

FIG. 1A

Host protein	Motif							Partner
Consensus	∓/X	X_1	X_2	Y	X_3	X_4	∓	
TFR	P	L	S	Y	T	R	F	AP2M1
P-selctin	L	G	T	Y	G	V	F	AP2M1
HLA-DM	H	S	S	Y	T	P	L	AP2M1

FIG. 1B

Virus/Protein	Motif				Host partner(s)
Consensus	Y	X	X	∓	
ELAV/Gag	Y	P	D	L	AP2M1
HIV-1/Gag	Y	P	I	V	AP2M1
HIV-1/Euv	Y	S	P	L	AP2M1,AP1M1,AP3M1

FIG. 1C

HCV/Core	Motif						
Consensus	ϕ	X1	X2	Y	X3	X4	∓
HCV consensus	L	M	G	Y	I	P	L/V
% conservation	99.3	98.9	99.4	98.9	98	99.6	86.71
Genotypes 1,3,4,5	L	M	G	Y	I	P	L
Genotypes 2,6,7,8	L	M	G	Y	I	P	V
Y136A mutant	L	M	G	A	I	P	V
ϕ139A mutant	L	M	G	Y	I	P	A
ϕ139L mutant	L	M	G	Y	I	P	L
YTPL mutant	L	M	G	Y	T	P	L
YRRL mutant	L	M	G	Y	R	R	L

FIG. 1D

SUBSTITUTE SHEET (RULE 26)

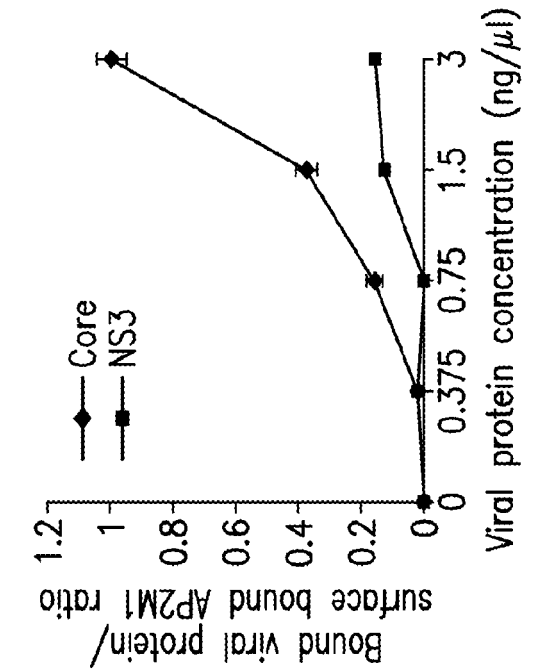

Bound viral protein/
surface bound AP2M1 ratio
1.2
1
0.8
0.6
0.4
0.2
0
Core
NS3
0
0.375
0.75
1.5
3
Viral protein concentration (ng/μl)

FIG. 1F

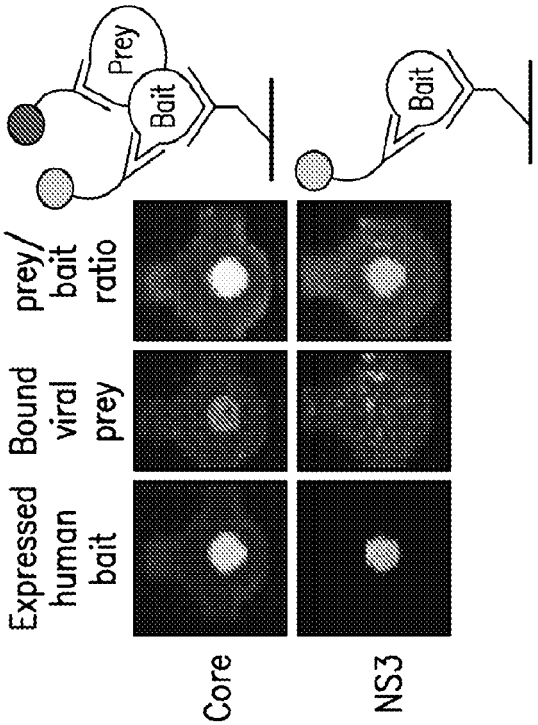

Expressed human bait
Bound viral prey
prey/ bait ratio
Prey
Bait
Bait
Core
NS3

FIG. 1E

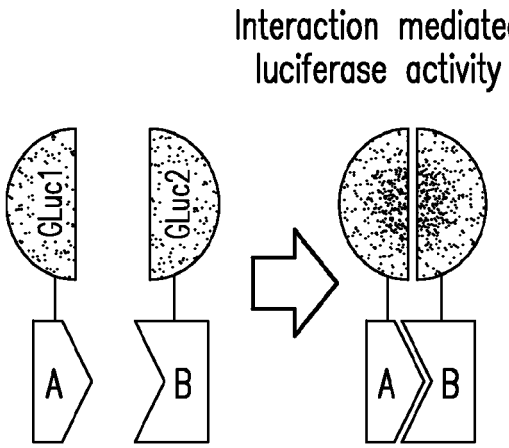


FIG. 2A

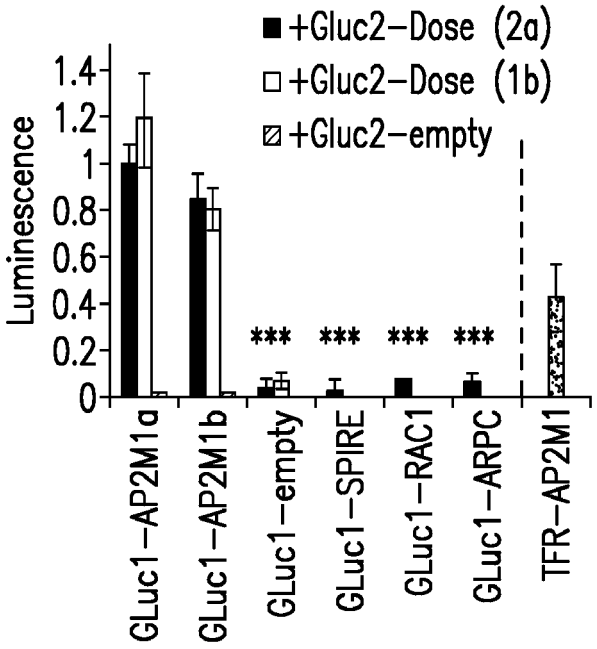


FIG. 2B

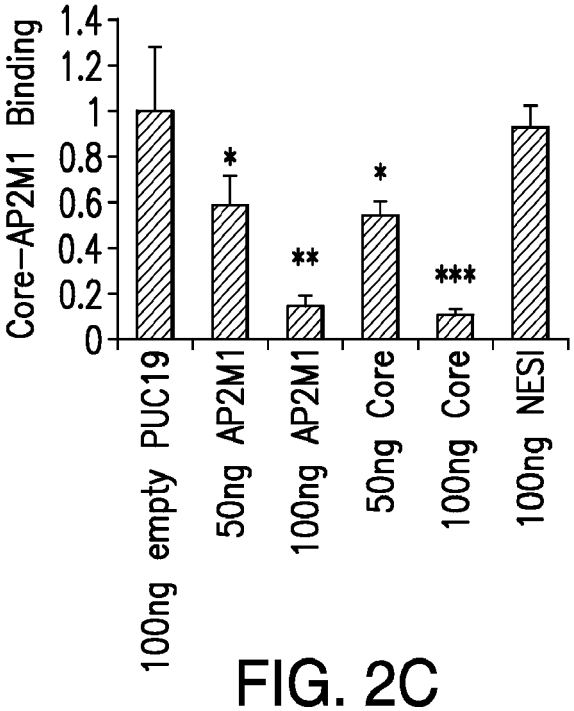


FIG. 2C

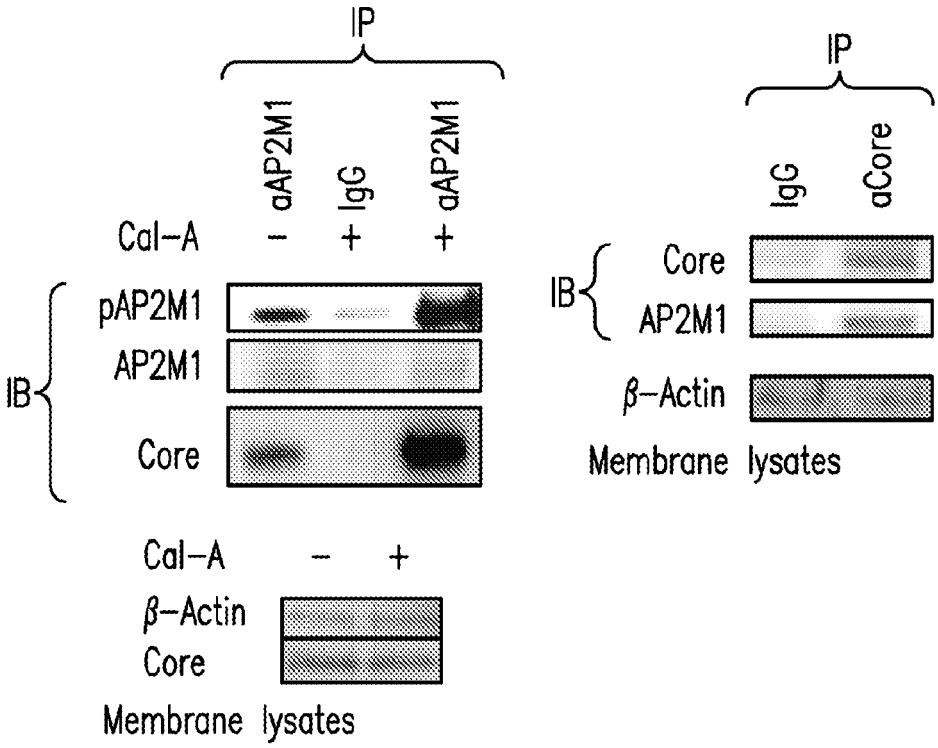

IP
- αAP2M1
+ IgG
+ αAP2M1
Cal-A
IB
pAP2M1
AP2M1
Core
Cal-A - +
β-Actin
Core
Membrane lysates
IP
IgG
αCore
IB
Core
AP2M1
β-Actin
Membrane lysates

FIG. 2D

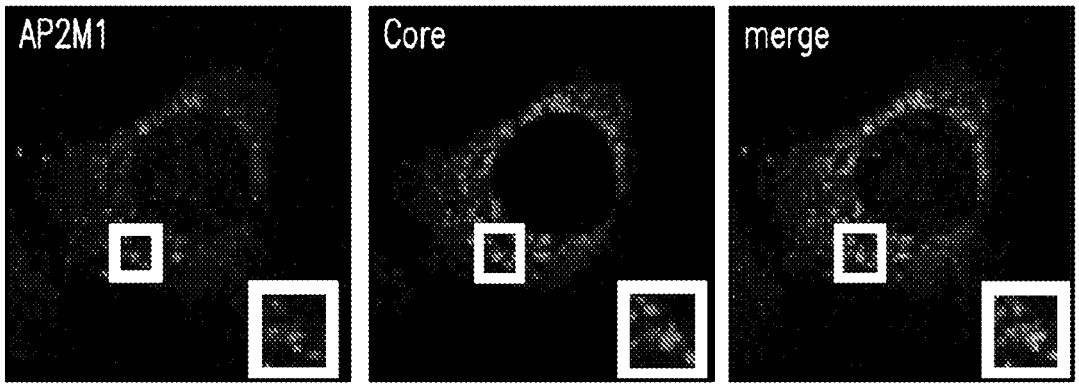

AP2M1
Core
merge

FIG. 2E

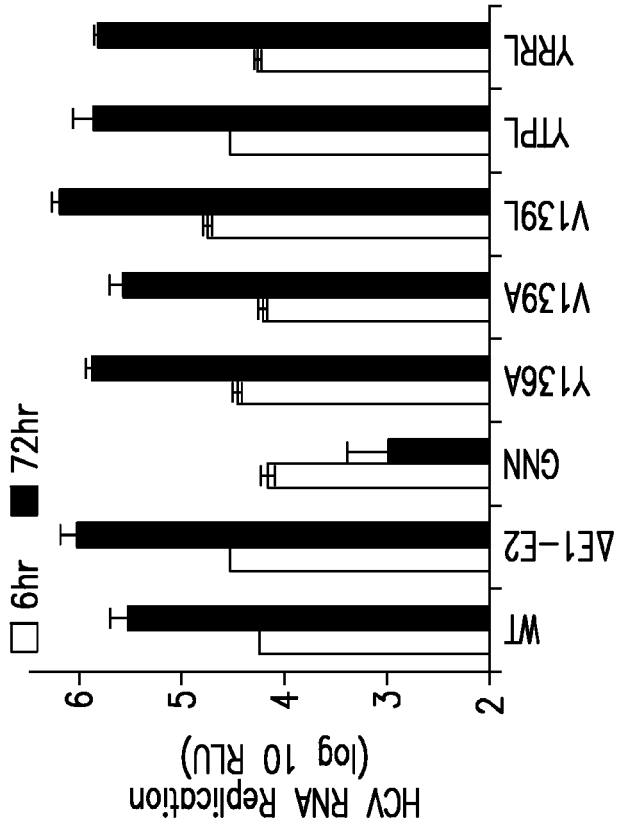

HCV RNA Replication
(log 10 RLU)
6
5
4
3
2
6hr
72hr
WT
Δ E1-E2
GNN
Y136A
V139A
V139L
YTPL
YRRL

