

FIG. 1A

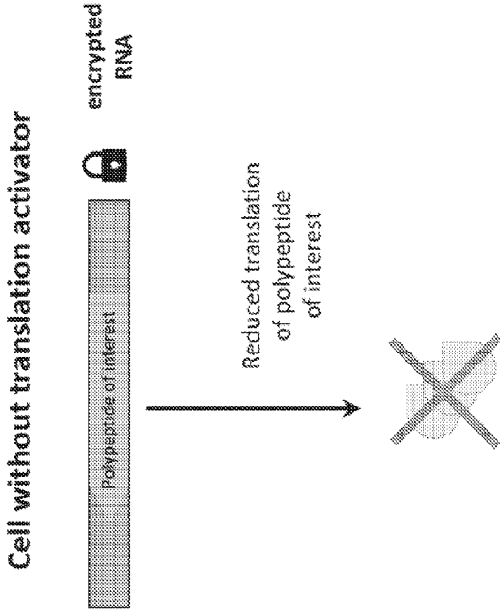


FIG. 1B

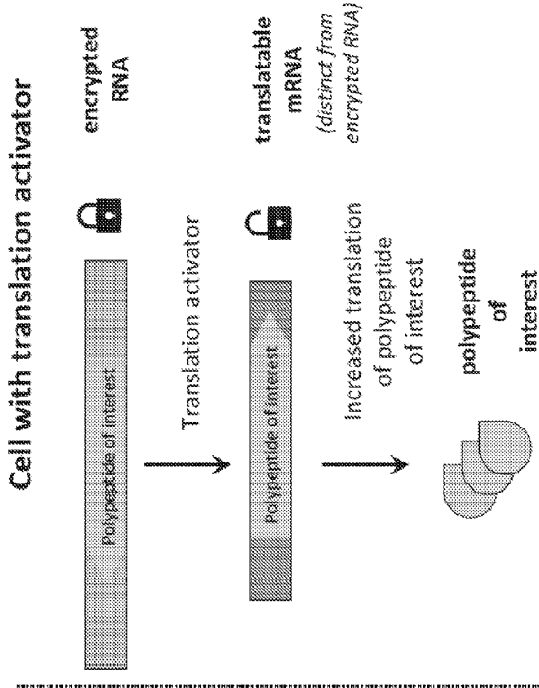


FIG. 2A

mRNA:
Protein production in all cells

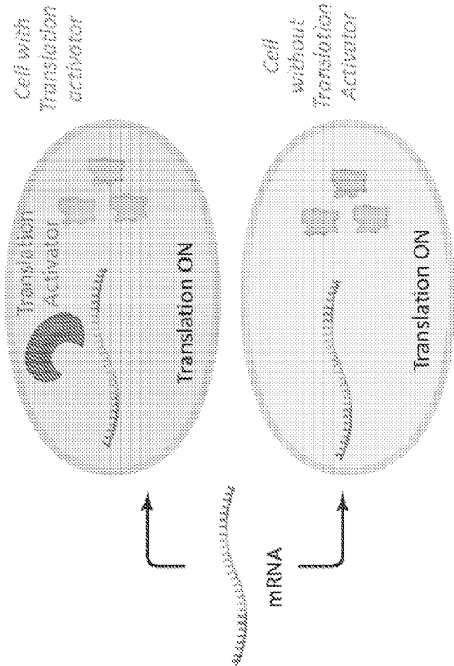
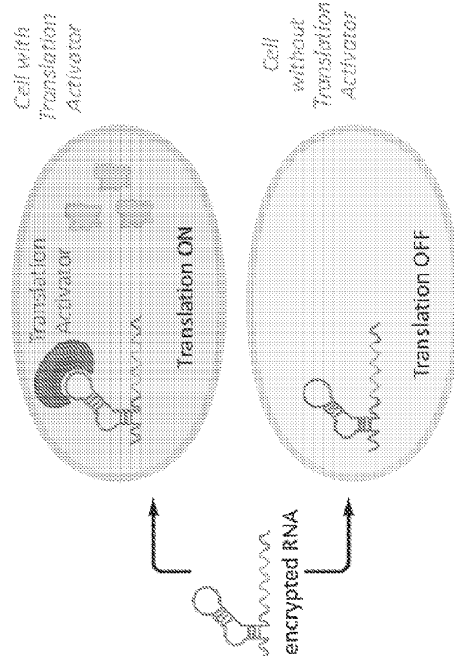


FIG. 2B

Encrypted RNA:
Increased translation of protein of interest in treated cells also provided with translation activator



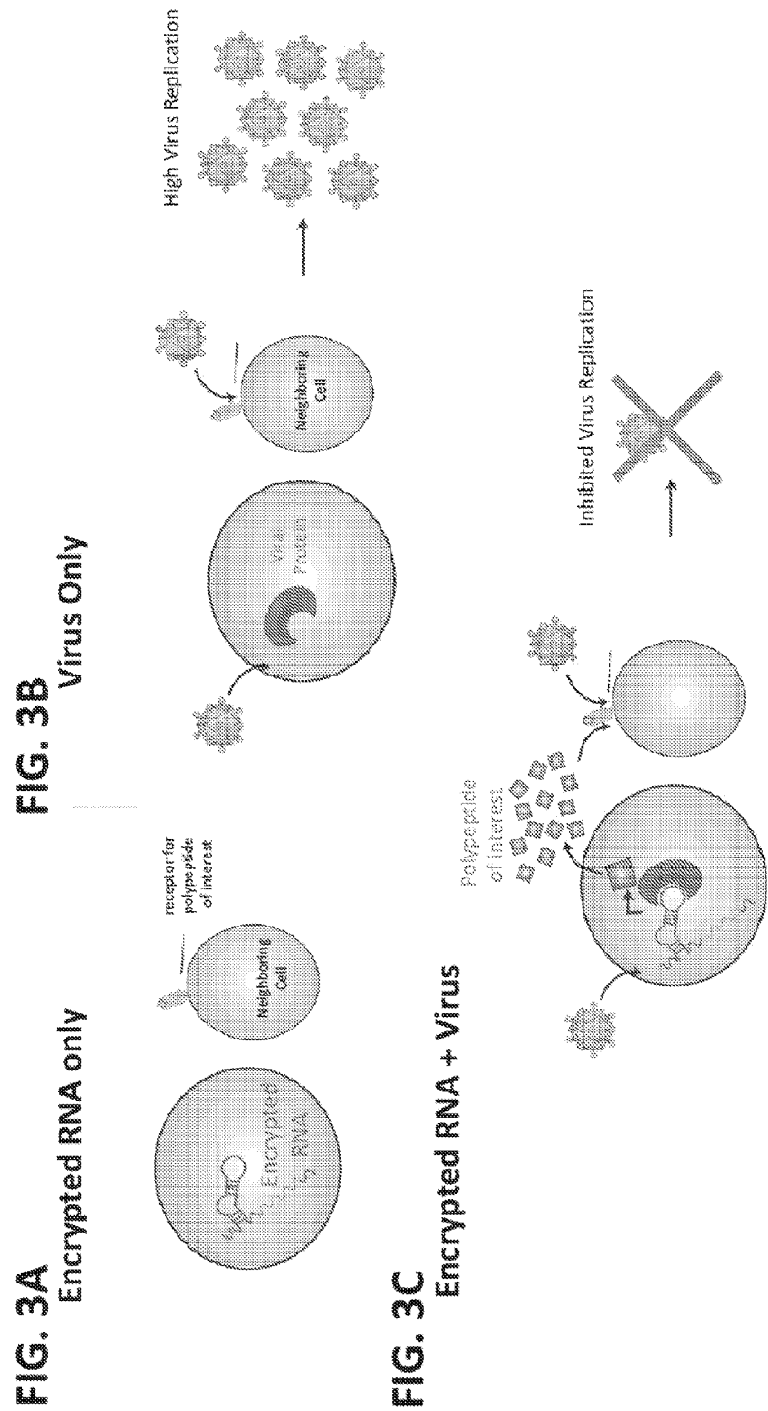


FIG. 4A

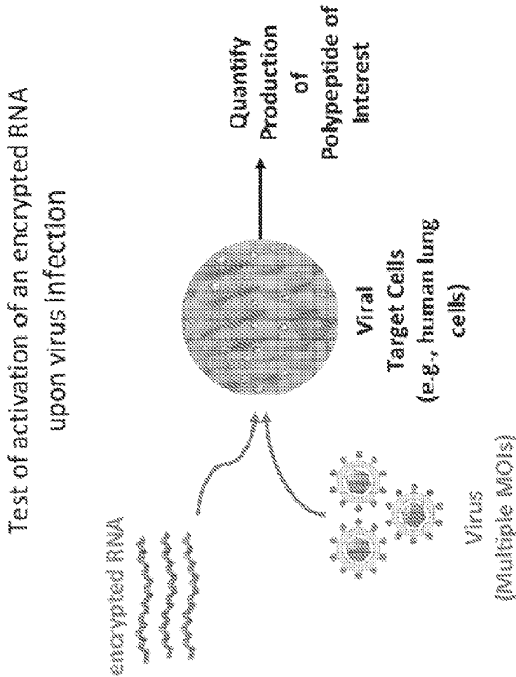


FIG. 4B

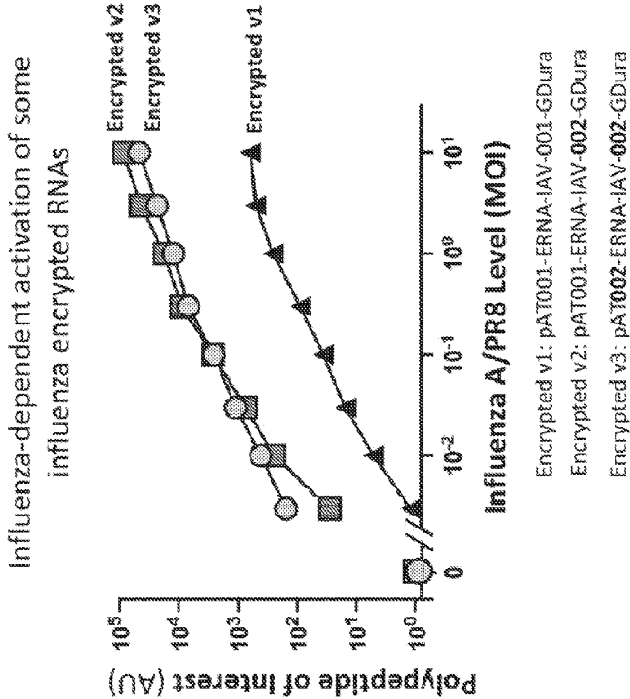


FIG. 5

Influenza Proteins Provided						Substantially Increased Translation of Polypeptide of Interest?
Pool	PB2	PB1	PA	NP	Encrypted RNA ERNA-1AY-002-GDura	
no TA	---	---	---	---	+	No
Pol _A -PB2	---	+	+	+	+	No
Pol _A -PB1	+	---	+	+	+	No
Pol _A -PA	+	+	---	+	+	No
Pol _A -ERNA	+	+	+	+	---	No
Pol _A	+	+	+	+	+	Yes

