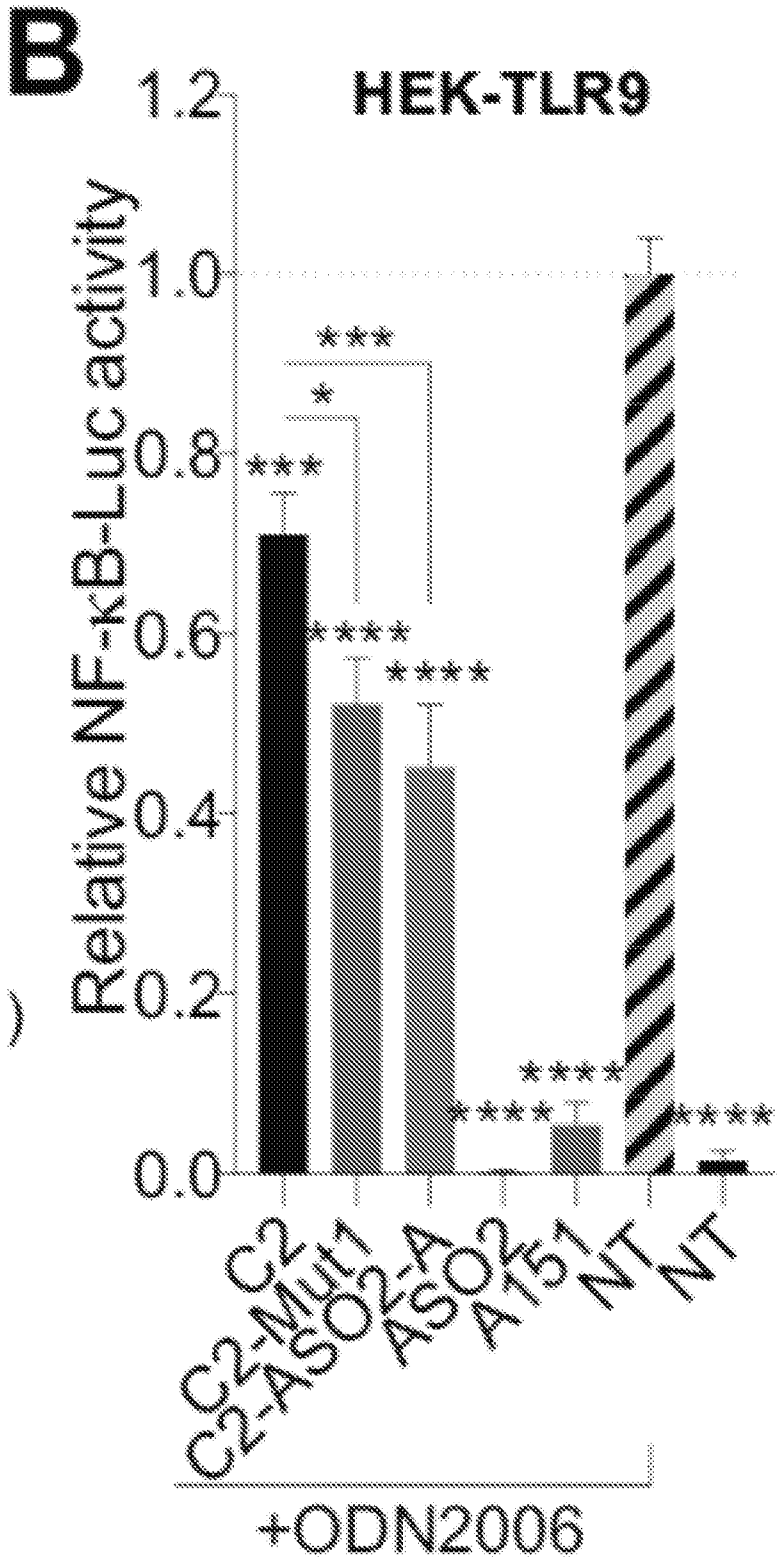

B
HEK-TLR9
Relative NF-κB-Luc activity
1.2
1.0
0.8
0.6
0.4
0.2
0.0
***
*
***
****
****
****
****
****
C2
C2-MUT1
C2-ASO2-A
ASO2
A151
NT
NT
+ODN2006

FIGURE 5B

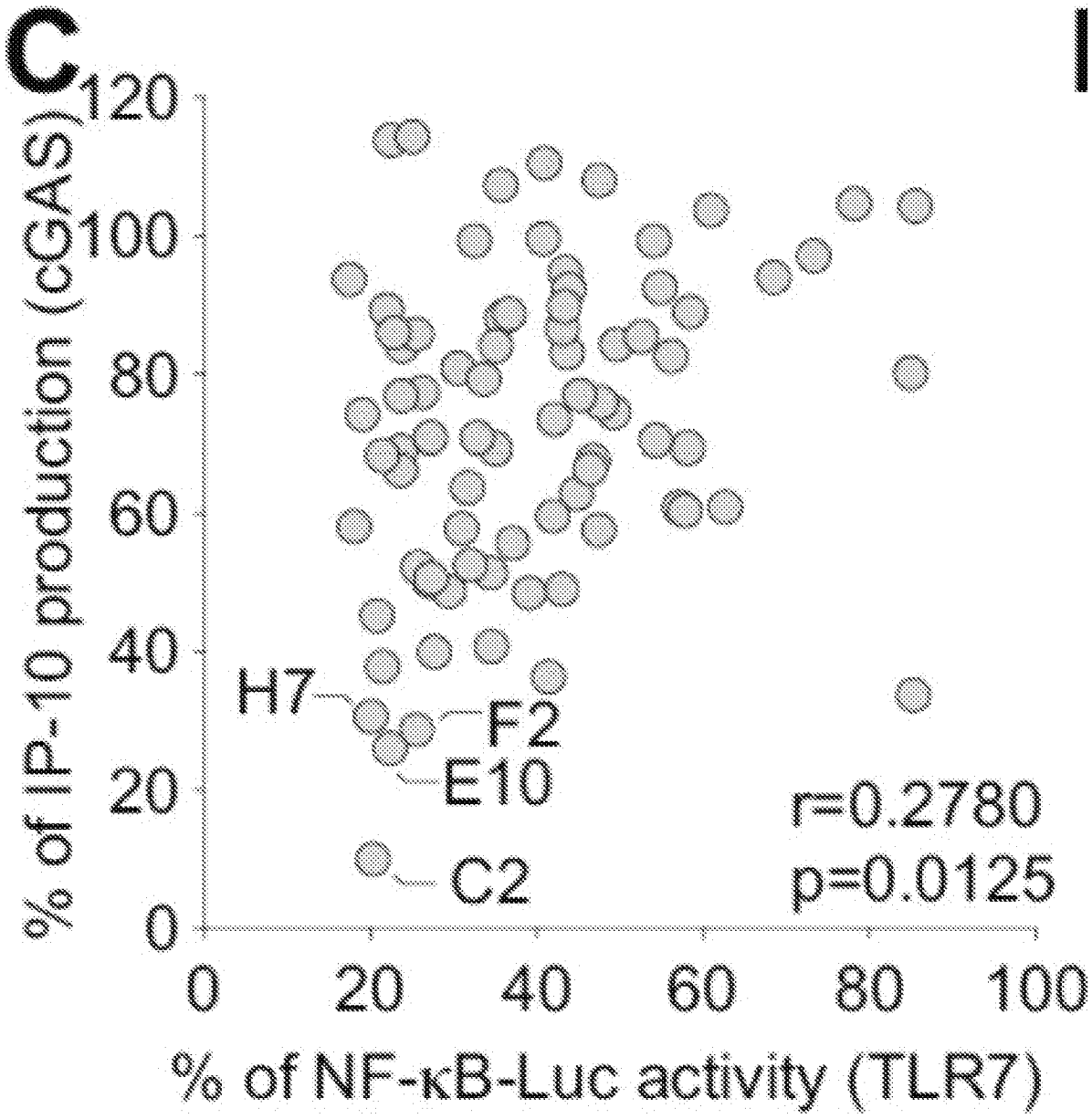

C
% of IP-10 production (cGAS)
120
100
80
60
40
20
0
H7
F2
E10
C2
r=0.2780
p=0.0125
0
20
40
60
80
100
% of NF-κB-Luc activity (TLR7)

FIGURE 5C

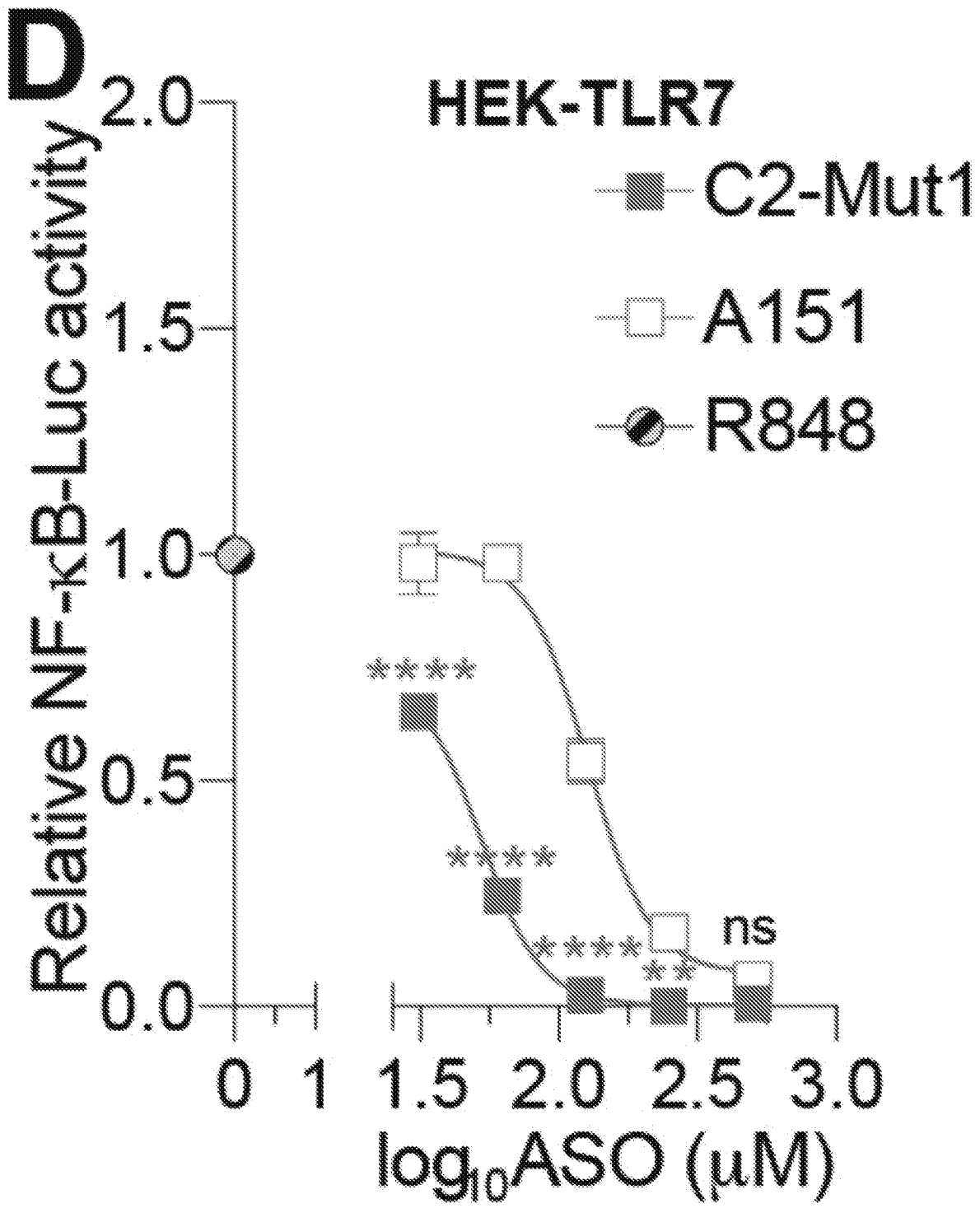

D
HEK-TLR7
C2-Mut1
A151
R848
Relative NF-κB-Luc activity
2.0
1.5
1.0
0.5
0.0
****
****
****
ns
**
0 1 1.5 2.0 2.5 3.0
log10ASO (μM)

FIGURE 5D

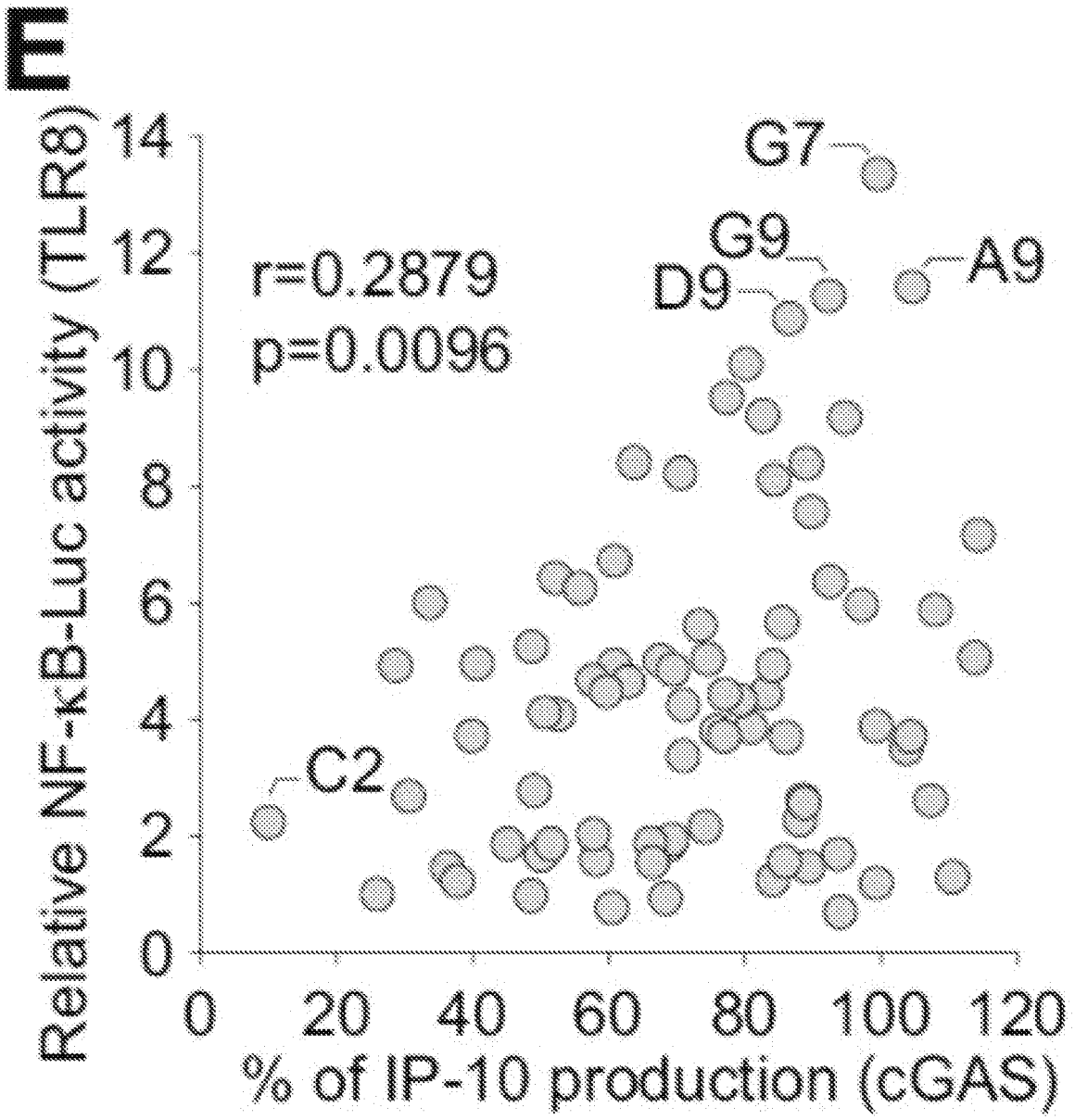

E
Relative NF-κB-Luc activity (TLR8)
14
12
10
8
6
4
2
0
r=0.2879
p=0.0096
G7
G9
D9
A9
C2
0
20
40
60
80
100
120
% of IP-10 production (cGAS)

FIGURE 5E

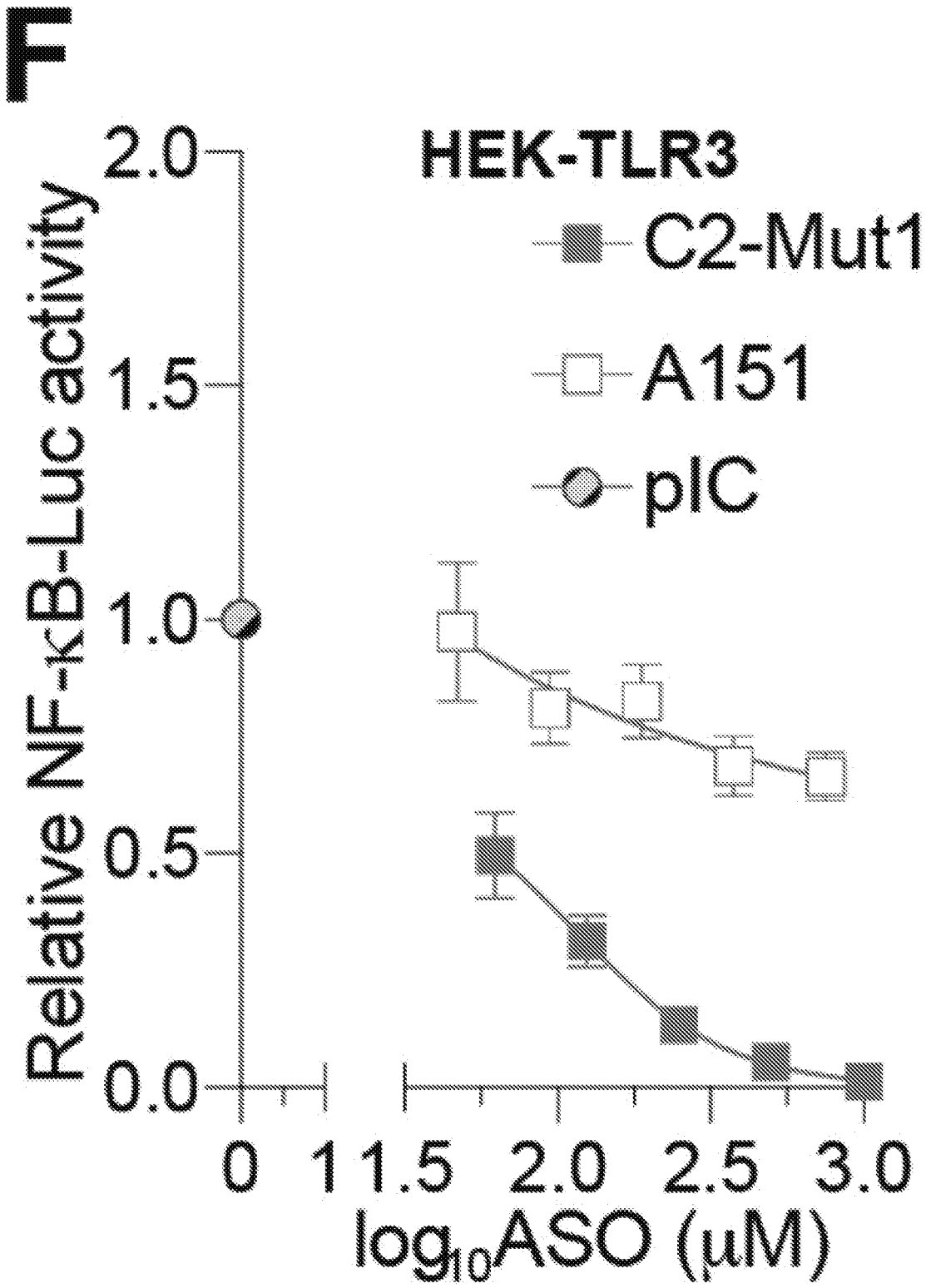
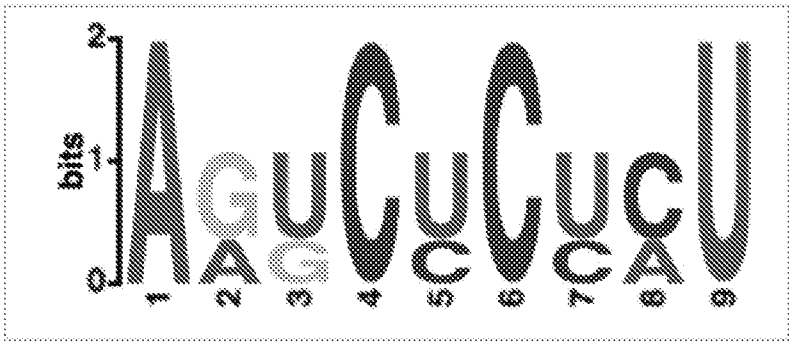

F
HEK-TLR3
C2-Mut1
A151
pIC
Relative NF-κB-Luc activity
2.0
1.5
1.0
0.5
0.0
0
1
1.5
2.0
2.5
3.0
log10ASO (μM)

FIGURE 5F

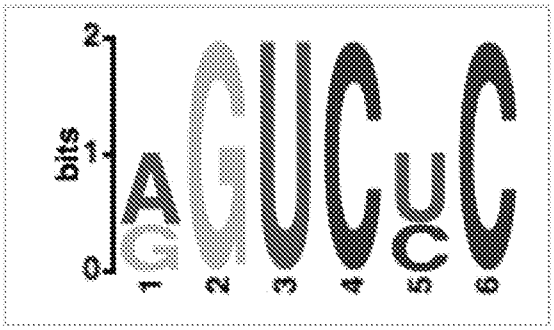
A



Log Likelihood Ratio: 27 Information Content: 13.4 Relative Entropy: 13 Bayes Threshold: 3.45943

Name	Start	p-value	Sites
3. ASO2	12	3.88e-5	CCGGCCTCGG AA CCCCCC
1. 196861965-C2	3	3.88e-5	GC A CCCCCAG GTCCCAGGC
2. 195513083-E10	10	7.24e-5	GAGGGTTCC A CCCCCCT GC

B

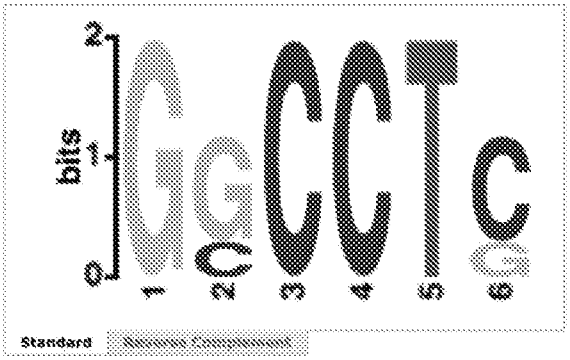


Log Likelihood Ratio: 33 Information Content: 10.1 Relative Entropy: 9.5 Bayes Threshold: 5.25873

Name	Start	p-value	Sites
3. P2-F2	4	2.97e-4	AGC A CCCC CATGTCCCAG
1. P2-C2	3	2.97e-4	GC A CCCC CATGTCCCAG
7. P2-E8	2	6.29e-4	G CCCC CTCCAGAGCC
2. P2-E10	10	1.03e-3	GAGGGTTCC A CCCC CCCC
10. P2-F9	1	1.48e-3	G CCCC ATCCCTTCTG

FIGURES 6A & 6B

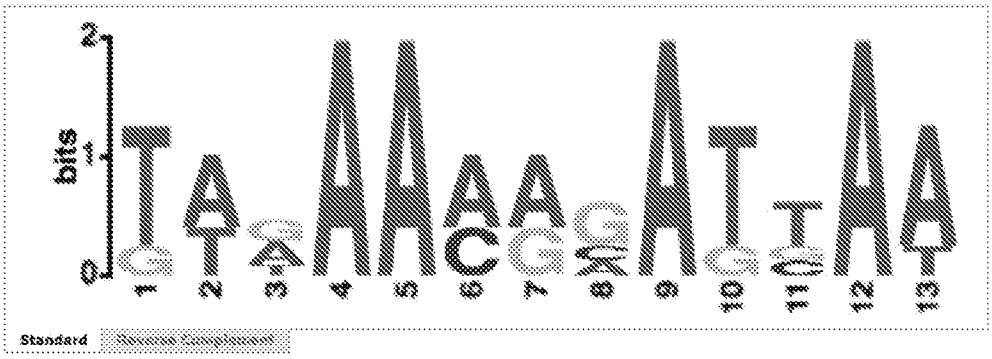
C



Log Likelihood Ratio: 31 Information Content: 10.4 Relative Entropy: 11.1 Bayes Threshold: 6.08215

	Name	Strand	Start	p-value	Sites
11.	ASO2	+	4	1.47e-4	TCC CCCTC GGAAGCTCTC
8.	P2-C4	+	11	1.47e-4	CCATGTCCCA CCCTC CAGT
4.	P2-C11	+	3	2.51e-4	TT CCCTC TGGATGCTTT
7.	P2-A11	+	11	4.58e-4	AAATGTCCTG CCCCTC ACTG

D

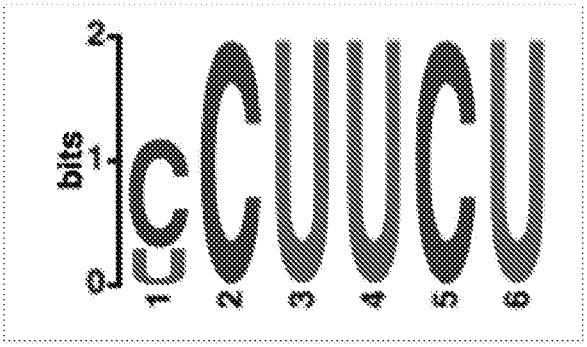


Log Likelihood Ratio: 55 Information Content: 16.7 Relative Entropy: 15 Bayes Threshold: 3.44518

	Name	Strand	Start	p-value	Sites
6.	P2-A6	+	4	3.25e-7	GAT TAAAACAATTAA TACA
1.	P2-C6	+	5	3.25e-7	GGAT TAAAACAATTAA TAC
3.	P2-E6	+	4	7.92e-6	CTT CTAAAACATTAT CTTC
5.	P2-C5	+	3	1.10e-5	CC TACAAACAACAA AGATT
10.	P2-D6	+	3	1.53e-5	AA TTTAAACCATCAA TATTA

FIGURES 6C & 6D

E



Log Likelihood Ratio: 50 Information Content: 11.2 Relative Entropy: 9 Bayes Threshold: 5.7039

	Name	Start	p-value	Sites
12.	P2-D10	4	1.17e-3	CAC CCUUCU CTCTGGTCCC
6.	P2-A8	1	1.17e-3	CCUUCU CTCTGGTCCC
6.	P2-A9	15	1.17e-3	GGGTCCCAATC CCUUCU
4.	P2-A3	15	1.17e-3	CTGCTGCCCA CCUUCU
2.	P2-H9	9	1.17e-3	GCCCCAGC CCUUCU GCTGCC
1.	P2-H8	14	1.17e-3	GCCTCCAGAC CCUUCU C
11.	P2-H2	14	2.11e-3	GCCTCCAGTG CCUUCU C
9.	P2-G7	8	2.11e-3	GCCCAAC CCUUCU AACCCGG