FIG. 3B

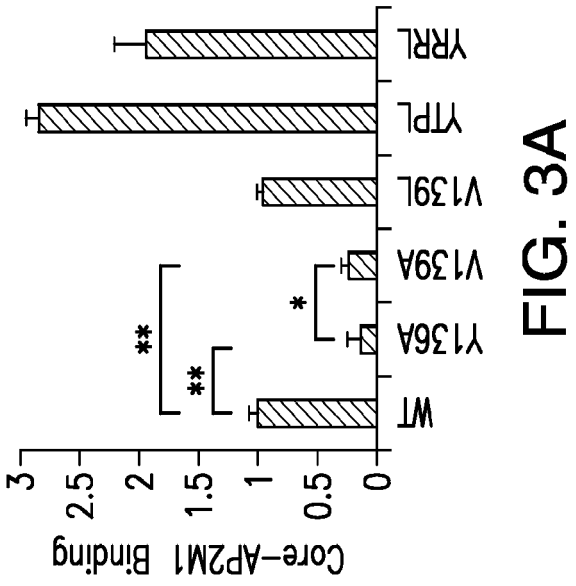

Core-AP2M1 Binding
3
2.5
2
1.5
1
0.5
0
WT
Y136A
V139A
V139L
YTPL
YRRL
**
**
*

FIG. 3A

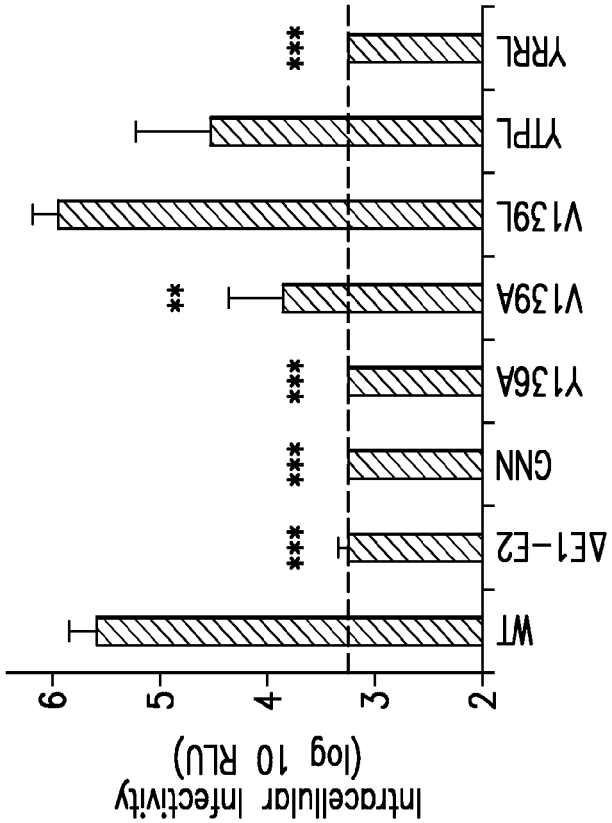

Intracellular Infectivity
(log 10 RLU)
6
5
4
3
2
WT
Δ E1–E2
GNN
Y136A
V139A
V139L
YTPL
YRRL
***
***
***
***
**

FIG. 3D

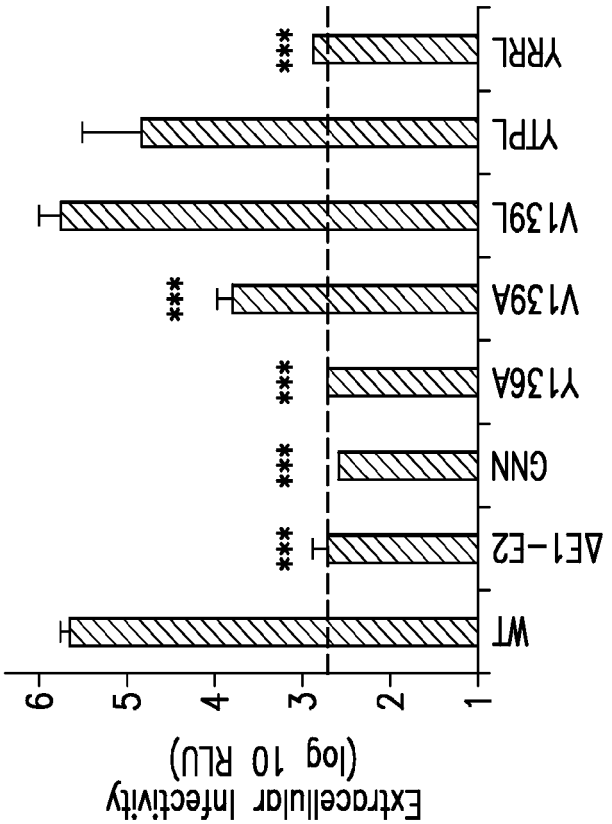

Extracellular Infectivity
(log 10 RLU)
6
5
4
3
2
1
WT
Δ E1–E2
GNN
Y136A
V139A
V139L
YTPL
YRRL
***
***
***
***
***

FIG. 3C

Mutant	$TCID_{50}$/ml	
	Extracellular	Intracellular
J6/JFH(p7-Rluc2A).....	$6.32x10^3$	$3.15x10^4$
J6/JFH(p7-Rluc2A)/ΔE1-E2.....	0	0
J6/JFH(p7-Rluc2A)/Y136A.....	0	0
J6/JFH(p7-Rluc2A)/V139A.....	$1.19x10^2$	$4.5x10^3$

FIG. 3E

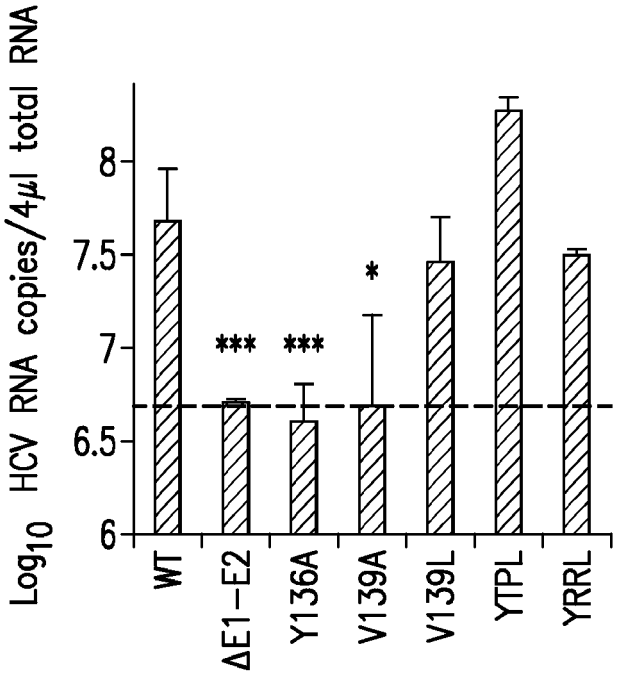


FIG. 3F

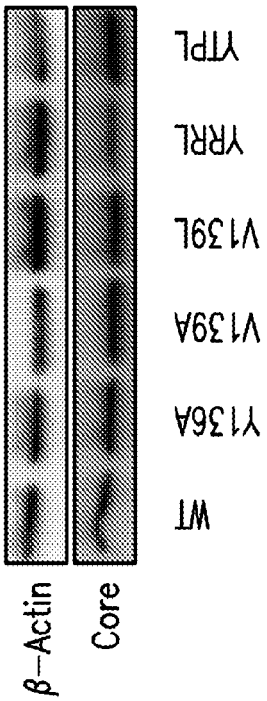

β−Actin
Core
WT
Y136A
V139A
V139L
YRRL
YTPL

FIG. 3H

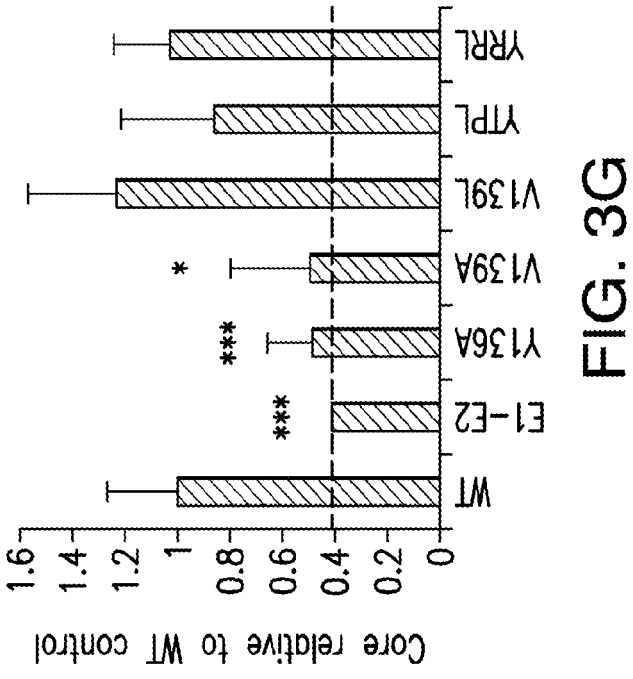

Core relative to WT control
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
WT
E1−E2
Y136A
V139A
V139L
YTPL
YRRL
***
***
*

FIG. 3G

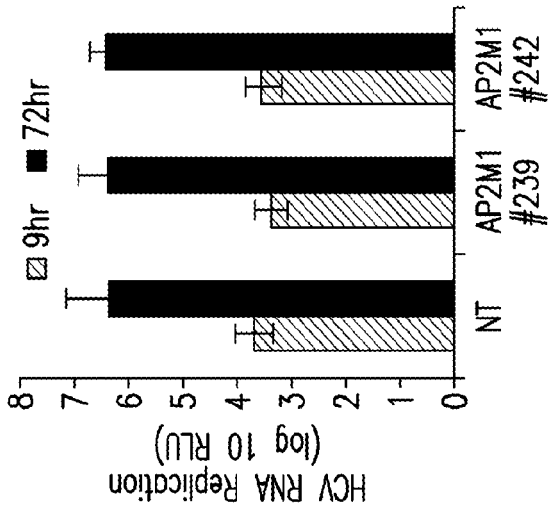


FIG. 4C

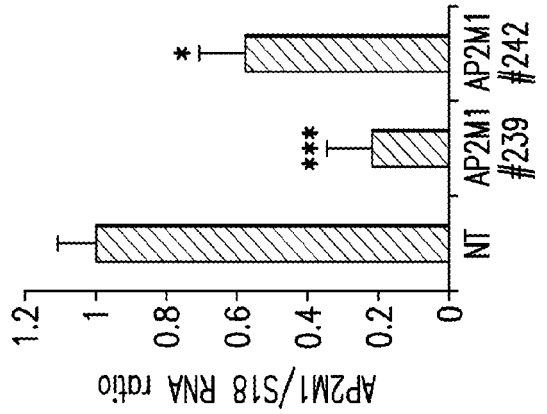


FIG. 4B

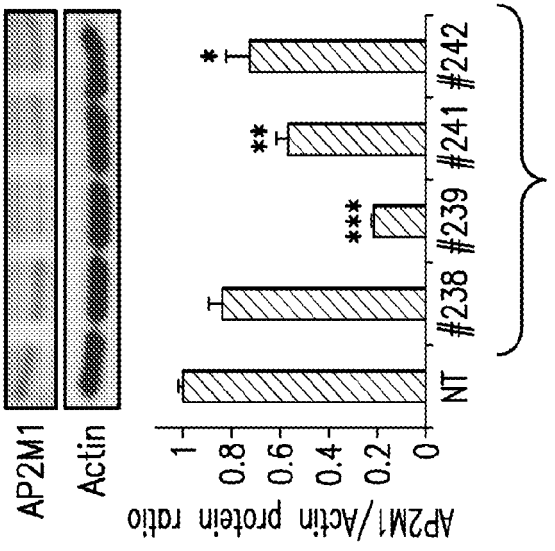


FIG. 4A

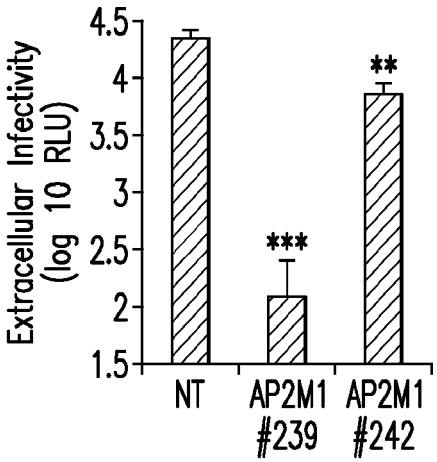


FIG. 4D

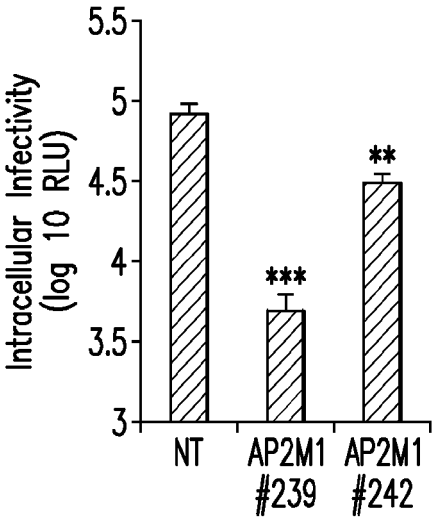


FIG. 4E

Clone	$TCID_{50}$/ml	
	Extracellular	Intracellular
NT.....	$6.32x10^3$	$2.14x10^4$
AP2M1 #239.....	$1.58x10^1$	$7.01x10^1$
AP2M1 #242.....	$1.79x10^2$	$2.05x10^3$