FIG. 6

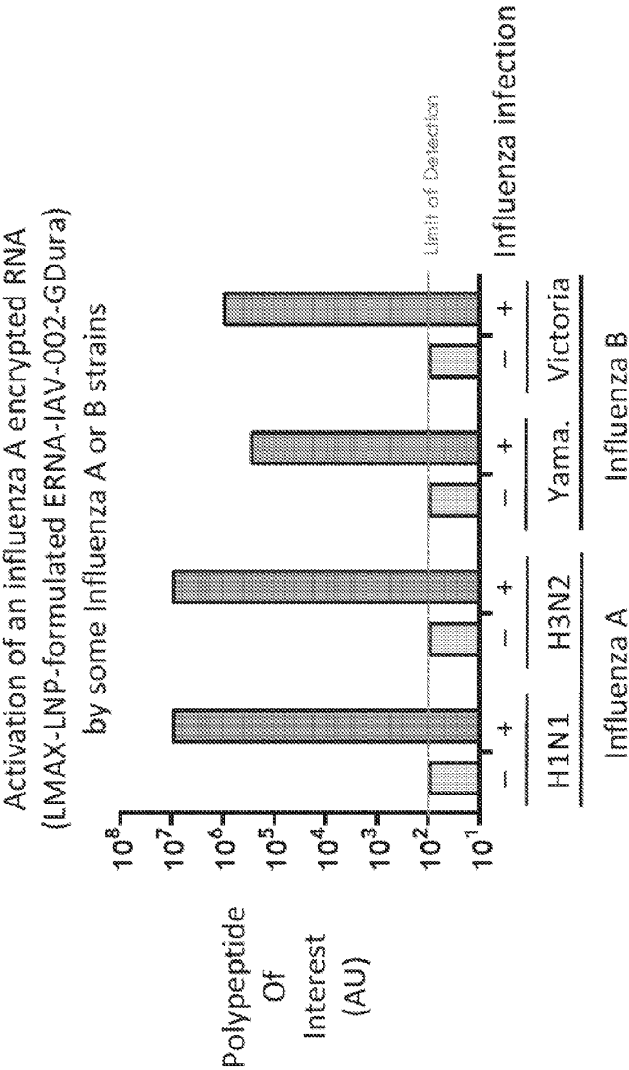


FIG. 7

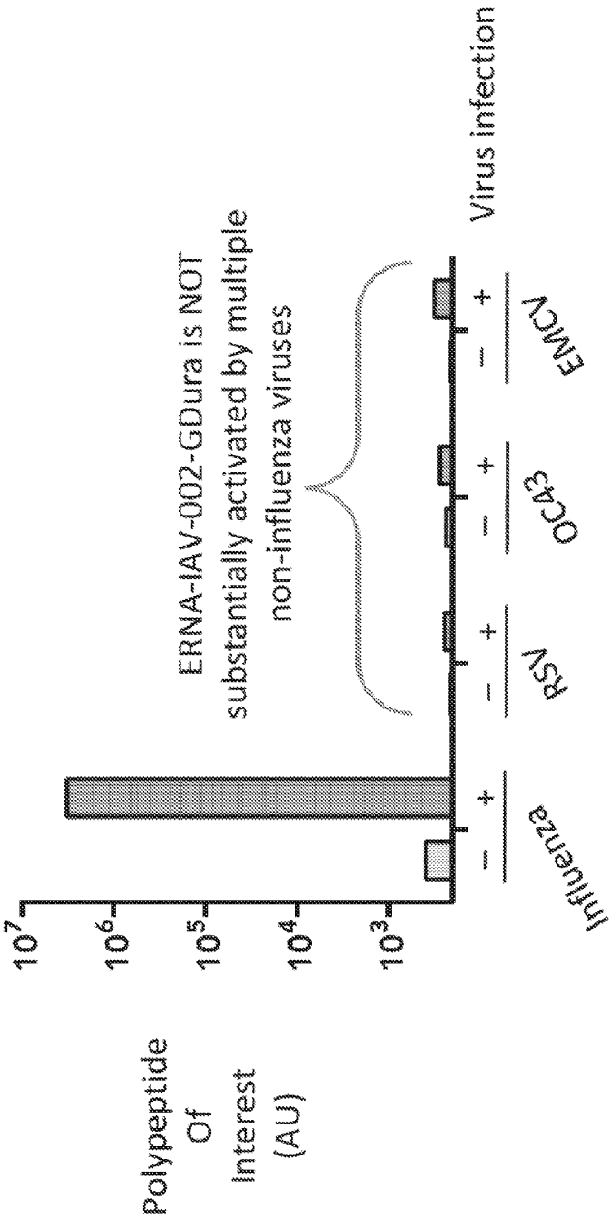


FIG. 8A

FIG. 8B

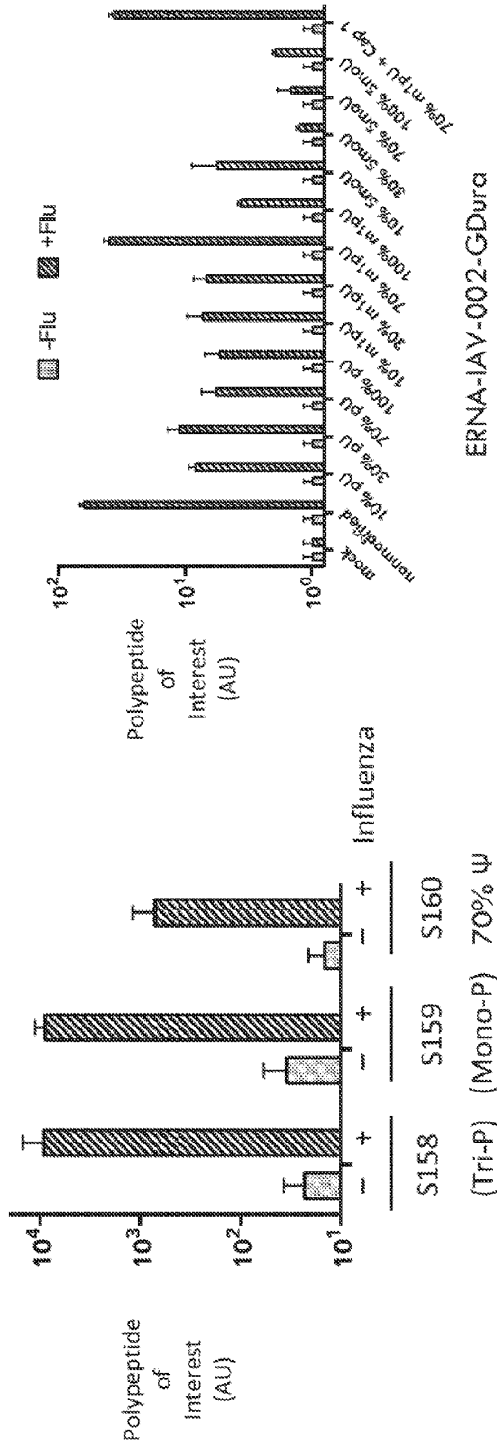


FIG. 9

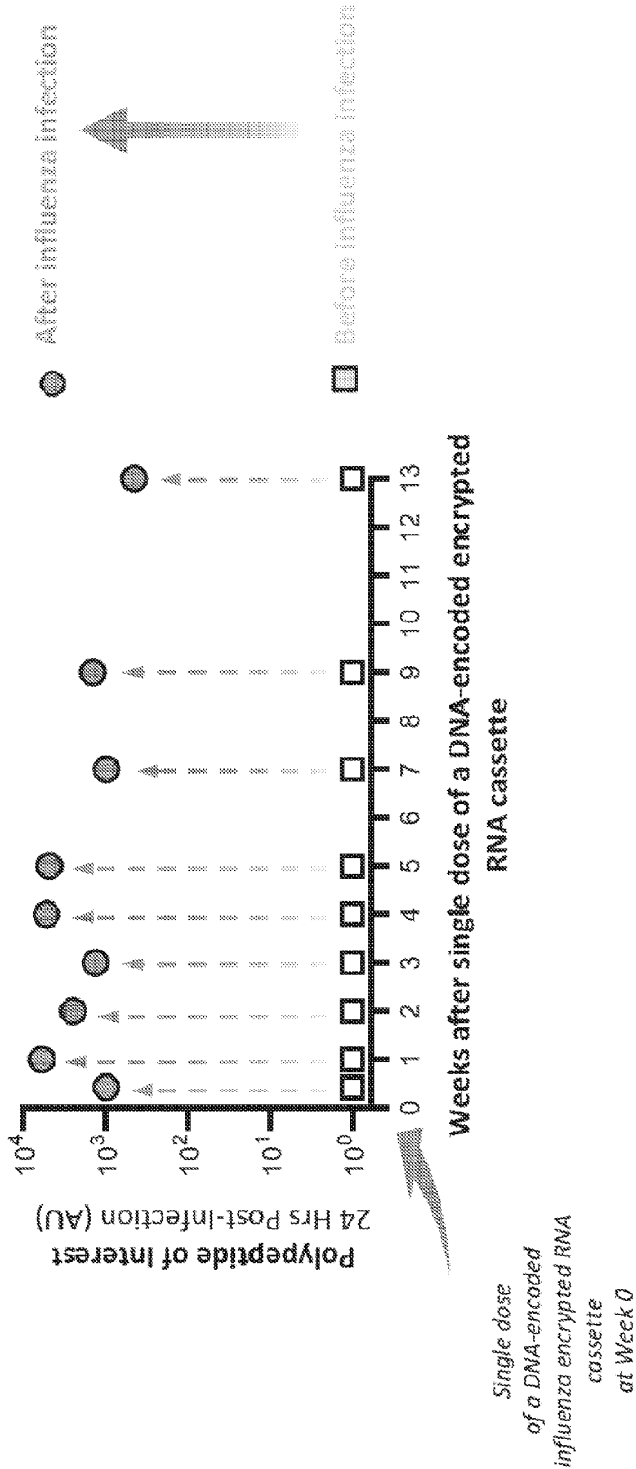
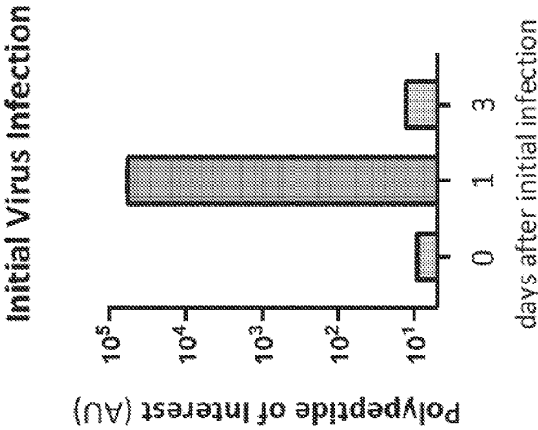


FIG. 10A



Rechallenge
w/virus
1 week
later

FIG. 10B

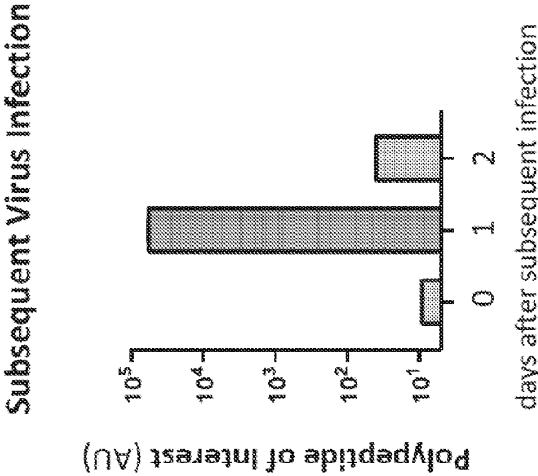
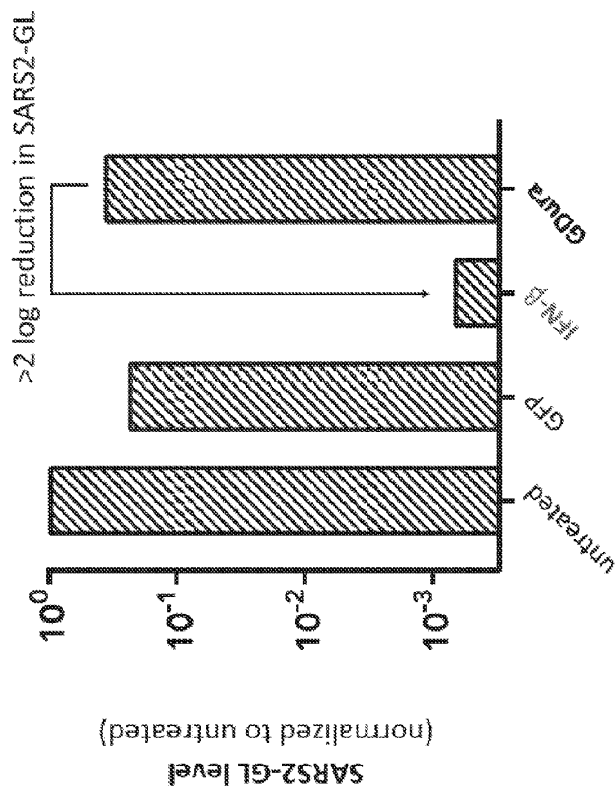
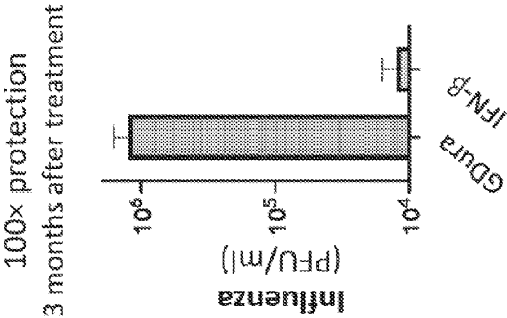


FIG. 11



GDura: LMAX-LNP-formulated uncapped ERNA-SARS2-101-GDura (sarbecovirus encrypted RNA encoding GDura)
IFN-β : LMAX-LNP-formulated uncapped ERNA-SARS2-101-hu__IFNB (sarbecovirus encrypted RNA encoding human IFN-β)
GFP: LMAX-LNP-formulated uncapped mRNA encoding a GFP

FIG. 12



GDura: DNA-encoded influenza encrypted RNA cassette encoding GDura
IFN-β : DNA-encoded influenza encrypted RNA cassette encoding human IFN-β

FIG. 13

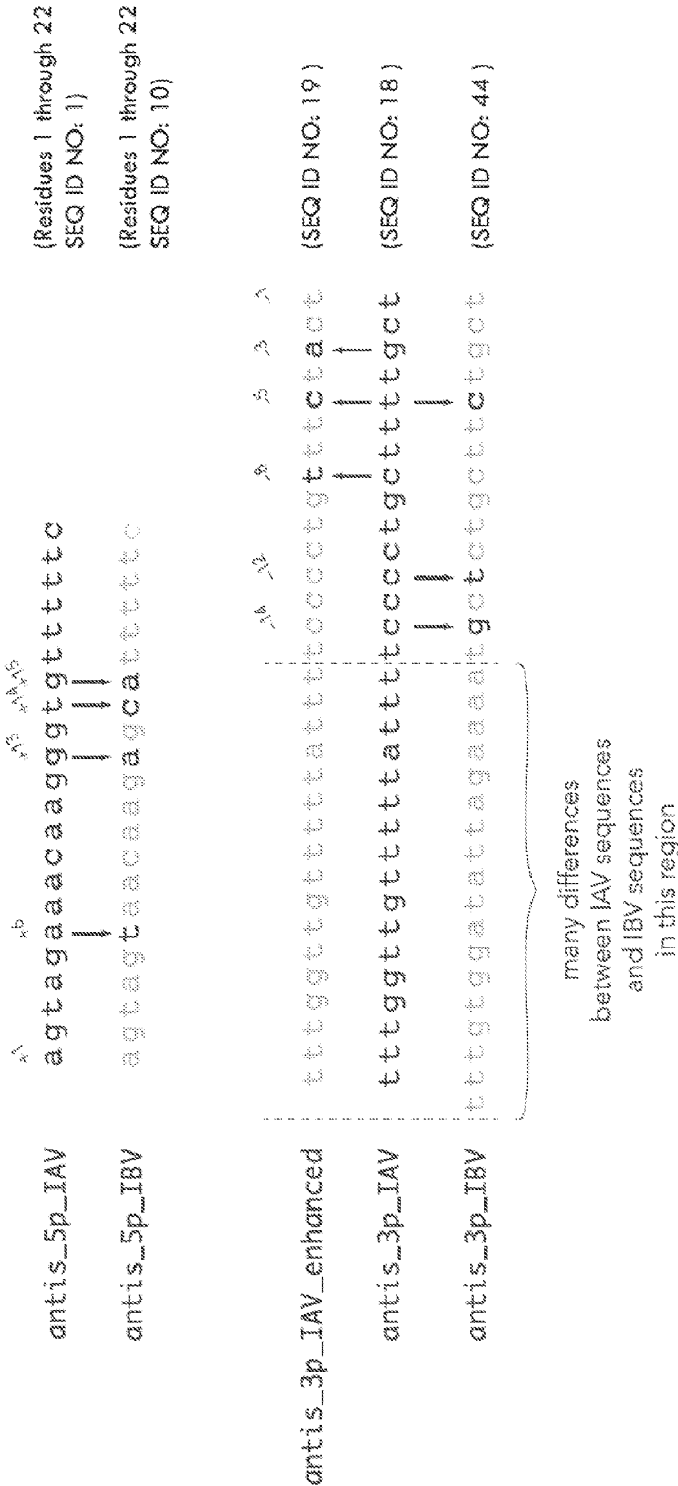
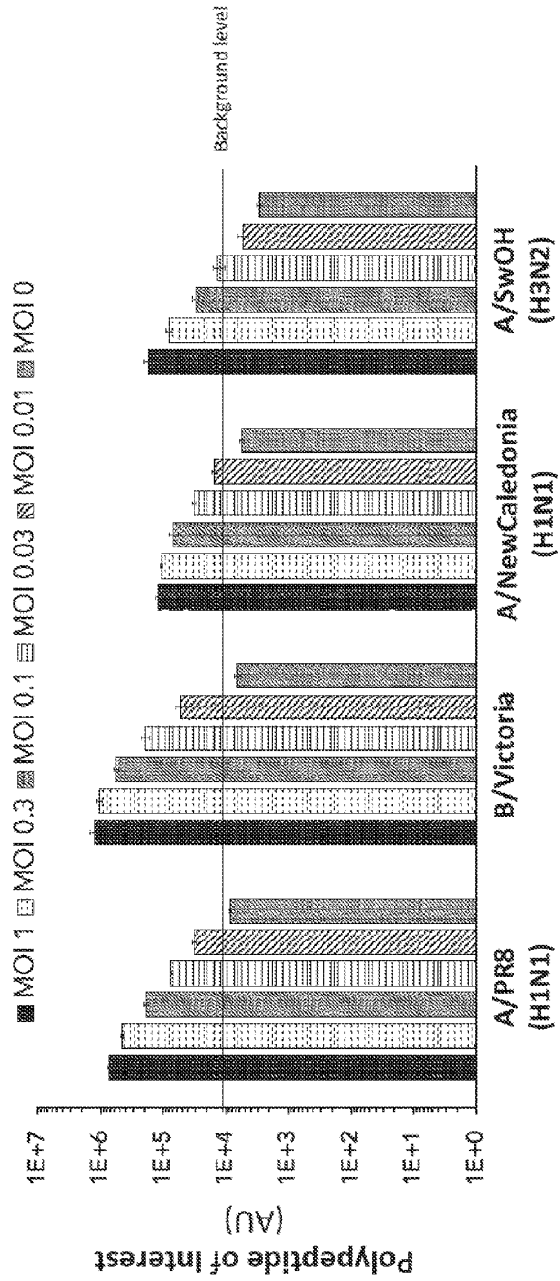