FIGURE 6E

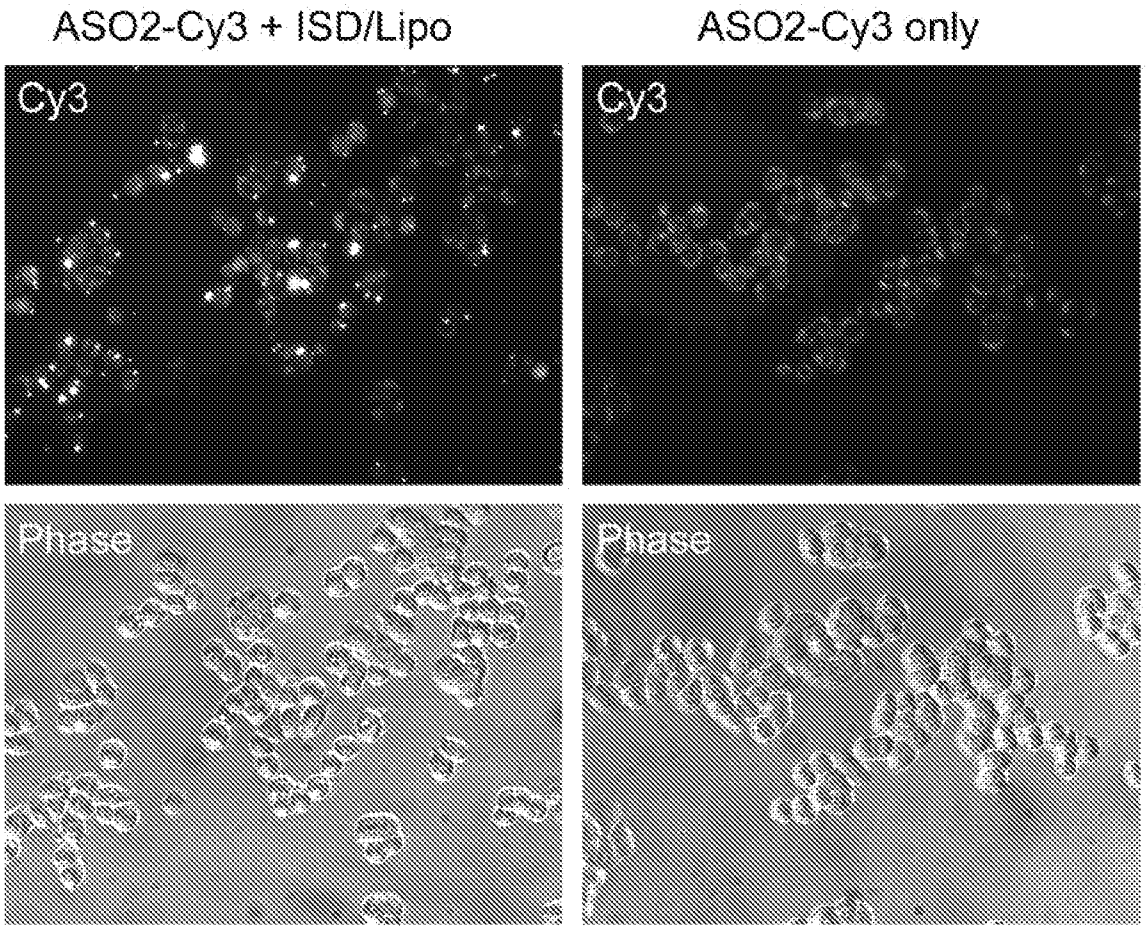


FIGURE 7

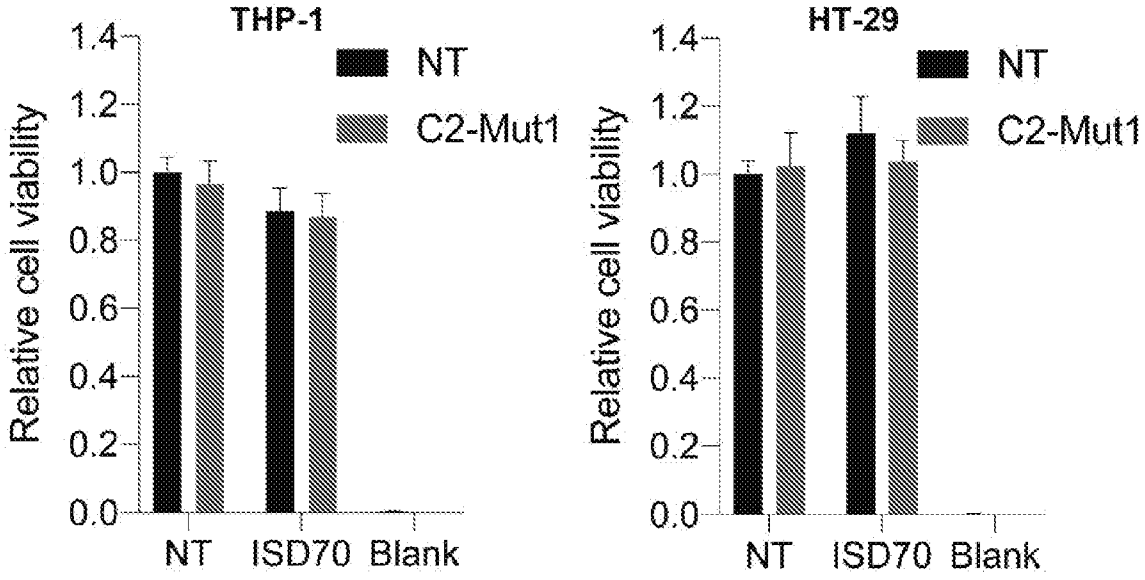

THP-1
HT-29
NT
C2-Mut1
Relative cell viability
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
NT
ISD70
Blank

FIGURE 8

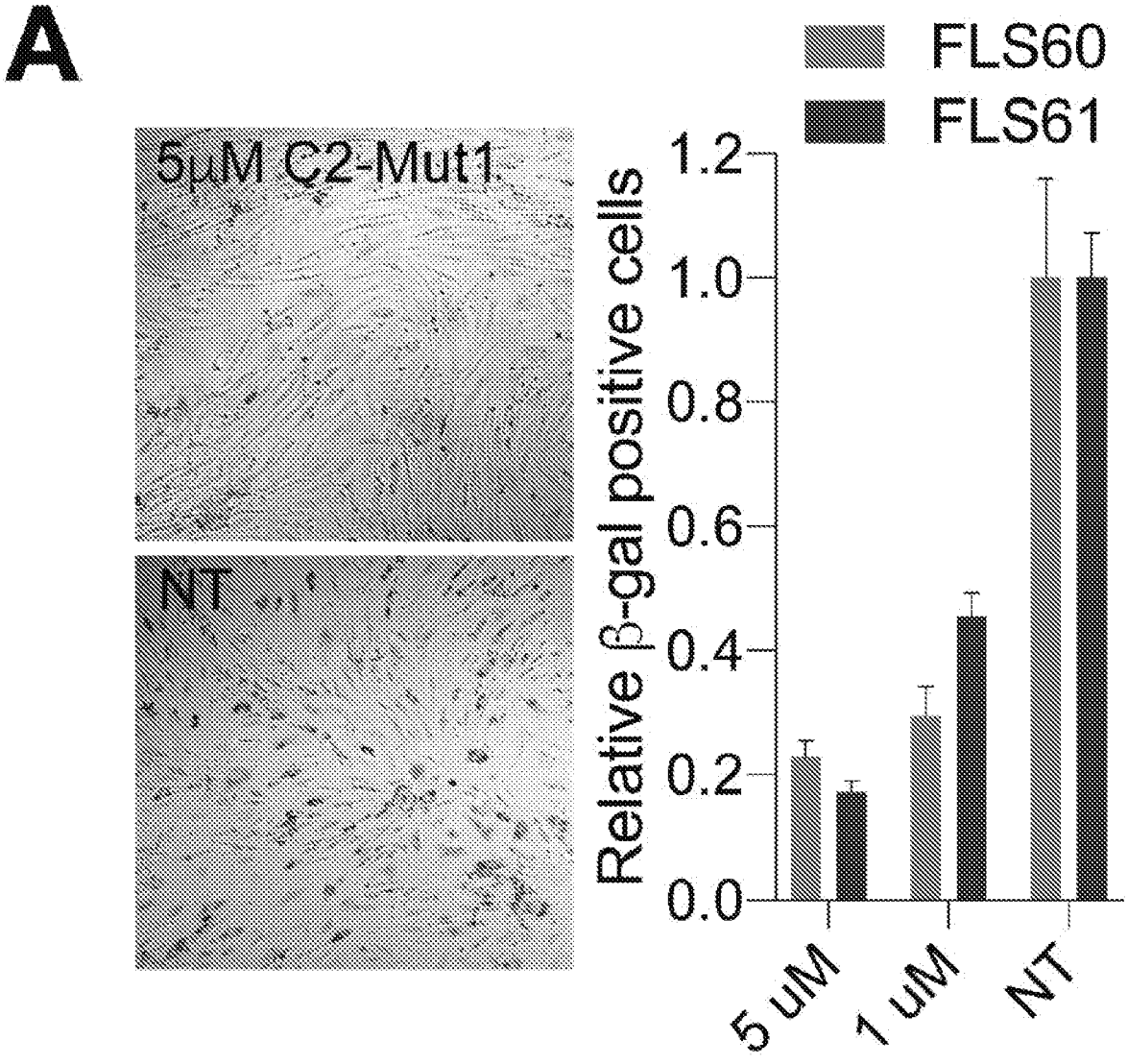
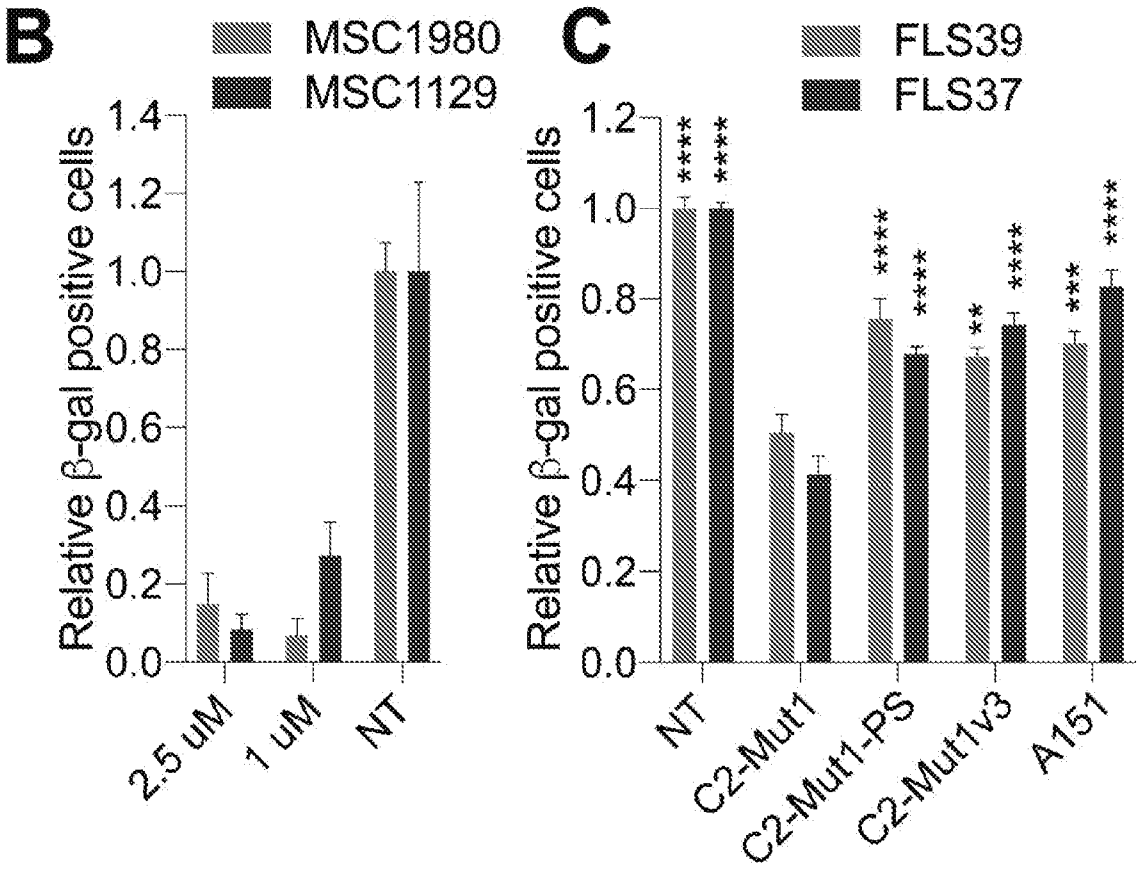

A
5μM C2-Mut1
NT
FLS60
FLS61
Relative β-gal positive cells
1.2
1.0
0.8
0.6
0.4
0.2
0.0
5 uM
1 uM
NT

FIGURE 9A



FIGURES 9B & 9C

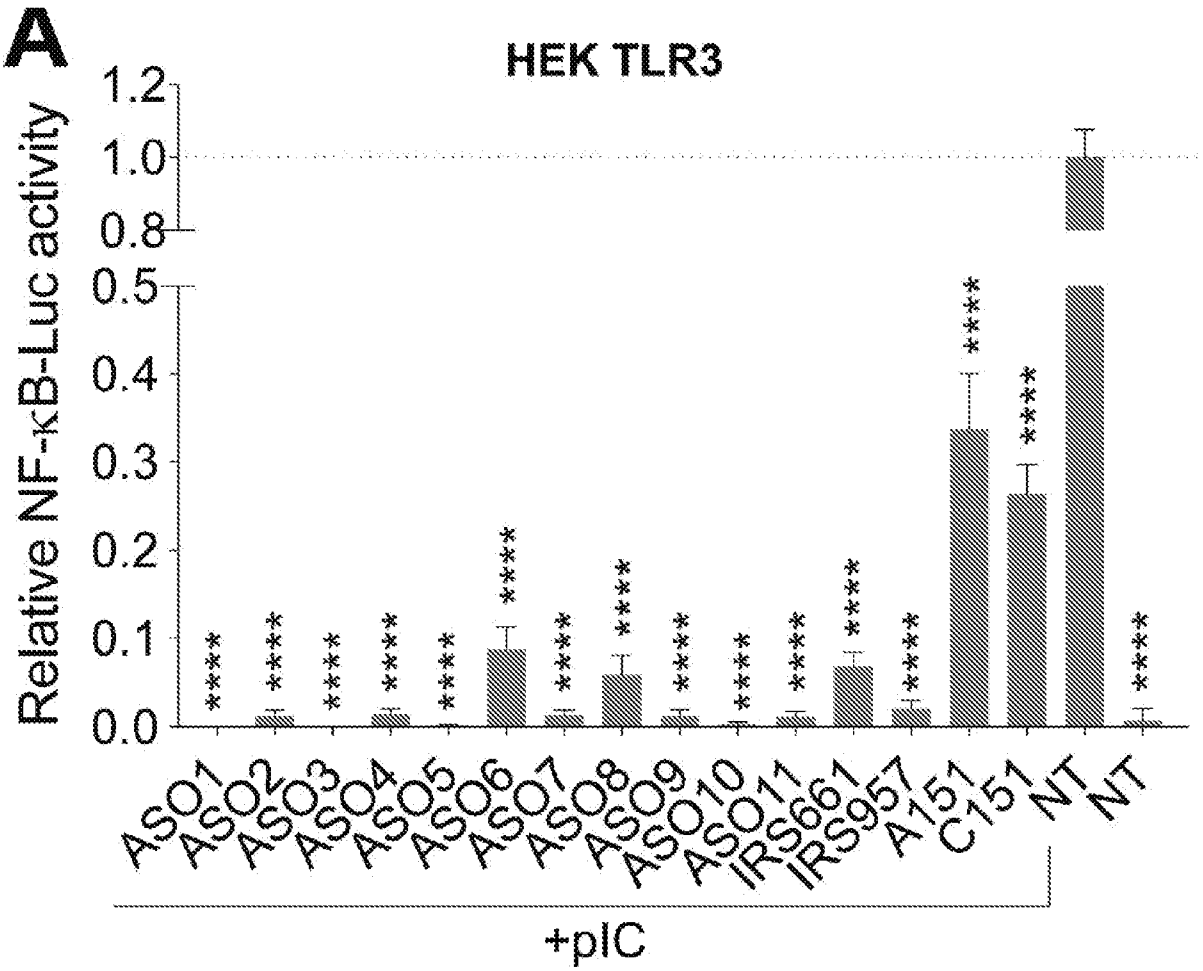

A
HEK TLR3
Relative NF-κB-Luc activity
1.2
1.0
0.8
0.5
0.4
0.3
0.2
0.1
0.0
ASO1
ASO2
ASO3
ASO4
ASO5
ASO6
ASO7
ASO8
ASO9
ASO10
ASO11
IRS661
IRS957
A151
C151
NT
NT
+pIC

FIGURE 10A

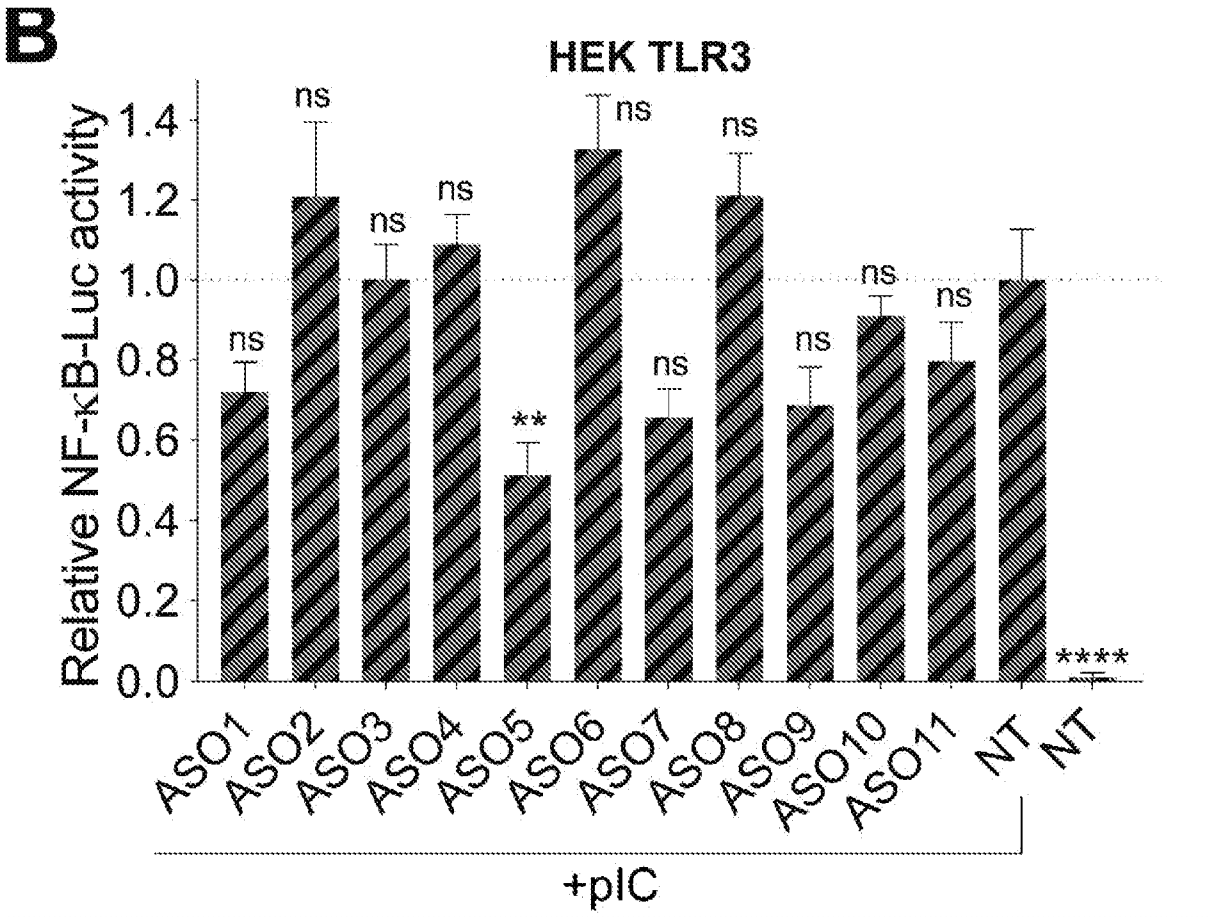

B
HEK TLR3
Relative NF-κB-Luc activity
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
ns
ns
ns
**
ns
ns
ns
ns
ns
ns
****
ASO1
ASO2
ASO3
ASO4
ASO5
ASO6
ASO7
ASO8
ASO9
ASO10
ASO11
NT
NT
+pIC

FIGURE 10B

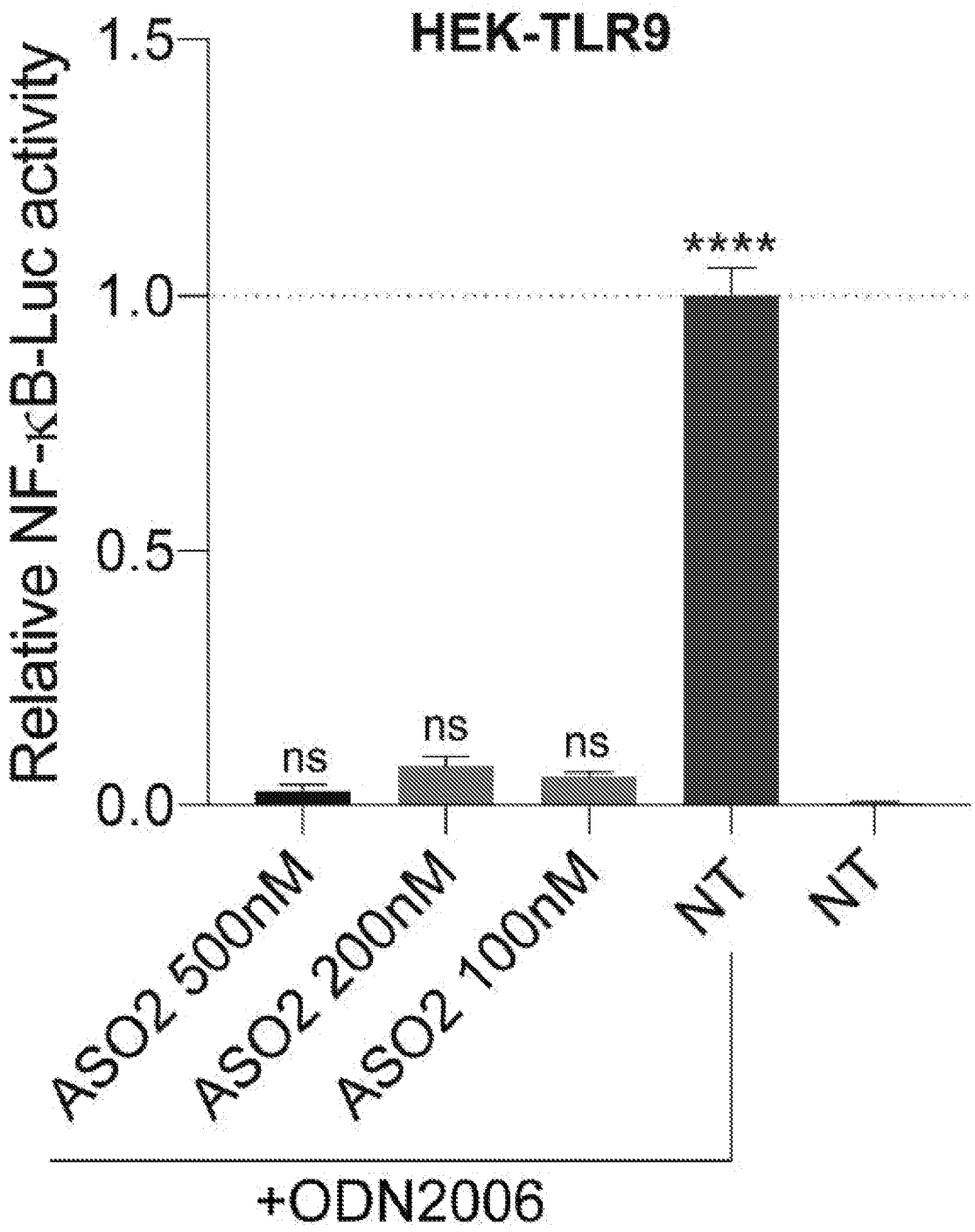

HEK-TLR9
Relative NF-κB-Luc activity
1.5
1.0
0.5
0.0
****
ns
ns
ns
ASO2 500nM
ASO2 200nM
ASO2 100nM
NT
NT
+ODN2006

FIGURE 11

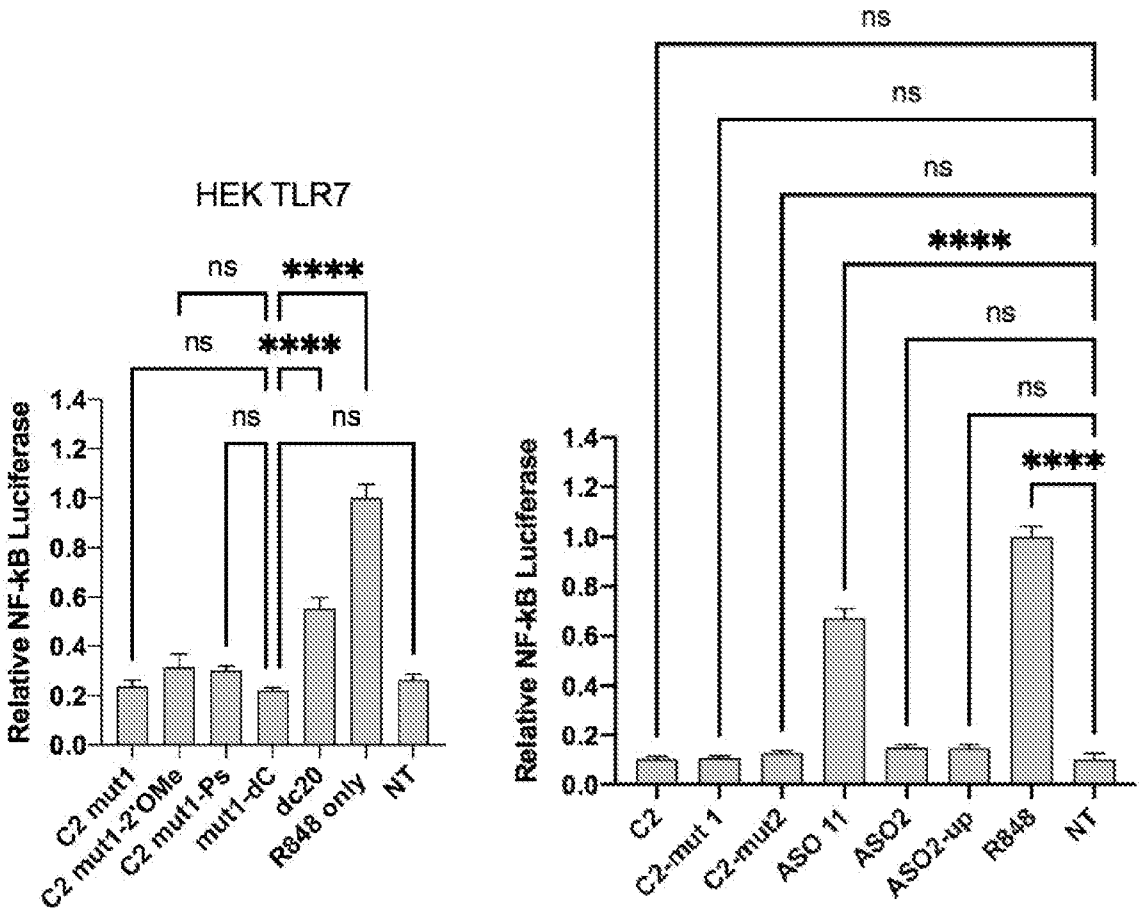

HEK TLR7
Relative NF-kB Luciferase
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
****
ns
****
ns
ns
C2 mut1
C2 mut1-2'OMe
C2 mut1-Ps
mut1-dC
dc20
R848 only
NT
Relative NF-kB Luciferase
ns
ns
ns
****
ns
ns
****
C2
C2-mut 1
C2-mut2
ASO 11
ASO2
ASO2-up
R848
NT