FIG. 4F

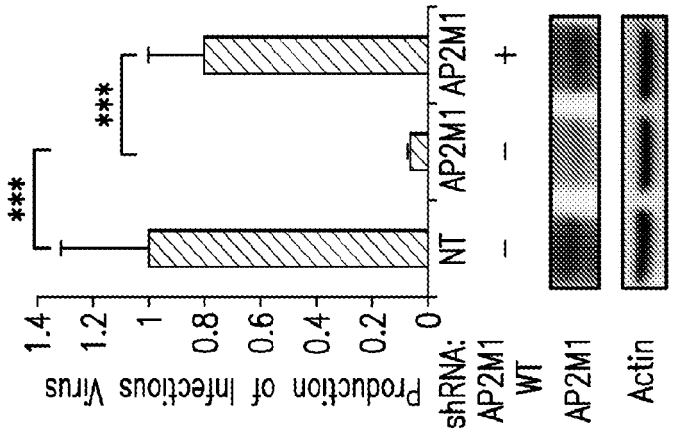


FIG. 4I

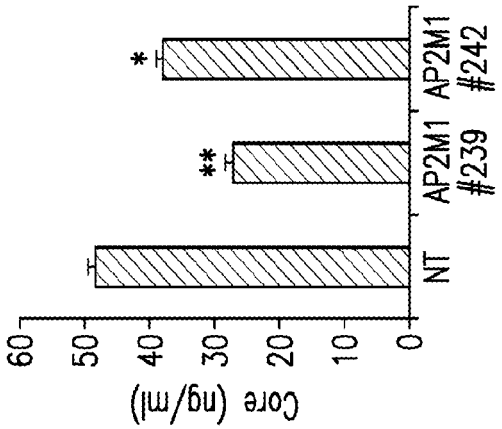


FIG. 4H

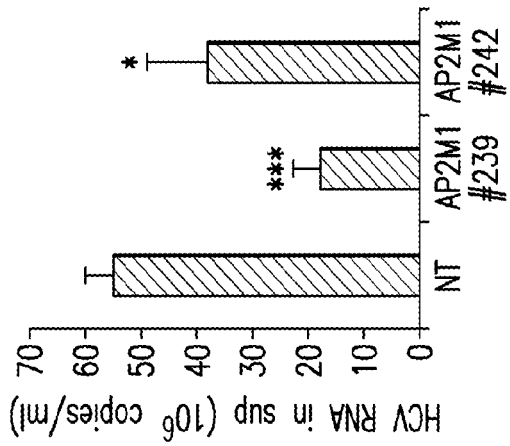


FIG. 4G

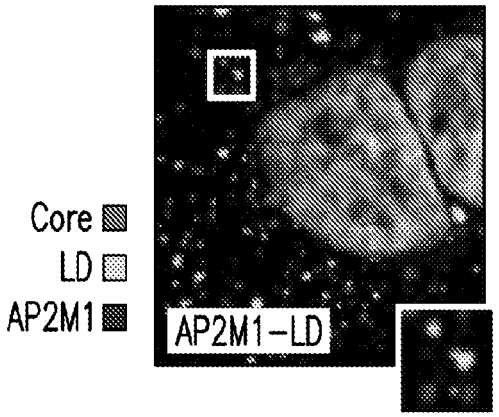


FIG. 5A

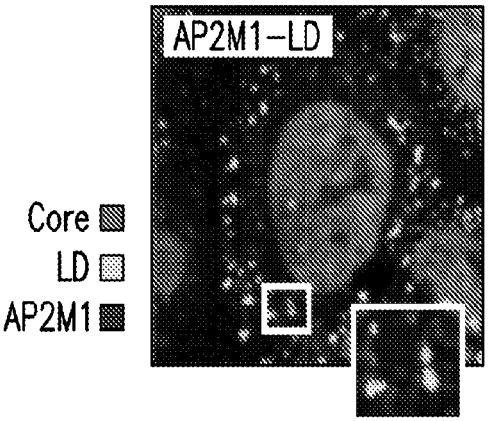


FIG. 5B

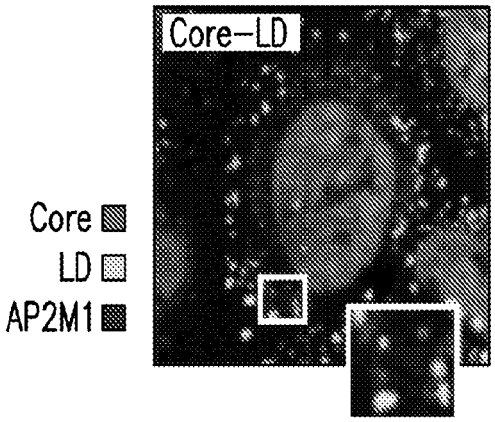


FIG. 5C

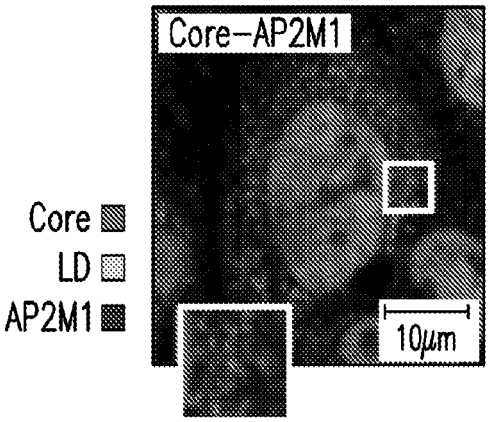


FIG. 5D

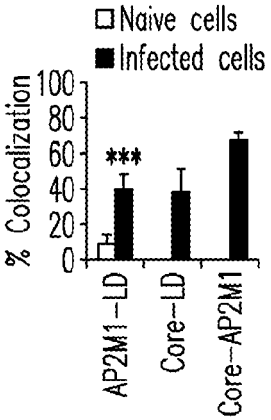


FIG. 5E

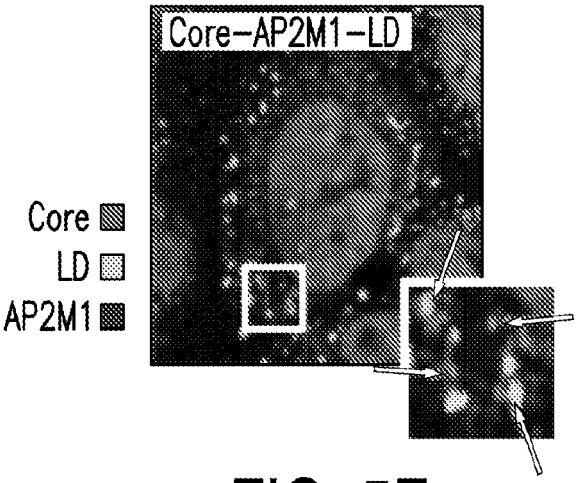


FIG. 5F

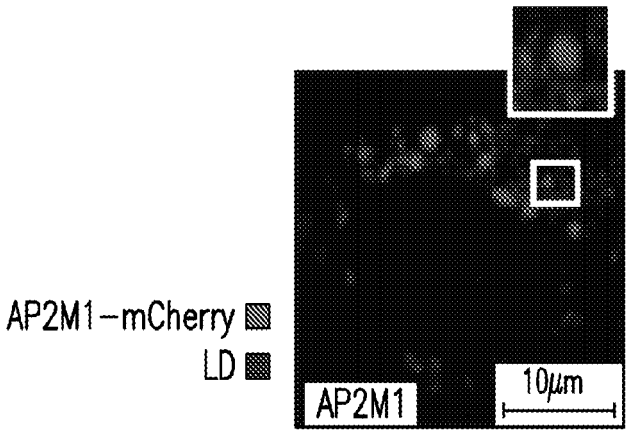

AP2M1−mCherry
LD
AP2M1
10μm

FIG. 5G

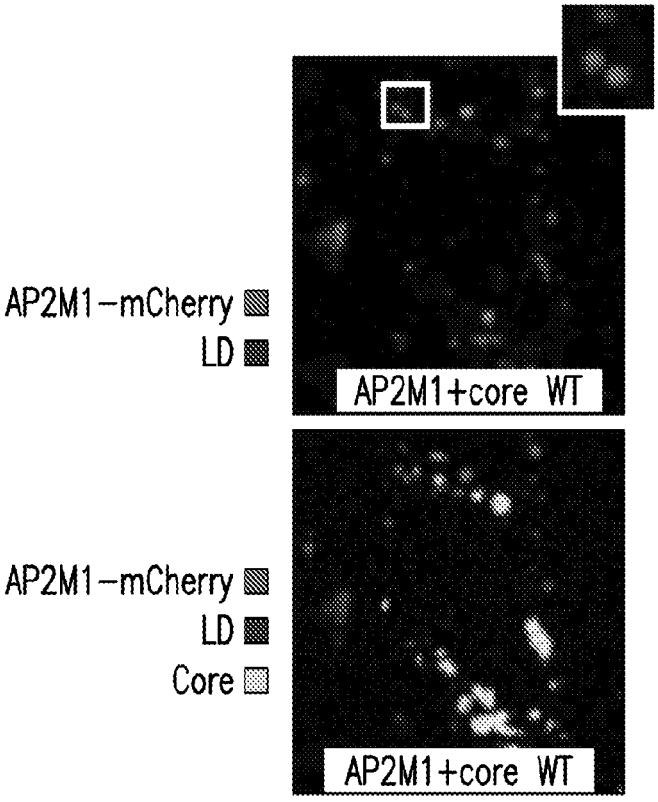

AP2M1−mCherry
LD
AP2M1+core WT
AP2M1−mCherry
LD
Core
AP2M1+core WT

FIG. 5H

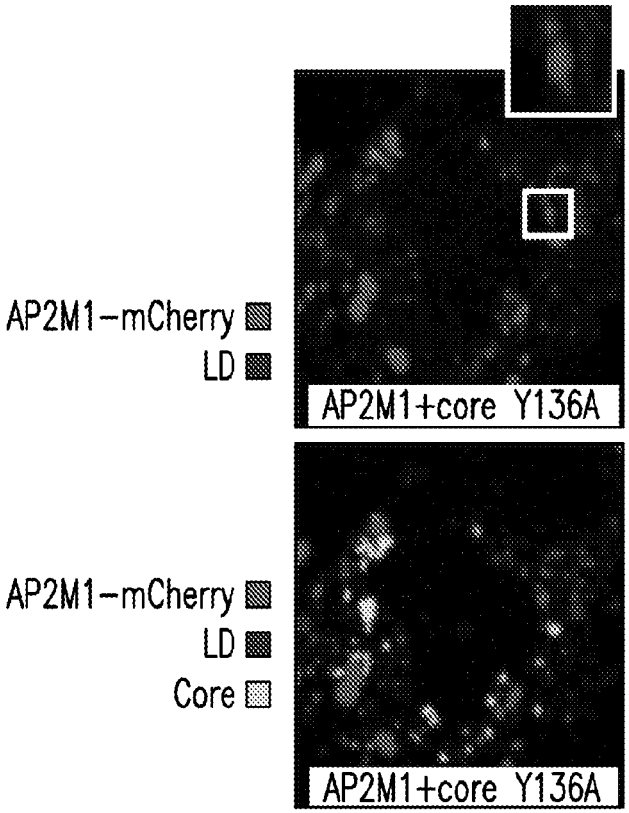

AP2M1-mCherry
LD
AP2M1+core Y136A
AP2M1-mCherry
LD
Core
AP2M1+core Y136A

FIG. 5I

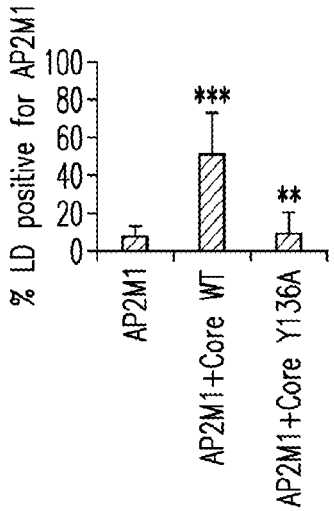

% LD positive for AP2M1
100
80
60
40
20
0
***
**
AP2M1
AP2M1+Core WT
AP2M1+Core Y136A