FIG. 14



5
4
3
2
1

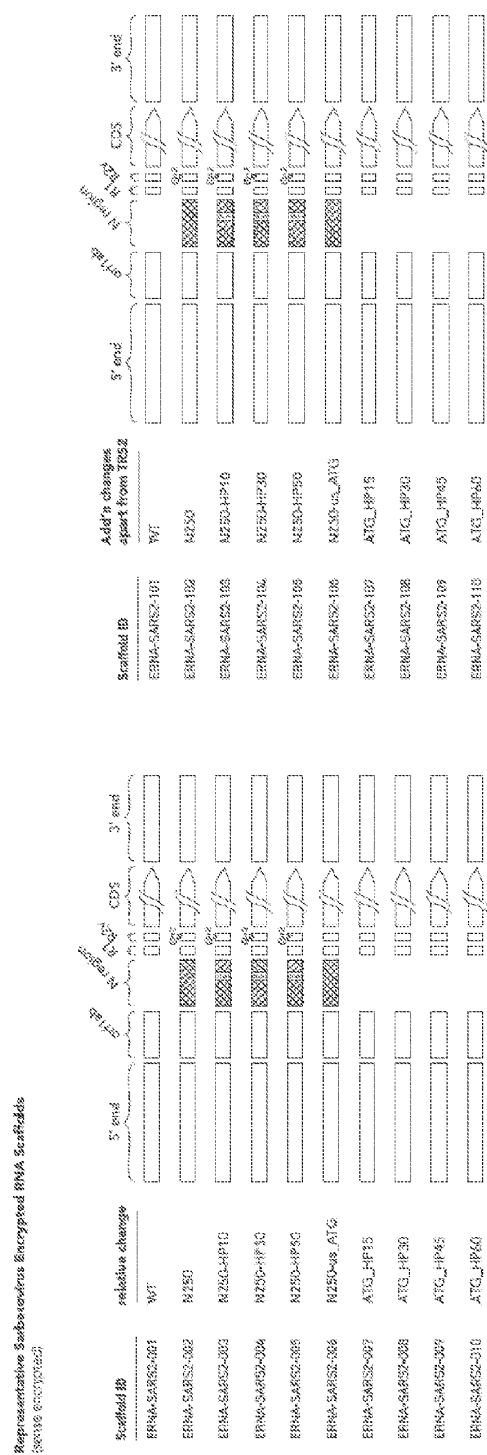


FIG. 16A

Virus-dependent activation of
encrypted RNA
(24 hpi)

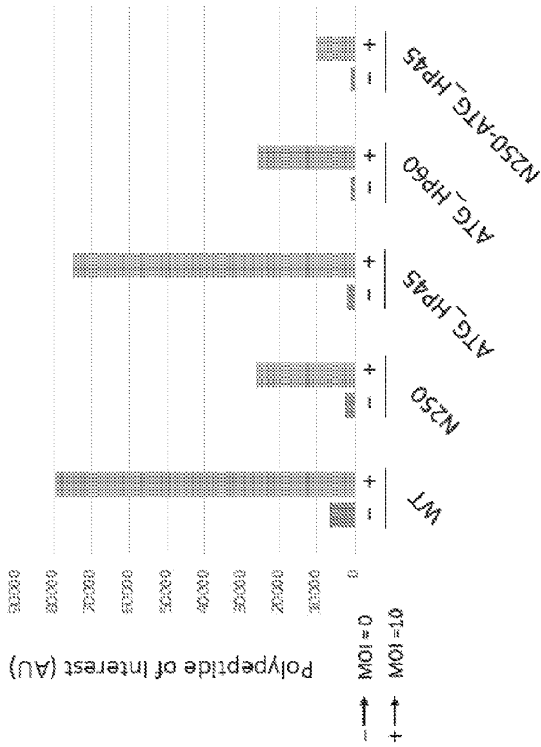


FIG. 16B

Virus-dependent activation of
encrypted RNA
(48 hpi)

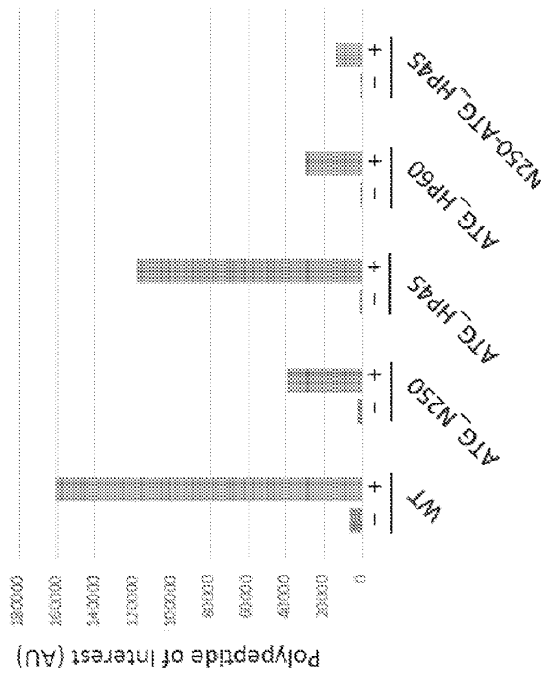


FIG. 17

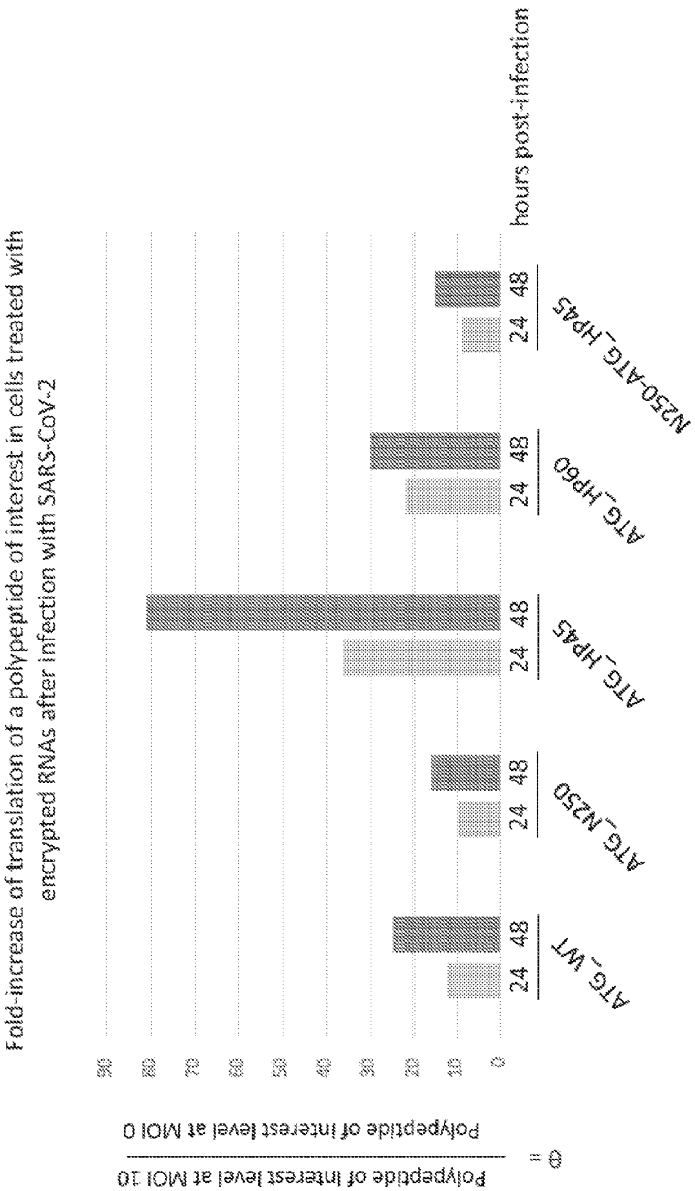


FIG. 18A

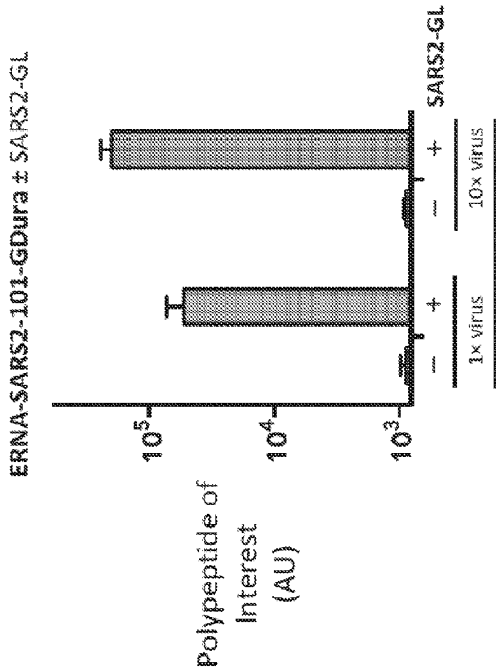


FIG. 18B

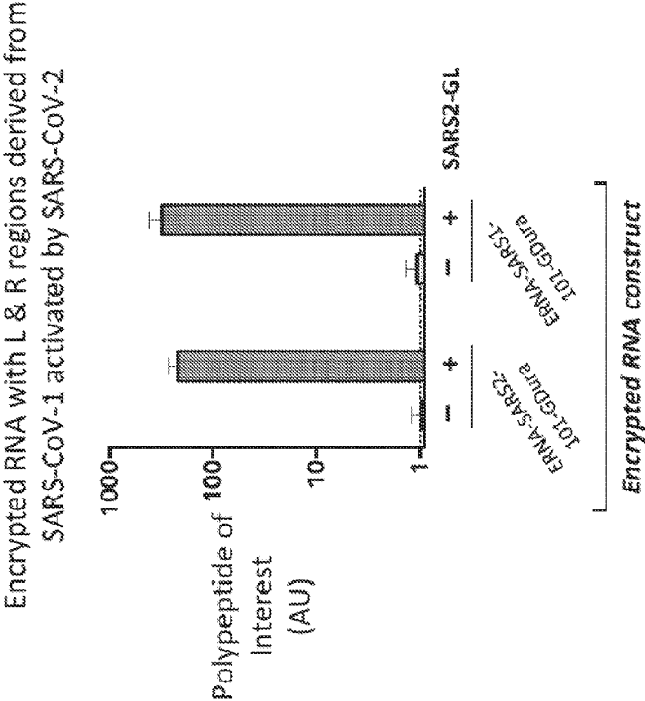


FIG. 19

Representative Sarbecovirus Encrypted RNA Scaffolds
(antisense protein CDS)

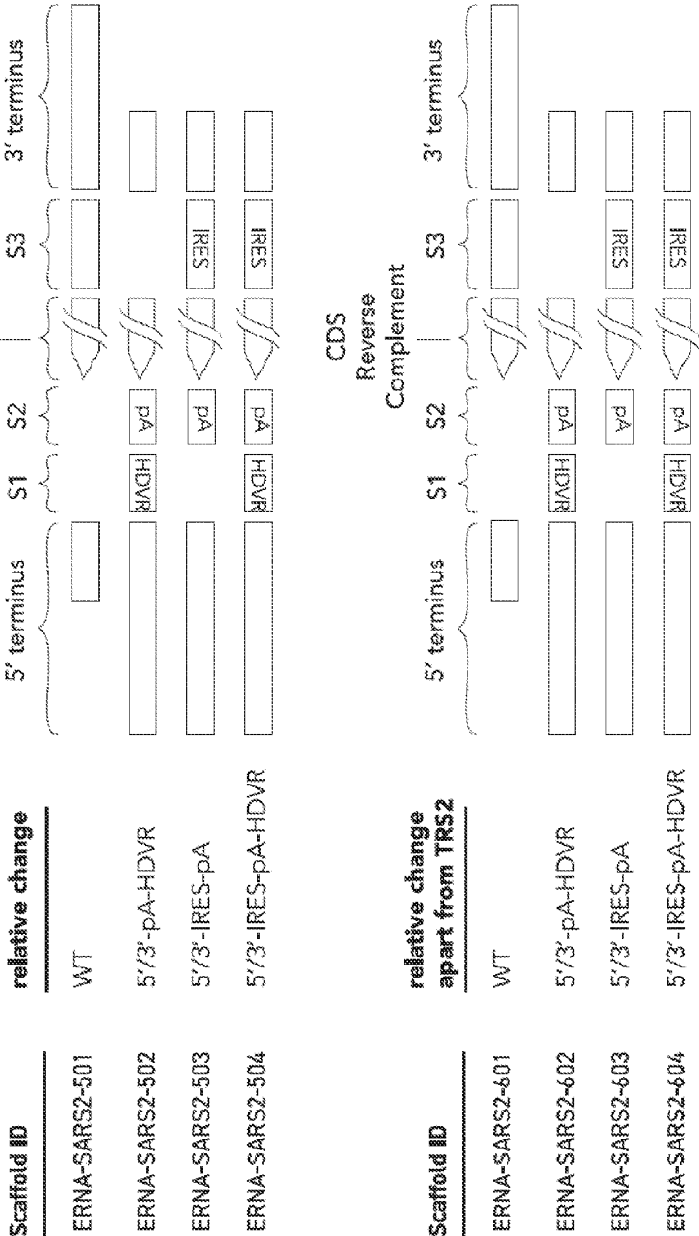


FIG. 20A

Translation activation of
encrypted RNA
(24 hpi)

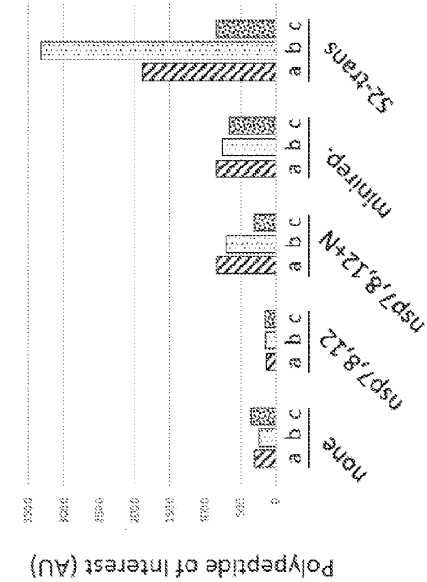
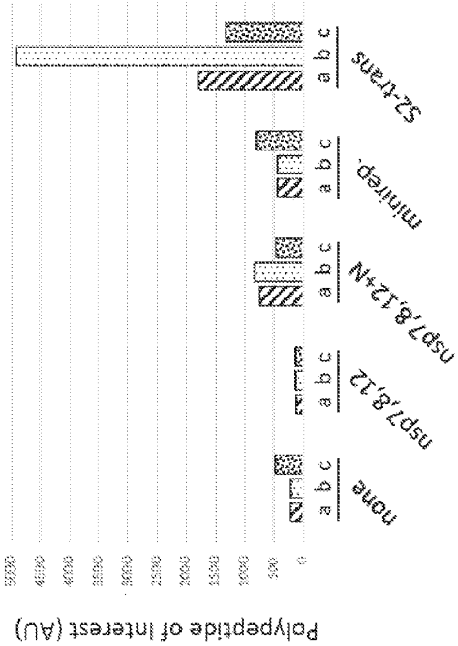


FIG. 20B

Translation activation of
encrypted RNA
(48 hpi)