FIGURE 12

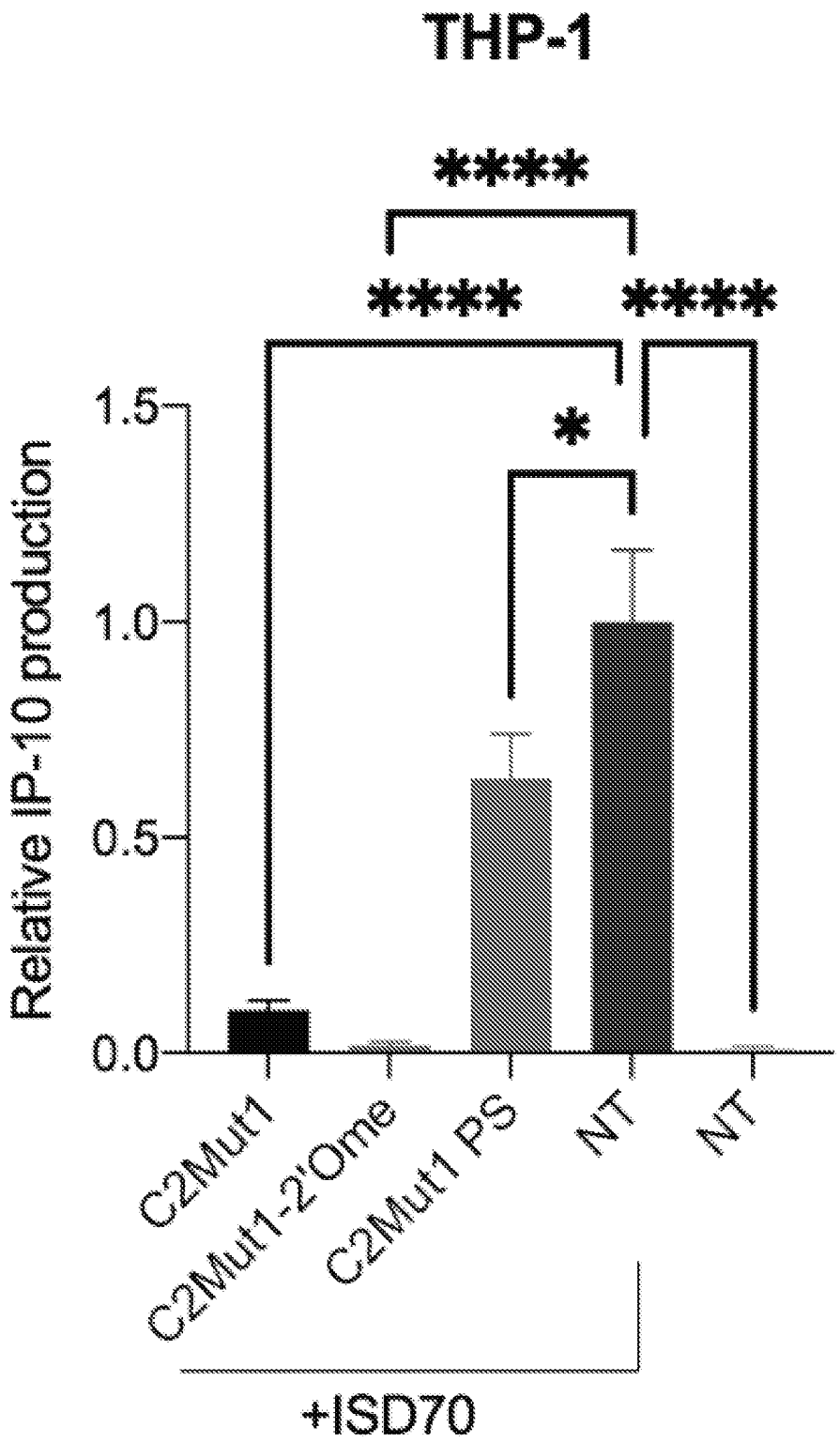

THP-1
****
****
****
*
Relative IP-10 production
1.5
1.0
0.5
0.0
C2Mut1
C2Mut1-2'Ome
C2Mut1 PS
NT
NT
+ISD70

FIGURE 13

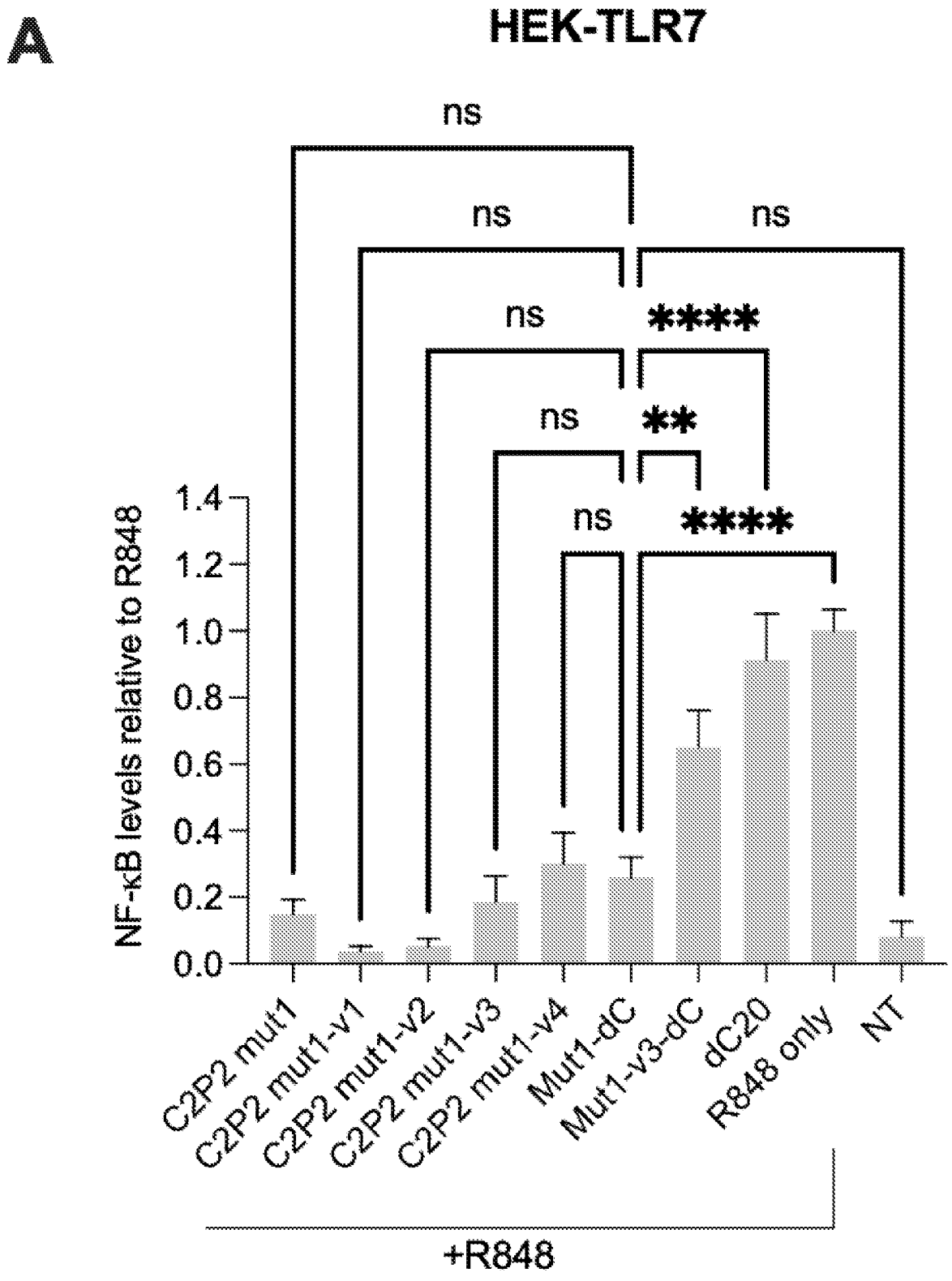
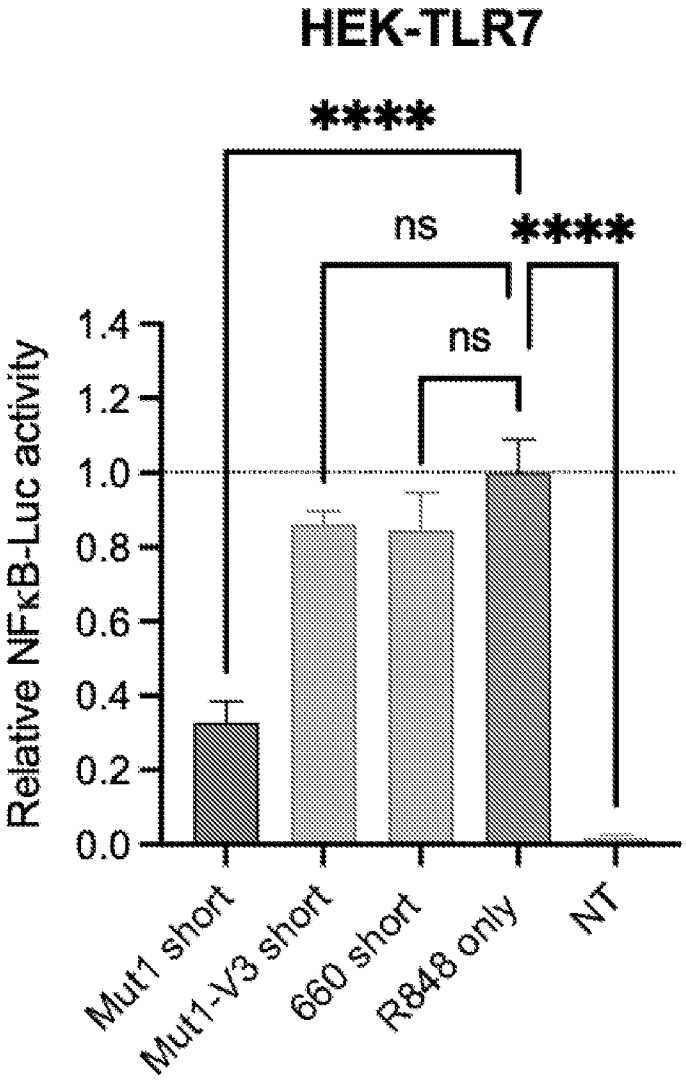

A
HEK-TLR7
ns
ns
ns
ns
****
ns
**
ns
****
NF-κB levels relative to R848
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
C2P2 mut1
C2P2 mut1-v1
C2P2 mut1-v2
C2P2 mut1-v3
C2P2 mut1-v4
Mut1-dC
Mut1-v3-dC
dC20
R848 only
NT
+R848

FIGURE 14A

B



ShortMut1: mG*mG*mU*mA*mU
ShortMut1v3:mC*mG*mU*mU*mU
Short660v1: mC*mU*mU*mC*mG

FIGURE 14B

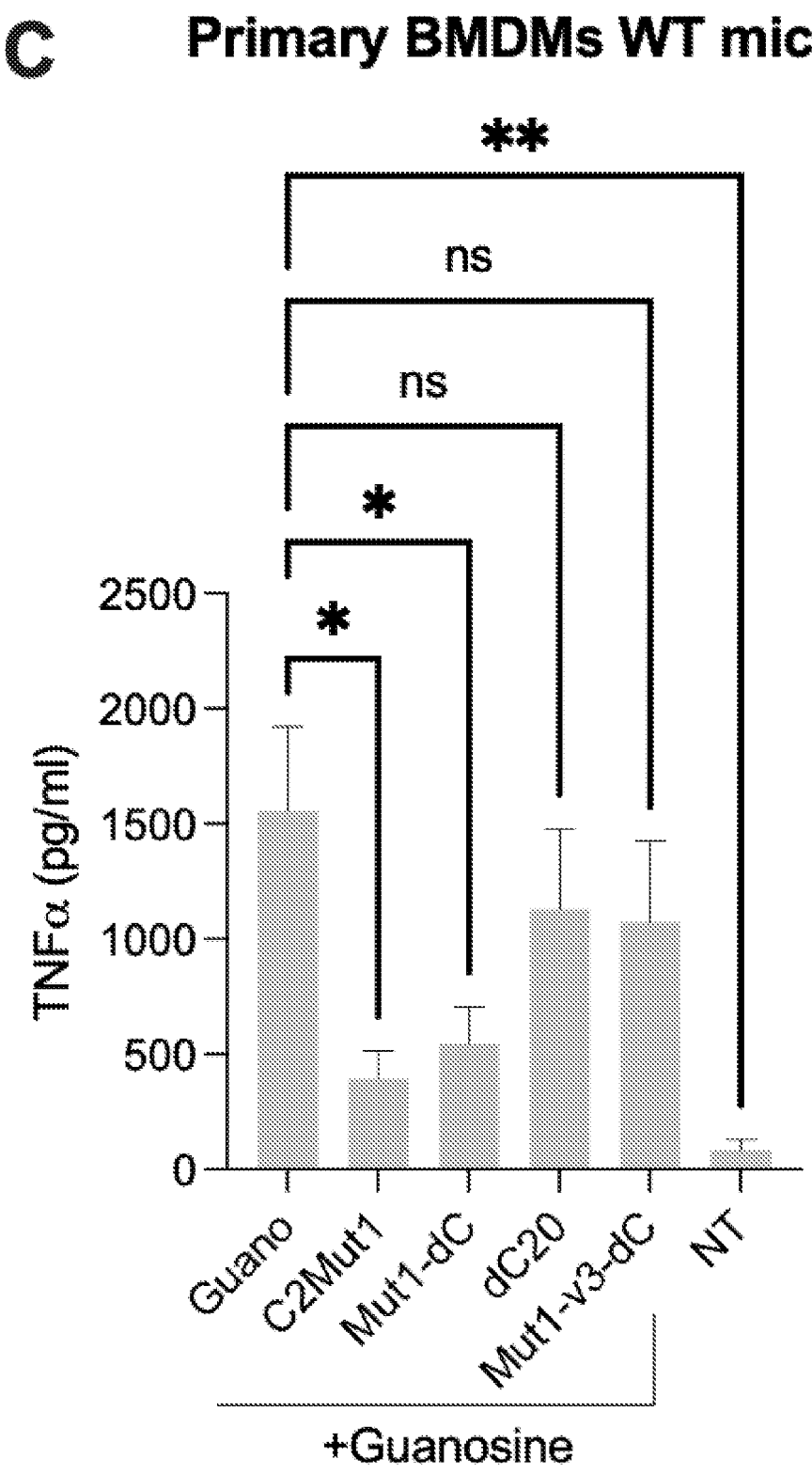

C
Primary BMDMs WT mice
**
ns
ns
*
*
2500
2000
1500
1000
500
0
TNFα (pg/ml)
Guano
C2Mut1
Mut1-dC
dC20
Mut1-v3-dC
NT
+Guanosine

FIGURE 14C

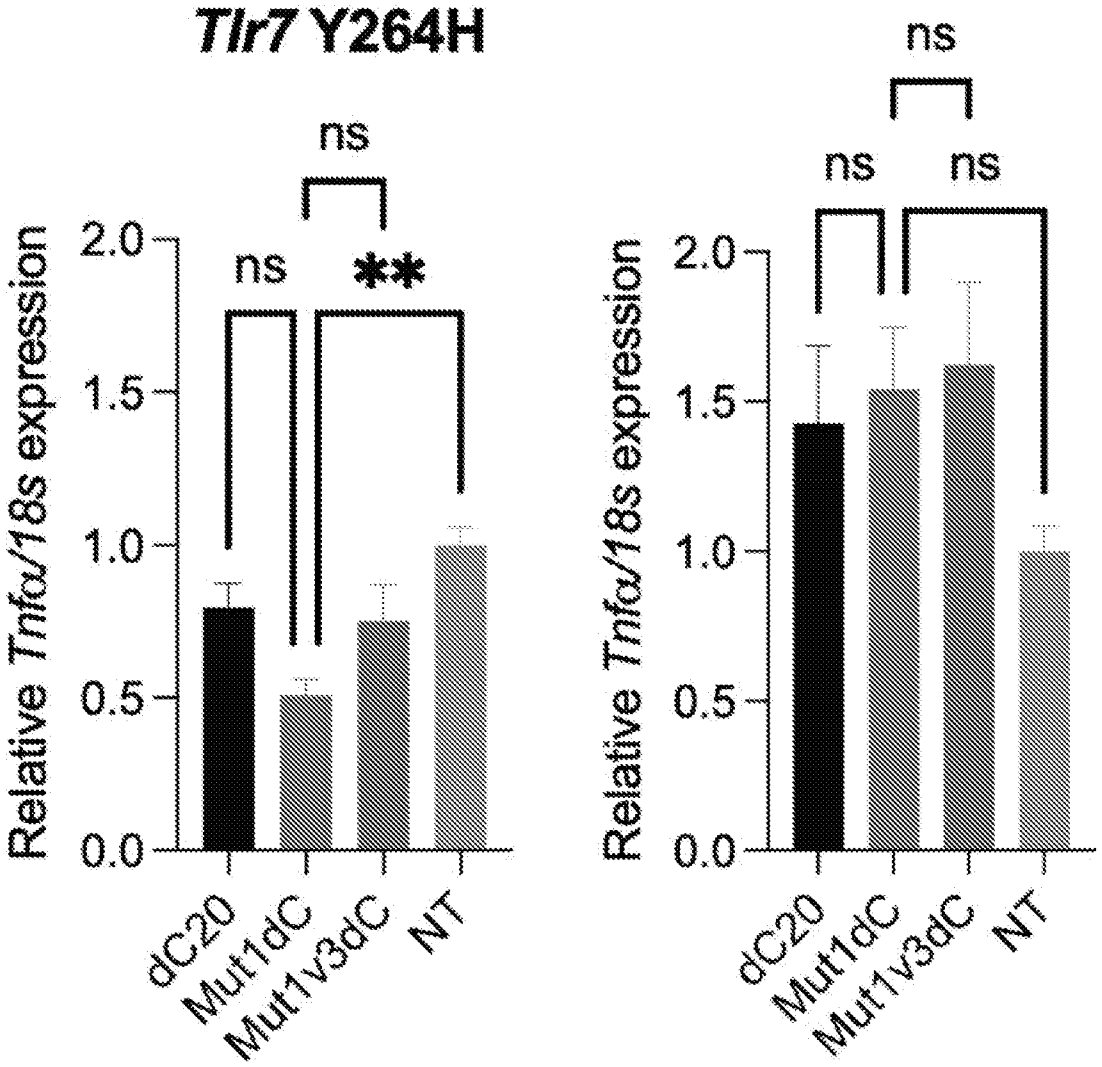

Tlr7 Y264H
ns
ns
**
Relative Tnfα/18s expression
2.0
1.5
1.0
0.5
0.0
dC20
Mut1dC
Mut1v3dC
NT
ns
ns
ns
Relative Tnfα/18s expression
2.0
1.5
1.0
0.5
0.0
dC20
Mut1dC
Mut1v3dC
NT

FIGURE 15

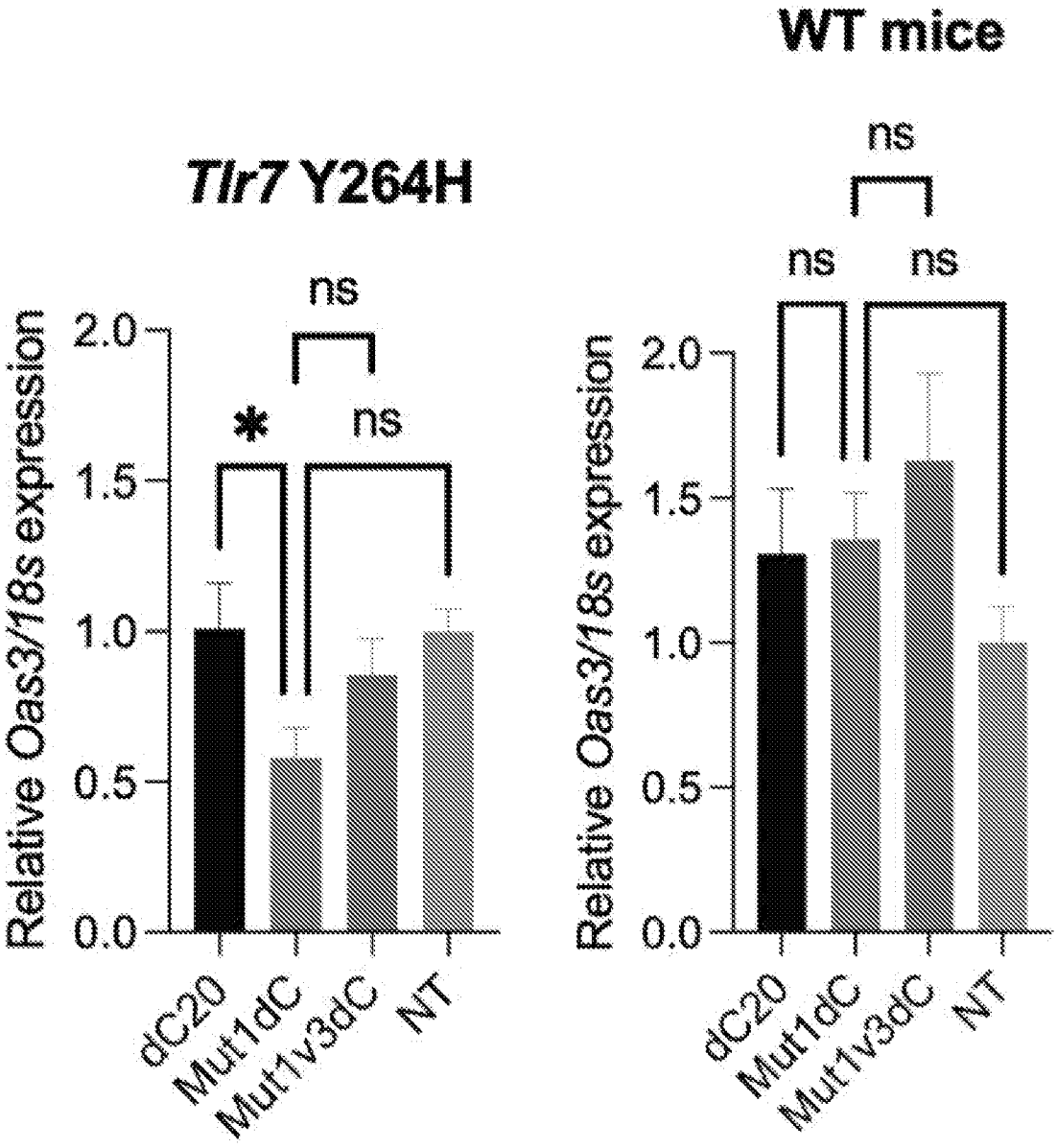
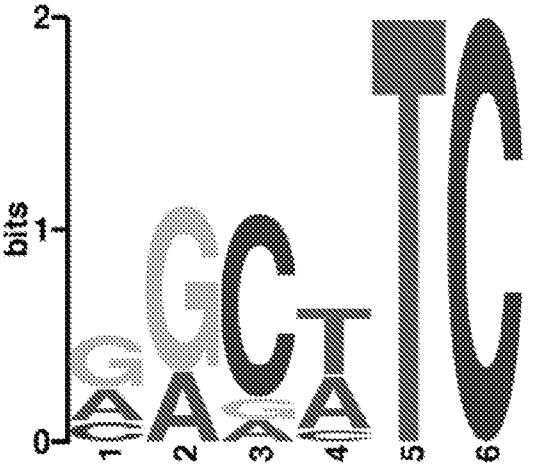


FIGURE 15 continued

	Name	Strand	Start	*p*-value	Sites
3.	G5	+	1	2.51e-4	GGCATC CACCACGTCG
4.	E6	+	13	1.17e-3	CCTTGCACGT GGCTTC GT
1.	F5	+	14	1.17e-3	CCTTGCACGT GGCTTC G
10.	E5	+	15	1.48e-3	ATTTCAGAGC AGCTTC
2.	F4	+	7	1.48e-3	TTCTGC AGCTTC CTTGTCCT
5.	D5	+	7	2.46e-3	TGGGCT GGAATC CGAGTTAT
8.	G8	+	4	2.77e-3	GTC CACATC CTGTGGCTCG
9.	E2	+	7	5.29e-3	TGTGAT GGCCTC CCATCTCC
6.	C8	+	7	5.29e-3	TTTGCA CACTTC GTACCCAA
7.	D3	+	5	6.22e-3	GTCC AACATC AGCAGTCTCA