FIG. 5J

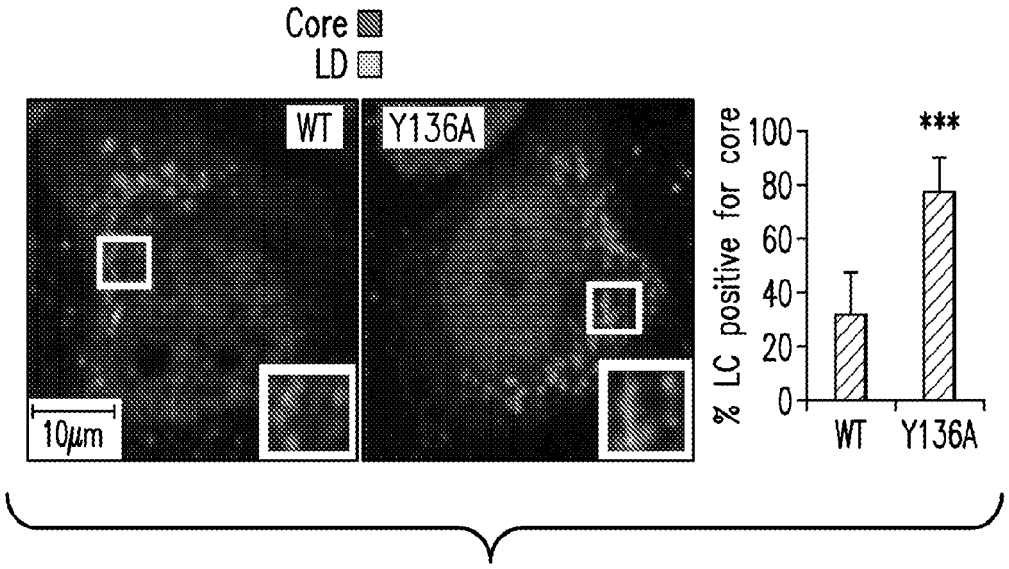

Core
LD
WT
Y136A
10μm
% LC positive for core
100
80
60
40
20
0
***
WT
Y136A

FIG. 5K

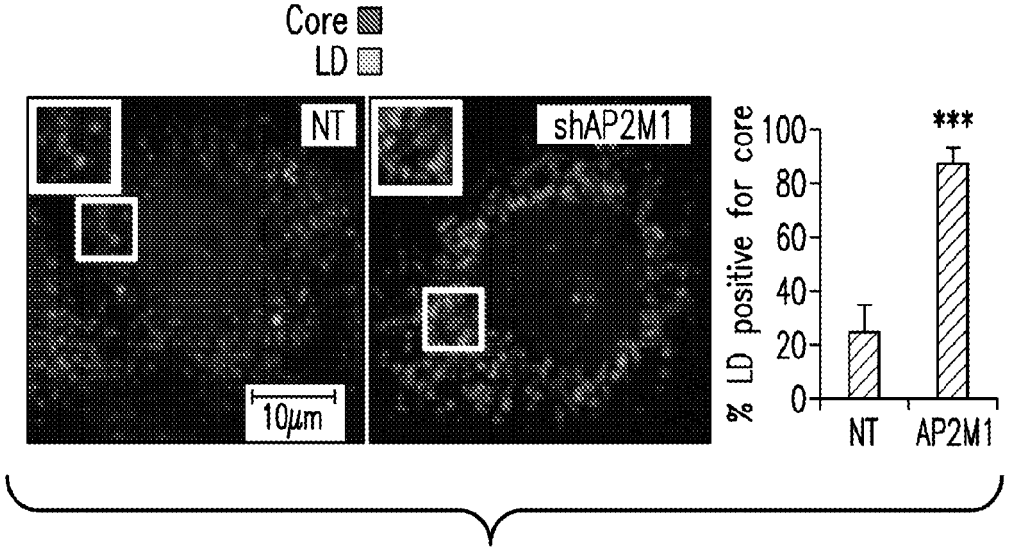

Core
LD
NT
shAP2M1
10μm
% LD positive for core
100
80
60
40
20
0
***
NT
AP2M1

FIG. 5L

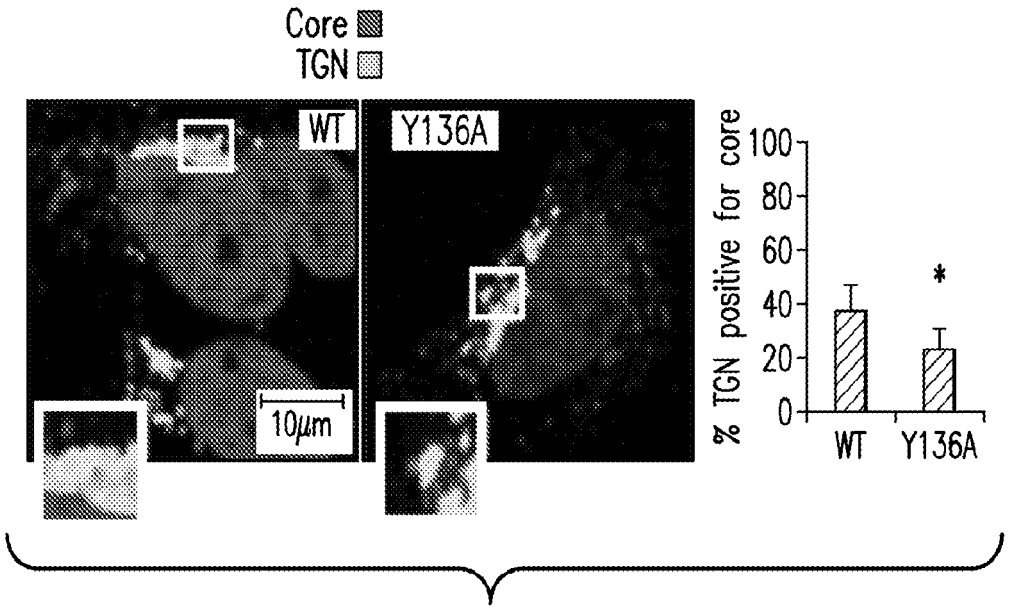

Core
TGN
WT
Y136A
10μm
% TGN positive for core
100
80
60
40
20
0
*
WT
Y136A

FIG. 5M

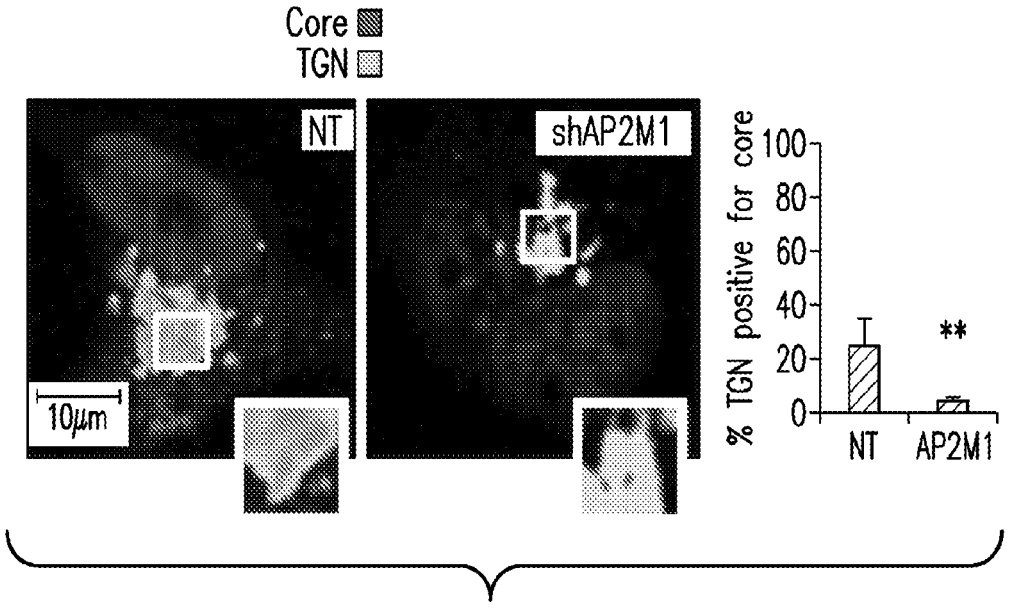

Core
TGN
NT
shAP2M1
10μm
% TGN positive for core
100
80
60
40
20
0
**
NT
AP2M1

FIG. 5N

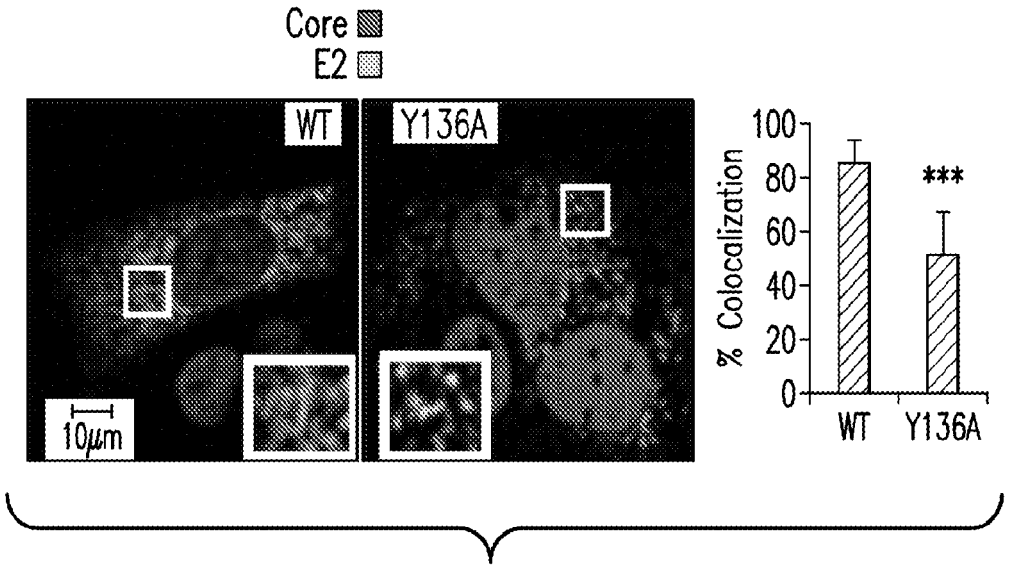

Core
E2
WT
Y136A
10μm
% Colocalization
100
80
60
40
20
0
***
WT
Y136A

FIG. 5O

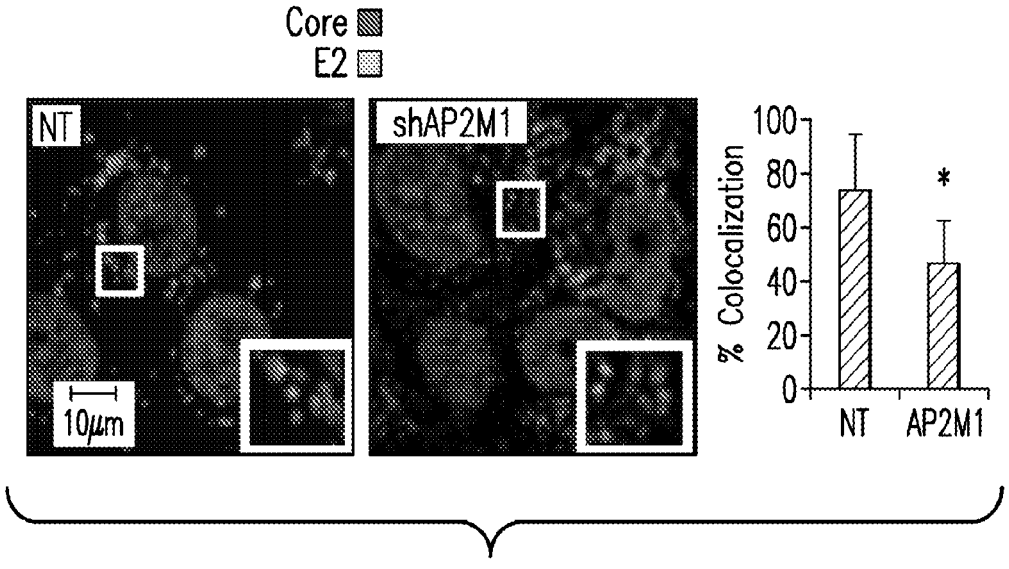

Core
E2
NT
shAP2M1
10μm
% Colocalization
100
80
60
40
20
0
*
NT
AP2M1

FIG. 5P

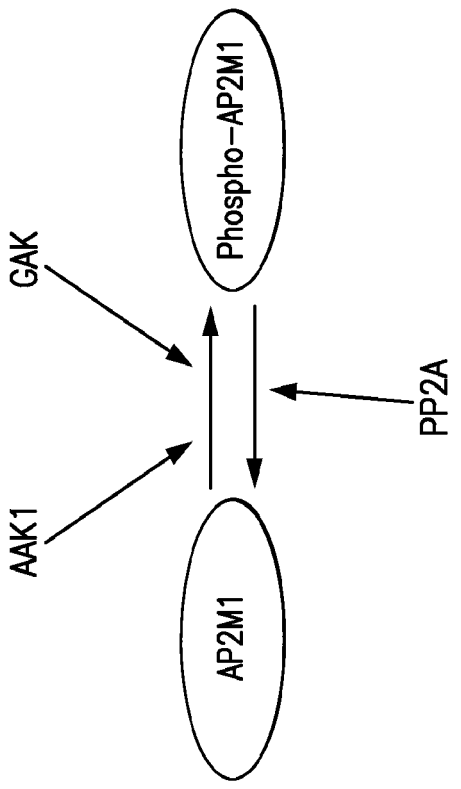


FIG. 6A

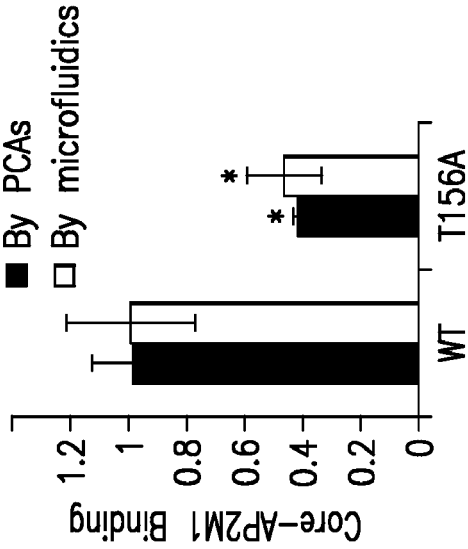


FIG. 6B

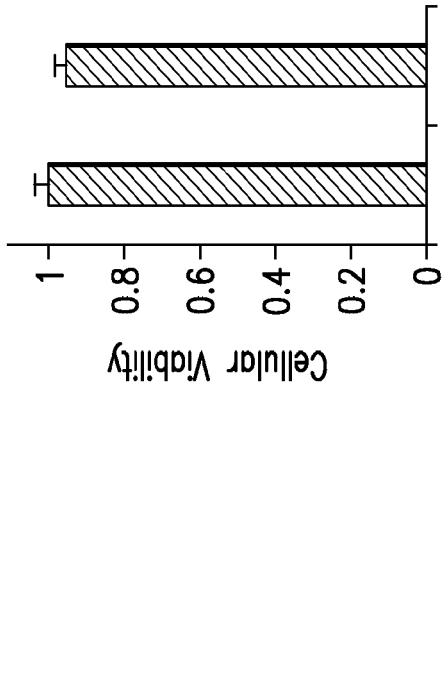


FIG. 6C

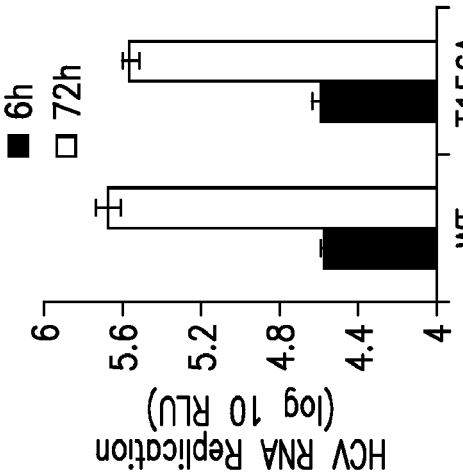