- a pAT401-ERNA-SARS2-601-GDura
- b pAT402-ERNA-SARS2-601-GDura
- c pAT402-ERNA-SARS2-604-GDura

FIG. 21

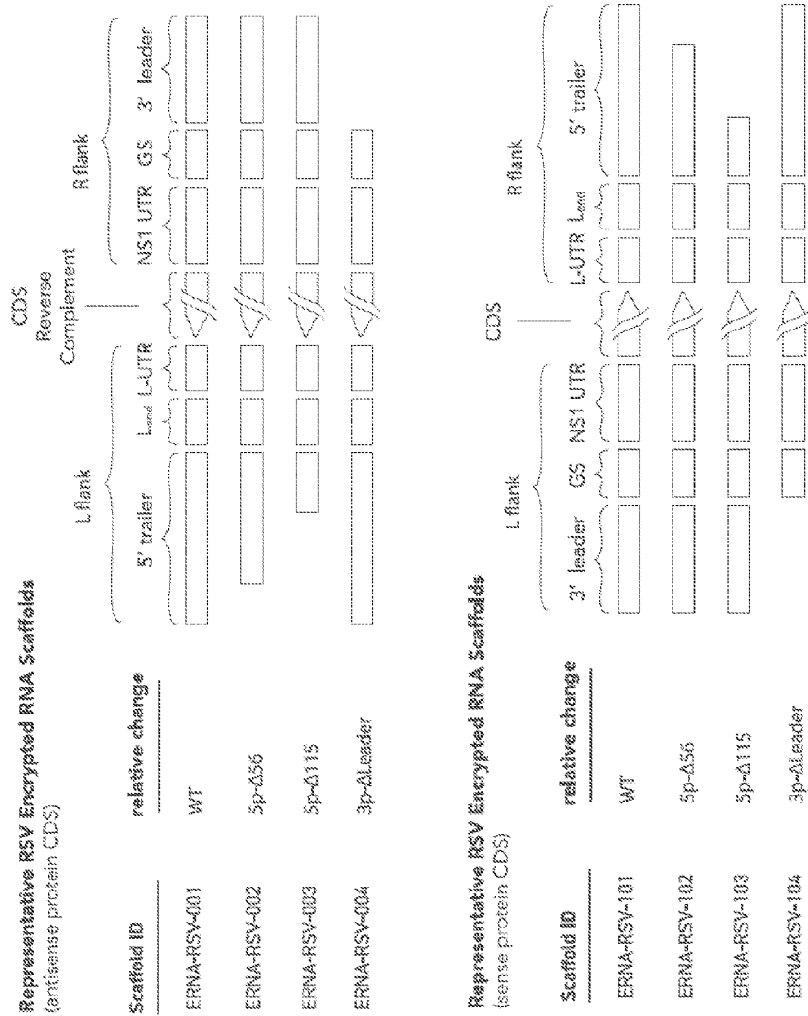
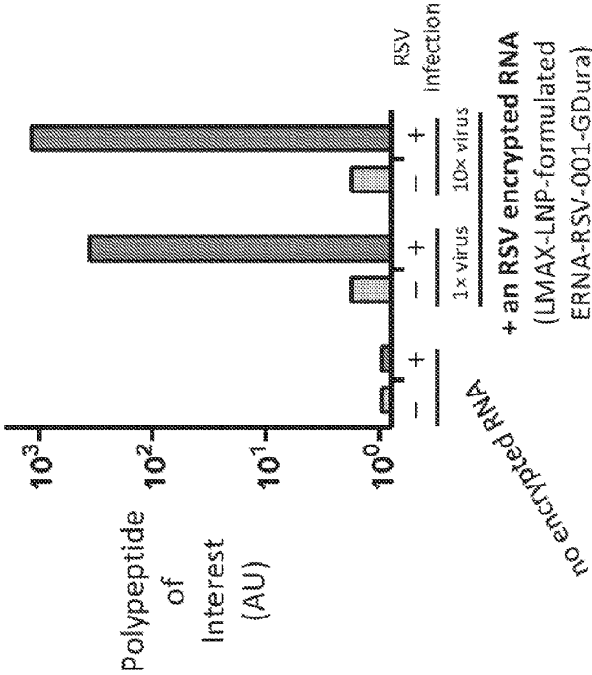
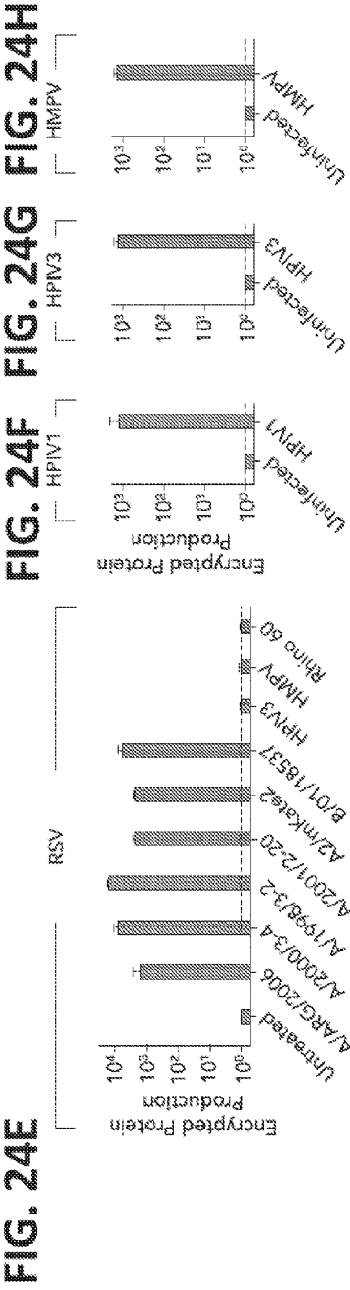
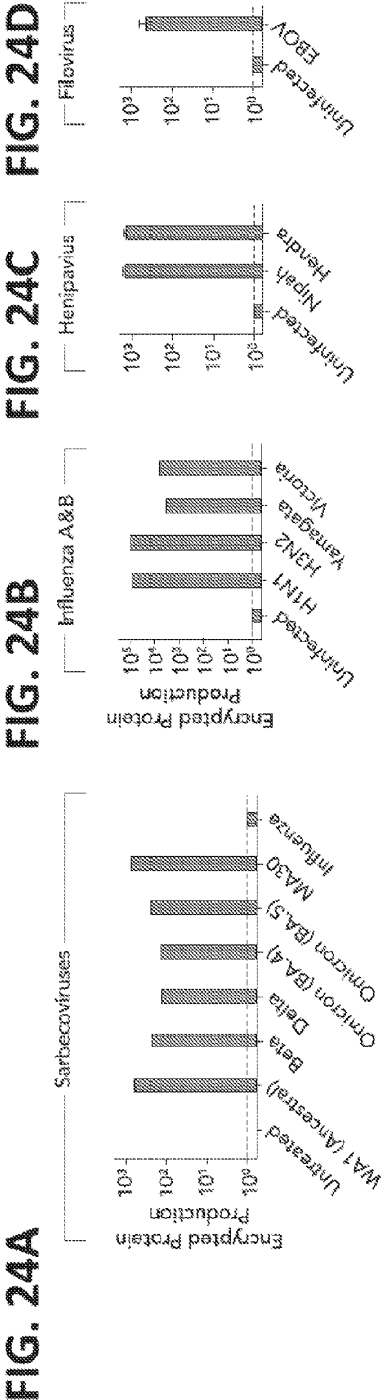
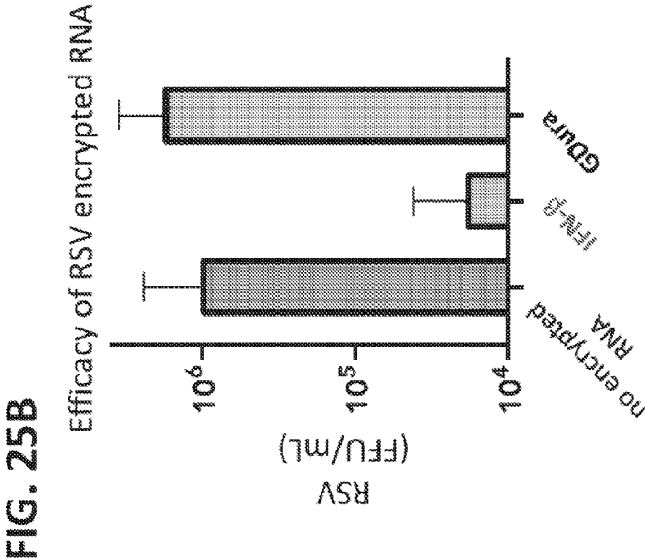
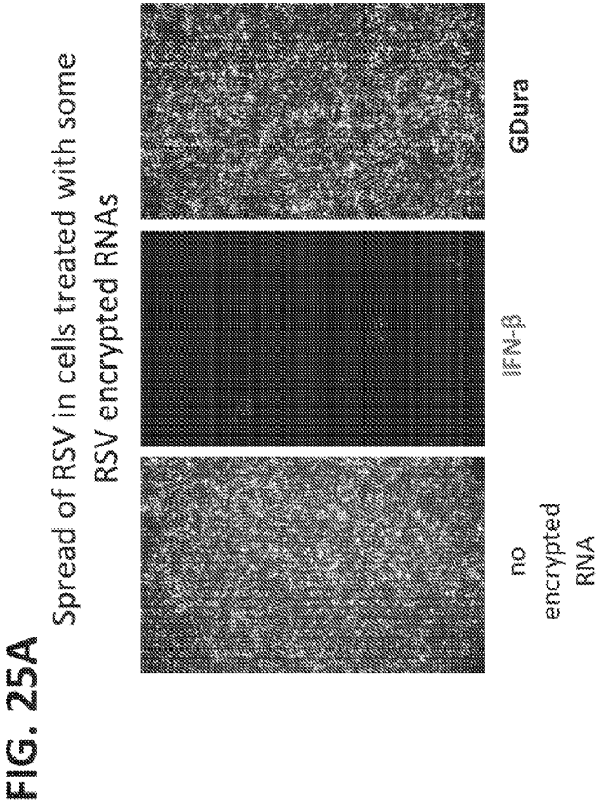


FIG. 22

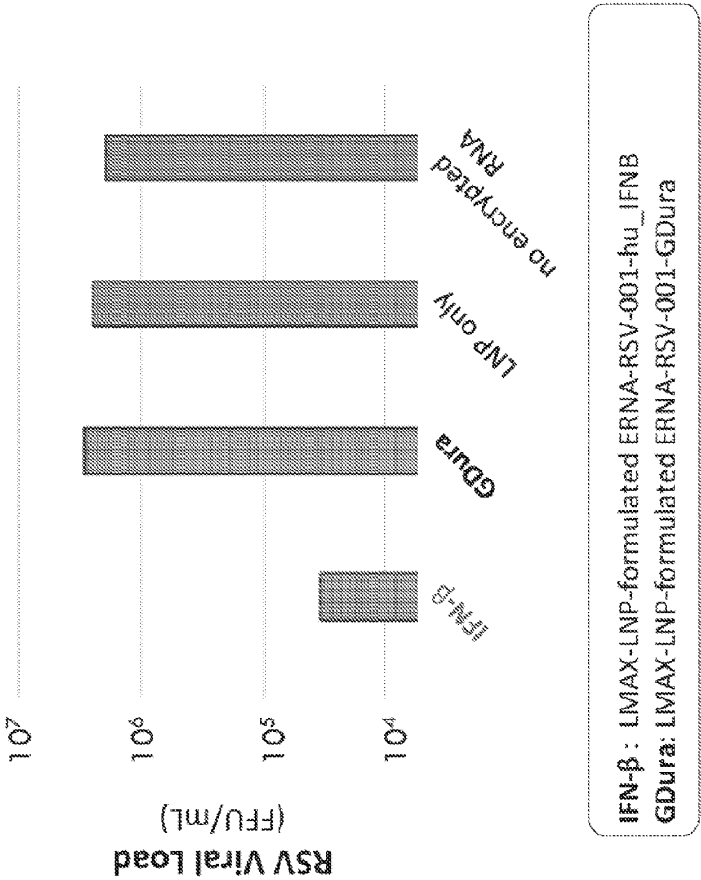


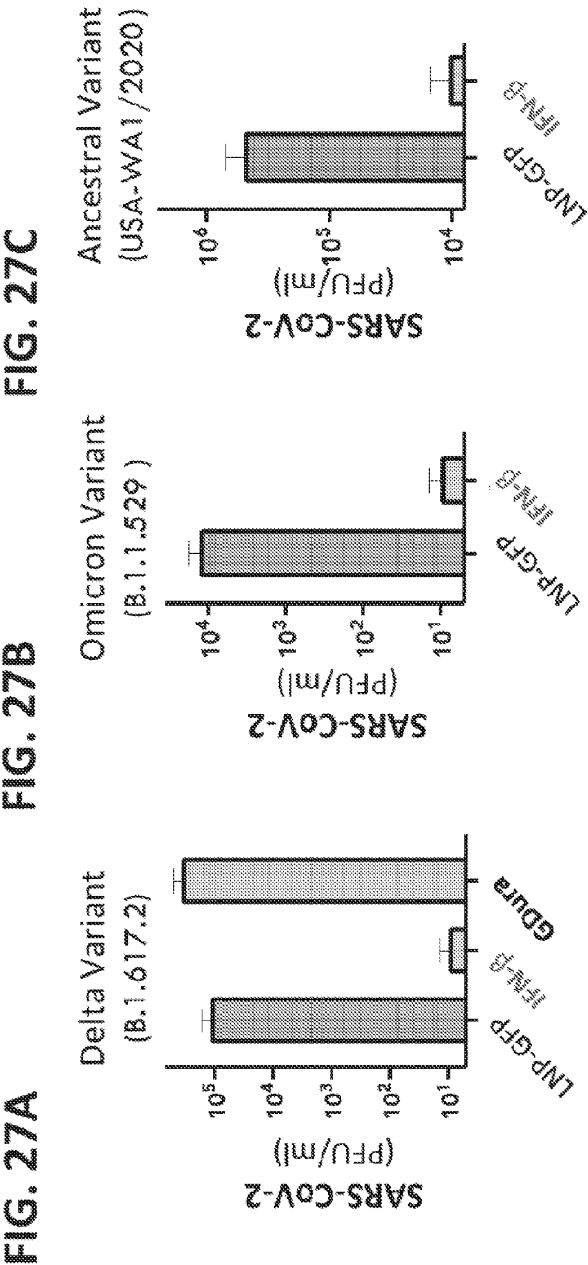




IFN-β : LMAX-LNP formulated ERNA-RSV-001-hu_IFNB (RSV encrypted RNA encoding human IFN-β)
GDura: LMAX-LNP formulated ERNA-RSV-001-GDura (RSV encrypted RNA encoding GDura)

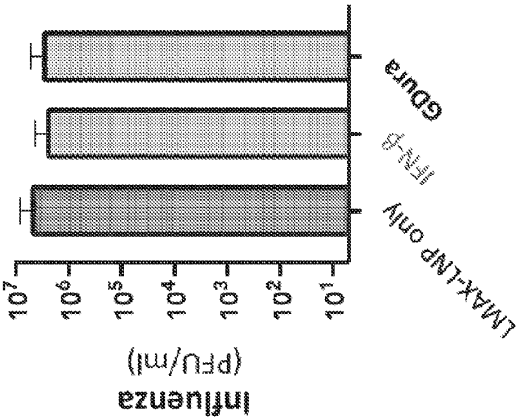
FIG. 26





GDura: LNP-formulated ERNA-SARS2-101-GDura (sarbecovirus encrypted RNA encoding GDura)
IFN-β : LNP-formulated ERNA-SARS2-101-hu_IFNB (sarbecovirus encrypted RNA encoding human IFN-β)
LNP-GFP: LNP-formulated mRNA encoding a GFP