>F5 TGTCCTTGCACGTGGCTTCG

>F5-Mut TGTCCTTGCACGTGCCTAAG



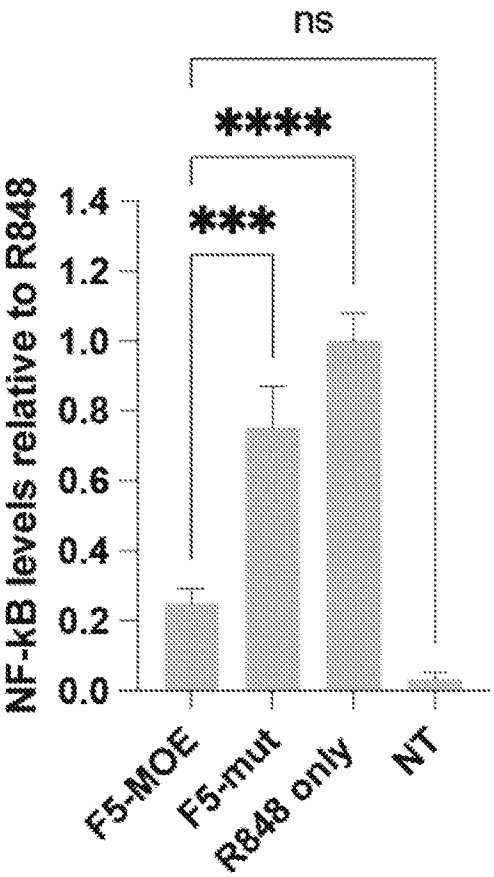


FIGURE 16

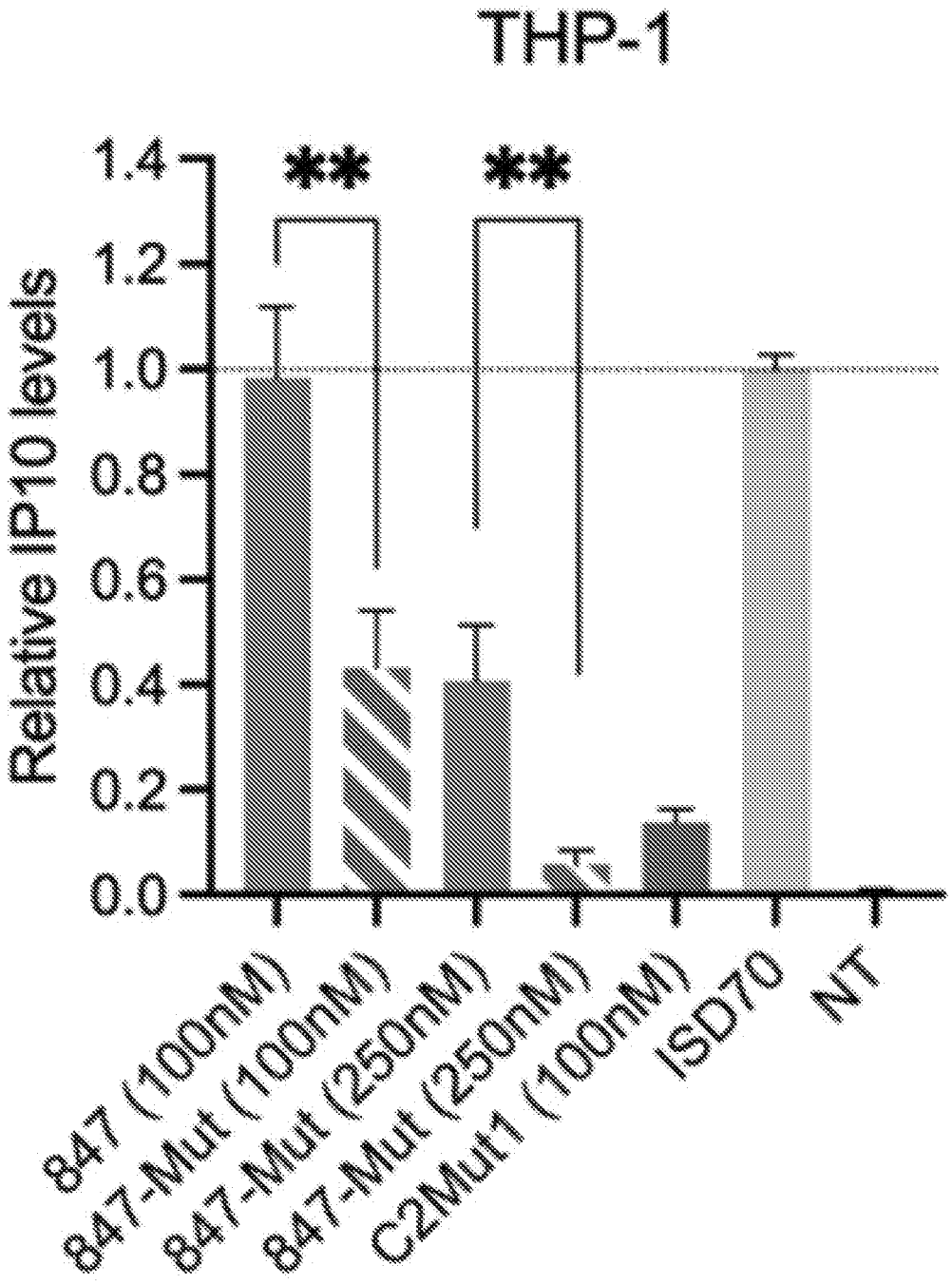

THP-1
Relative IP10 levels
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
**
**
847 (100nM)
847-Mut (100nM)
847-Mut (250nM)
847-Mut (250nM)
C2Mut1 (100nM)
ISD70
NT

FIGURE 17

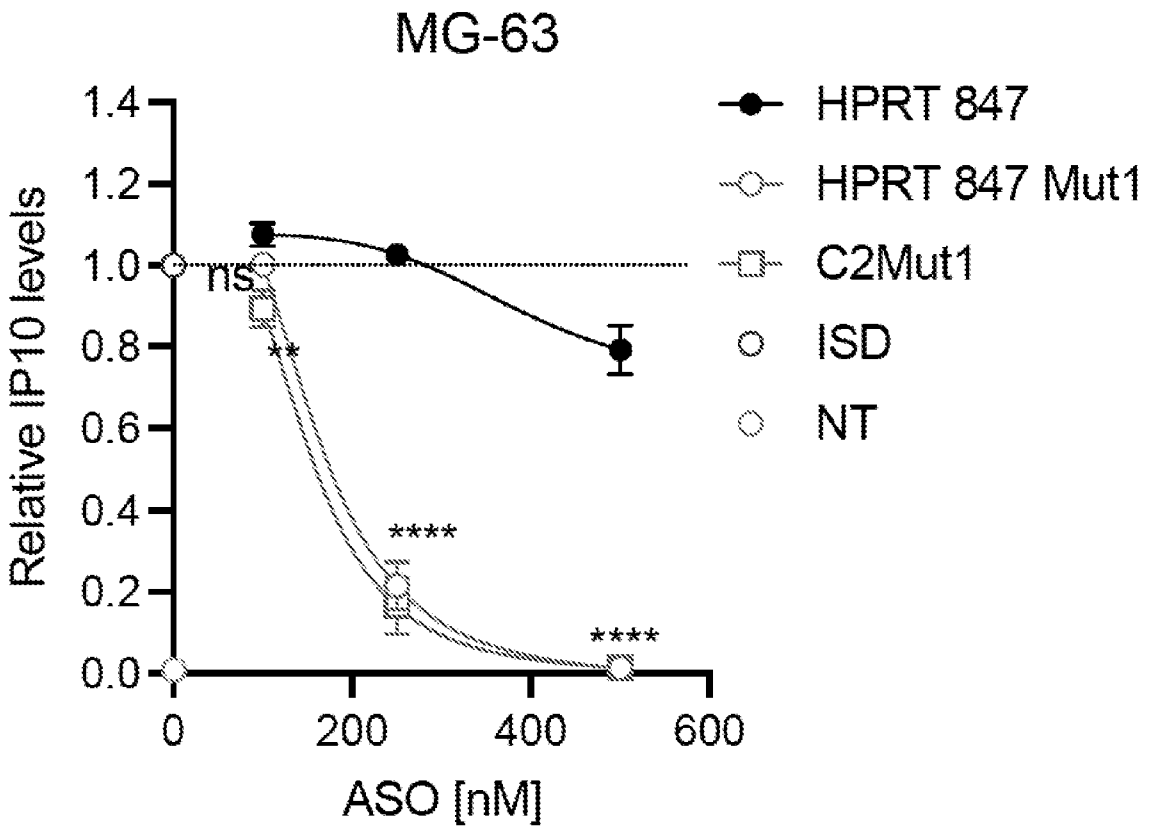
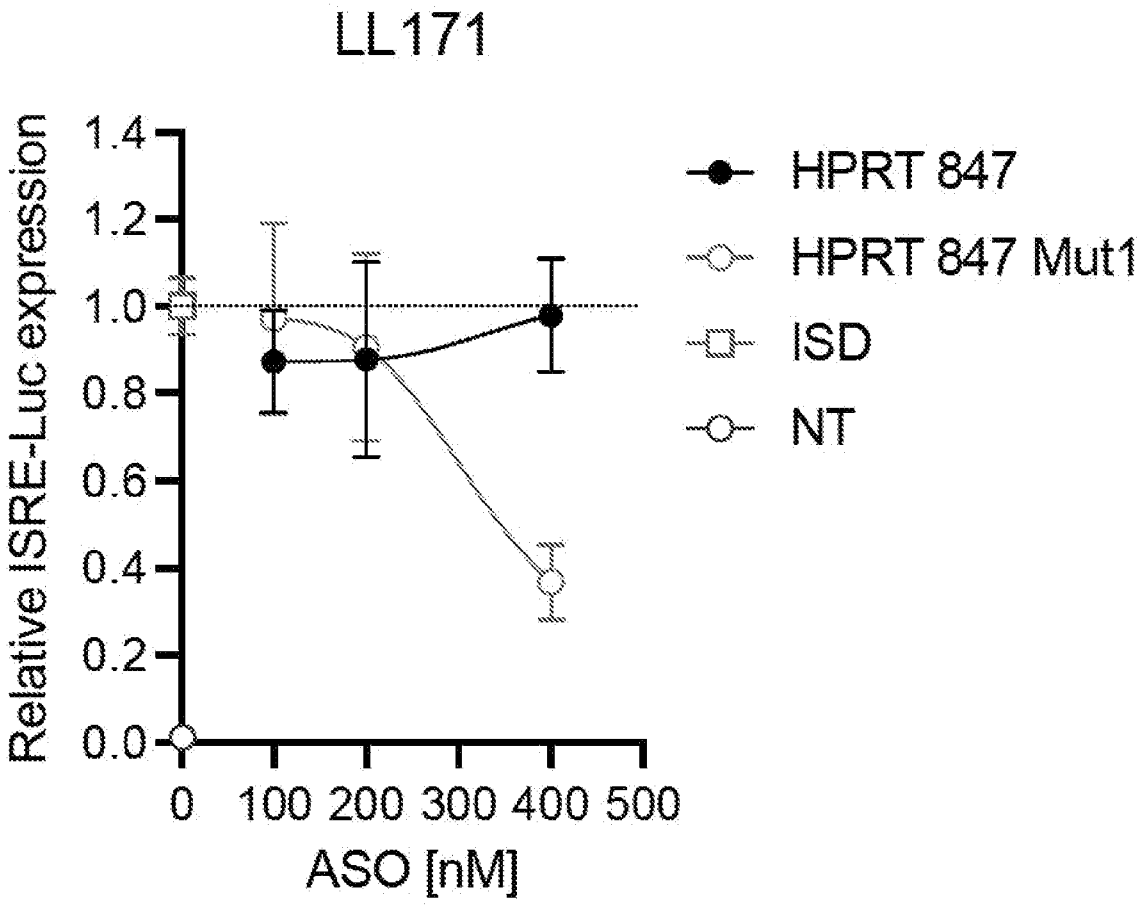


FIGURE 17 continued



HPRT-2OMe-847:
mA*mU*mA*mG*mG*A*C*T*C*C*A*G*A*T*G*mU*mU*mU*mC*mC

HPRT-2OMe-847-Mut1:
mG*mG*mU*mA*mU*mA*mG*mG*A*C*T*C*C*A*G*A*T*G*mU*mU*mU*mC*mC

FIGURE 17 continued

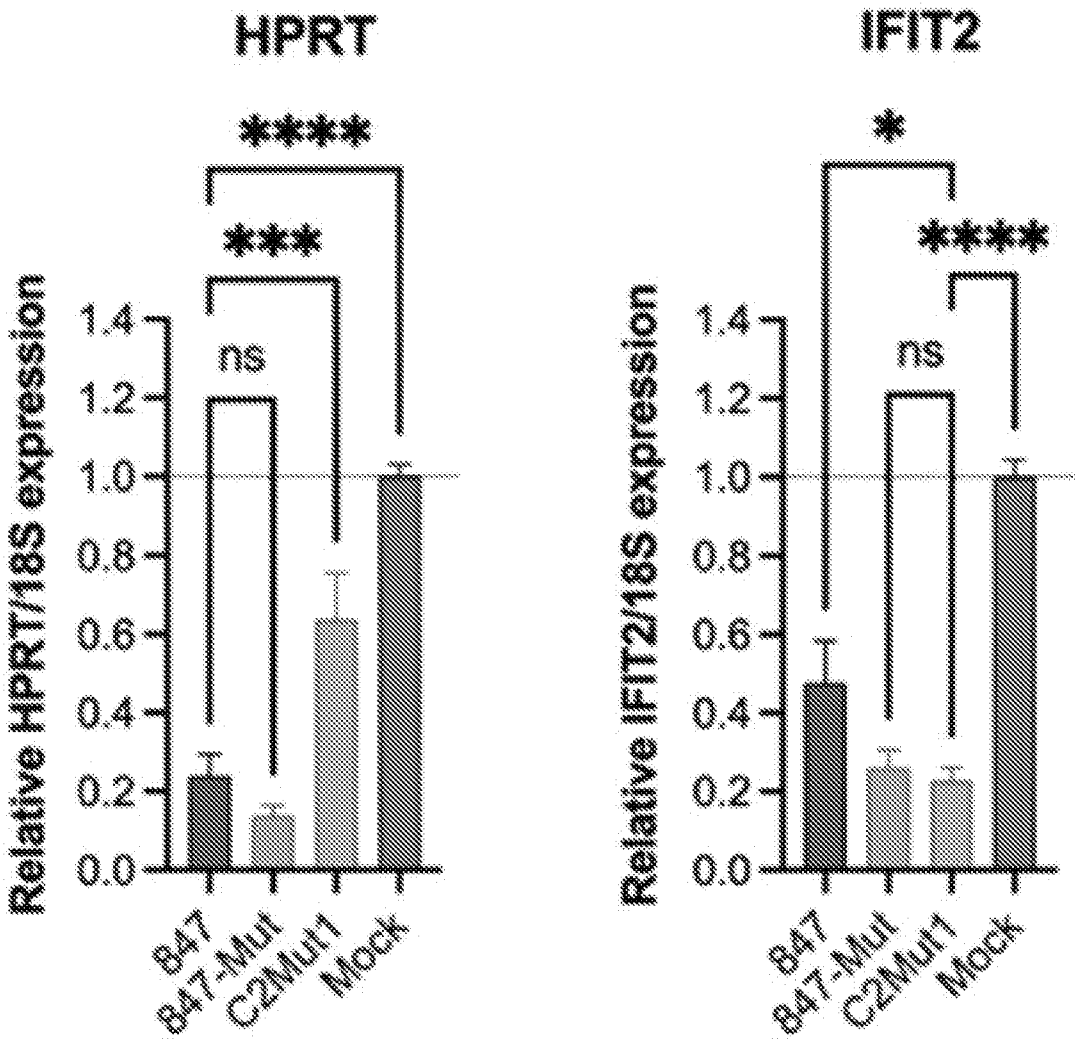
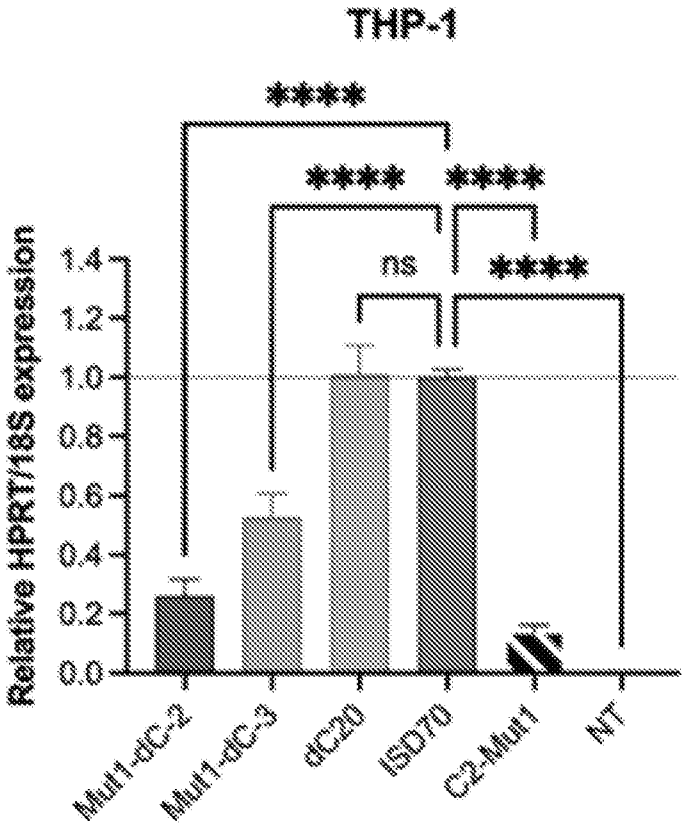

HPRT
IFIT2
****
***
*
****
ns
ns
Relative HPRT/18S expression
Relative IFIT2/18S expression
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
847
847-Mut
C2Mut1
Mock

FIGURE 18



C2Mut1-dC-2:
mG*mG*mU*A*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C

C2Mut1-dC-3:
mG*mG*mU*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C

FIGURE 19

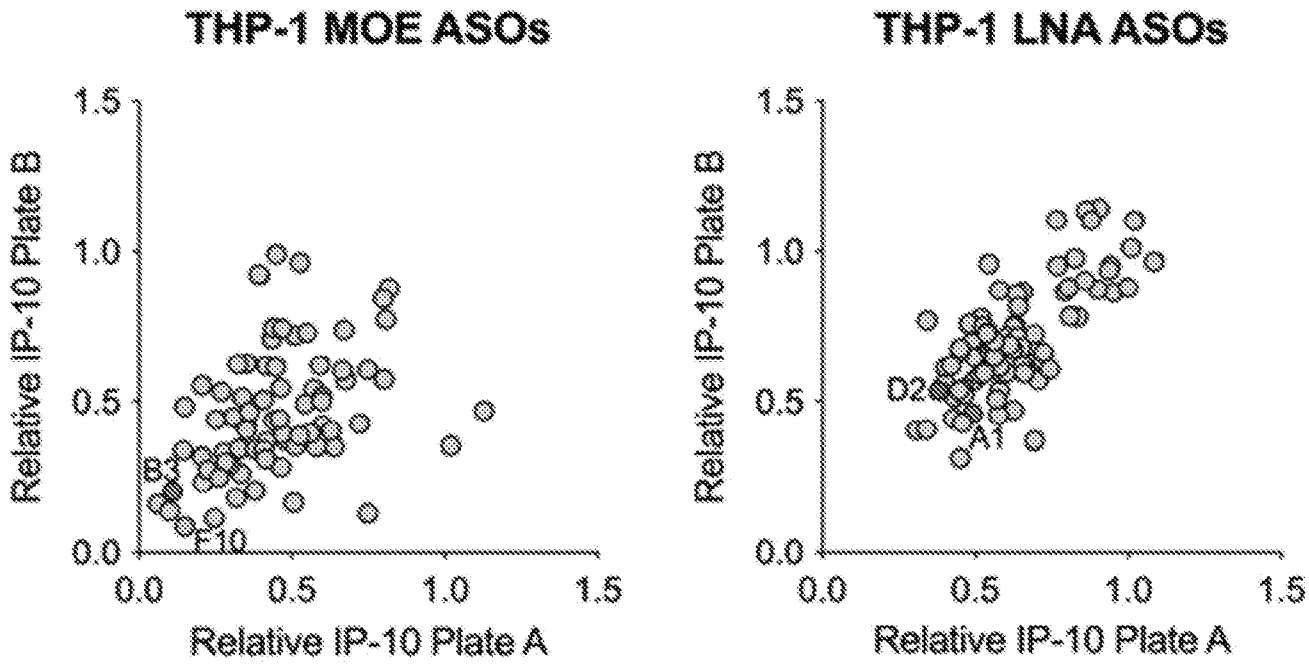

THP-1 MOE ASOs
Relative IP-10 Plate B
Relative IP-10 Plate A
0.0
0.5
1.0
1.5
B4
F10
THP-1 LNA ASOs
Relative IP-10 Plate B
Relative IP-10 Plate A
D2
A1

FIGURE 20

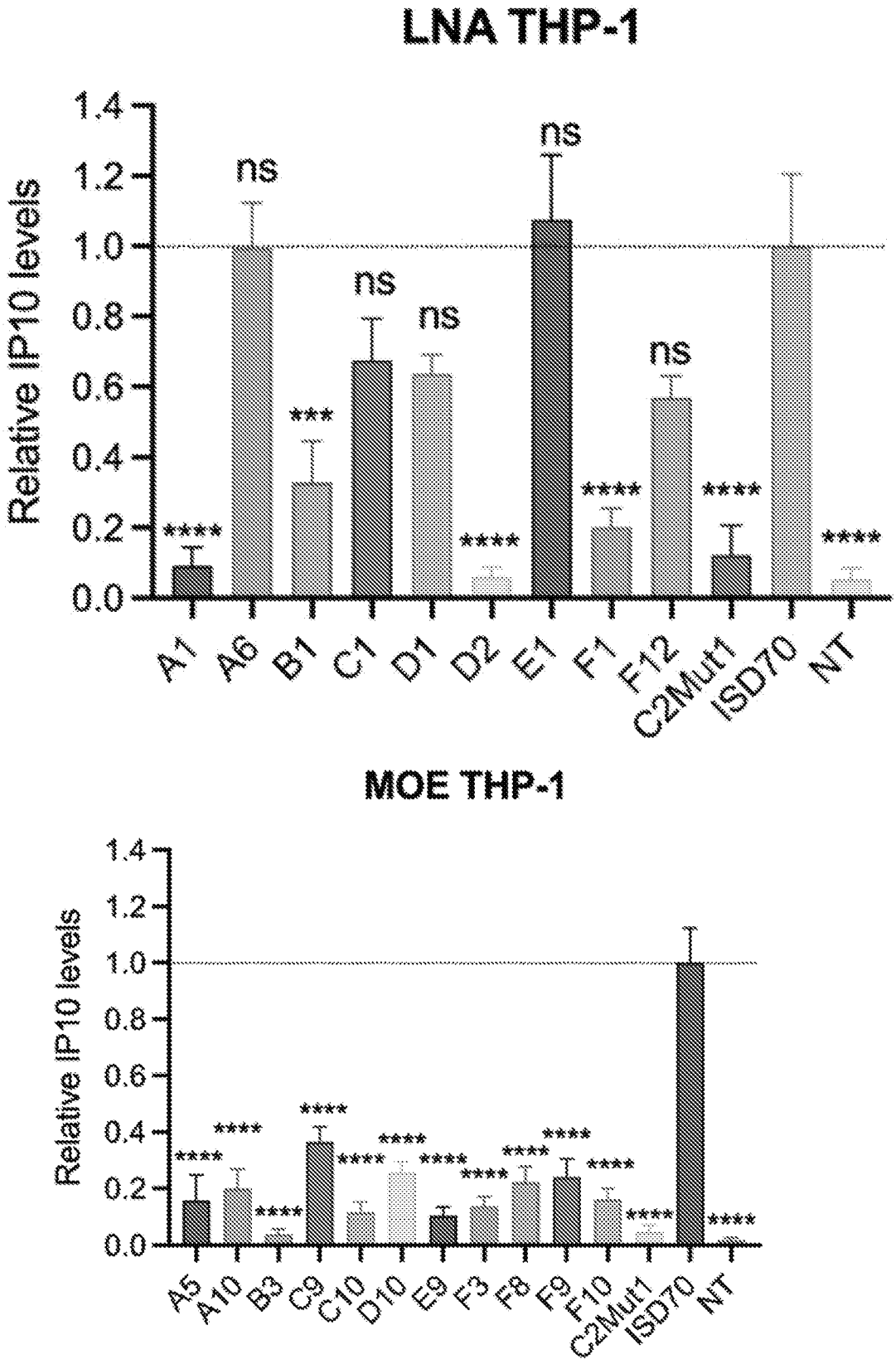

LNA THP-1
Relative IP10 levels
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
ns
ns
ns
ns
***
****
****
****
****
****
A1
A6
B1
C1
D1
D2
E1
F1
F12
C2Mut1
ISD70
NT
MOE THP-1
Relative IP10 levels
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
****
A5
A10
B3
C9
C10
D10
E9
F3
F8
F9
F10
C2Mut1
ISD70
NT

FIGURE 21

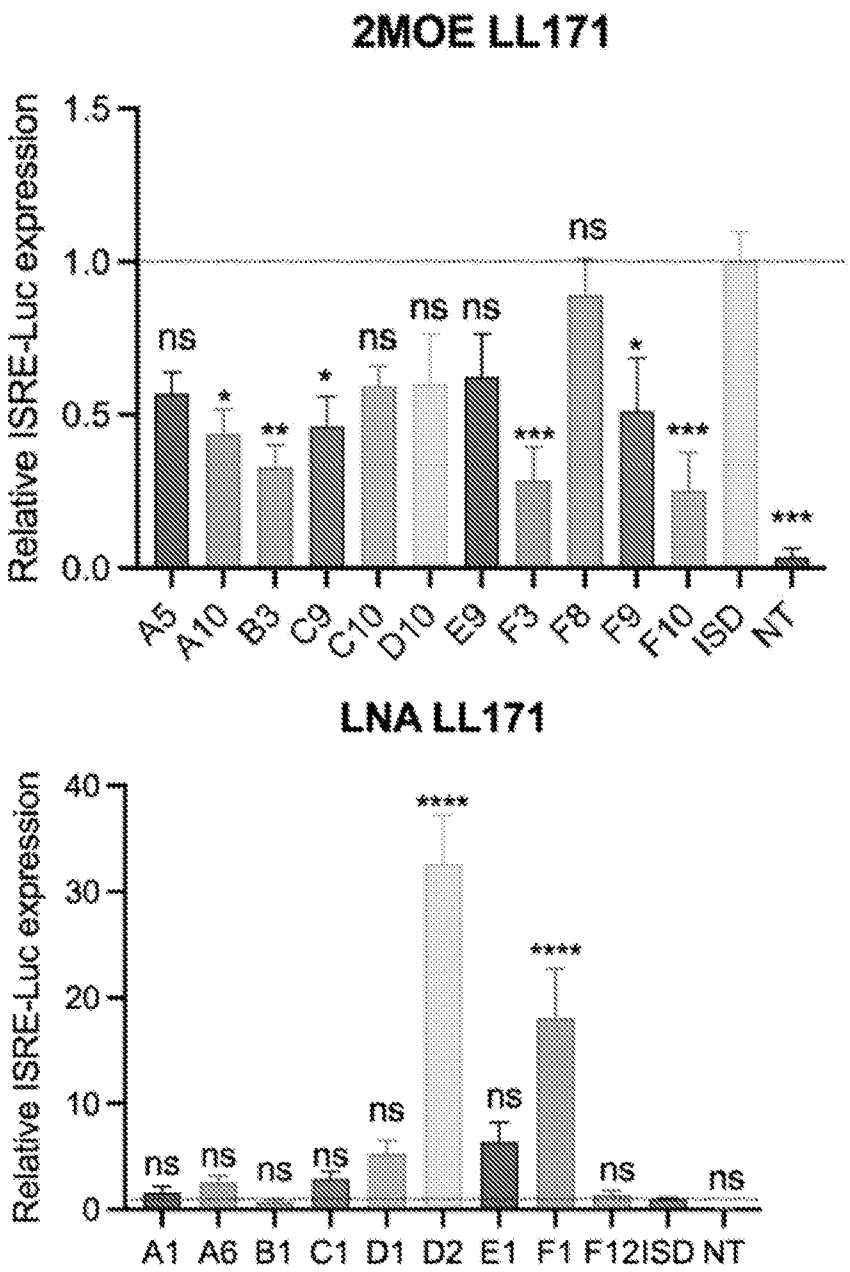

2MOE LL171
Relative ISRE-Luc expression
1.5
1.0
0.5
0.0
ns
*
**
*
ns
ns ns
***
ns
*
***
***
A5 A10 B3 C9 C10 D10 E9 F3 F8 F9 F10 ISD NT
LNA LL171
Relative ISRE-Luc expression
40
30
20
10
0
ns ns ns ns ns
****
ns
****
ns ns
A1 A6 B1 C1 D1 D2 E1 F1 F12 ISD NT