FIG. 6D

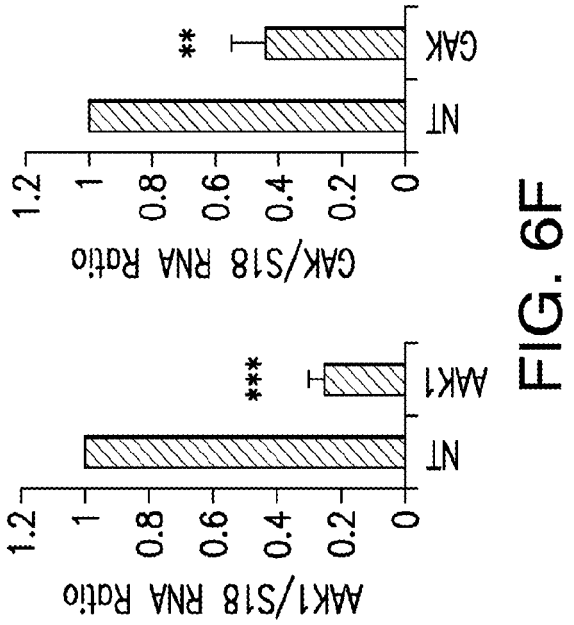


FIG. 6F

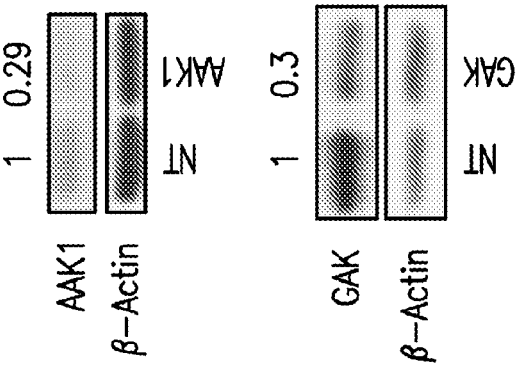


FIG. 6G

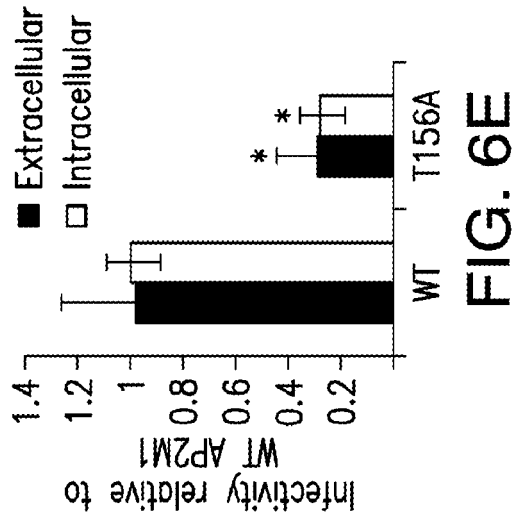


FIG. 6E

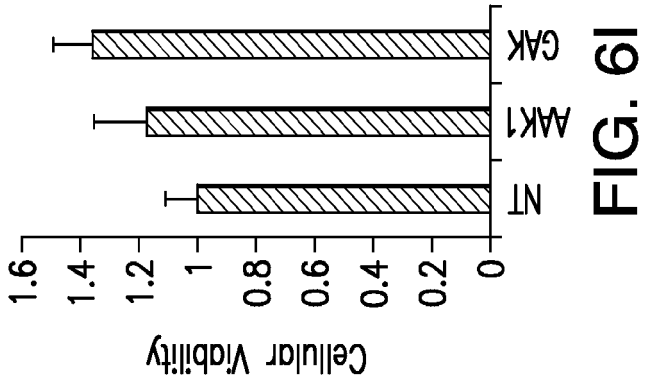


FIG. 6I

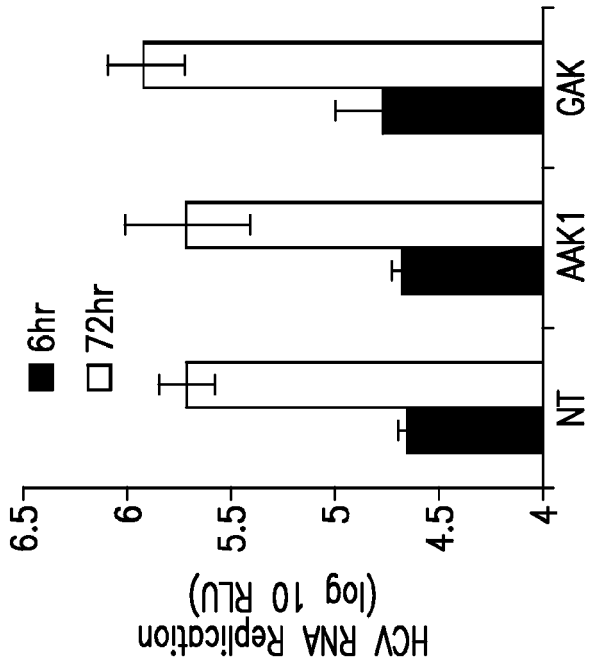


FIG. 6J

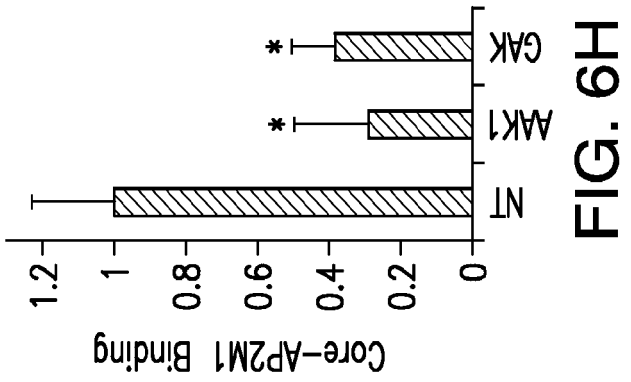


FIG. 6H

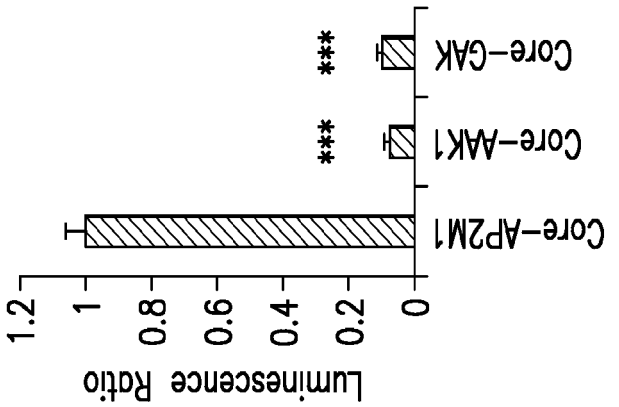

Luminescence Ratio
1.2
1
0.8
0.6
0.4
0.2
0
Core–AP2M1
Core–AAK1
Core–GAK
***
***

FIG. 6L

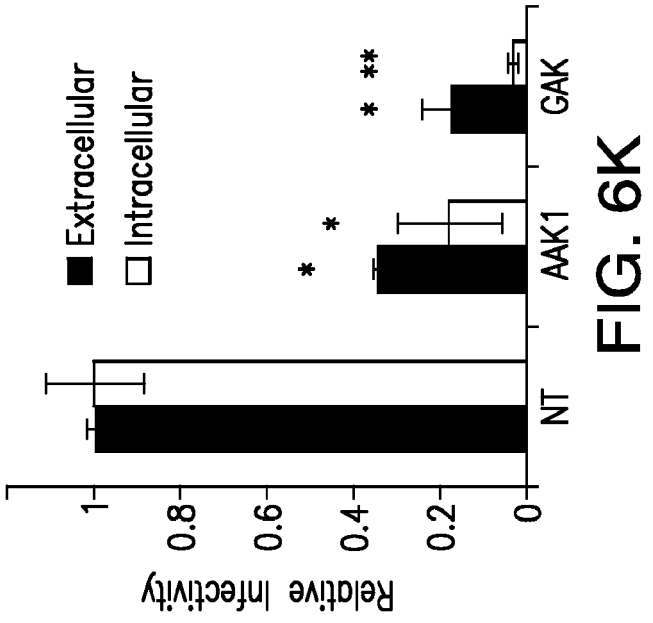

Relative Infectivity
1
0.8
0.6
0.4
0.2
0
Extracellular
Intracellular
NT
AAK1
GAK
*
*
*
**

FIG. 6K

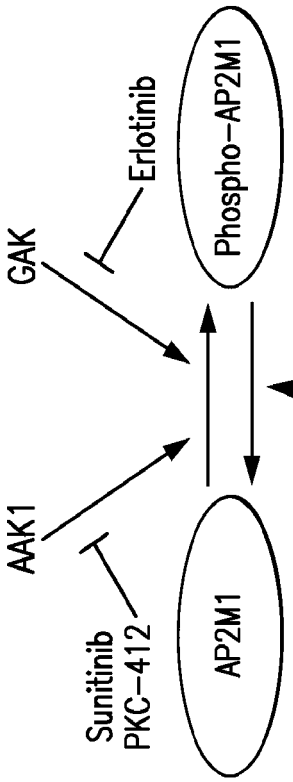


FIG. 7A

Compound	Target	Kd of binding (nM)	IC50 (μM)	EC50 for Extracellular Infectinity (μM)	EC50 for Intracellular Infectivity (μM)	EC50 for HCVcc infection (μM)
Erlotinib	GAK	3.1	0.038±0.01	0.6±0.12	0.45±0.13	0.6±0.12
Sunitinib malate	AAK1	11	0.045±0.02	0.2±0.03	0.155±0.06	1.2±0.3
PKC–412	AAK1	48	0.2±0.07	1.6±0.4	1.79±0.4	4.6±2