FIG. 28



GDura: LMAX-LNP-formulated ERNA-SARS2-101-GDura (sarbecovirus encrypted RNA encoding GDura)
IFN-β : LMAX-LNP-formulated ERNA-SARS2-101-hu_IFNB (therapeutic sarbecovirus encrypted RNA encoding human IFN-β)
LMAX-LNP only: LMAX-LNP only

FIG. 29A

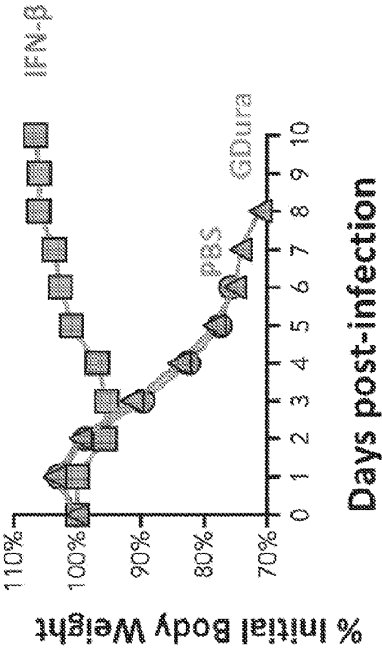
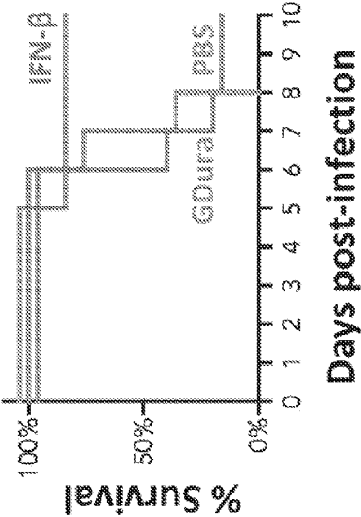


FIG. 29B



IFN-β : LNP-formulated capped ERNA-SARS2-001-m_IFNB
GDura: LNP-formulated capped ERNA-SARS2-001-GDura
PBS: PBS + 5% sucrose (vehicle only)

FIG. 30

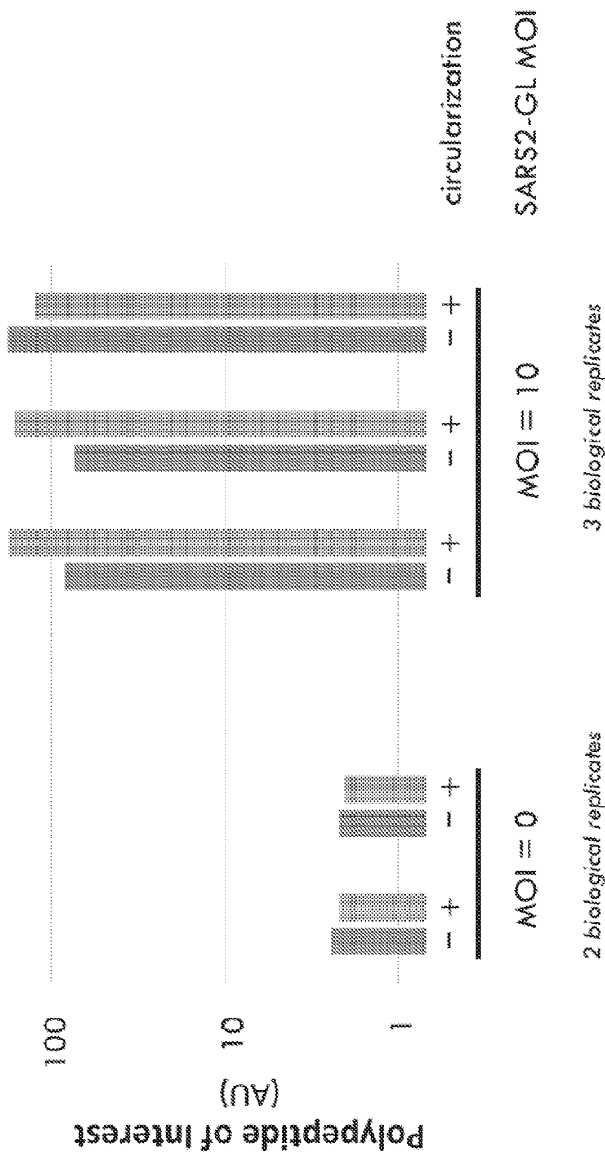


FIG. 31

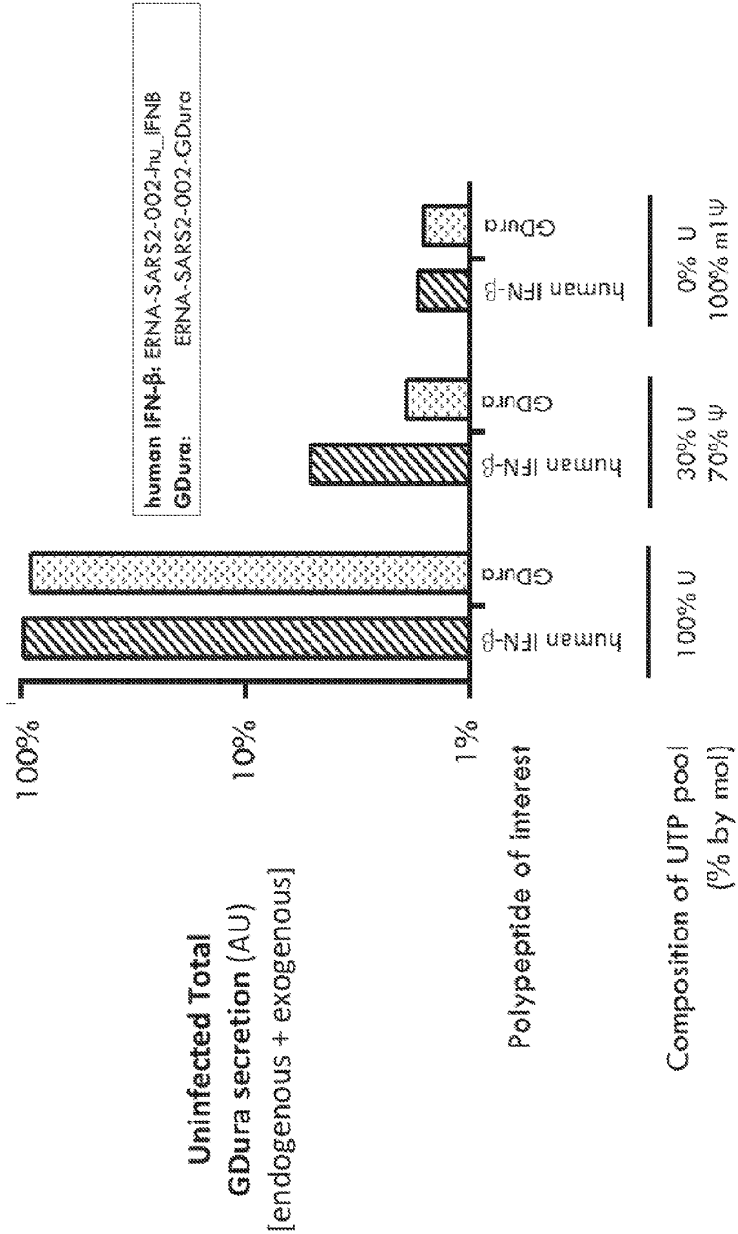


FIG. 32

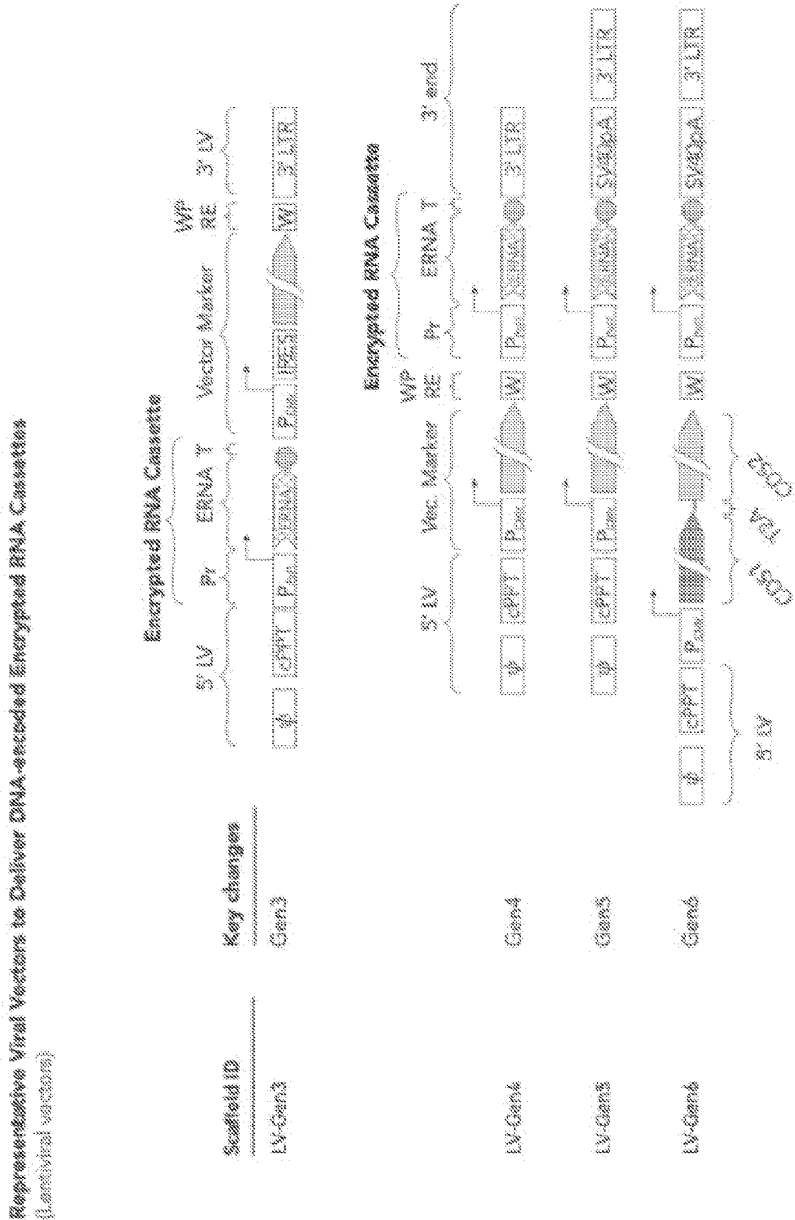


FIG. 33

Sequence of 3' end of RNA transcript (3'-RACE)		Poll terminator sequence		Statistics of interpreted genotypes of 3'-RACE sequences		
3' end of desired sequence	Extra nt in transcript	ccaccccccacttcggag... (Residues 1 through 17 of SEQ ID NO: 355) mouse terminator			cccaacttcggag... (Residues 1 through 13 of SEQ ID NO: 357) mouse enhanced terminator (d4)	
		ccaccccccacttcggag... (Residues 1 through 12 of SEQ ID NO: 356) mouse enhanced terminator			cccaacttcggag... (Residues 1 through 12 of SEQ ID NO: 356) mouse enhanced terminator	
...gcu <u>cccc</u>	5 extra C	73% (8 of 11)	0% (0 of 8)	0%	(0 of 10)	
...gcu <u>cccc</u>	4 extra C	18% (2 of 11)	0% (0 of 8)	0%	(0 of 10)	
...gcu <u>ccc</u>	3 extra C	0% (0 of 11)	0% (0 of 8)	0%	(0 of 10)	
...gcu <u>cc</u>	2 extra C	9% (1 of 11)	0% (0 of 8)	0%	(0 of 10)	
...gcu <u>c</u>	1 extra C	0% (0 of 11)	50% (4 of 8)	0%	(0 of 10)	
...gcu	0 extra C	0% (0 of 11)	50% (4 of 8)	100%	(10 of 10)	

34
G.
L

An RSV encrypted RNA with a 5'-monophosphate is competent for activation

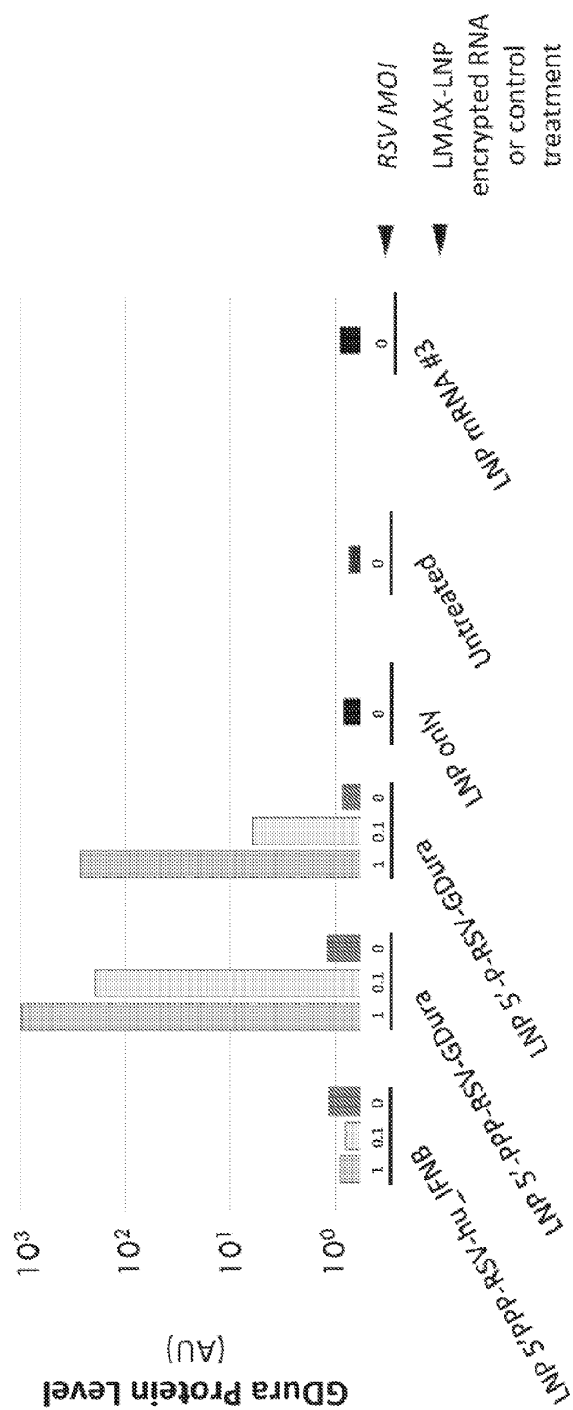


FIG. 35

An RSV encrypted RNA lacking a RIG-I agonist (5'-triphosphate) is competent for activation