FIGURE 22

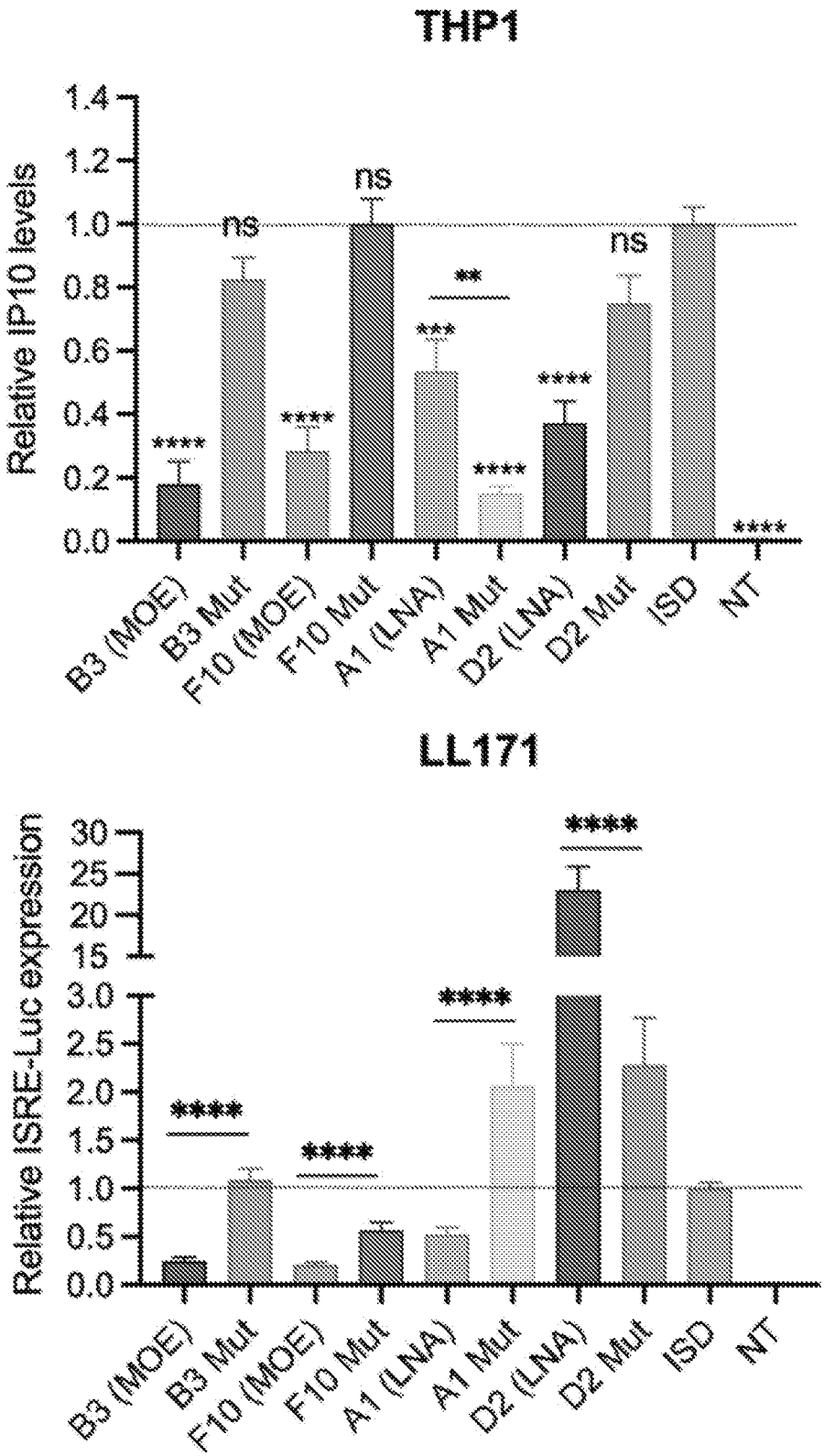
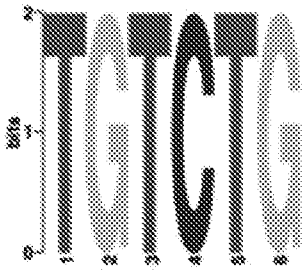

THP1
Relative IP10 levels
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
ns
ns
**
***
****
****
****
****
B3 (MOE)
B3 Mut
F10 (MOE)
F10 Mut
A1 (LNA)
A1 Mut
D2 (LNA)
D2 Mut
ISD
NT
LL171
Relative ISRE-Luc expression
30
25
20
15
3.0
2.5
2.0
1.5
1.0
0.5
0.0
****
****
****
****
B3 (MOE)
B3 Mut
F10 (MOE)
F10 Mut
A1 (LNA)
A1 Mut
D2 (LNA)
D2 Mut
ISD
NT

FIGURE 23

LNA Motif 1

Name	Strand	Start	p-value	Sites
5. F1	+	2	5.60e-4	G T TCTC GAAGCTTCC
4. A1	+	9	5.60e-4	CGCTTTTC T TCTC GT



A1-LNA: +C*+G*+C*T*T*T*T*C*T*G*T*C*T*+G*+G*+T

A1-Mut-LNA: +C*+G*+C*T*T*T*T*C*T*C*T*C*C*+G*+G*+T

LNA Motif 2

Name	Strand	Start	p-value	Sites
2. B1	+	2	4.88e-5	G AAA TTA TGCAAGG
5. F1	+	8	6.12e-5	GTGTCTG CAA CTTC C
1. D2	+	1	2.01e-4	CA CTC AGTGATGT



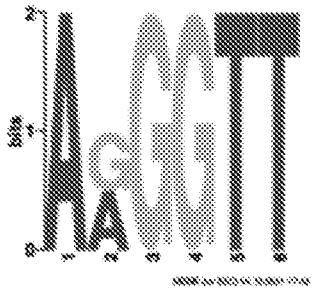
D2-LNA: +G*+C*+A*G*G*C*T*C*A*G*T*G*A*+T*+G*+T

D2-Mut-LNAt: +G*+C*+C*C*G*C*T*C*A*G*T*G*A*+T*+G*+T

FIGURE 23 continued

MOE Motif 1

	Name	Strand	Start	p-value	Sites
3.	B3	+	5	1.72e-4	GCGA AA[redacted]TT ATGCAAGGTC
6.	E9	+	14	4.01e-4	GACTGTCTTG A[redacted]TT C

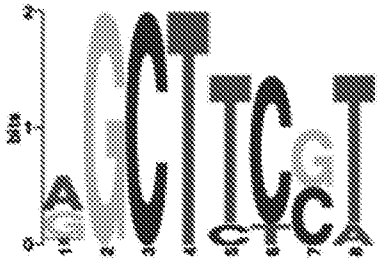


B3-MOE: /G*/G*/G*/A*/A*A*G*G*T*T*A*T*G*C*A*/A*/G*/G*/T*/C

B3-Mut-MOE: /G*/G*/G*/A*/A*A*C*G*C*T*A*T*G*C*A*/A*/G*/G*/T*/C

MOE Motif 2

	Name	Strand	Start	p-value	Sites
2.	F3	+	12	1.63e-5	CGTGTCTGGA A[redacted]CTTCCT T
1.	F8	+	11	1.63e-5	GAGTCTCTGG A[redacted]CTTCCT CT
11.	F10	+	3	9.50e-5	GG A[redacted]CTTC[redacted]A GGCCCCAGGC
10.	A10	+	11	1.47e-4	CGGAGGTCTT [redacted]CTTC[redacted]T GG
9.	C10	+	8	1.47e-4	AGGTCTT [redacted]CTTC[redacted]T GGAGC
8.	F9	+	7	1.47e-4	GGTCTT [redacted]CTTC[redacted]T GGAGCA
5.	C9	+	10	2.33e-4	AGTCGTAGT T[redacted]CTTCCT AAC
7.	D10	+	13	6.24e-4	CGGCCTCGGA A[redacted]CTCTCT



F10-MOE: /G*/G*/A*/G*/C*T*T*C*G*A*G*G*C*C*C*/C*/A*/G*/G*/C

F10-Mut-MOE: /G*/G*/A*/C*/C*C*T*C*G*A*G*G*C*C*C*/C*/A*/G*/G*/C

FIGURE 23 continued

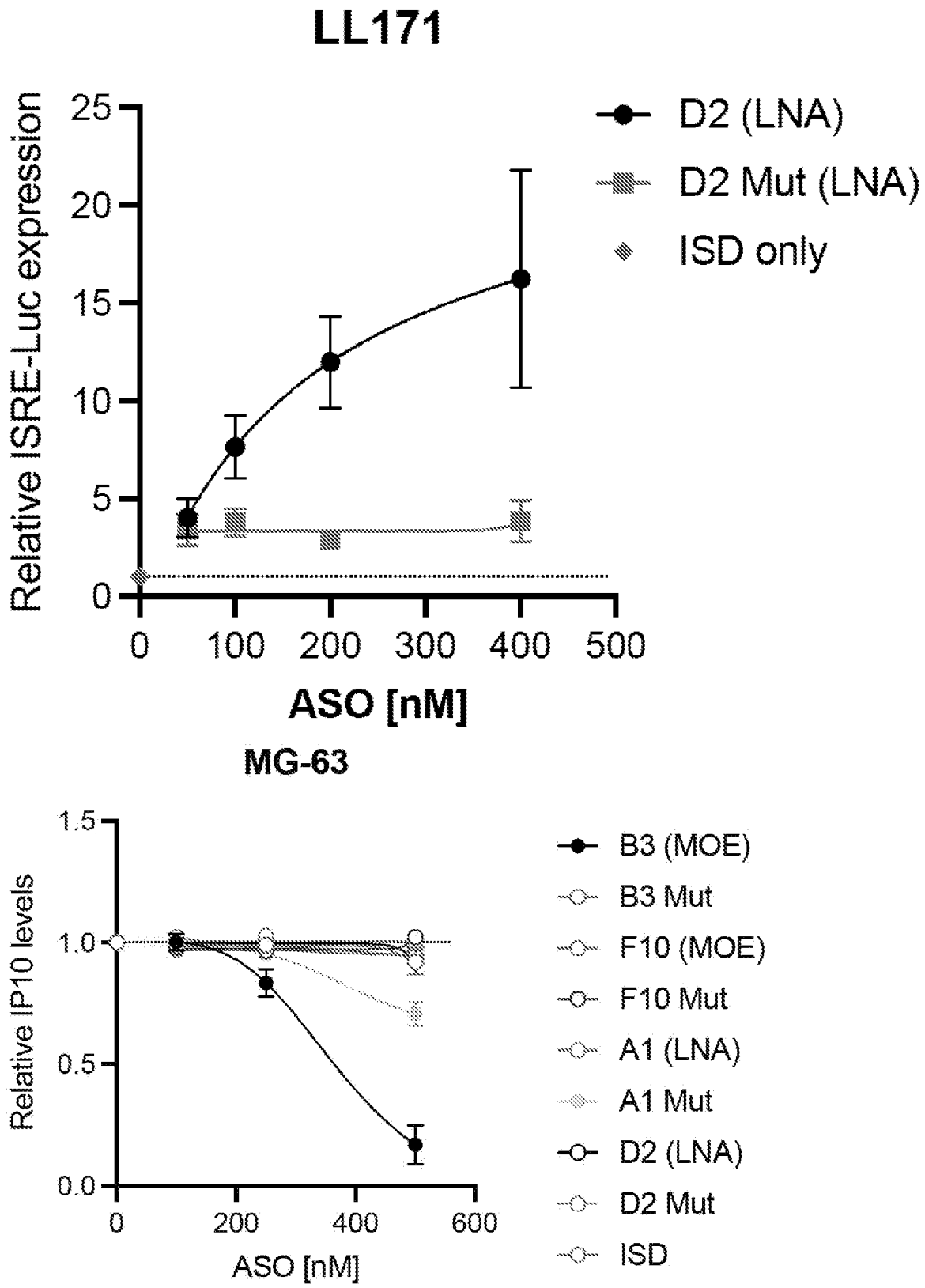

LL171
Relative ISRE-Luc expression
25
20
15
10
5
0
0
100
200
300
400
500
ASO [nM]
D2 (LNA)
D2 Mut (LNA)
ISD only
MG-63
Relative IP10 levels
1.5
1.0
0.5
0.0
0
200
400
600
ASO [nM]
B3 (MOE)
B3 Mut
F10 (MOE)
F10 Mut
A1 (LNA)
A1 Mut
D2 (LNA)
D2 Mut
ISD

FIGURE 24

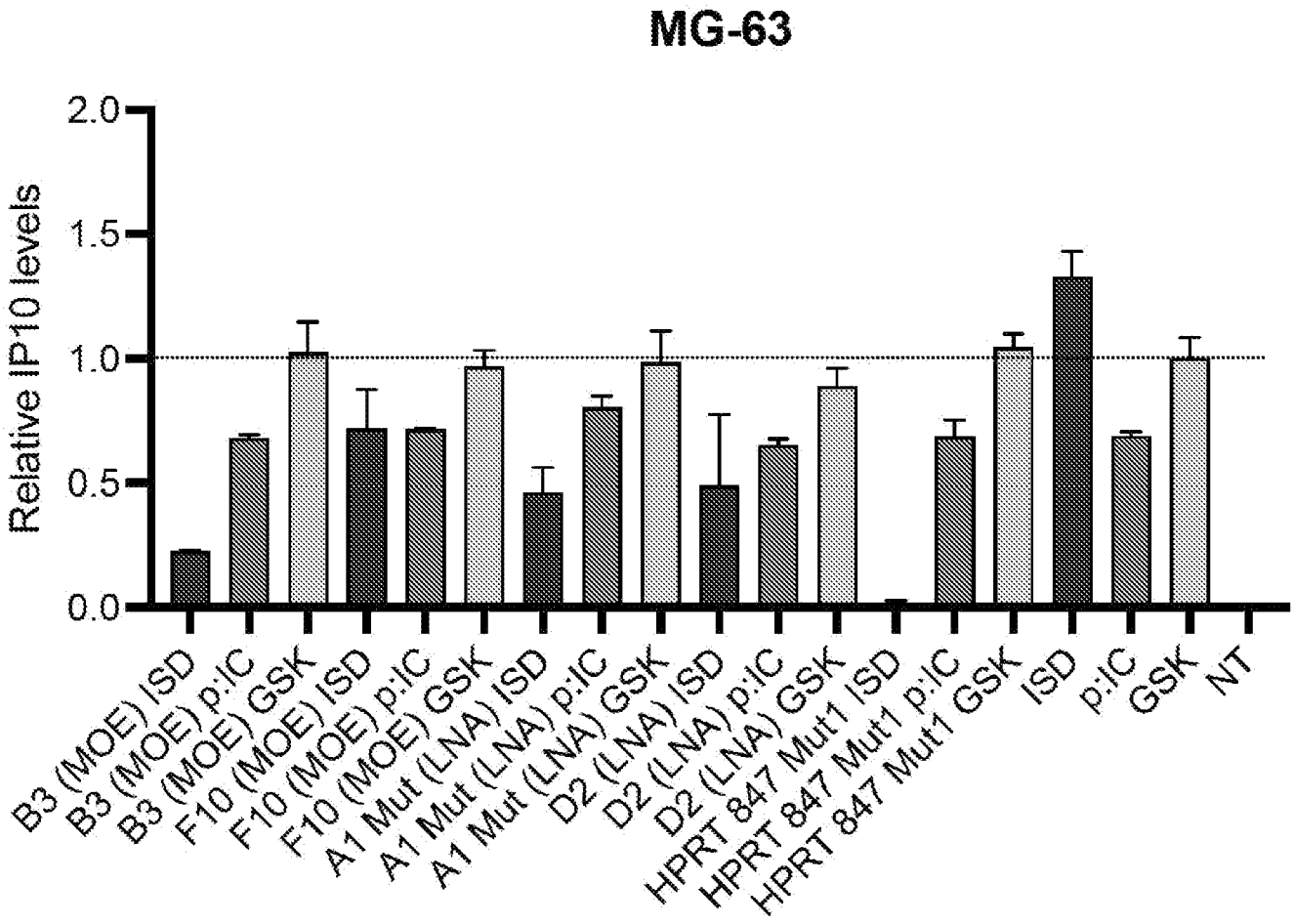

MG-63
Relative IP10 levels
2.0
1.5
1.0
0.5
0.0
B3 (MOE) ISD
B3 (MOE) p:IC
B3 (MOE) GSK
F10 (MOE) ISD
F10 (MOE) p:IC
F10 (MOE) GSK
A1 Mut (LNA) ISD
A1 Mut (LNA) p:IC
A1 Mut (LNA) GSK
D2 (LNA) ISD
D2 (LNA) p:IC
D2 (LNA) GSK
HPRT 847 Mut1 ISD
HPRT 847 Mut1 p:IC
HPRT 847 Mut1 GSK
ISD
p:IC
GSK
NT

FIGURE 25

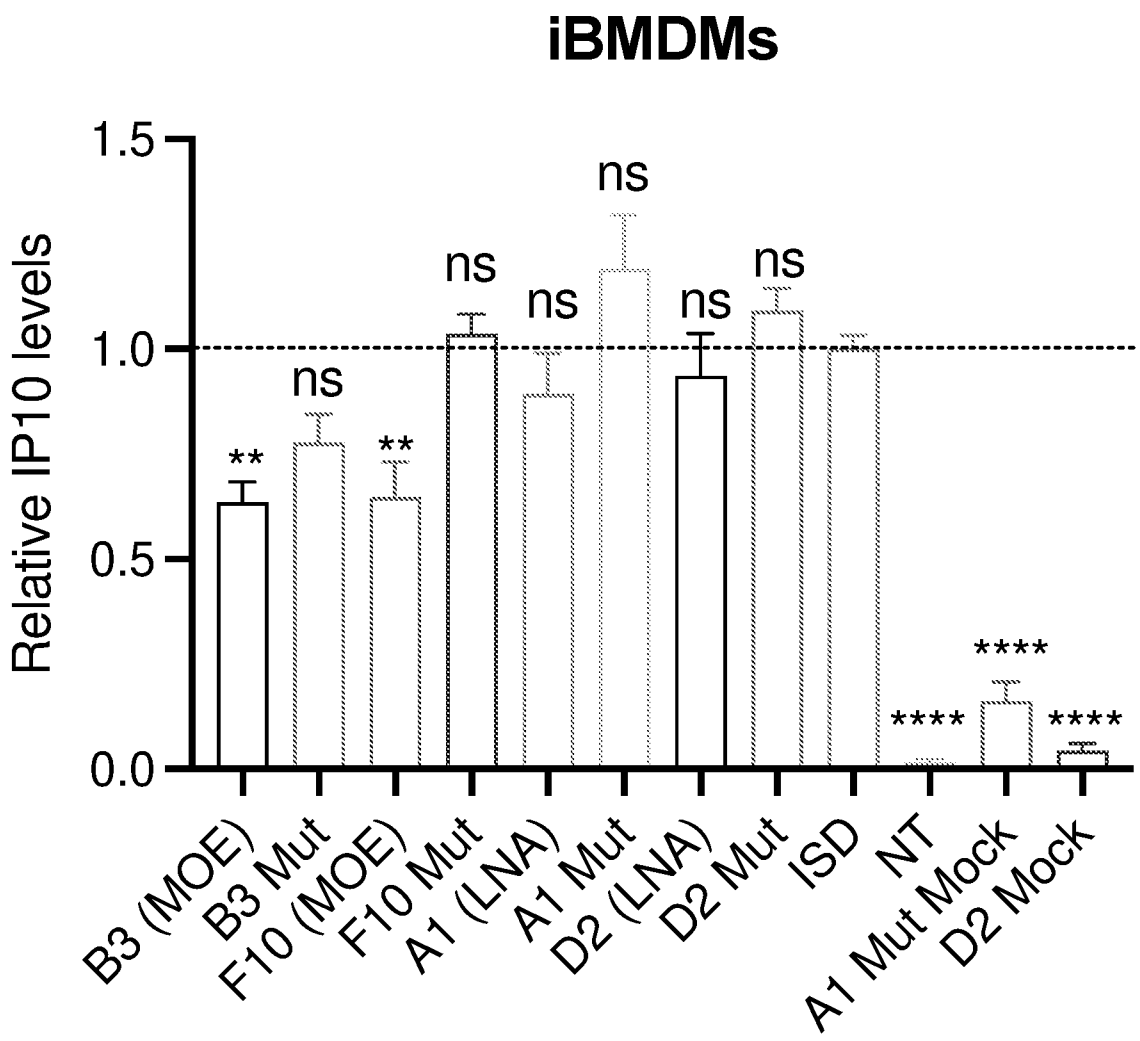

iBMDMs
Relative IP10 levels
1.5
1.0
0.5
0.0
**
ns
**
ns
ns
ns
ns
ns
****
****
****
B3 (MOE)
B3 Mut
F10 (MOE)
F10 Mut
A1 (LNA)
A1 Mut
D2 (LNA)
D2 Mut
ISD
NT
A1 Mut Mock
D2 Mock

FIGURE 26

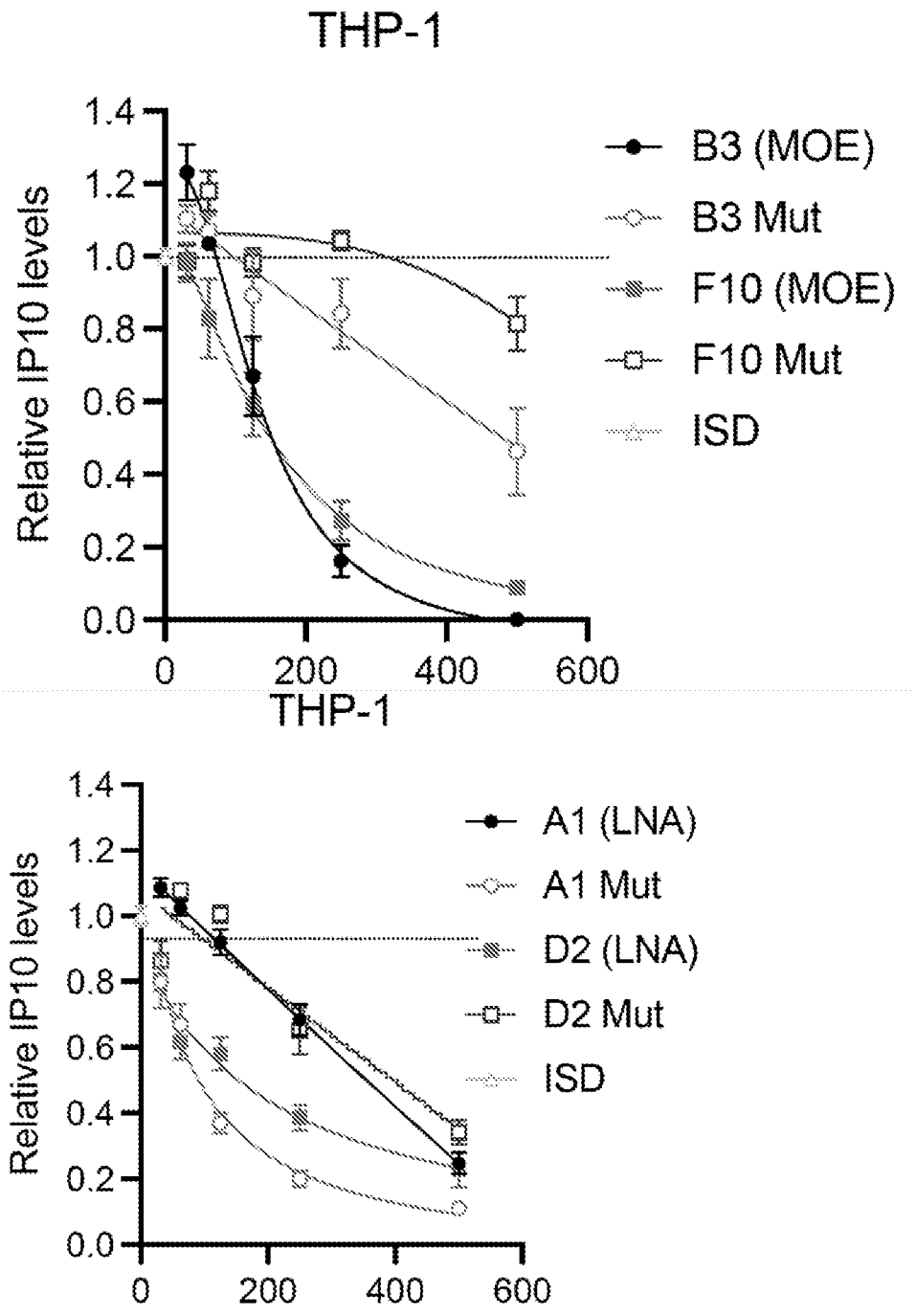

THP-1
Relative IP10 levels
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
THP-1
B3 (MOE)
B3 Mut
F10 (MOE)
F10 Mut
ISD
Relative IP10 levels
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
200
400
600
A1 (LNA)
A1 Mut
D2 (LNA)
D2 Mut
ISD

FIGURE 27

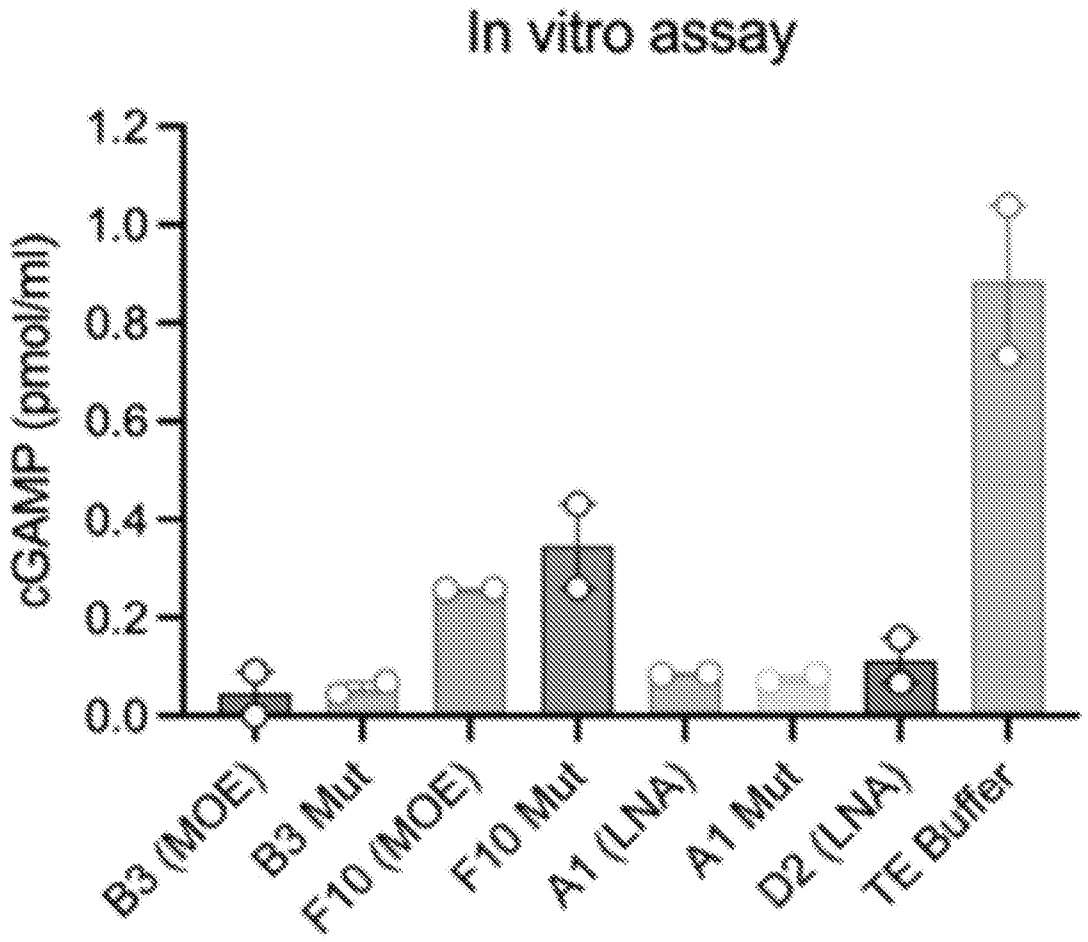

In vitro assay
cGAMP (pmol/ml)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
B3 (MOE)
B3 Mut
F10 (MOE)
F10 Mut
A1 (LNA)
A1 Mut
D2 (LNA)
TE Buffer