FIG. 7B

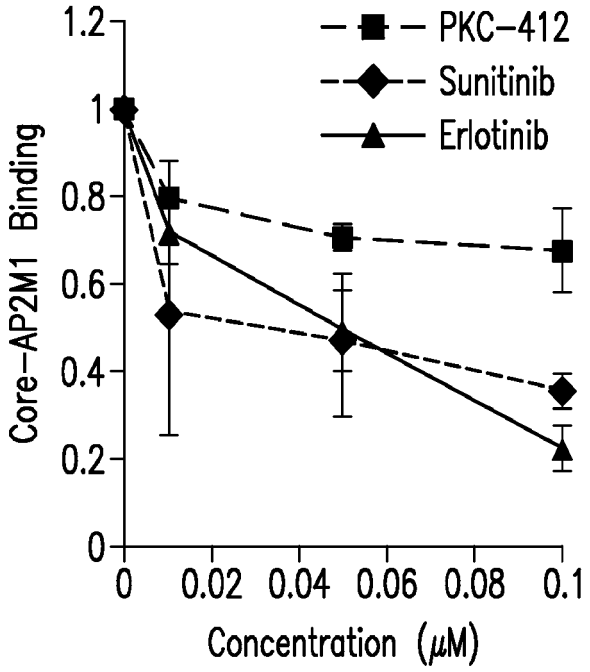


FIG. 7C

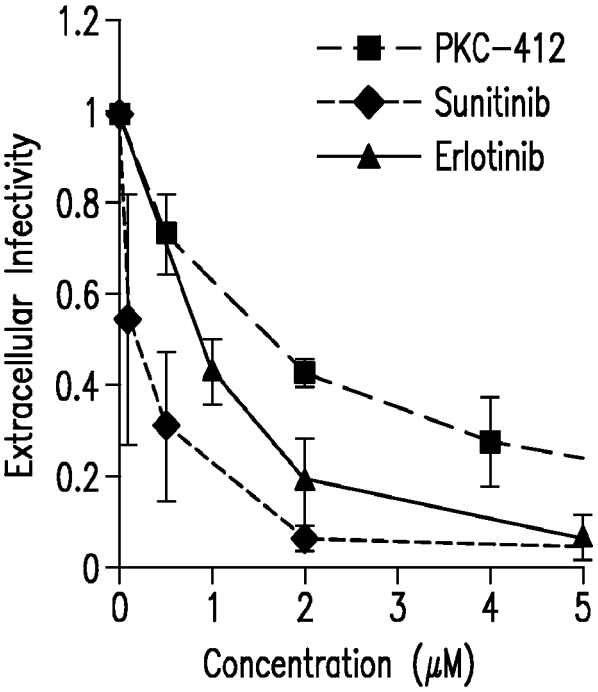


FIG. 7D

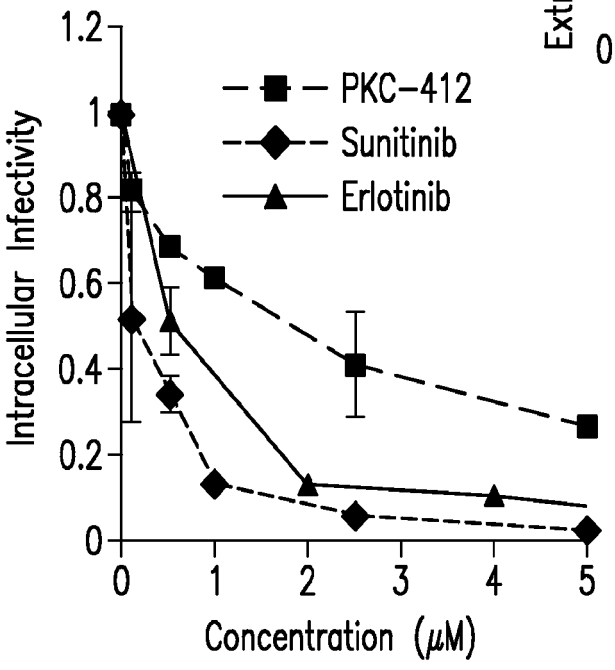


FIG. 7E

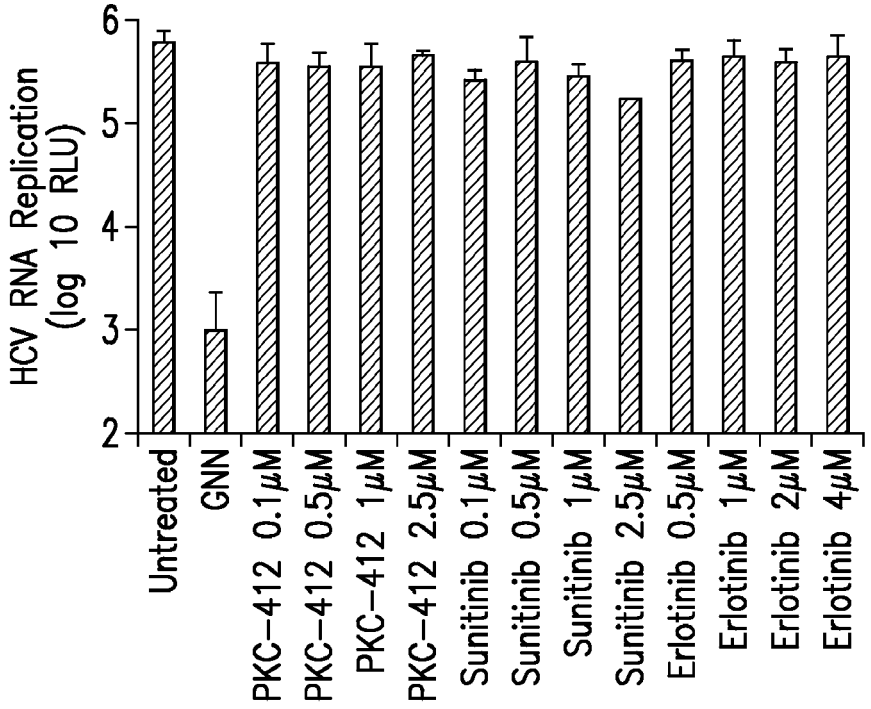

HCV RNA Replication
(log 10 RLU)
6
5
4
3
2
Untreated
GNN
PKC−412 0.1μM
PKC−412 0.5μM
PKC−412 1μM
PKC−412 2.5μM
Sunitinib 0.1μM
Sunitinib 0.5μM
Sunitinib 1μM
Sunitinib 2.5μM
Erlotinib 0.5μM
Erlotinib 1μM
Erlotinib 2μM
Erlotinib 4μM

FIG. 7F

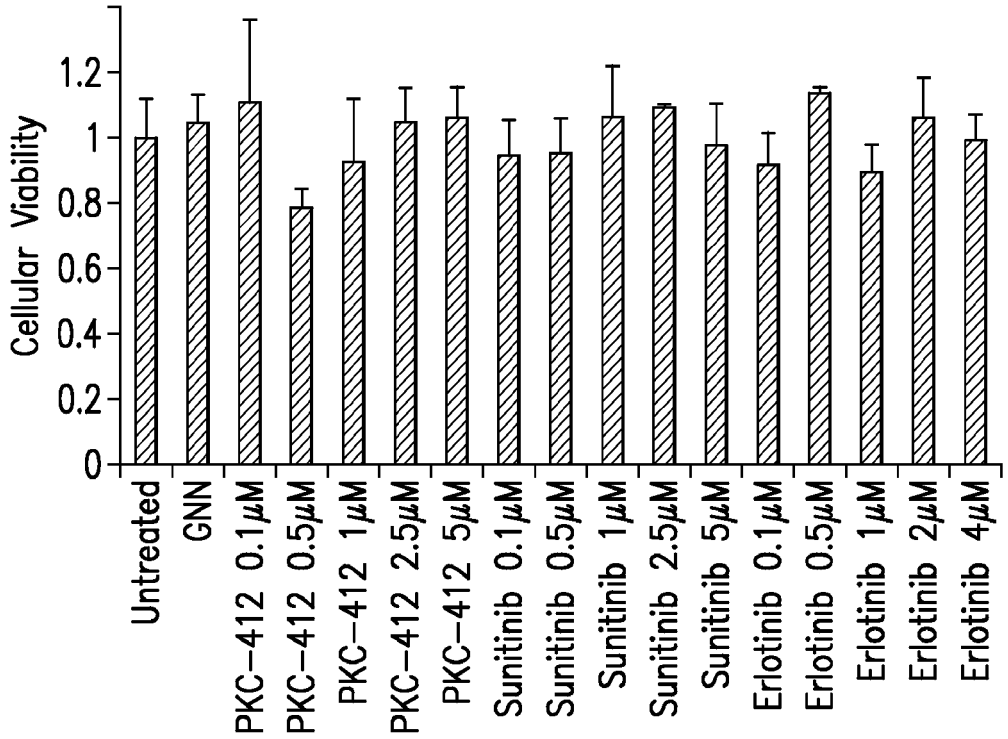

Cellular Viability
1.2
1
0.8
0.6
0.4
0.2
0
Untreated
GNN
PKC−412 0.1μM
PKC−412 0.5μM
PKC−412 1μM
PKC−412 2.5μM
PKC−412 5μM
Sunitinib 0.1μM
Sunitinib 0.5μM
Sunitinib 1μM
Sunitinib 2.5μM
Sunitinib 5μM
Erlotinib 0.1μM
Erlotinib 0.5μM
Erlotinib 1μM
Erlotinib 2μM
Erlotinib 4μM

FIG. 7G

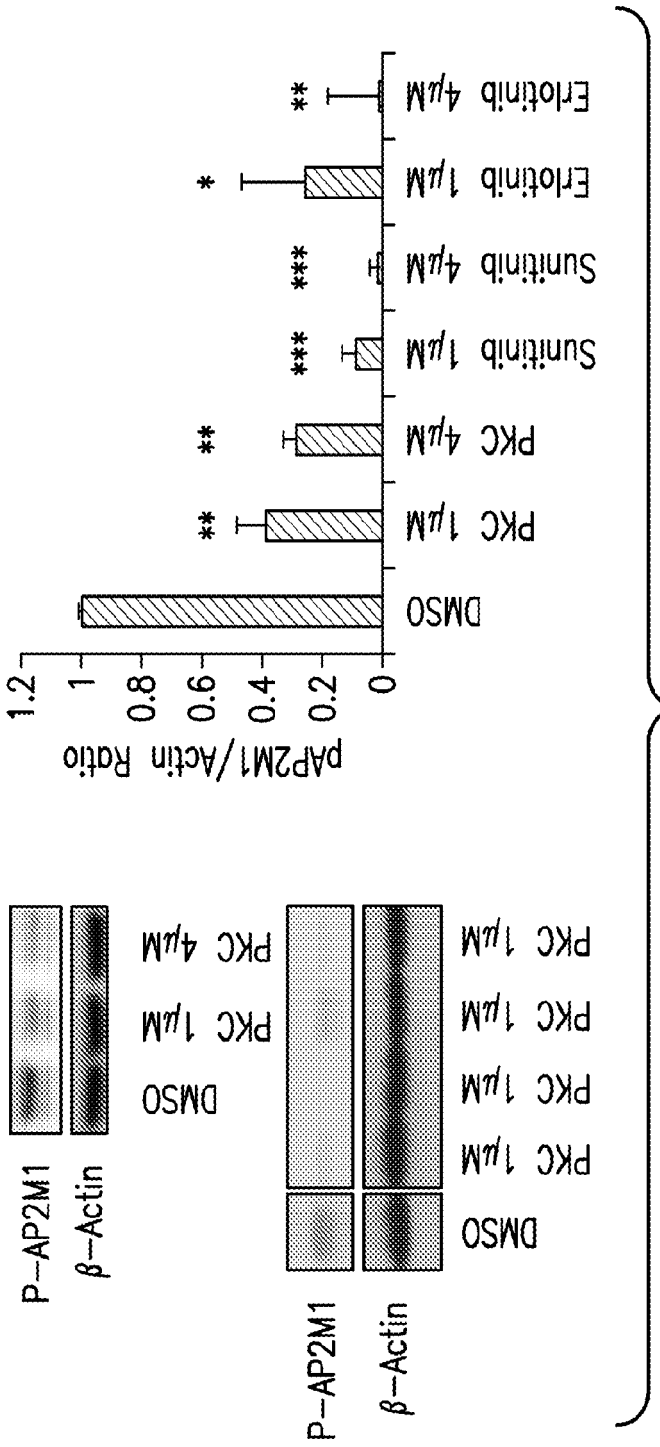

pAP2M1/Actin Ratio
1.2
1
0.8
0.6
0.4
0.2
0
DMSO
PKC 1μM
PKC 4μM
Sunitinib 1μM
Sunitinib 4μM
Erlotinib 1μM
Erlotinib 4μM
P-AP2M1
β-Actin
DMSO
PKC 1μM
PKC 1μM
PKC 1μM
PKC 1μM
P-AP2M1
β-Actin
DMSO
PKC 1μM
PKC 4μM