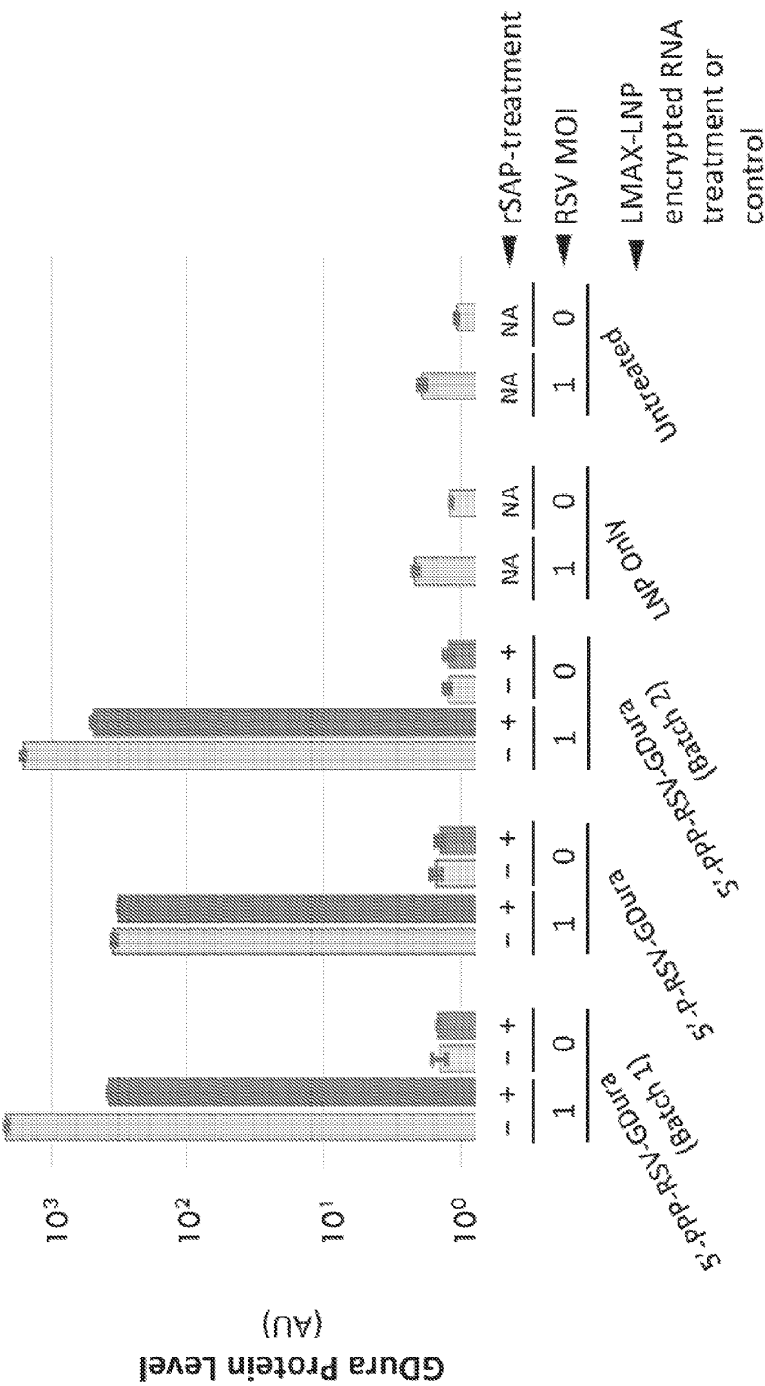


FIG. 37

An RSV encrypted RNA can be activated by distinct RSV strains

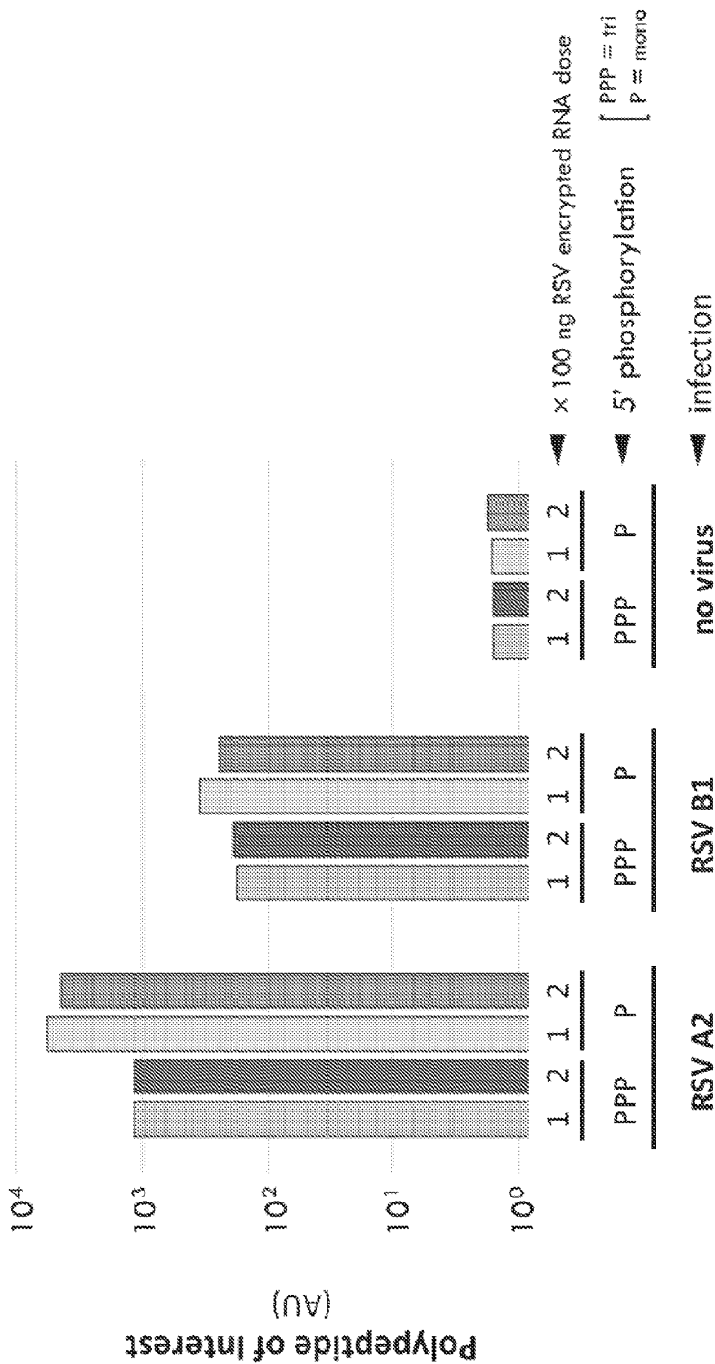


FIG. 38

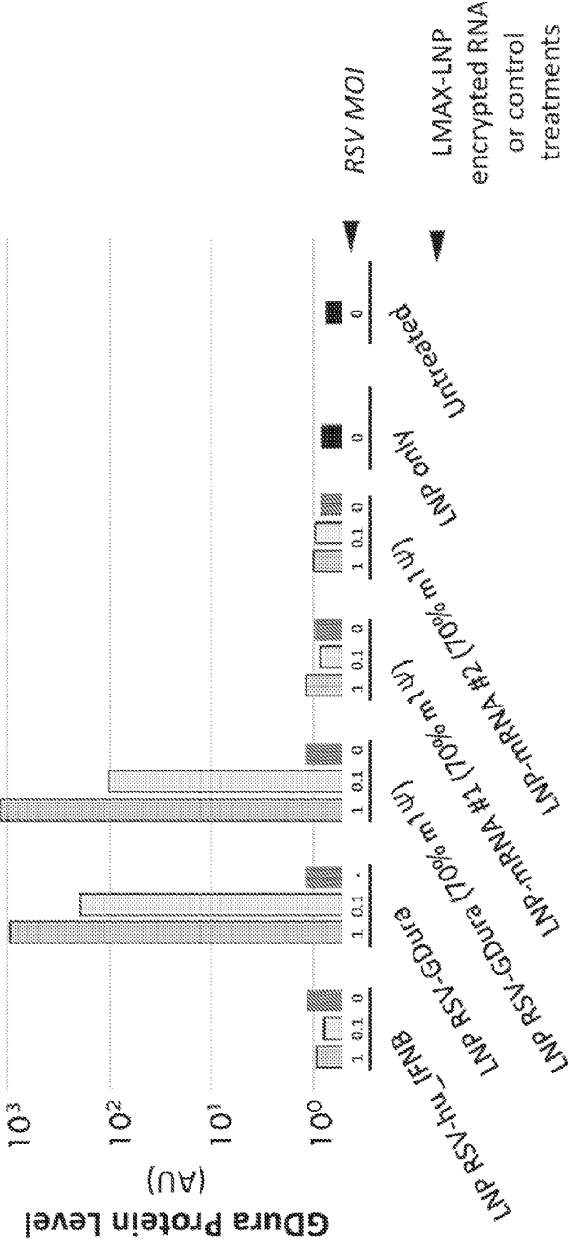


FIG. 39
Lipid-formulated RSV encrypted RNA can be activated days after dosing

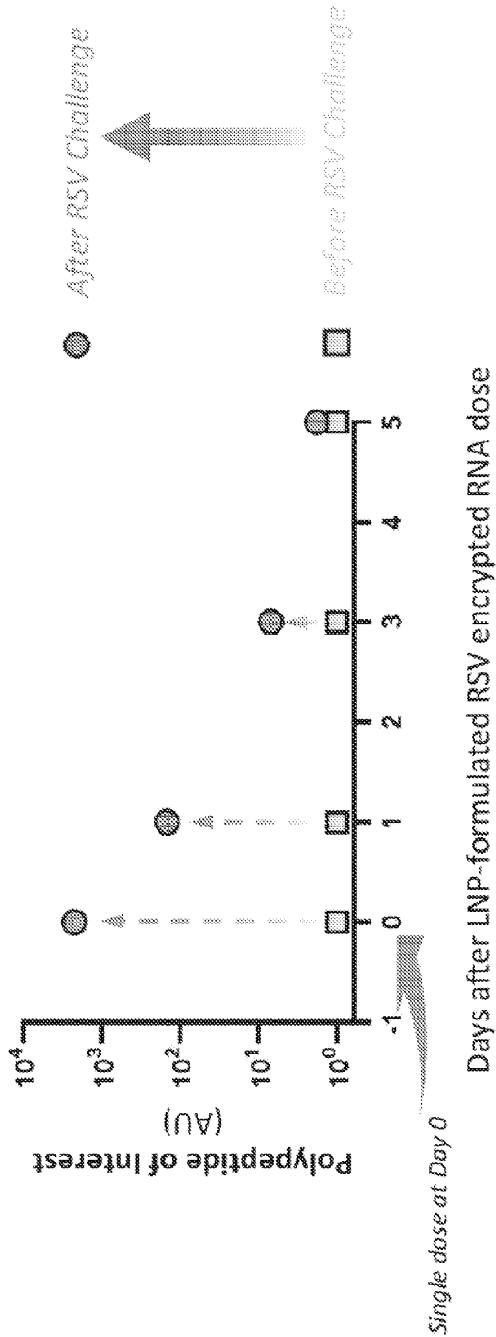


FIG. 40A

Activation with non-cognate TRS

Encrypted RNA: WT TRS (ERNA-SARS2-002-GDura)
Virus challenge: SARS2-GL

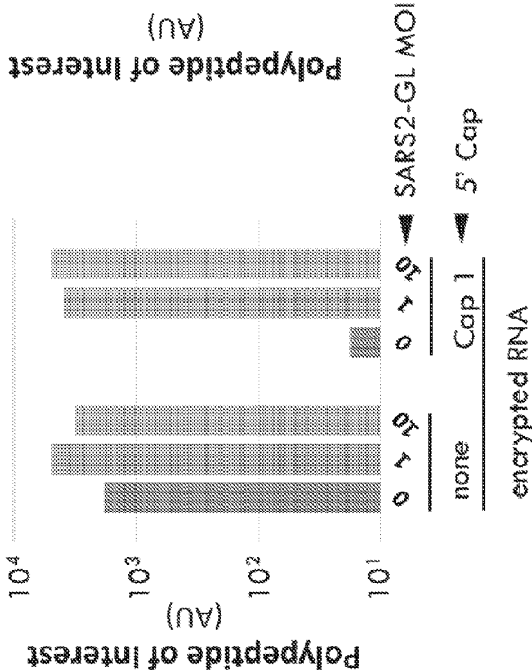


FIG. 40B

Activation with cognate SARS2-GL TRS