FIGURE 28

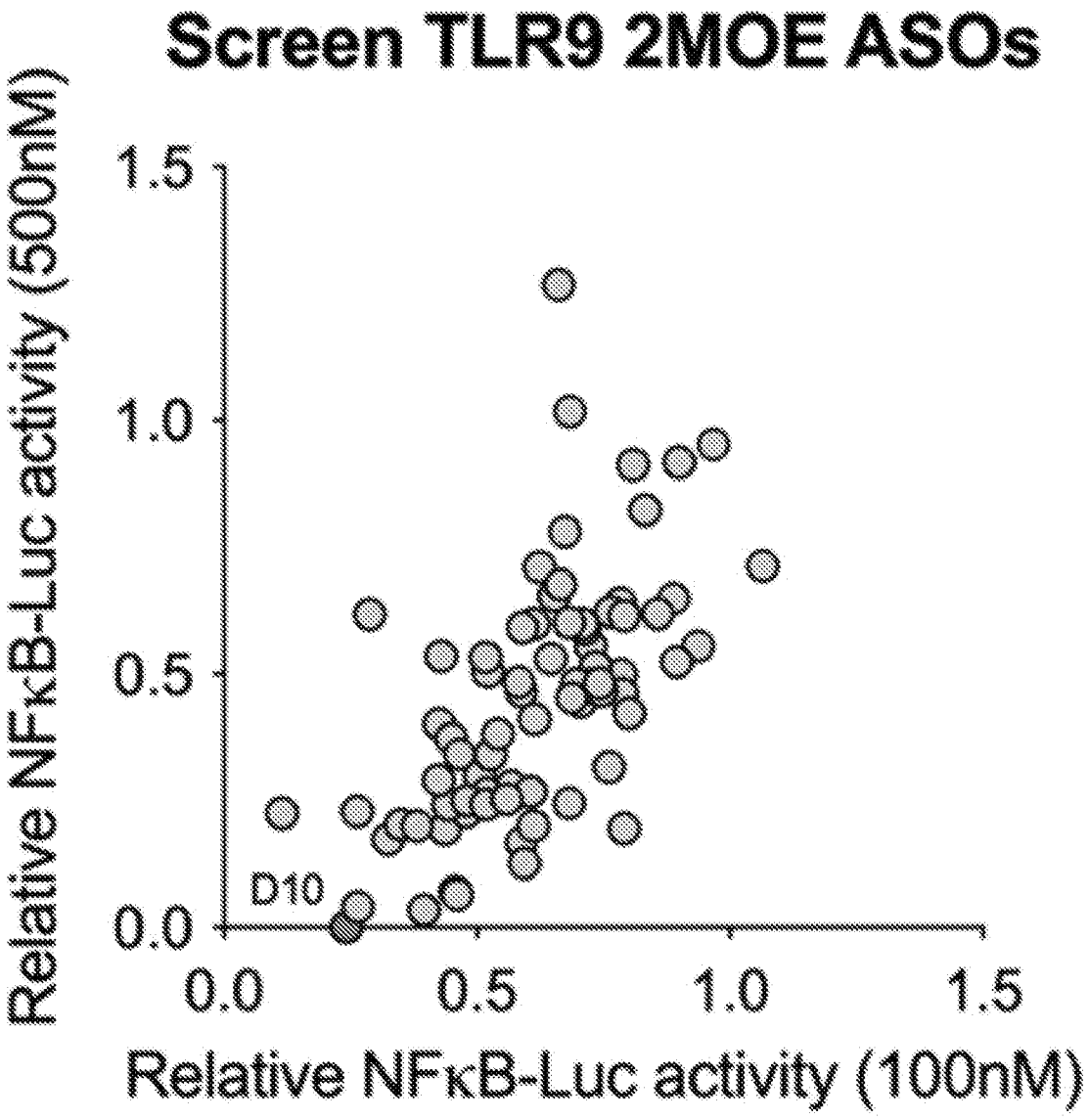

Screen TLR9 2MOE ASOs
Relative NFκB-Luc activity (500nM)
1.5
1.0
0.5
0.0
D10
0.0
0.5
1.0
1.5
Relative NFκB-Luc activity (100nM)

FIGURE 29

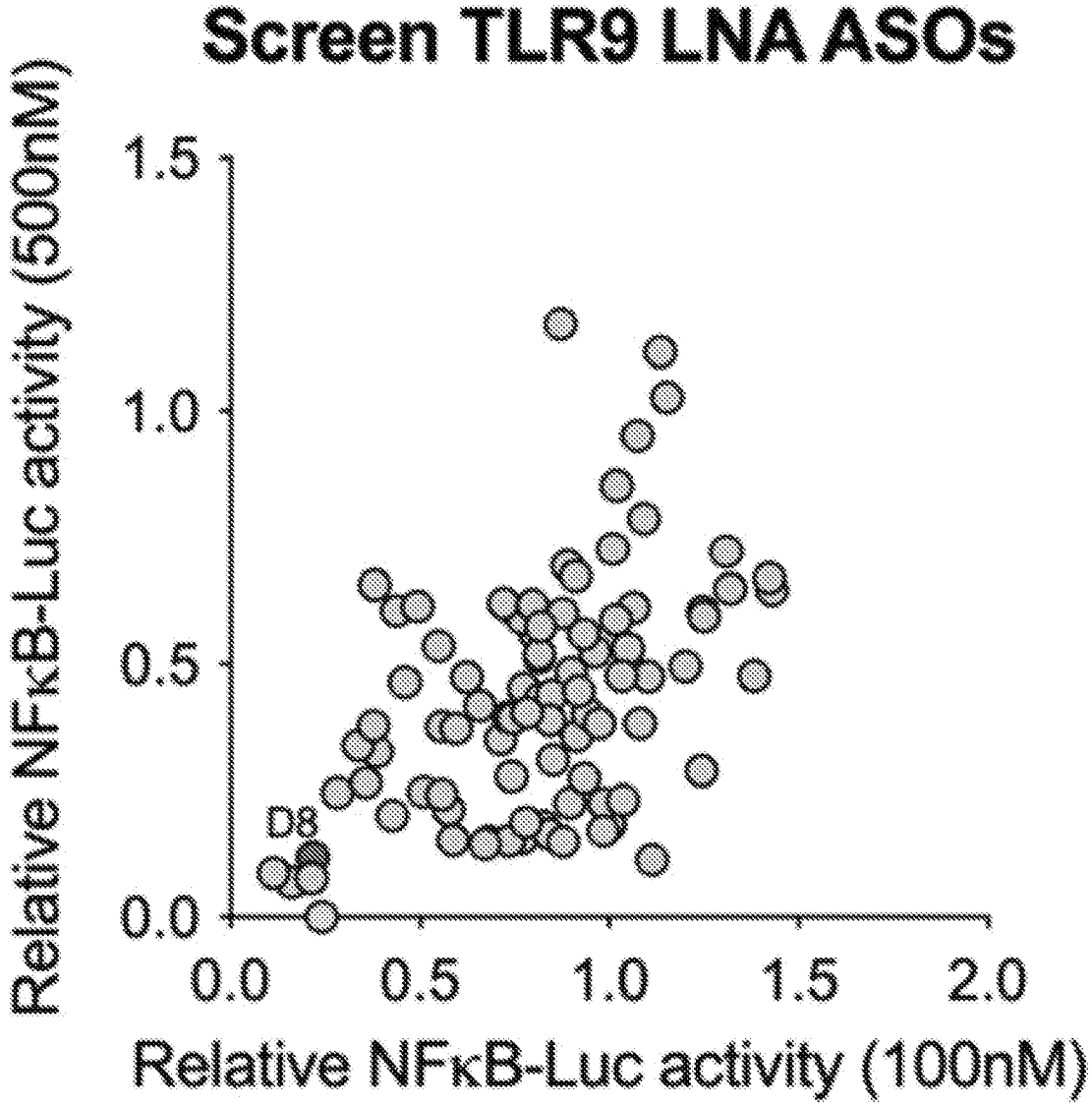
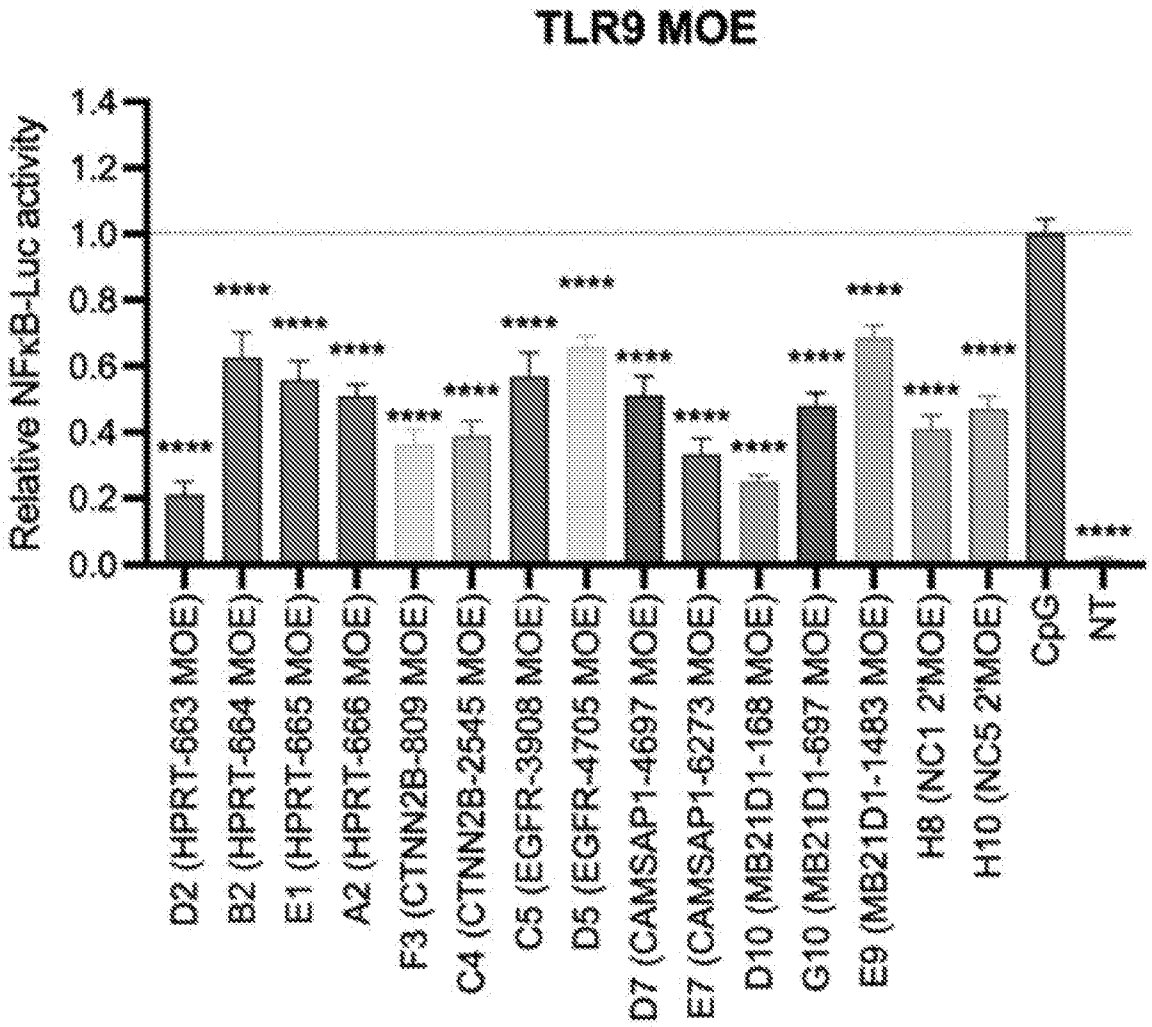
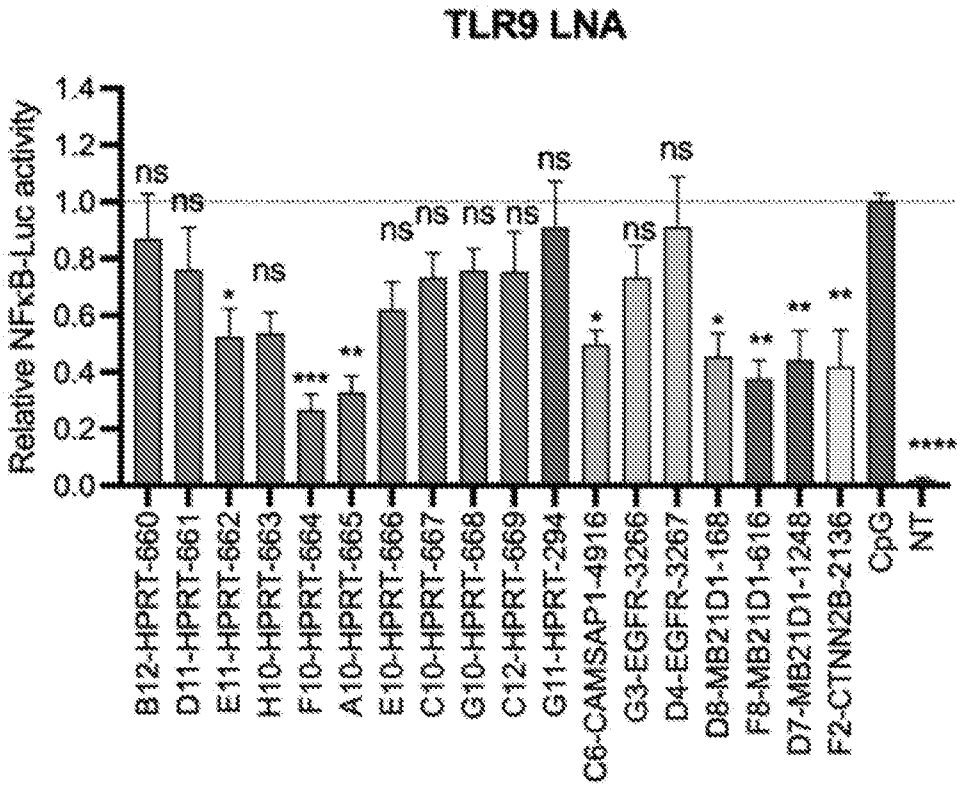


FIGURE 29 continued



HPRT-663 MOE ACACTTCGTGGGGTCCTTTT
HPRT-664 MOE AACACTTCGTGGGGTCCTTT
HPRT-665 MOE CAACACTTCGTGGGGTCCTT
HPRT-666 MOE CCAACACTTCGTGGGGTCCT

FIGURE 30



660 TCGTGGGGTCCTTTTC
661 TTCGTGGGGTCCTTTT
662 CTTCGTGGGGTCCTTT
663 ACTTCGTGGGGTCCTT
664 CACTTCGTGGGGTCCT
665 ACACTTCGTGGGGTCC
666 AACACTTCGTGGGGTC
667 CAACACTTCGTGGGGT
668 CCAACACTTCGTGGGG
669 TCCAACACTTCGTGGG

FIGURE 30 continued

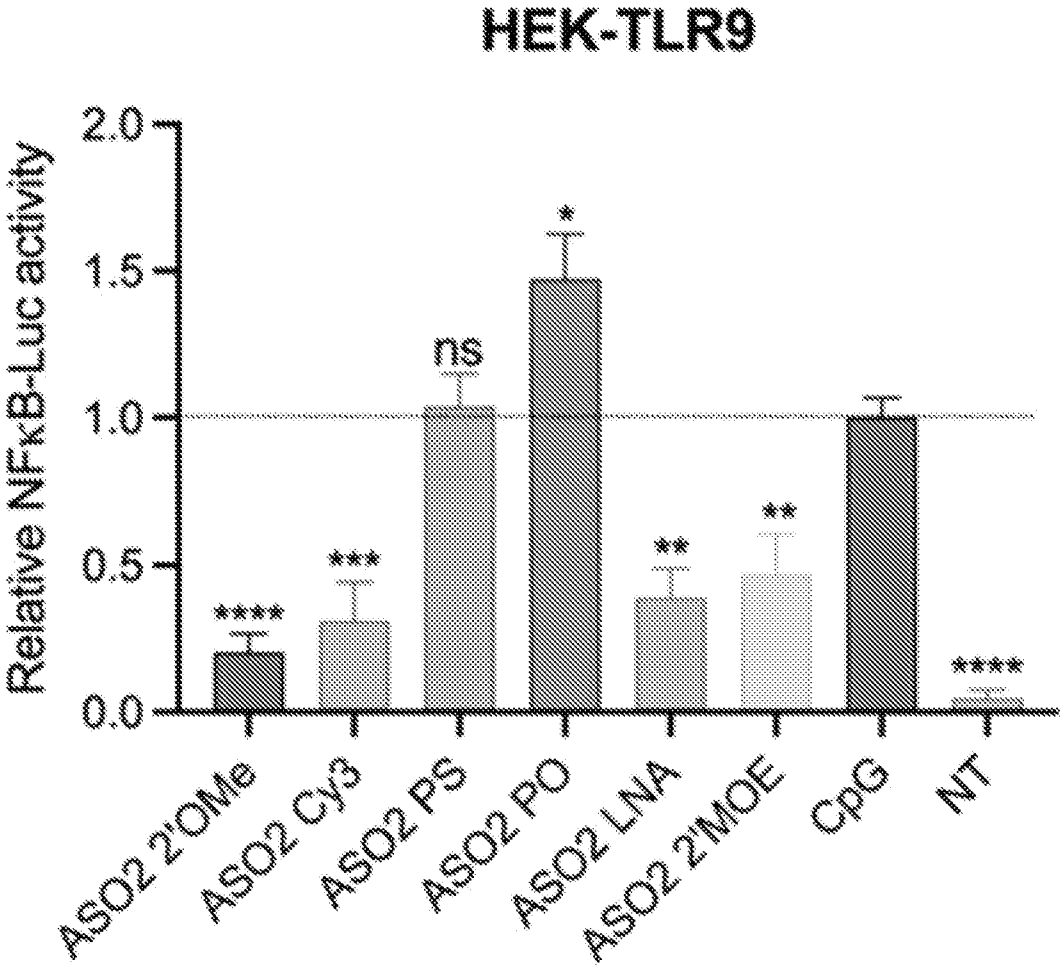

HEK-TLR9
Relative NFκB-Luc activity
2.0
1.5
1.0
0.5
0.0
****
***
ns
*
**
**
****
ASO2 2'OMe
ASO2 Cy3
ASO2 PS
ASO2 PO
ASO2 LNA
ASO2 2'MOE
CpG
NT

FIGURE 31

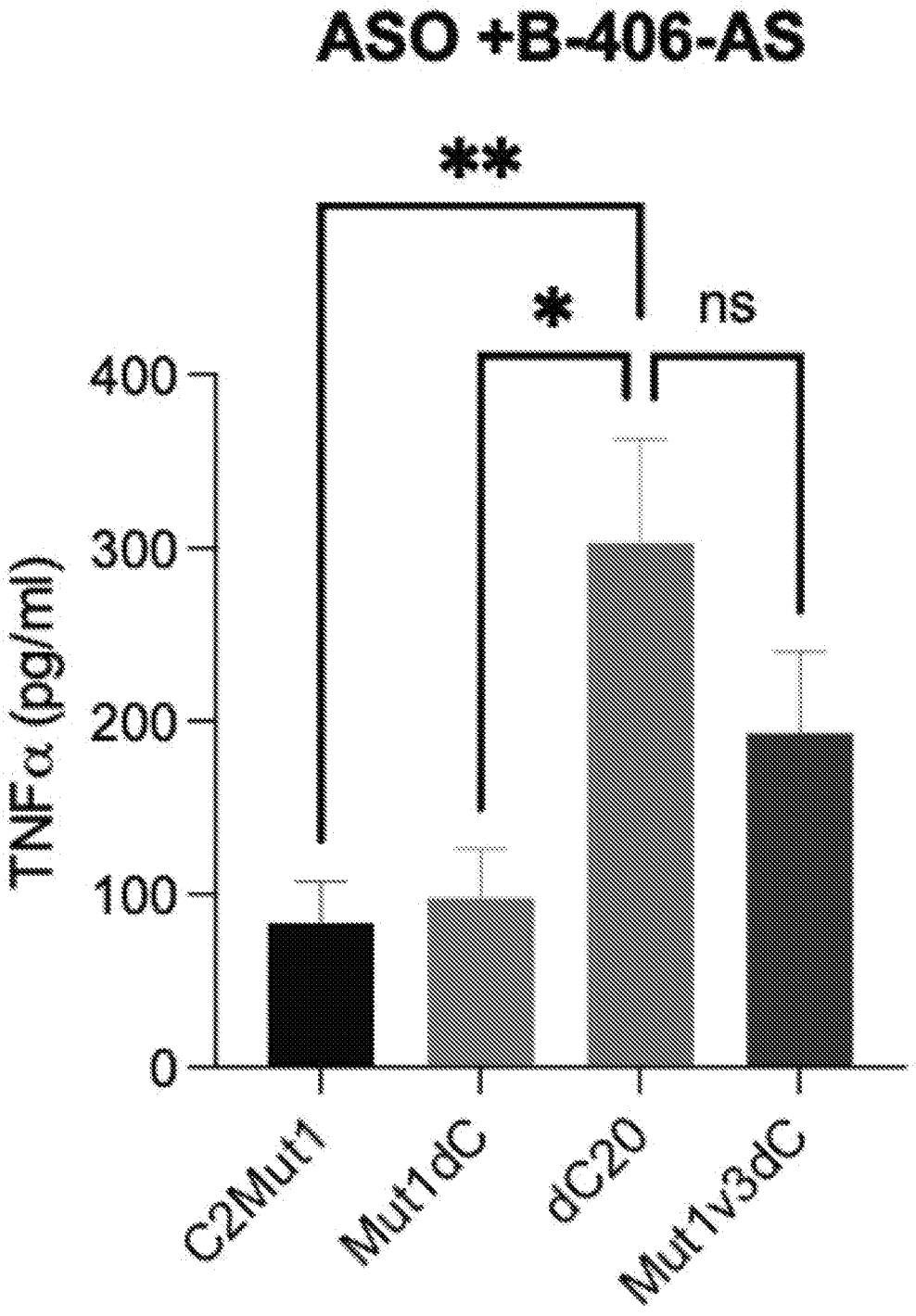
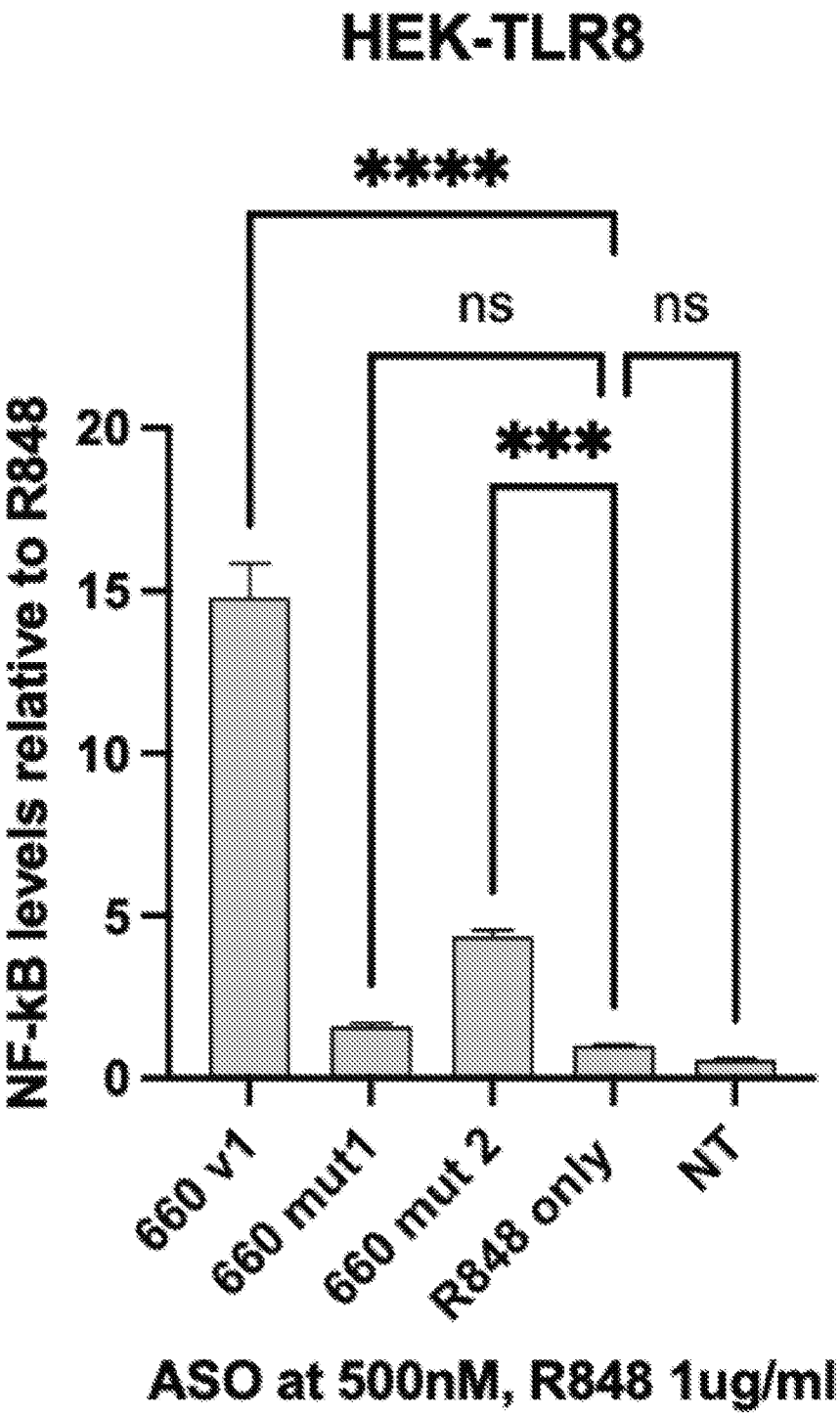