FIG. 7H

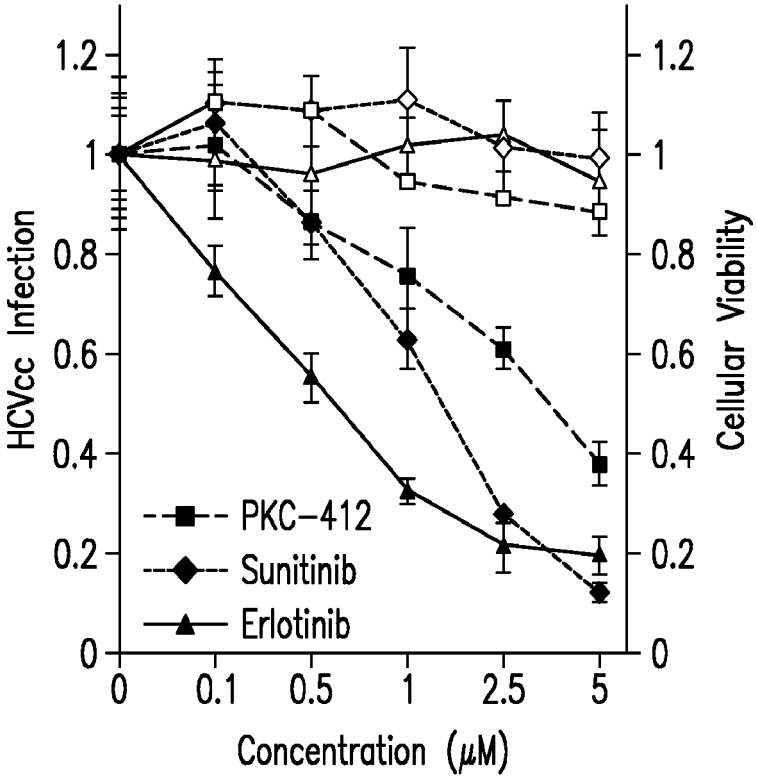

HCVcc Infection
Cellular Viability
1.2
1
0.8
0.6
0.4
0.2
0
0
0.1
0.5
1
2.5
5
Concentration (μM)
PKC-412
Sunitinib
Erlotinib

FIG. 7I

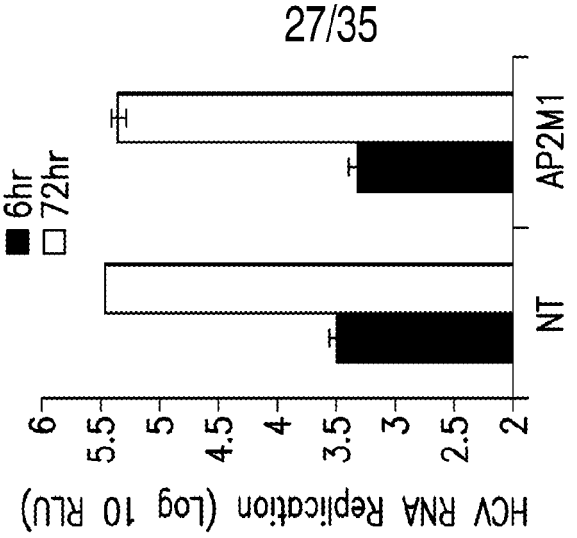


FIG. 8D

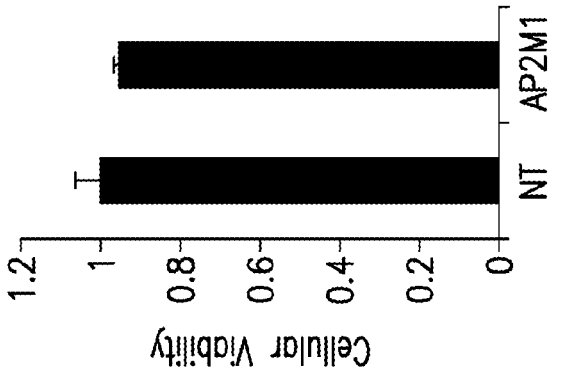


FIG. 8C

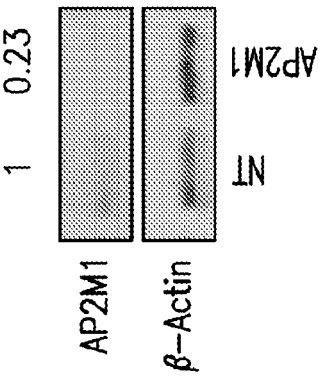


FIG. 8B

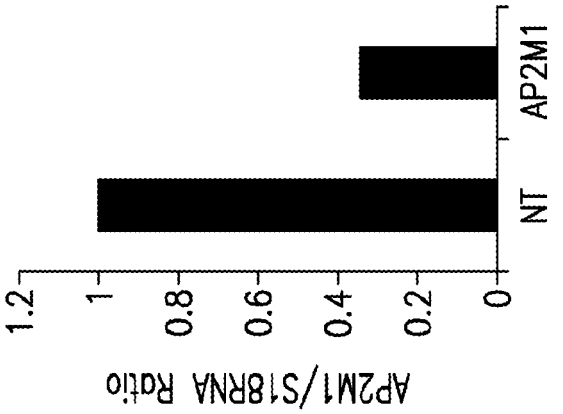


FIG. 8A

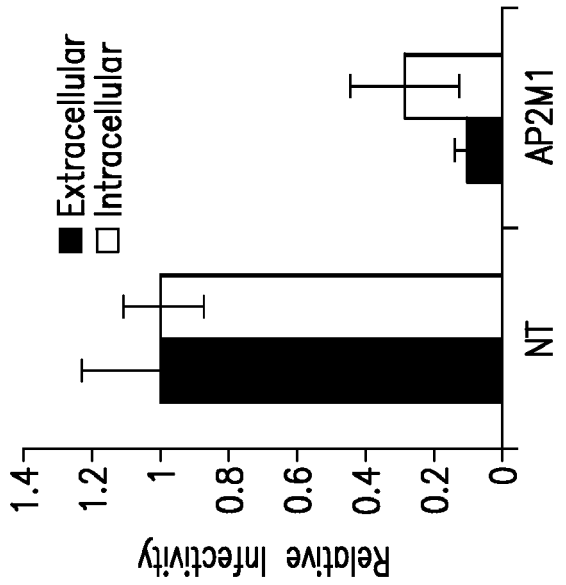


FIG. 8G

siRNAs	$TCID_{50}/ml$
NT.....	$6.32x10^3$
AP2M1.....	$1.12x10^2$

FIG. 8F

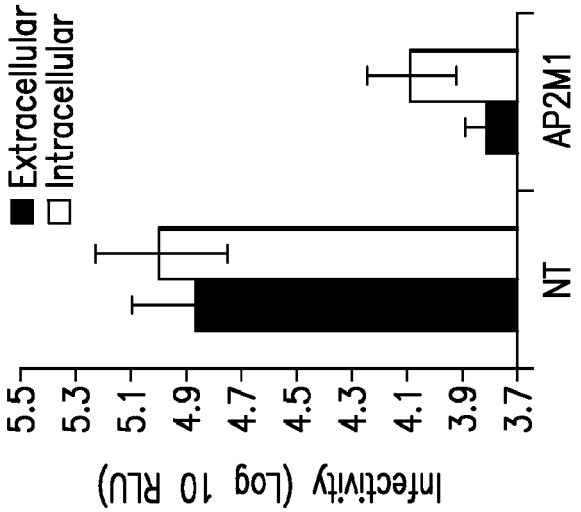


FIG. 8E

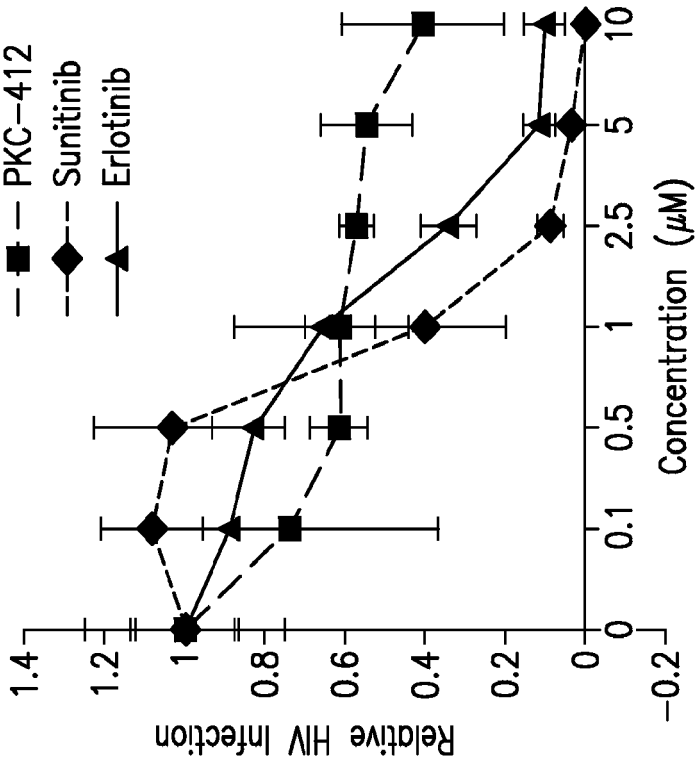

PKC−412
Sunitinib
Erlotinib
Relative HIV Infection
1.4
1.2
1
0.8
0.6
0.4
0.2
0
−0.2
0
0.1
0.5
1
2.5
5
10
Concentration (μM)