Encrypted RNA: SARS2-GL TRS (ERNA-SARS2-102-GDura)
Virus challenge: SARS2-GL

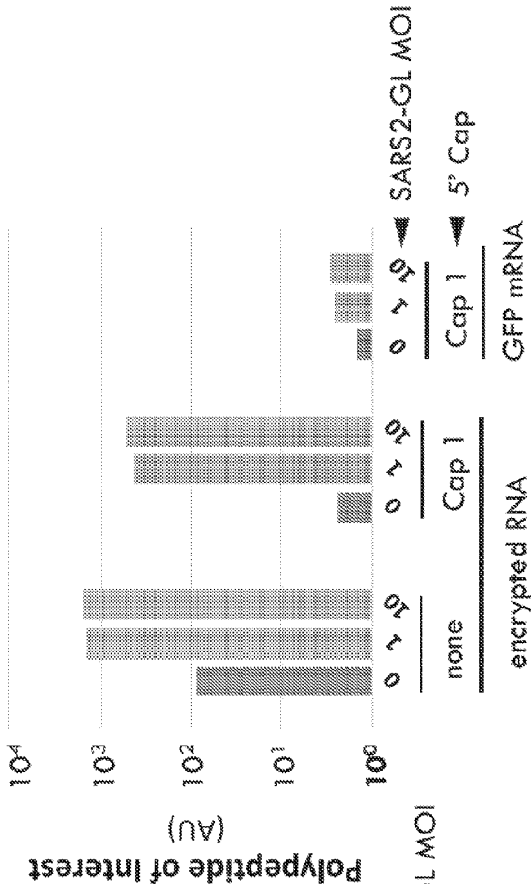


FIG. 41

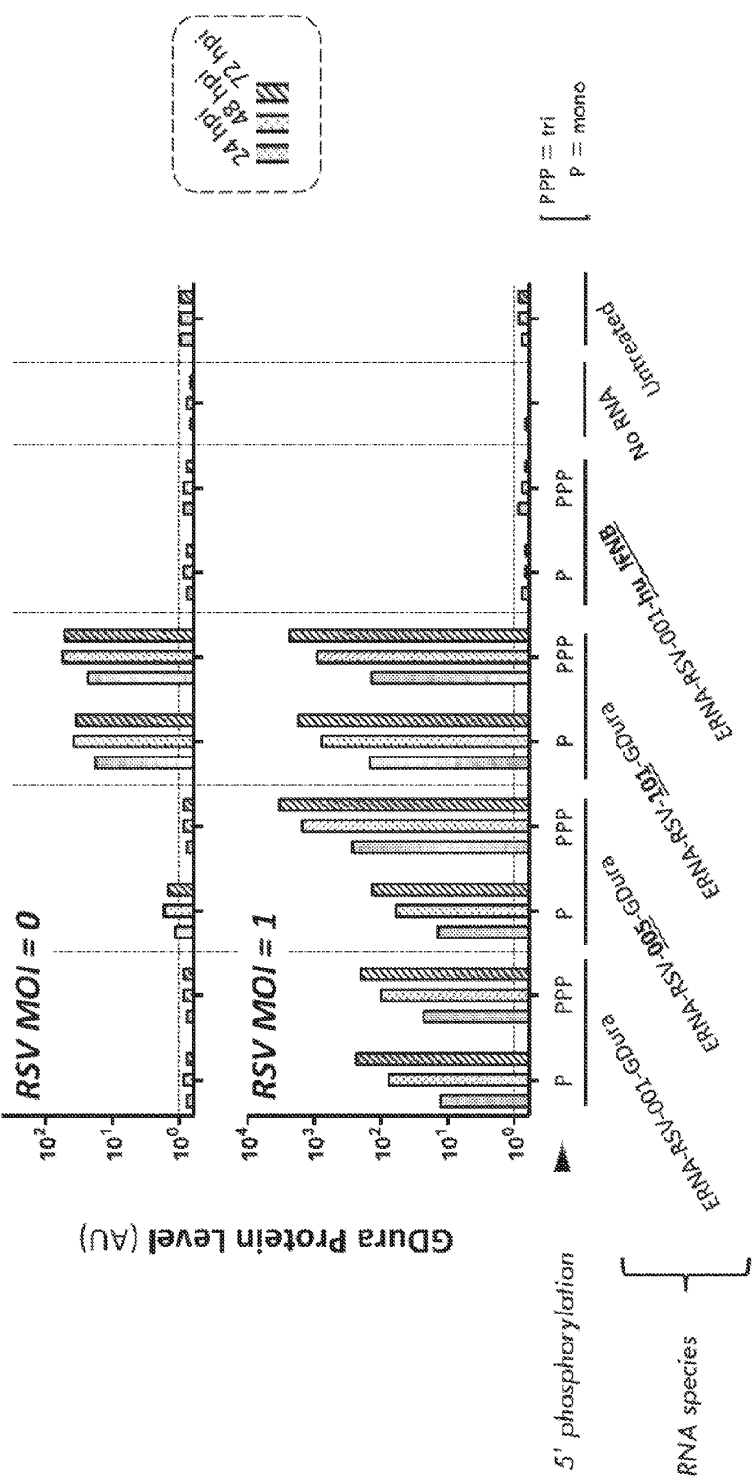


FIG. 42

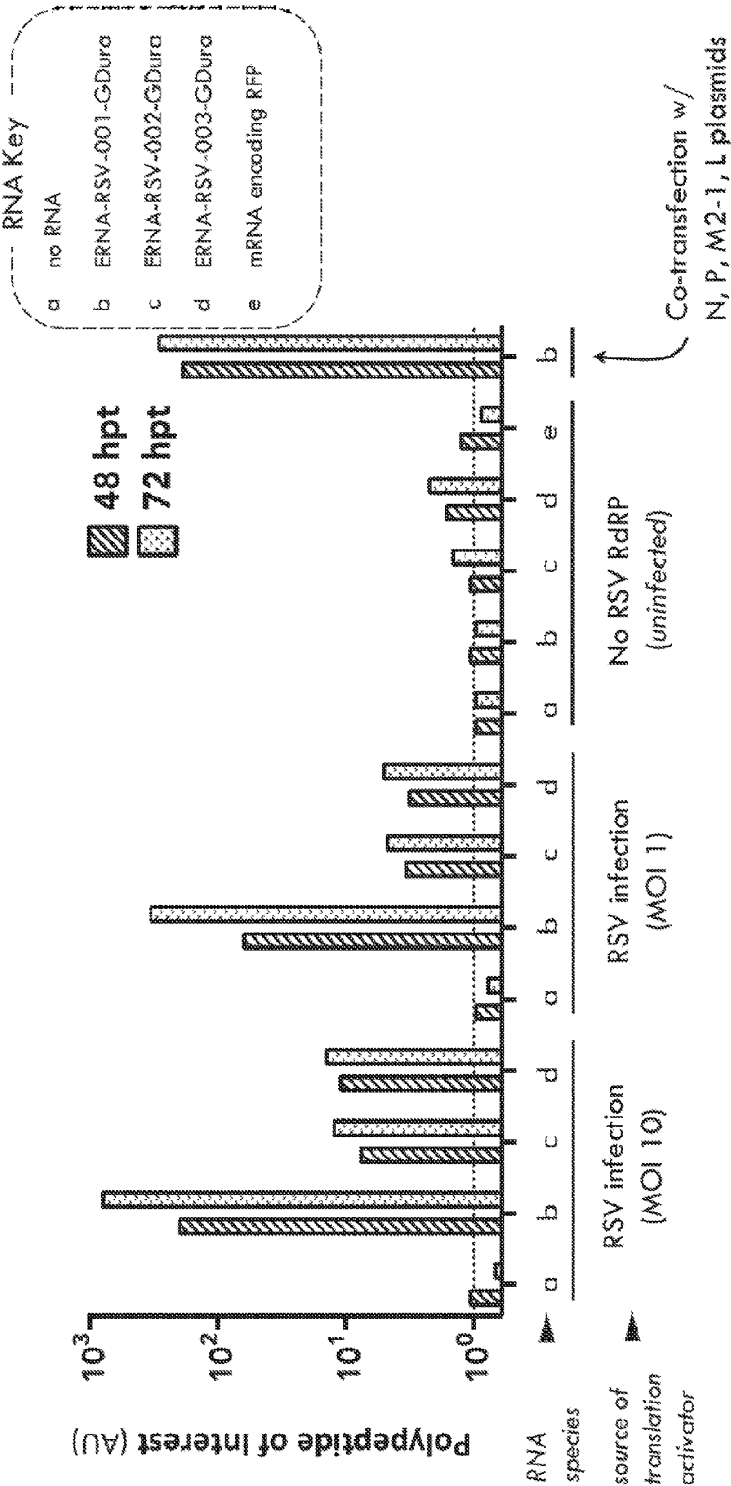


FIG. 43

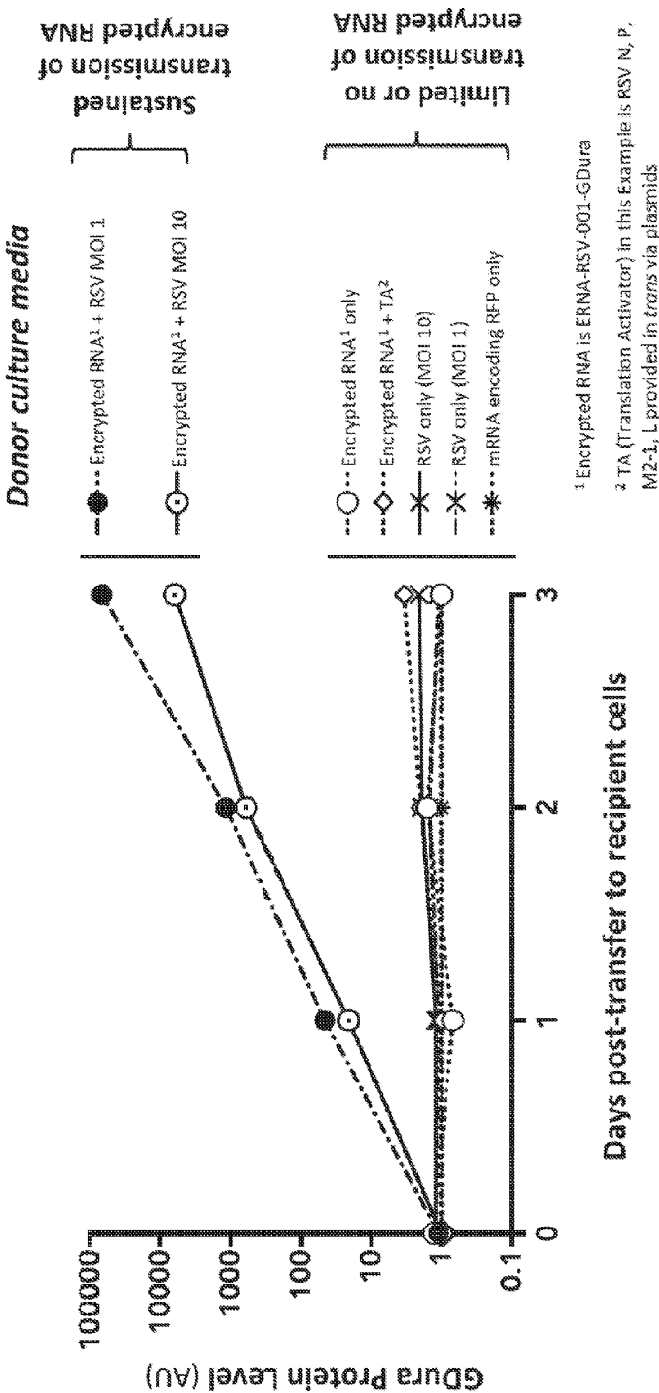


FIG. 44C

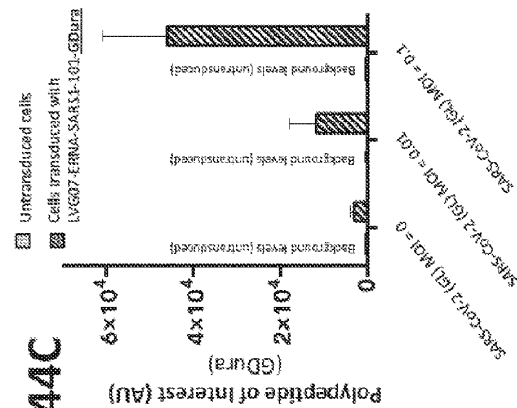


FIG. 44B

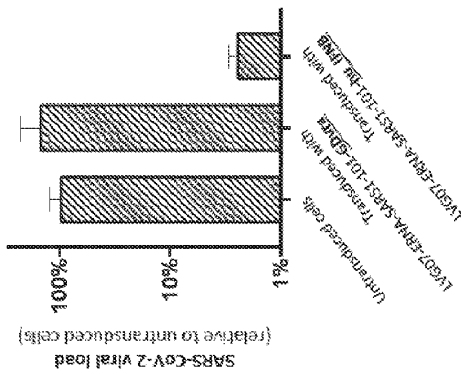


FIG. 44A

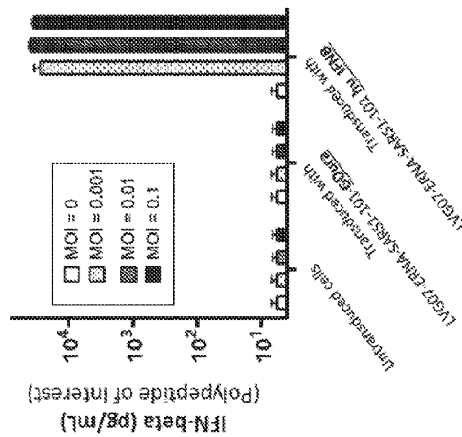


FIG. 45

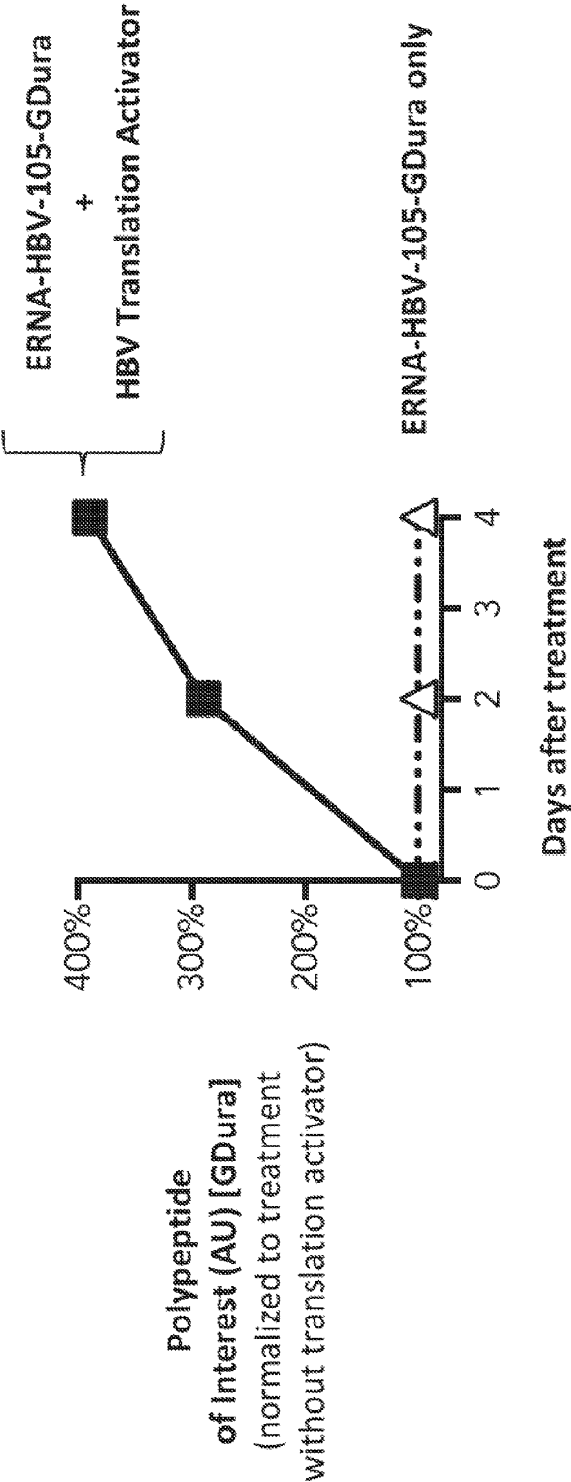
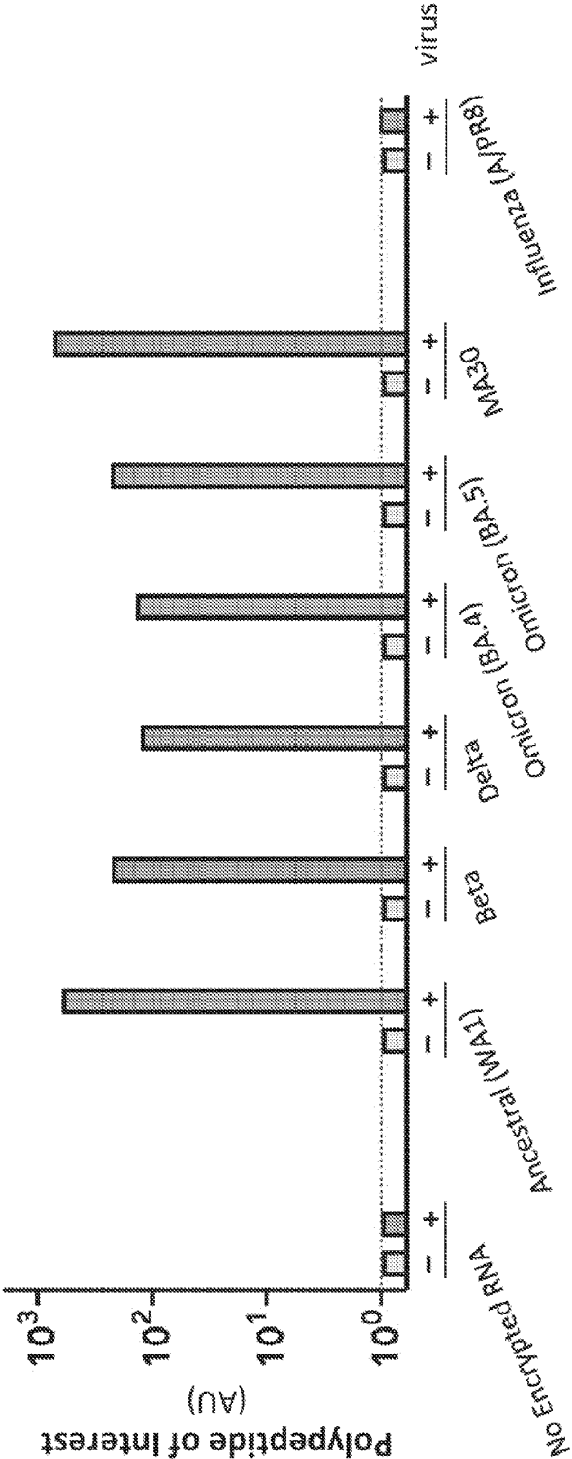