ASO +B-406-AS
**
*
ns
400
300
200
100
0
TNFα (pg/ml)
C2Mut1
Mut1dC
dC20
Mut1v3dC

FIGURE 32

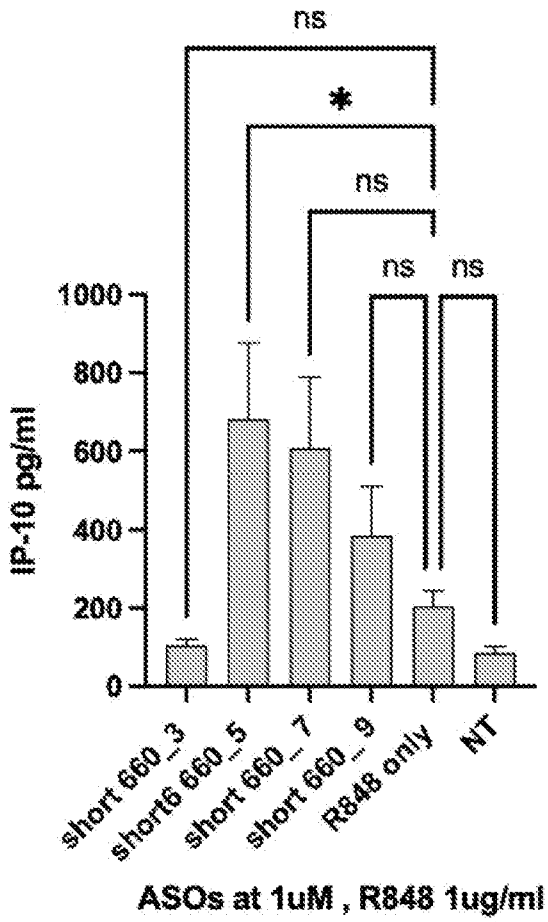


660v1: mC*mU*mU*mC*mG*T*G*G*G*G*T*C*C*T*T*mU*mU*mC*mA*mC

660-Mut1: mG*mA*mA*mC*mG*T*G*G*G*G*T*C*C*T*T*mU*mU*mC*mA*mC

660-Mut2: mC*mU*mU*+C*+G*T*G*G*G*G*T*C*C*T*T*mU*mU*mC*mA*mC

FIGURE 33



Short 660_3: mC*mU*mU

Short 660_5: mC*mU*mU*mC*mG

Short-660_7: mC*mU*mU*mC*mG*T*G

Short-660_9: mC*mU*mU*mC*mG*T*G*G*G

FIGURE 34

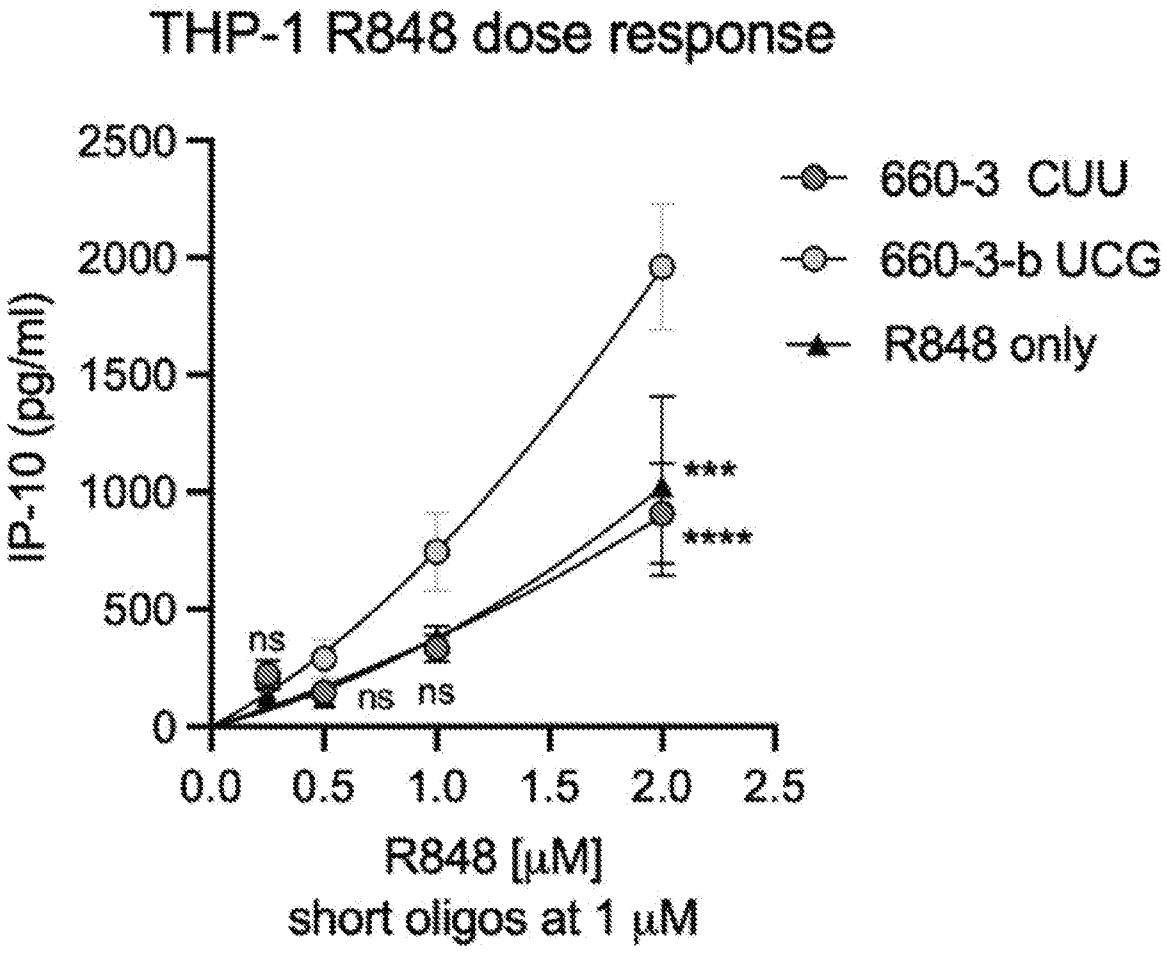

THP-1 R848 dose response
IP-10 (pg/ml)
2500
2000
1500
1000
500
0
0.0
0.5
1.0
1.5
2.0
2.5
R848 [μM]
short oligos at 1 μM
660-3 CUU
660-3-b UCG
R848 only
ns
ns
ns
***
****

FIGURE 35

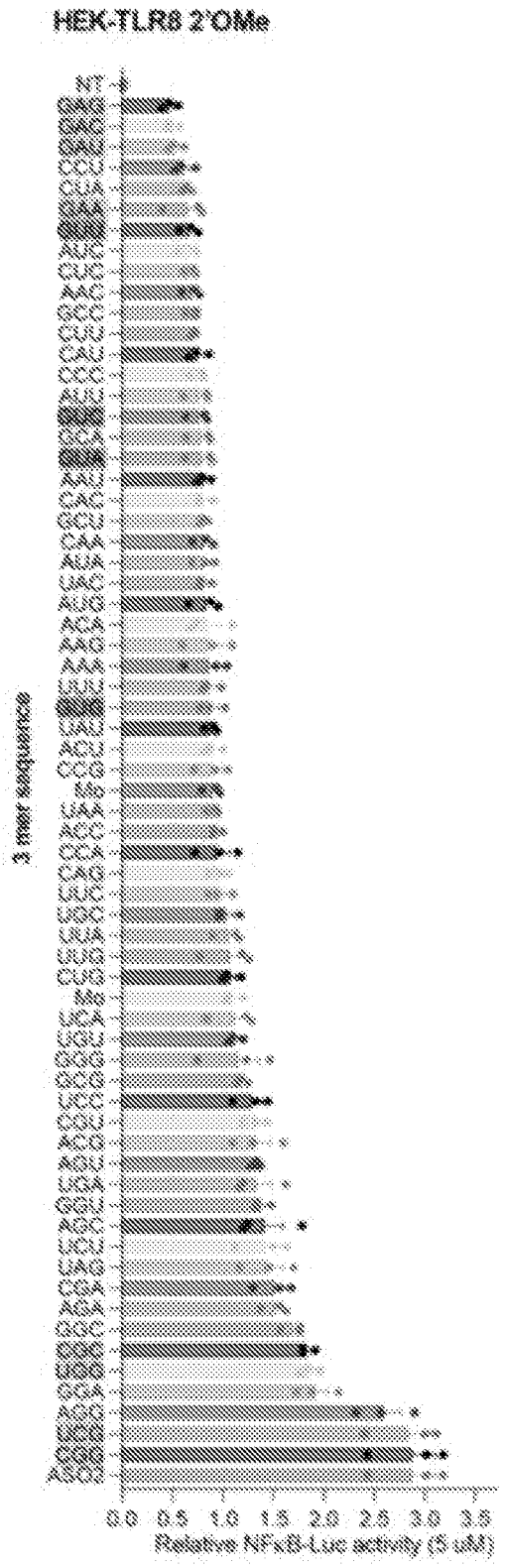

HEK-TLR8 2'OMe
NT
3 mer sequence
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5
Relative NFκB-Luc activity (5 uM)

FIGURE 36A

B

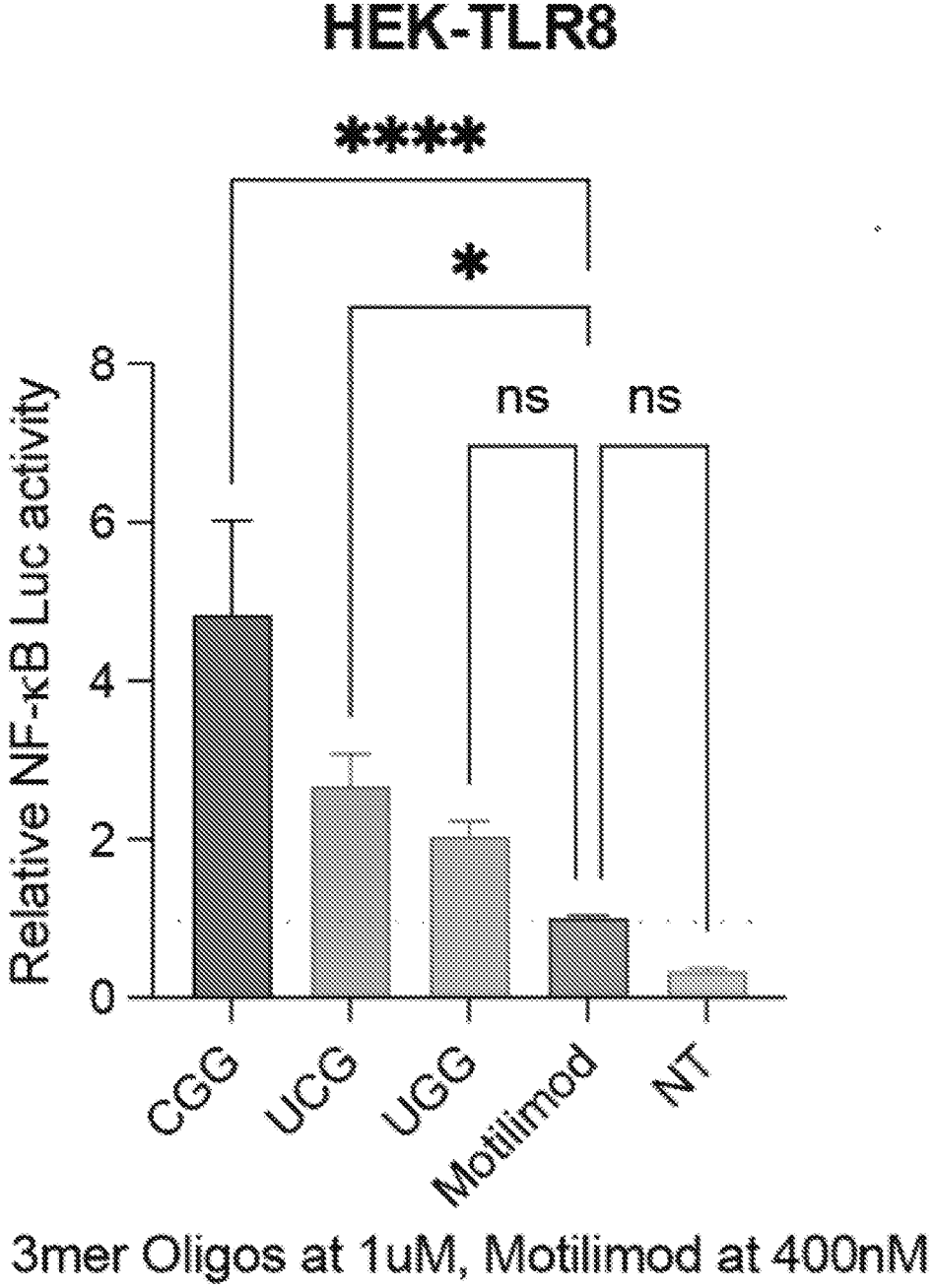

HEK-TLR8
****
*
ns
ns
Relative NF-κB Luc activity
0
2
4
6
8
CGG
UCG
UGG
Motilimod
NT
3mer Oligos at 1uM, Motilimod at 400nM

FIGURE 36B

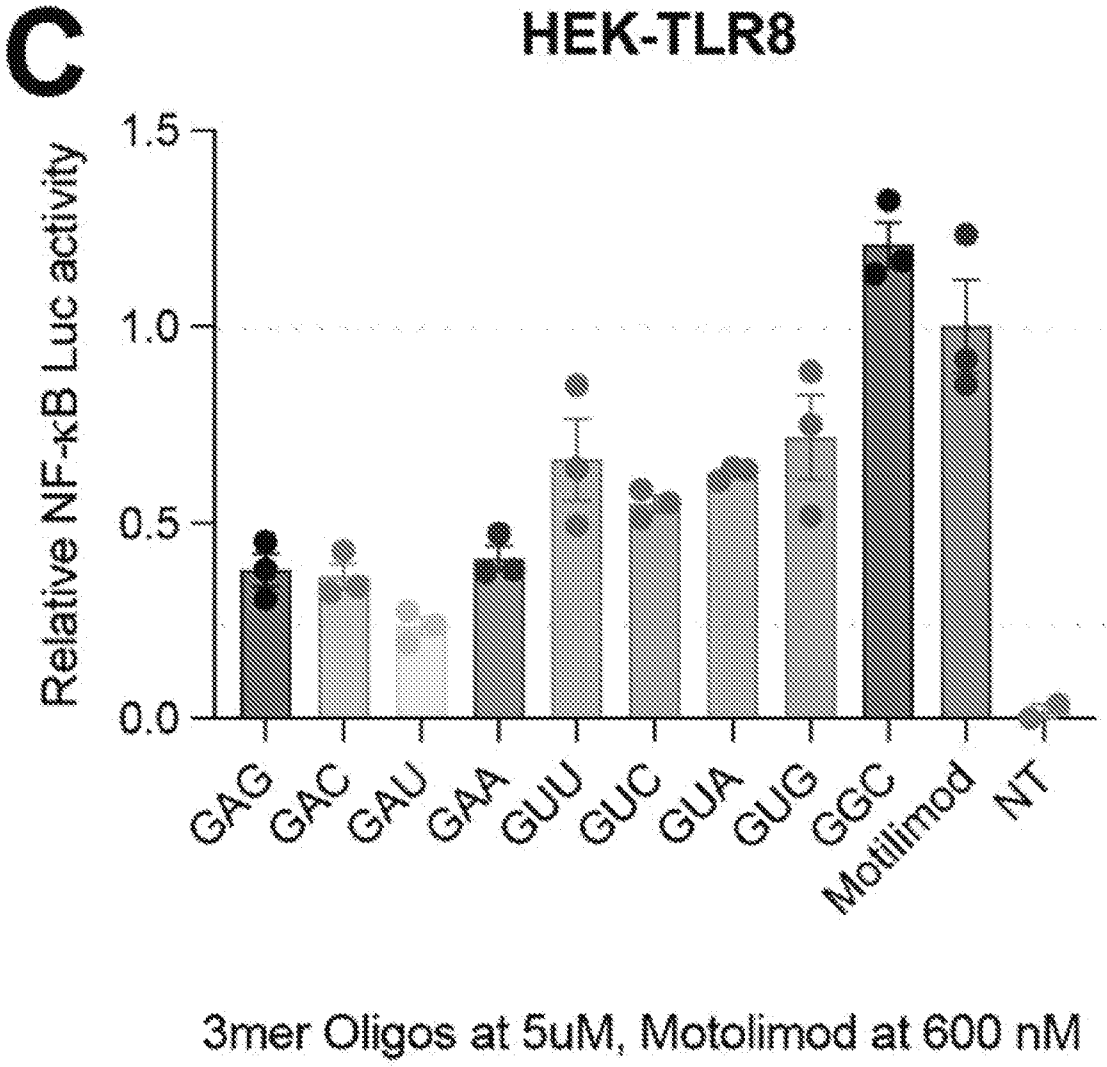

C
HEK-TLR8
Relative NF-κB Luc activity
1.5
1.0
0.5
0.0
GAG
GAC
GAU
GAA
GUU
GUC
GUA
GUG
GGC
Motilimod
NT
3mer Oligos at 5uM, Motolimod at 600 nM

FIGURE 36C

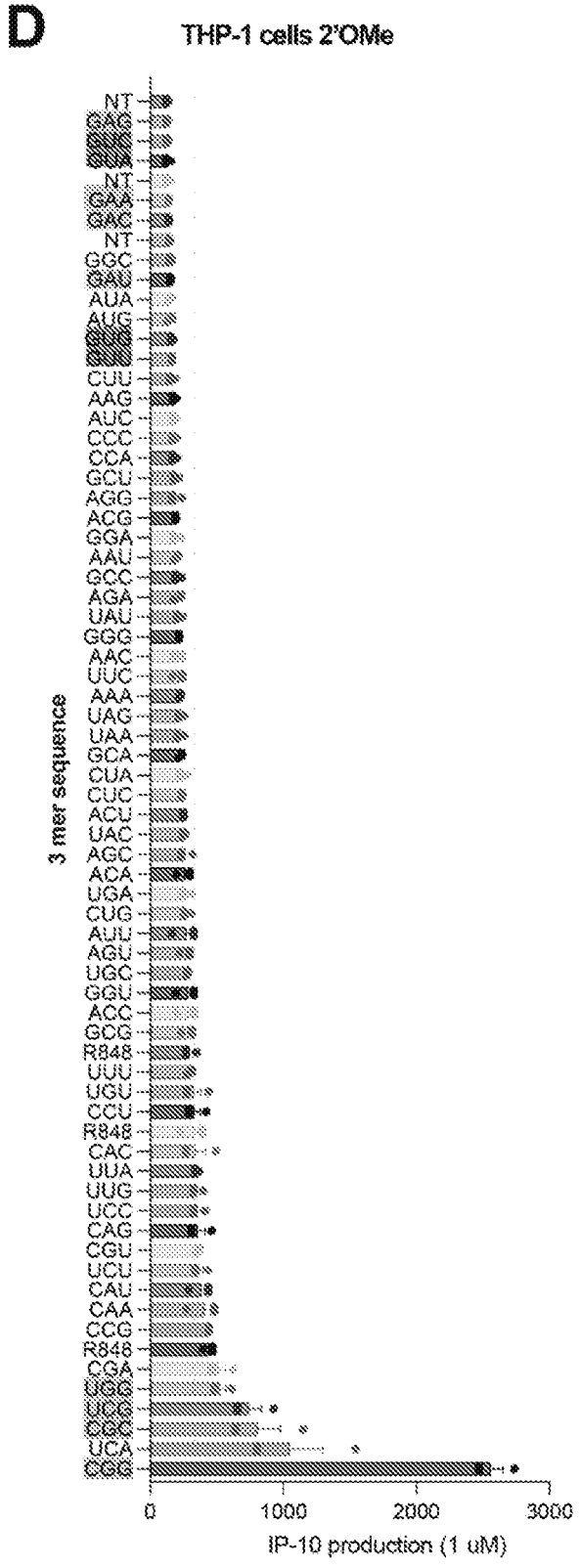

D
THP-1 cells 2'OMe
3 mer sequence
NT
GAG
NT
GAA
GAC
NT
GGC
GAU
AUA
AUG
CUU
AAG
AUC
CCC
CCA
GCU
AGG
ACG
GGA
AAU
GCC
AGA
UAU
GGG
AAC
UUC
AAA
UAG
UAA
GCA
CUA
CUC
ACU
UAC
AGC
ACA
UGA
CUG
AUU
AGU
UGC
GGU
ACC
GCG
R848
UUU
UGU
CCU
R848
CAC
UUA
UUG
UCC
CAG
CGU
UCU
CAU
CAA
CCG
R848
CGA
UGG
UCG
CGC
UCA
CGG
0
1000
2000
3000
IP-10 production (1 uM)

FIGURE 36D

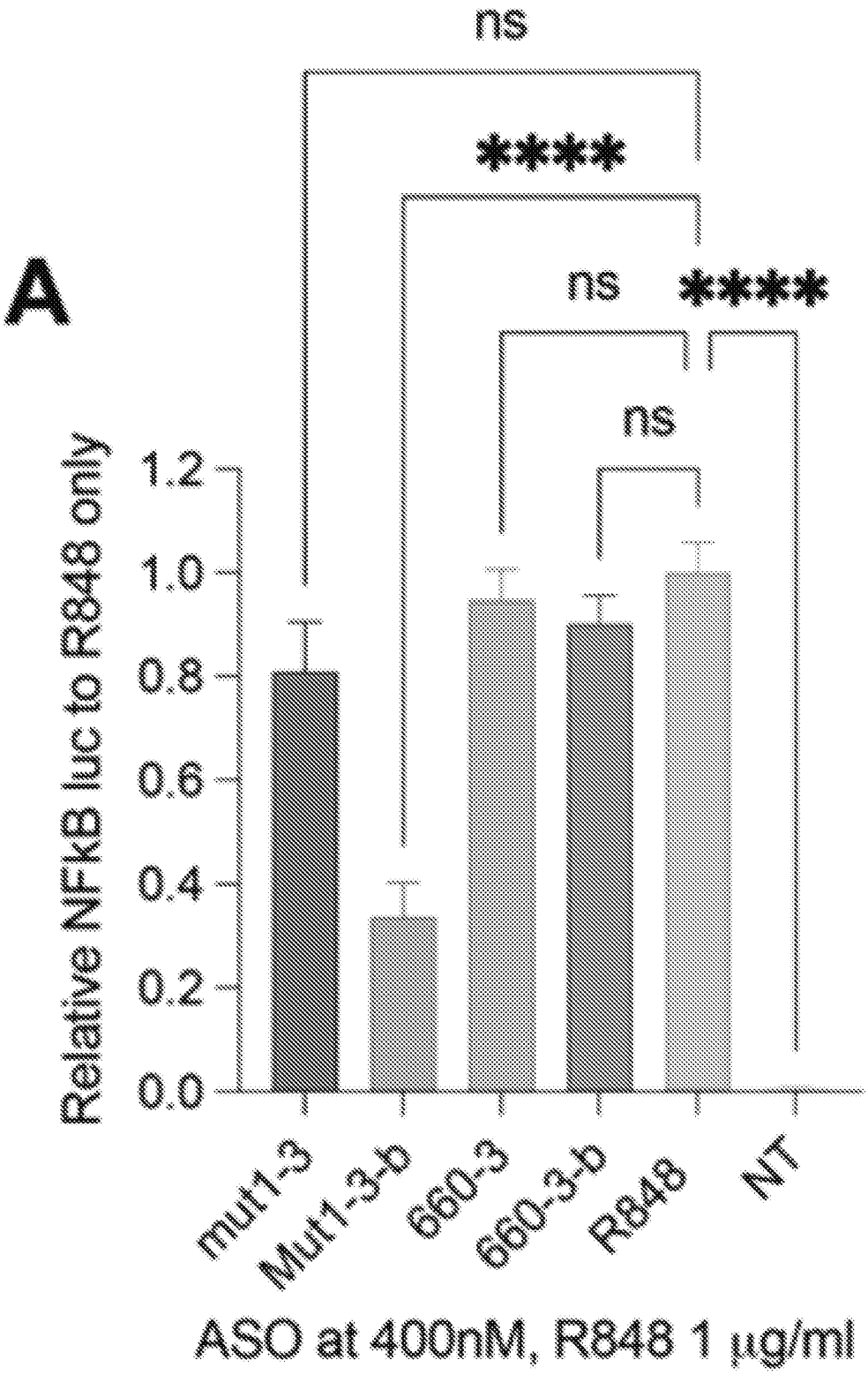

A
ns
****
ns
****
ns
Relative NFkB luc to R848 only
1.2
1.0
0.8
0.6
0.4
0.2
0.0
mut1-3
Mut1-3-b
660-3
660-3-b
R848
NT
ASO at 400nM, R848 1 μg/ml

FIGURE 37A

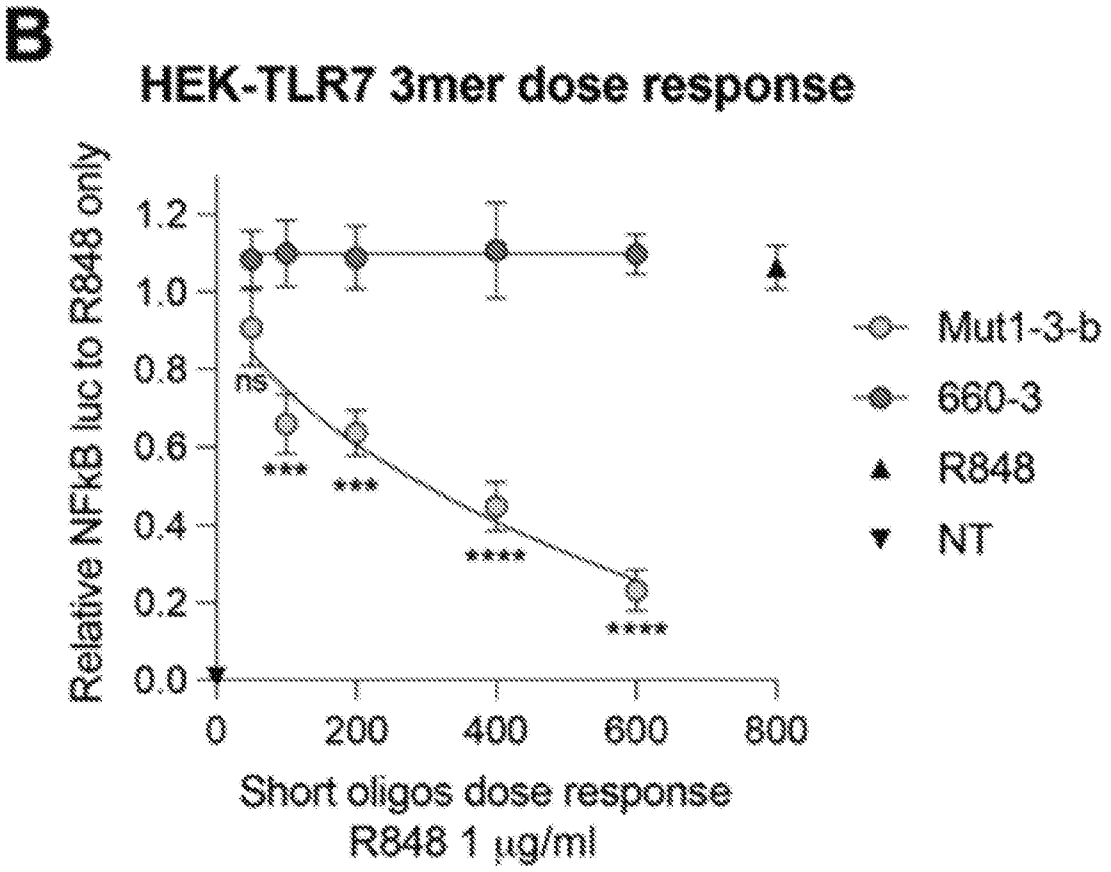

B
HEK-TLR7 3mer dose response
Relative NFkB luc to R848 only
1.2
1.0
0.8
0.6
0.4
0.2
0.0
ns
***
***
****
****
0
200
400
600
800
Short oligos dose response
R848 1 µg/ml
Mut1-3-b
660-3
R848
NT