FIG. 9B

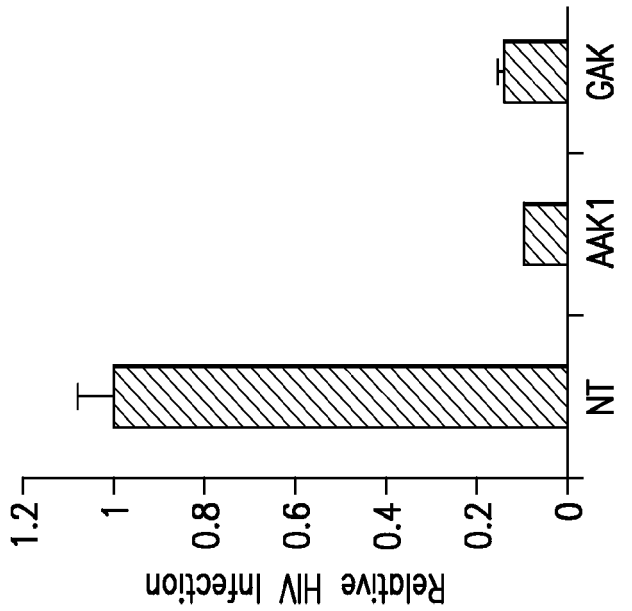

Relative HIV Infection
1.2
1
0.8
0.6
0.4
0.2
0
NT
AAK1
GAK

FIG. 9A

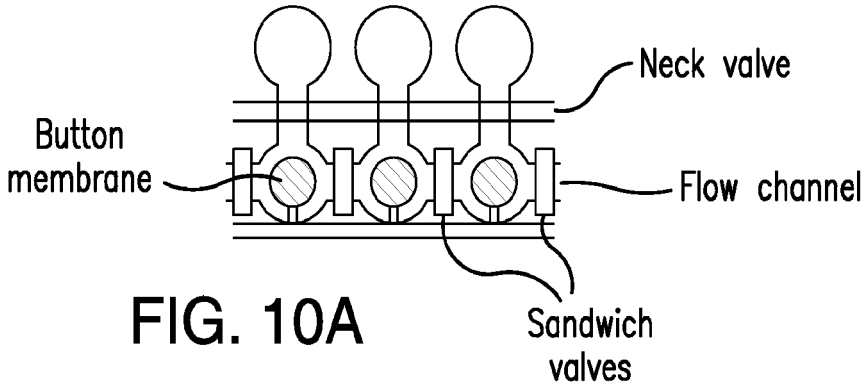


FIG. 10A

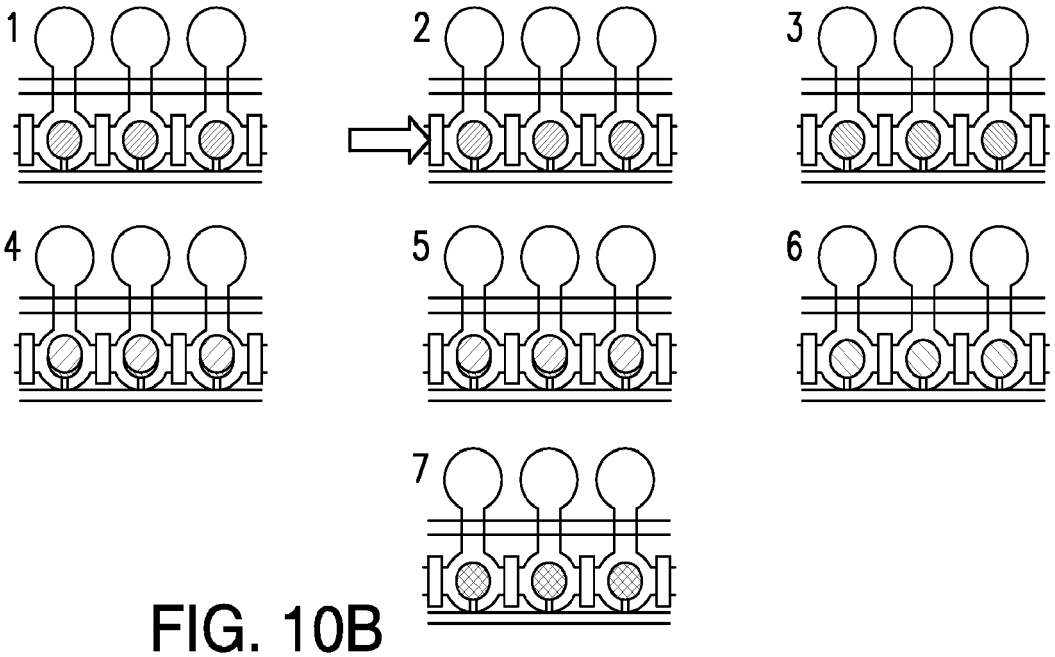


FIG. 10B

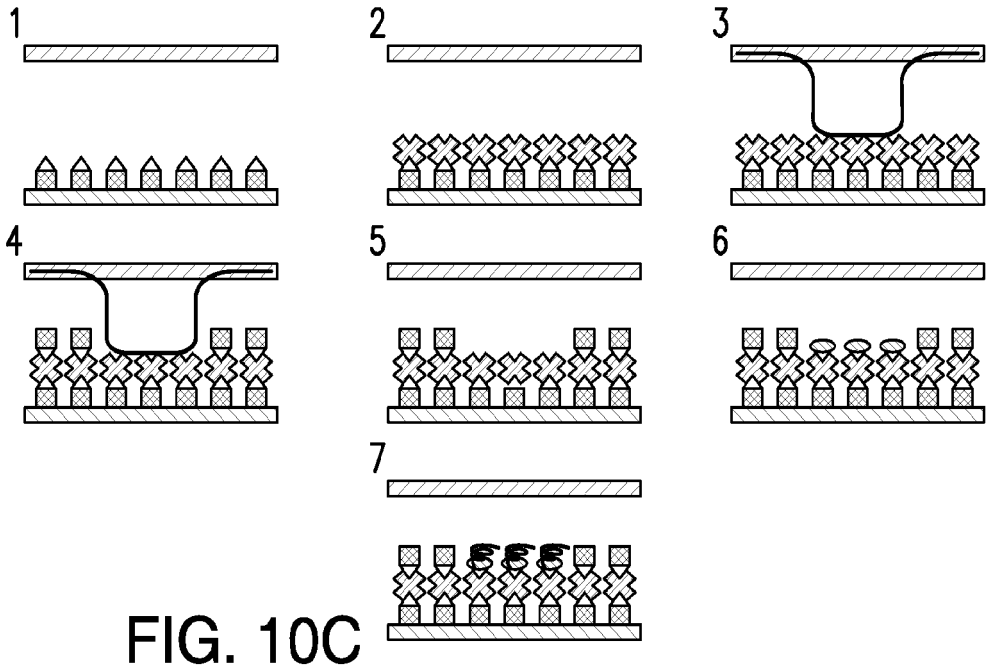


FIG. 10C

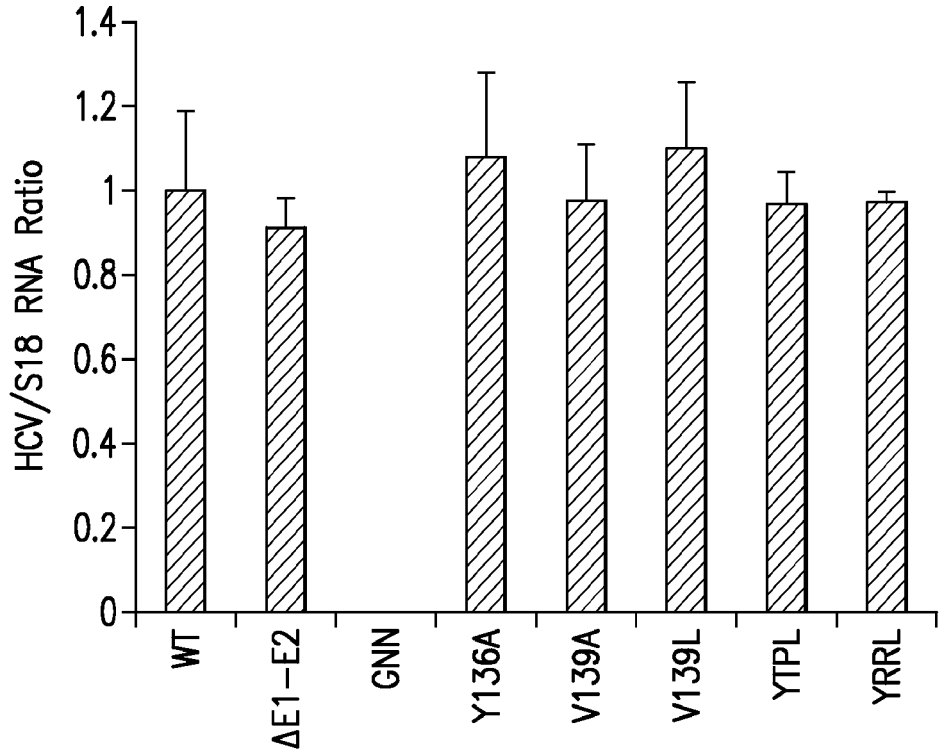

HCV/S18 RNA Ratio
1.4
1.2
1
0.8
0.6
0.4
0.2
0
WT
ΔE1–E2
GNN
Y136A
V139A
V139L
YTPL
YRRL

FIG. 11

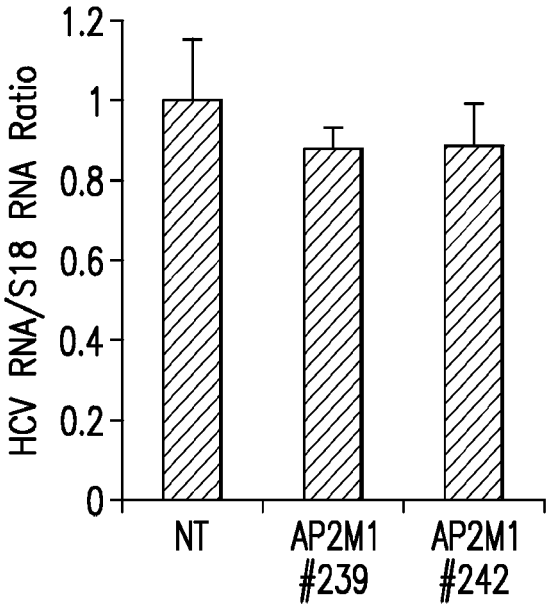


FIG. 12

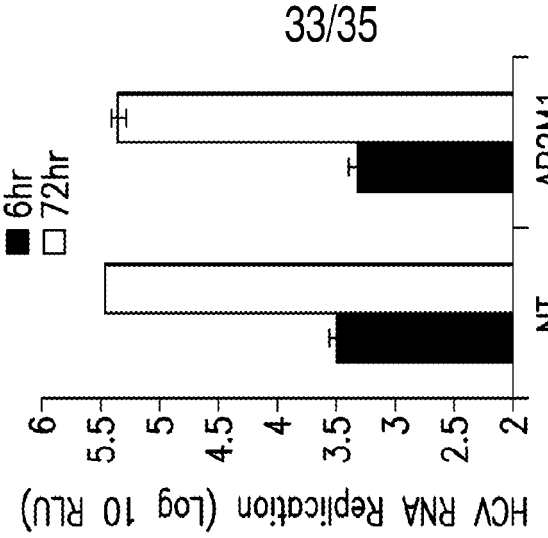


FIG. 13D

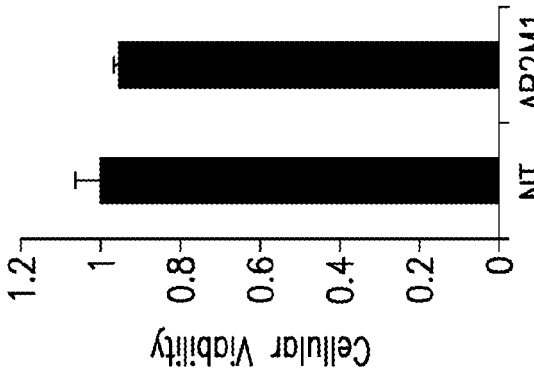


FIG. 13C

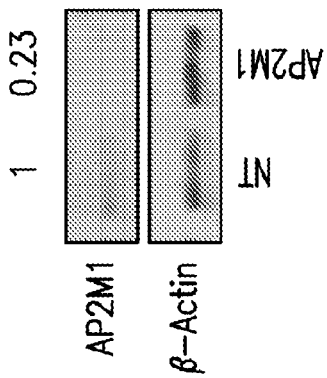


FIG. 13B

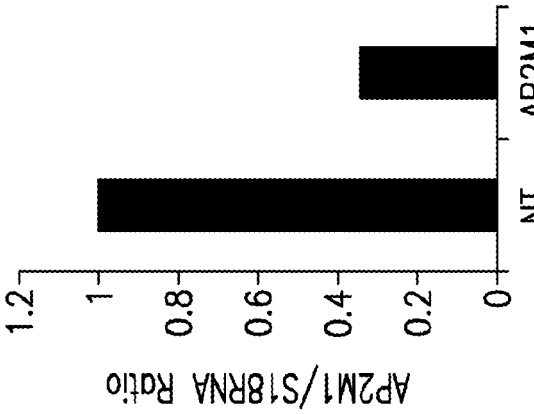


FIG. 13A

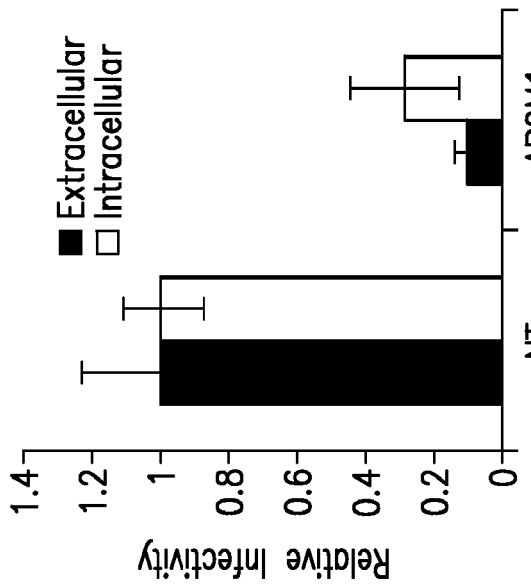


FIG. 13G

siRNAs	$TCID_{50}/ml$
NT.....	$6.32x10^3$
AP2M1.....	$1.12x10^2$

FIG. 13F

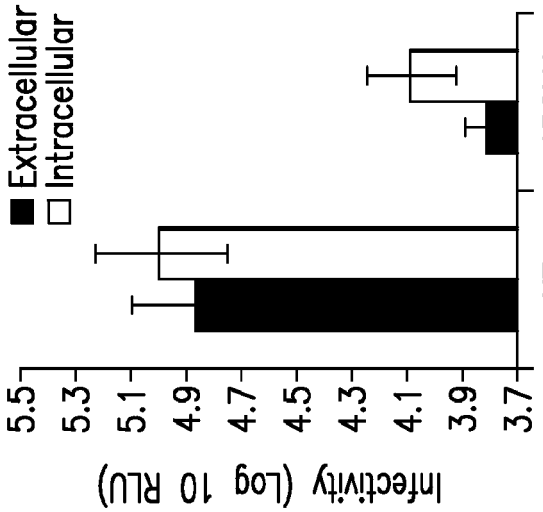


FIG. 13E

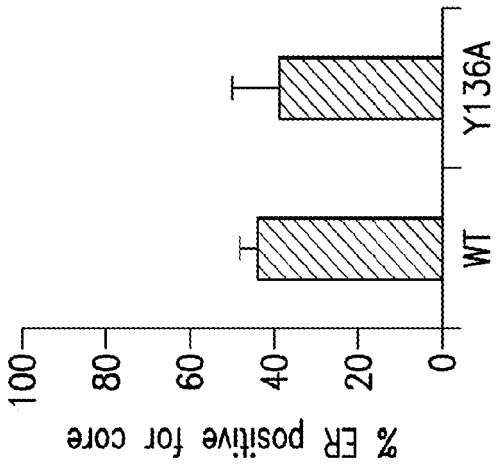


FIG. 14C

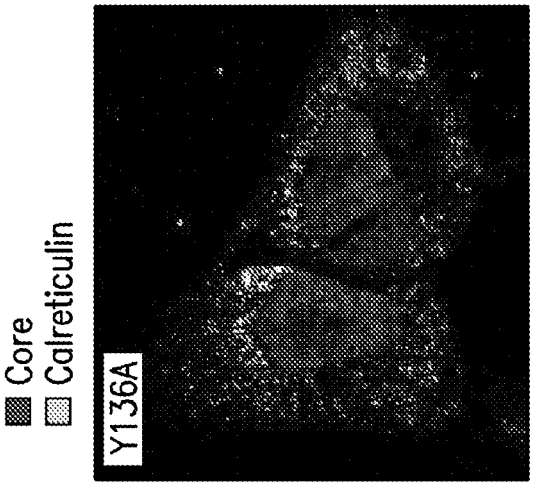


FIG. 14B

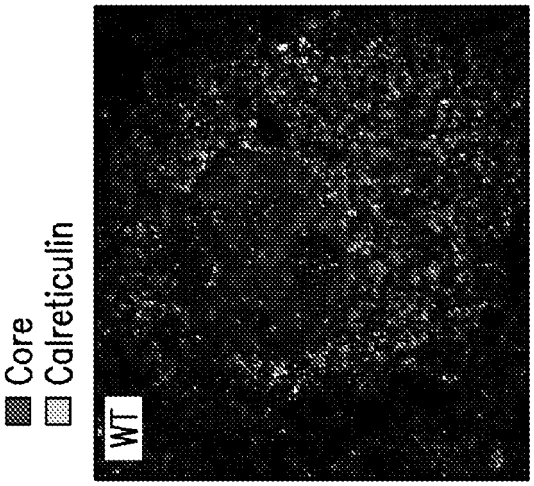


FIG. 14A