FIGURE 37B

C

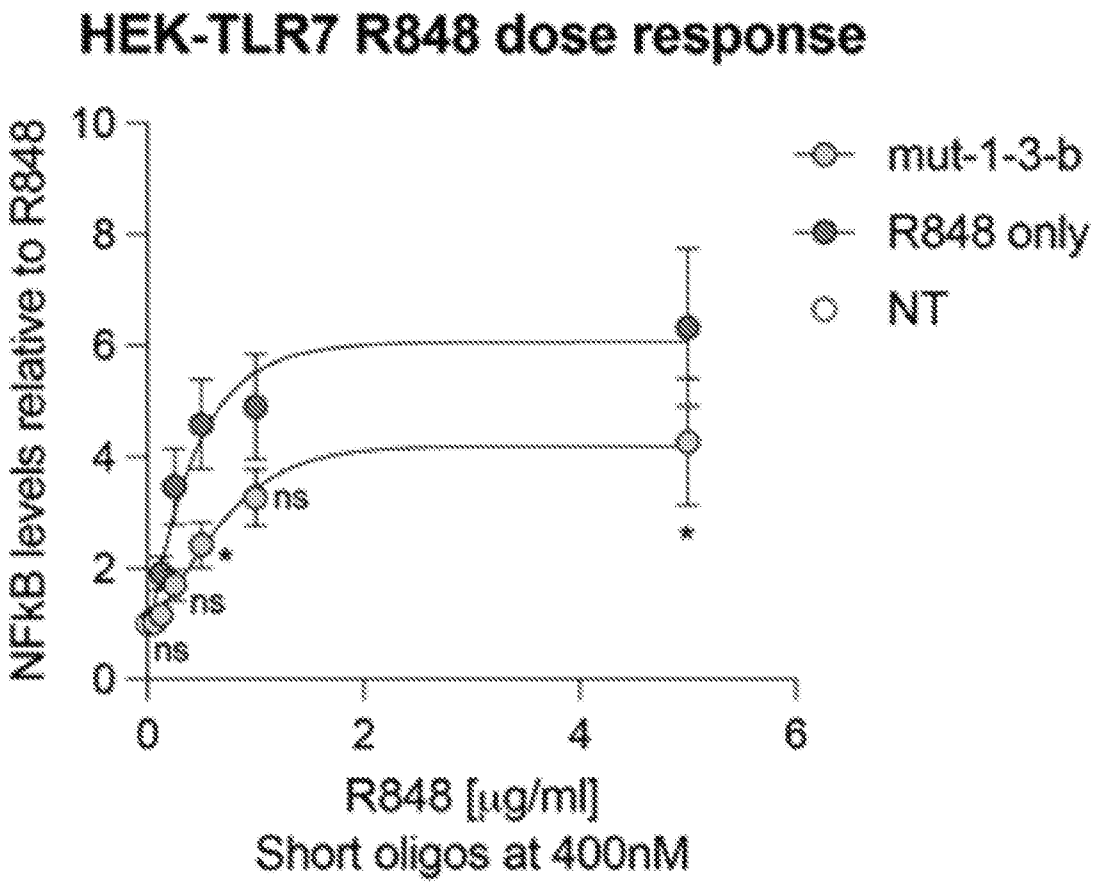

HEK-TLR7 R848 dose response
NFkB levels relative to R848
10
8
6
4
2
0
0
2
4
6
R848 [µg/ml]
Short oligos at 400nM
mut-1-3-b
R848 only
NT
ns
ns
ns
*
*

FIGURE 37C

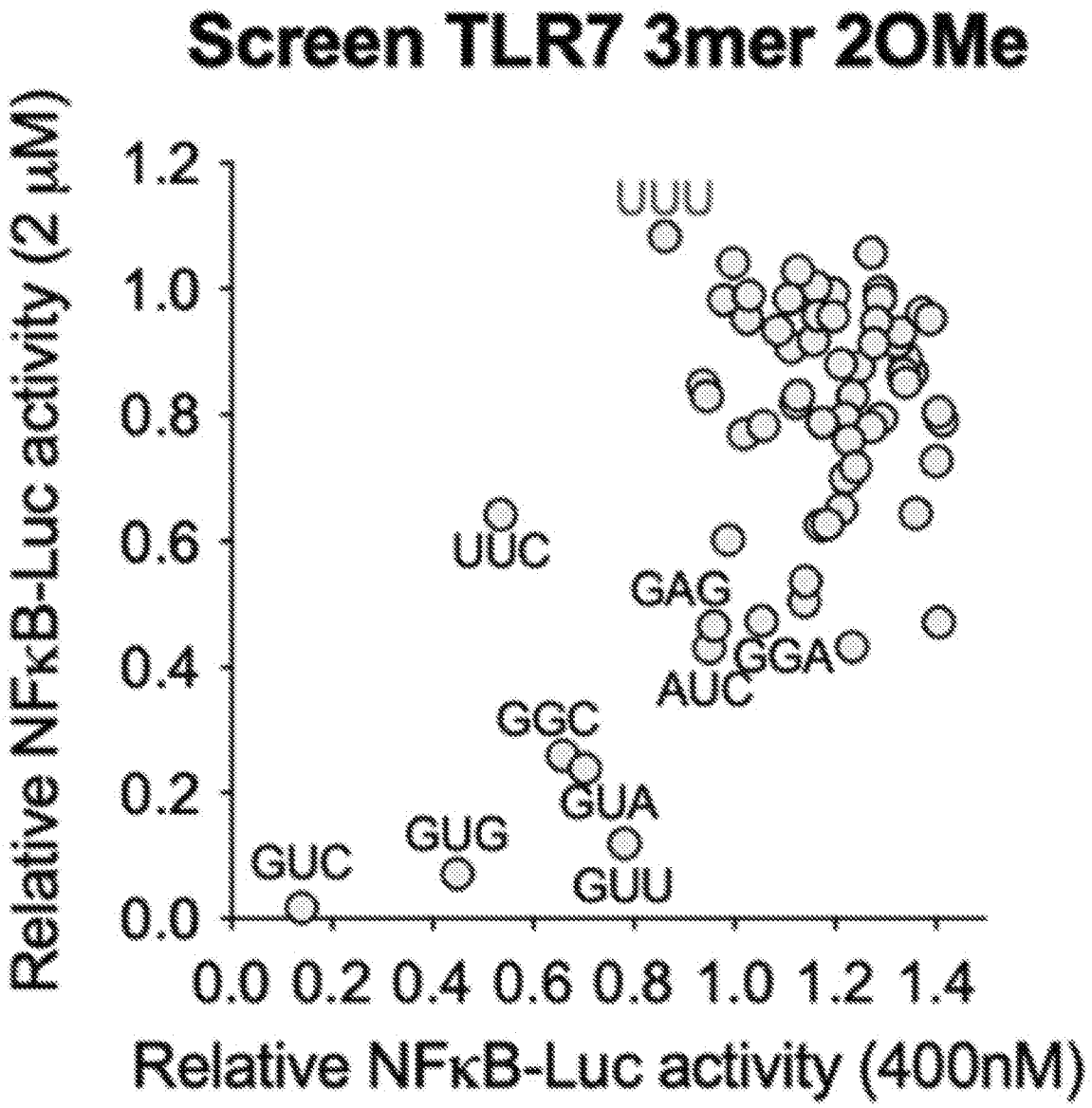
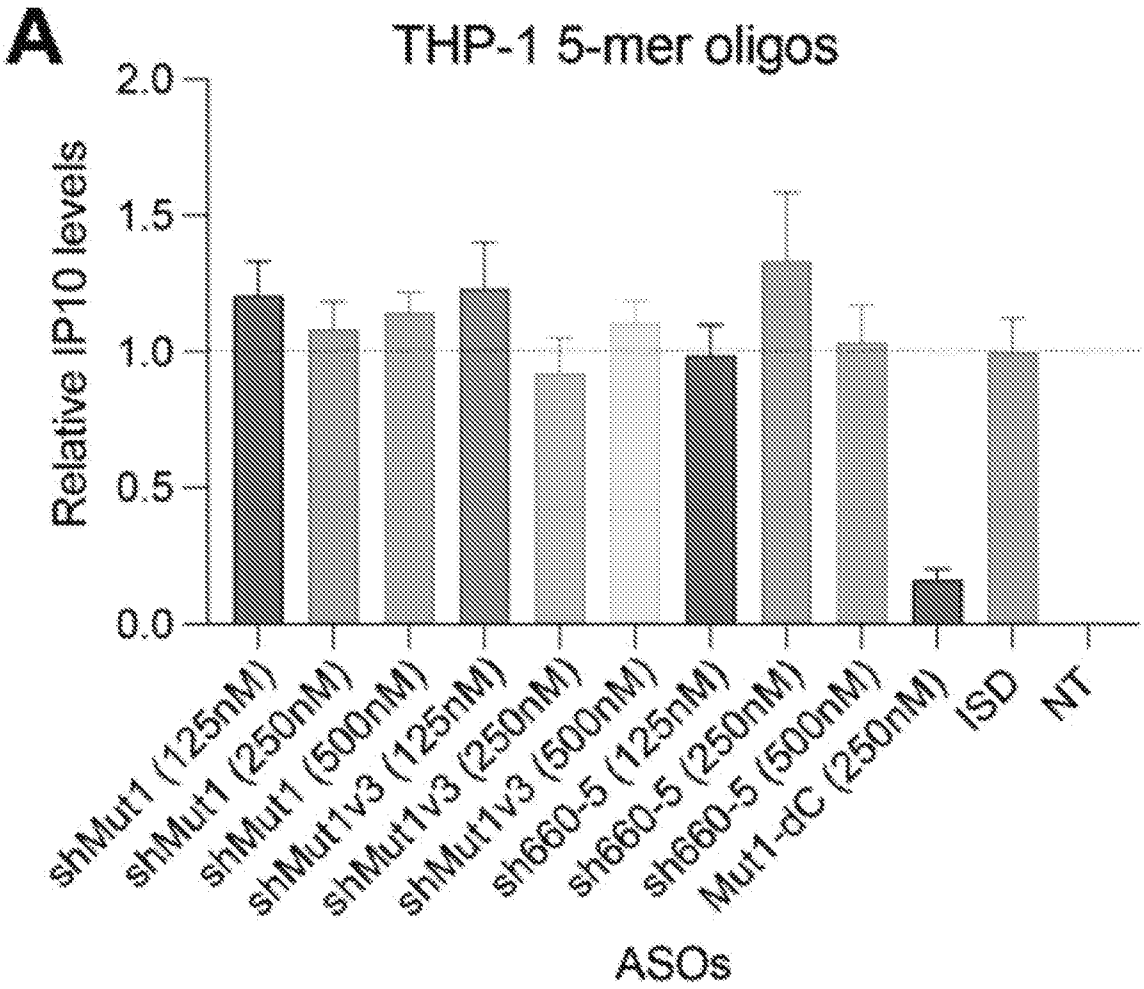
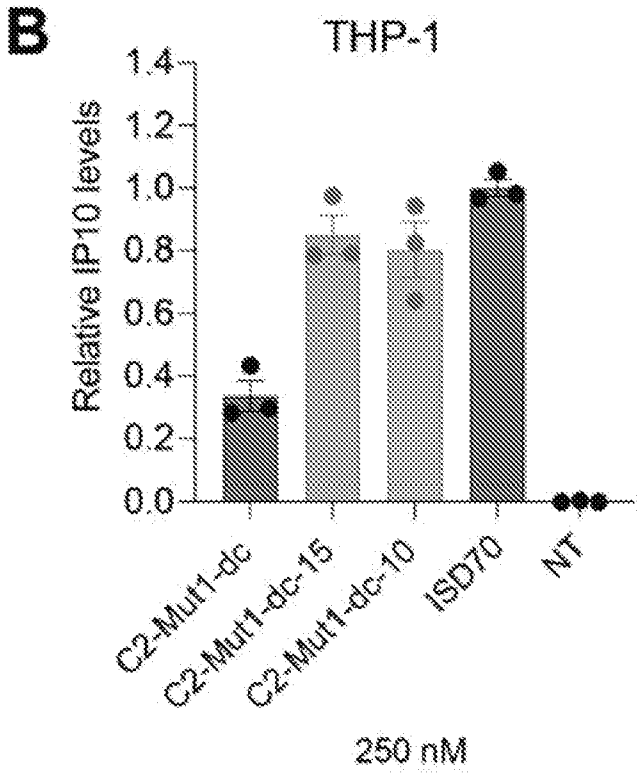

Screen TLR7 3mer 2OMe
Relative NFκB-Luc activity (2 μM)
1.2
1.0
0.8
0.6
0.4
0.2
0.0
UUU
UUC
GAG
GGA
AUC
GGC
GUA
GUG
GUC
GUU
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
Relative NFκB-Luc activity (400nM)

FIGURE 38



ShortMut1 : mG*mG*mU*mA*mU
ShortMut1v3: mC*mG*mU*mU*mU
Short660-5: mC*mU*mU*mC*mG

FIGURE 39A



C2Mut1-dC: mG*mG*mU*A*T*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C*C
C2Mut1-dC-15: mG*mG*mU*A*T*C*C*C*C*C*C*C*C*C*C*C
C2Mut1-dC-10: mG*mG*mU*A*T*C*C*C*C*C

FIGURE 39B

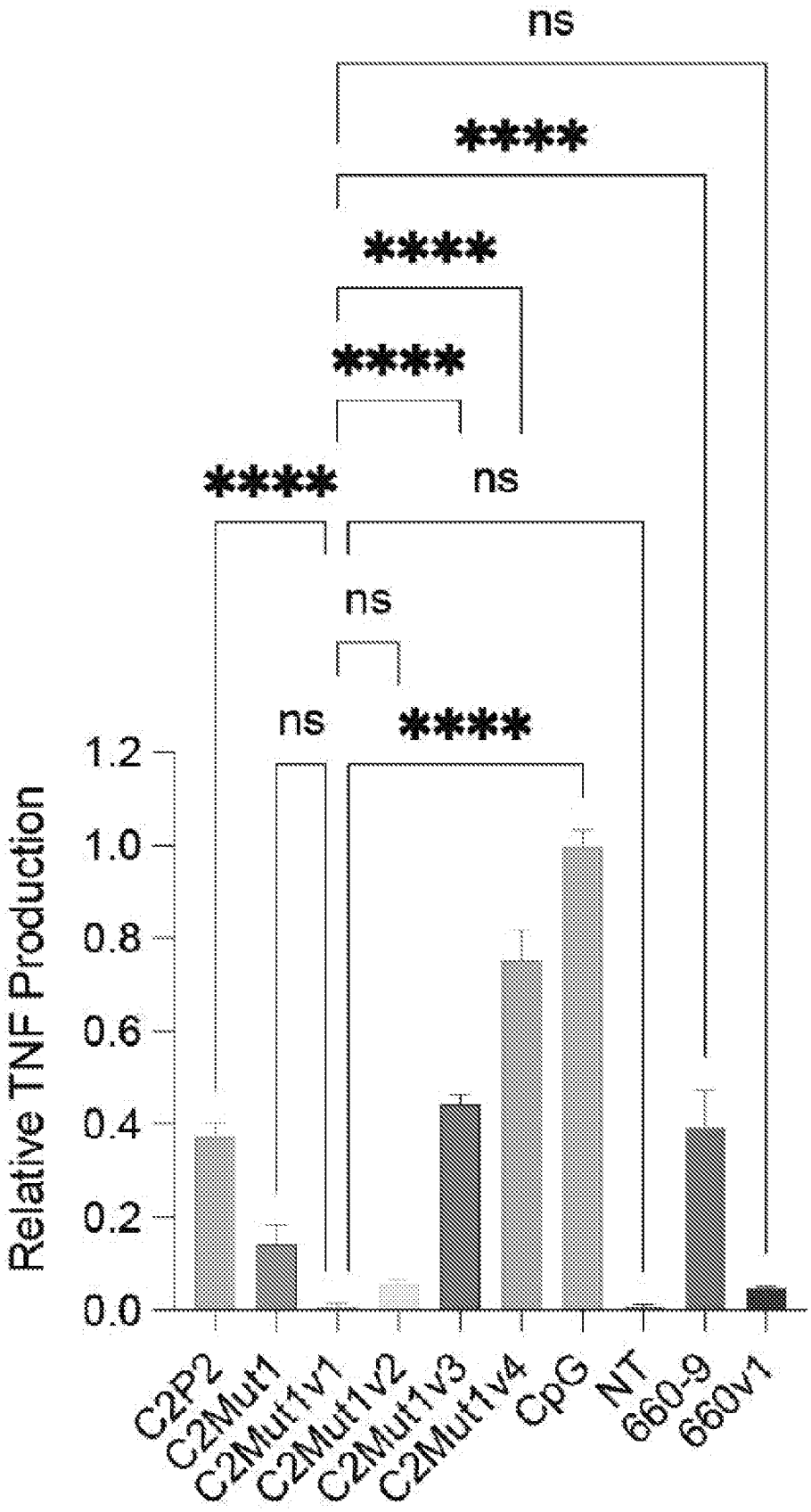

ns
****
****
****
****
ns
ns
ns
****
Relative TNF Production
1.2
1.0
0.8
0.6
0.4
0.2
0.0
C2P2
C2Mut1
C2Mut1v1
C2Mut1v2
C2Mut1v3
C2Mut1v4
CpG
NT
660-9
660v1

FIGURE 40

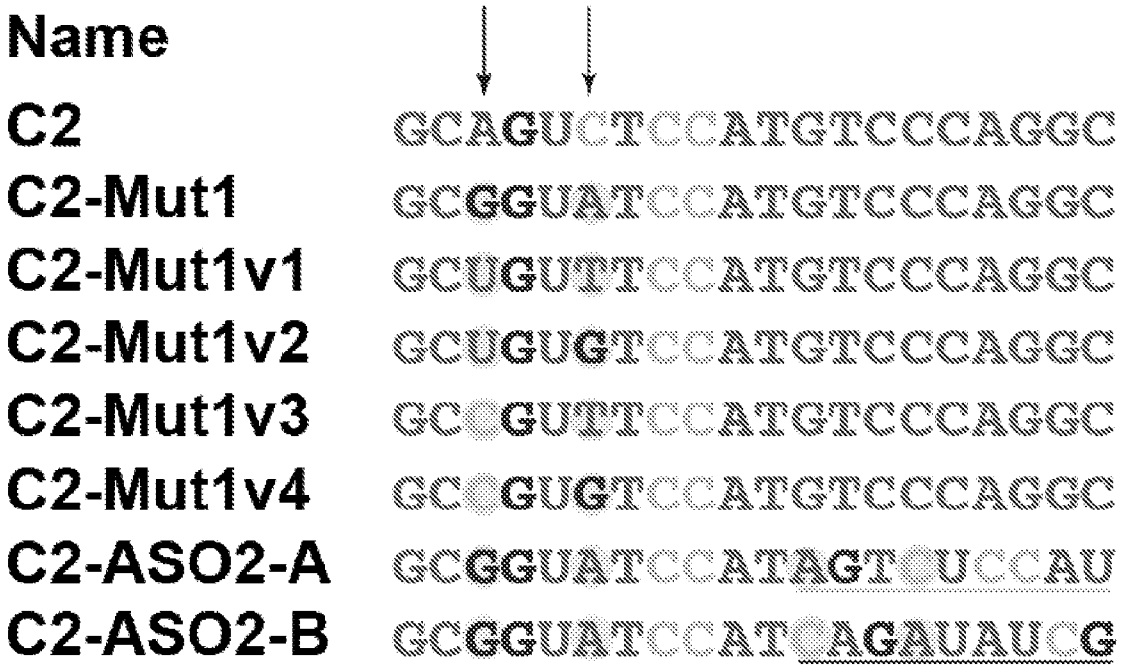


FIGURE 40 continued

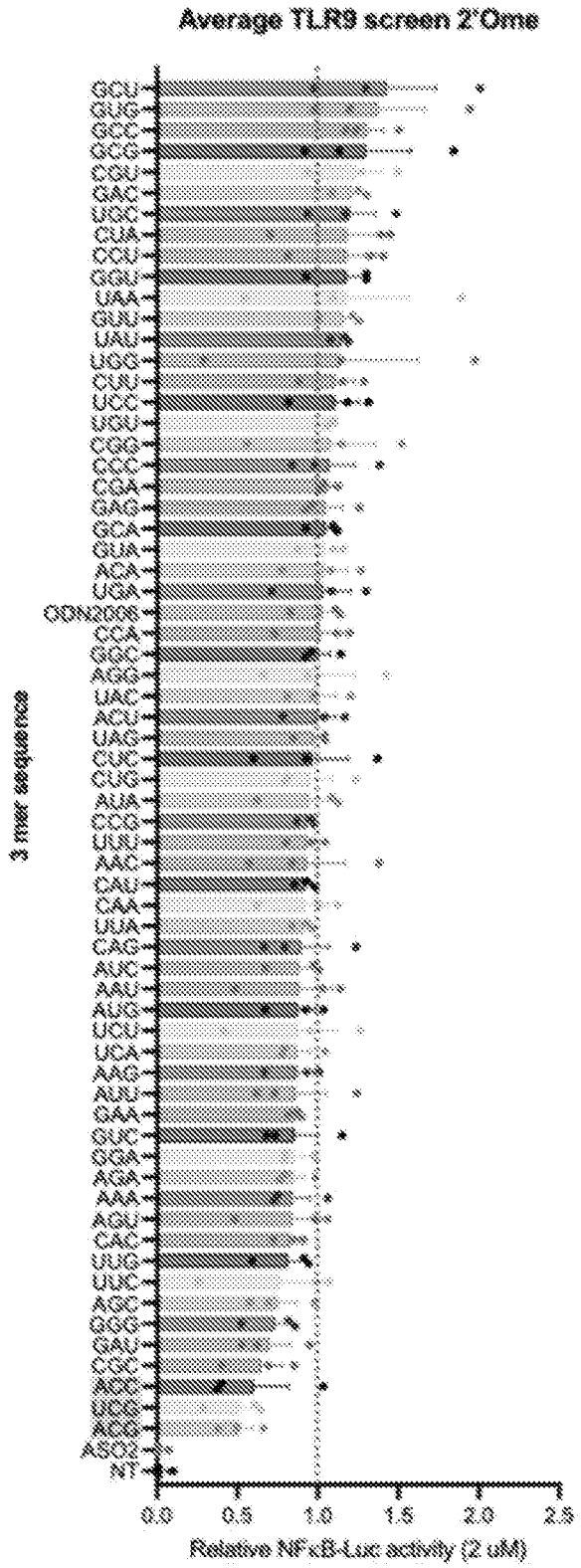

Average TLR9 screen 2'Ome
3 mer sequence
GCU
GUG
GCC
GCG
CGU
GAC
UGC
CUA
CCU
GGU
UAA
GUU
UAU
UGG
CUU
UCC
UGU
CGG
CCC
CGA
GAG
GCA
GUA
ACA
UGA
ODN2006
CCA
GGC
AGG
UAC
ACU
UAG
CUC
CUG
AUA
CCG
UUU
AAC
CAU
CAA
UUA
CAG
AUC
AAU
AUG
UCU
UCA
AAG
AUU
GAA
GUC
GGA
AGA
AAA
AGU
CAC
UUG
UUC
AGC
GGG
GAU
CGC
ACC
UCG
ACG
ASO2
NT
0.0
0.5
1.0
1.5
2.0
2.5
Relative NFκB-Luc activity (2 uM)

FIGURE 41

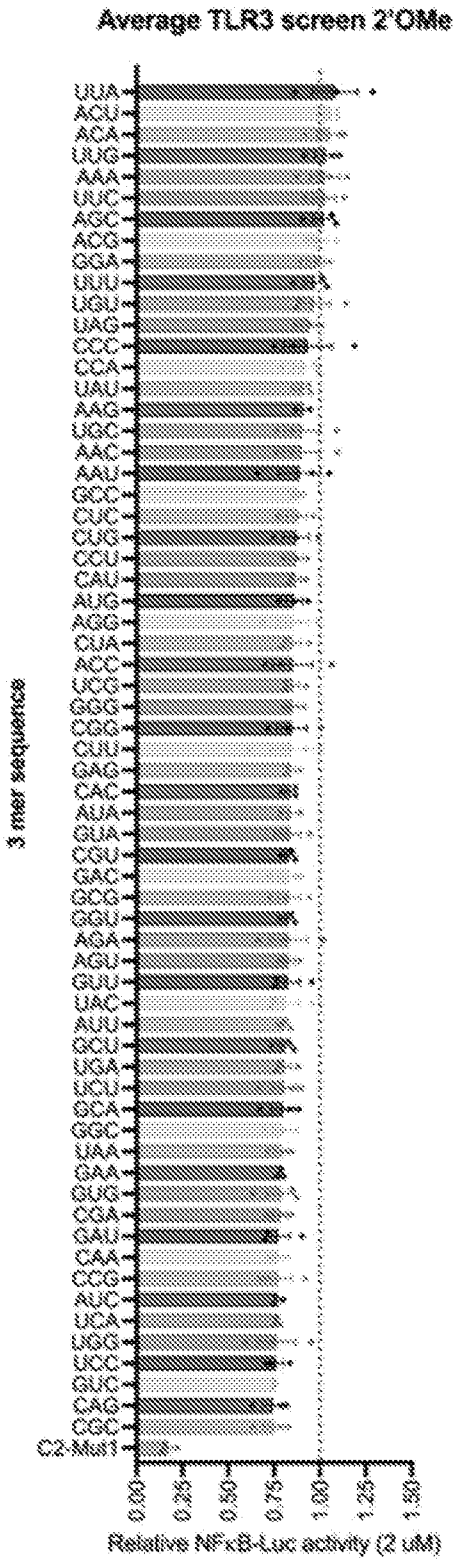

Average TLR3 screen 2'OMe
3 mer sequence
UUA
ACU
ACA
UUG
AAA
UUC
AGC
ACG
GGA
UUU
UGU
UAG
CCC
CCA
UAU
AAG
UGC
AAC
AAU
GCC
CUC
CUG
CCU
CAU
AUG
AGG
CUA
ACC
UCG
GGG
CGG
CUU
GAG
CAC
AUA
GUA
CGU
GAC
GCG
GGU
AGA
AGU
GUU
UAC
AUU
GCU
UGA
UCU
GCA
GGC
UAA
GAA
GUG
CGA
GAU
CAA
CCG
AUC
UCA
UGG
UCC
GUC
CAG
CGC
C2-Mus1
0.00
0.25
0.50
0.75
1.00
1.25
1.50
Relative NFκB-Luc activity (2 uM)

FIGURE 42

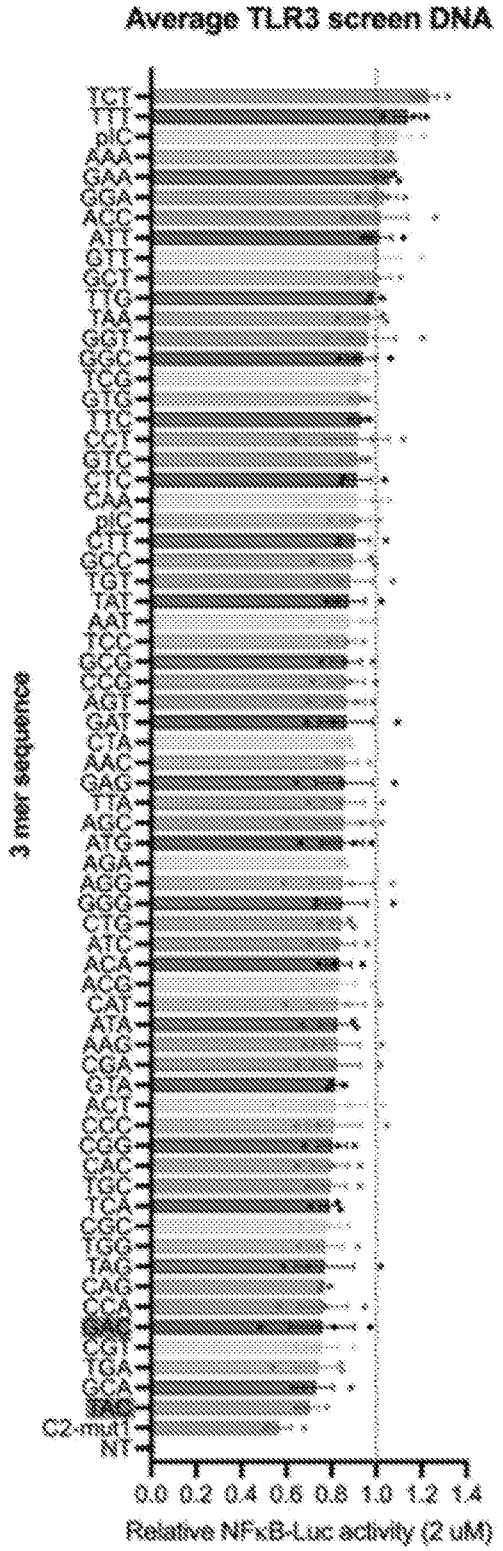

Average TLR3 screen DNA
3 mer sequence
C2-mut1
NT
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
Relative NFκB-Luc activity (2 uM)

FIGURE 43