FIG. 46



LNP-formulated ERNA-SARS2-001-GDura ($\pm$ a SARS-CoV-2 or influenza variant)

WA1, Beta, Delta, BA.4, BA.5, and MA30 are variants of SARS-CoV-2

FIG. 47A

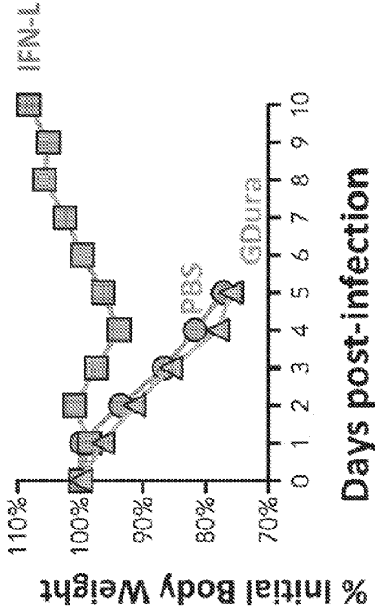
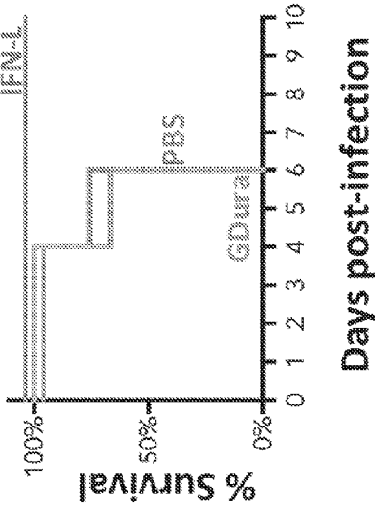


FIG. 47B



IFN-L : LNP-formulated capped ERNA-SARS2-001-m_IFN_lambda_2
GDura: LNP-formulated capped ERNA-SARS2-001-GDura
PBS: PBS + 5% sucrose (vehicle only)

FIG. 48A

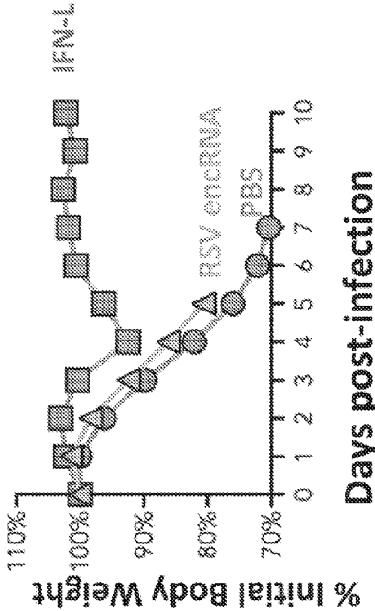


FIG. 48B



IFN-L : LNP-formulated capped ERNA-SARS2-001-m_IFN_lambda_2
RSV encRNA: LNP-formulated capped ERNA-RSV-005-m_IFN_lambda_2
PBS: PBS + 5% sucrose (vehicle only)

FIG. 49A

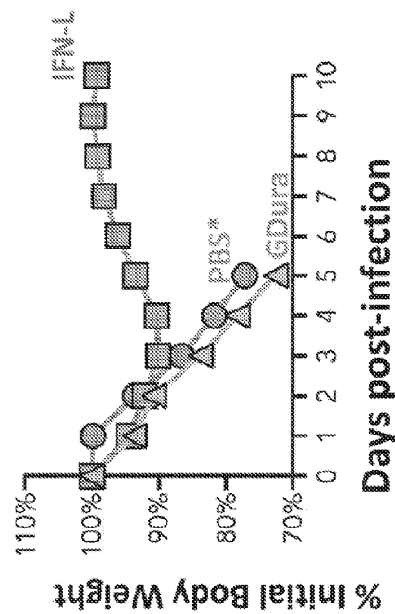
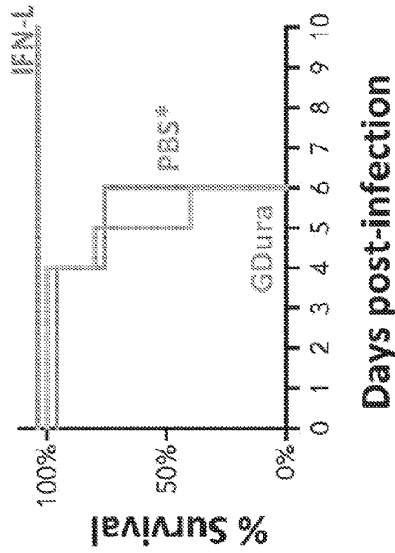


FIG. 49B



*shared control

IFN-L : LNP-formulated capped ERNA-SARS2-001-m_IFN_lambda_2

GDura: LNP-formulated capped ERNA-SARS2-001-GDura

PBS: PBS + 5% sucrose (vehicle only)

FIG. 50A

Encrypted RNA safety in hamsters

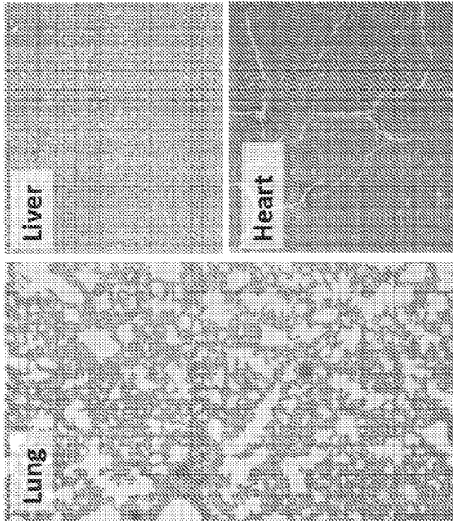
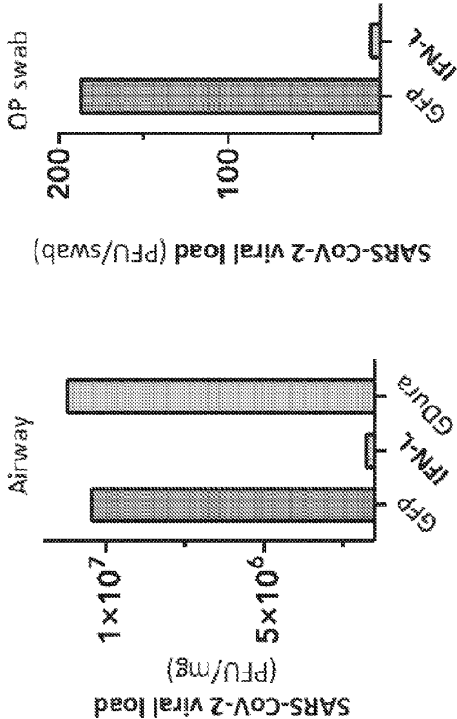


FIG. 50B

Encrypted RNA efficacy in hamsters



IFN-L: LNP-formulated capped ERNA-SARS2-001-hamster_1IFN_lambda_3
GDura: LNP-formulated capped ERNA-SARS2-001-GDura
GFP: LNP-formulated capped mRNA encoding a GFP

FIG. 51A

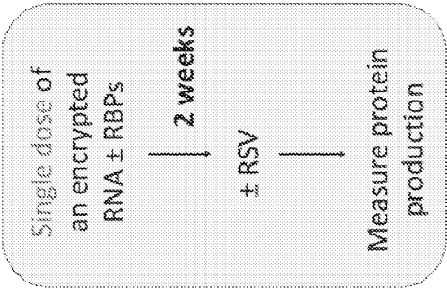


FIG. 51B

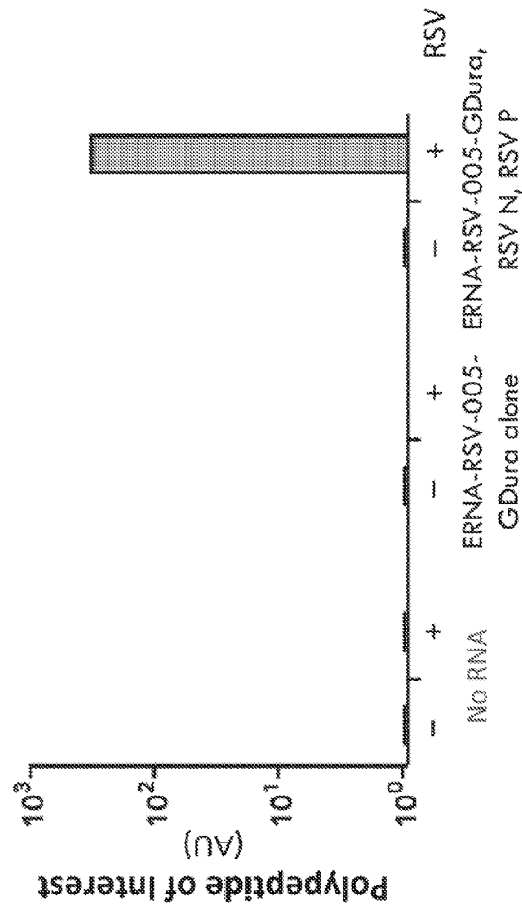


FIG. 52

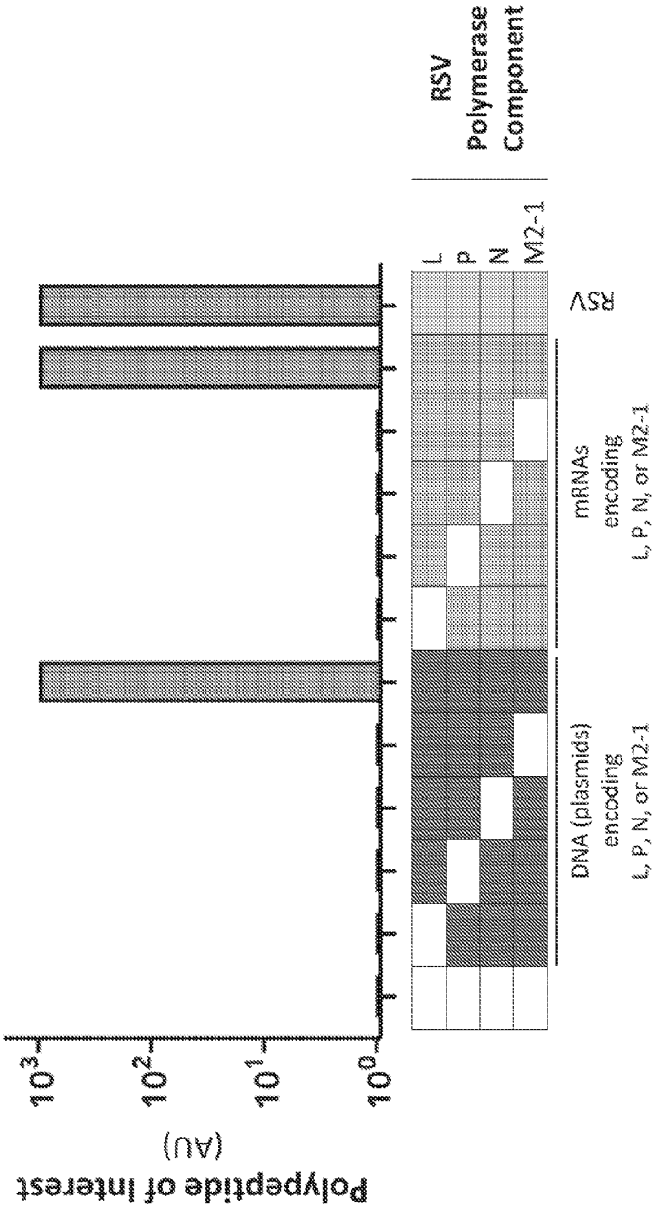
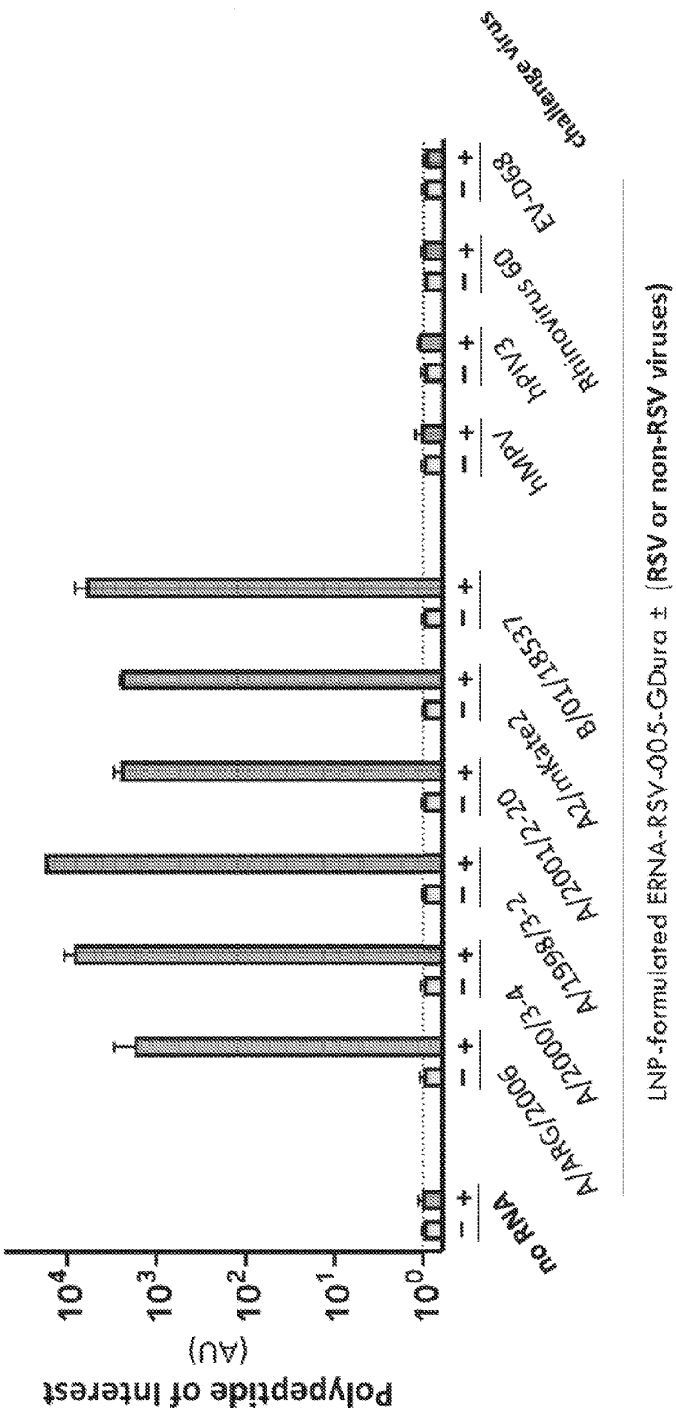


FIG. 53



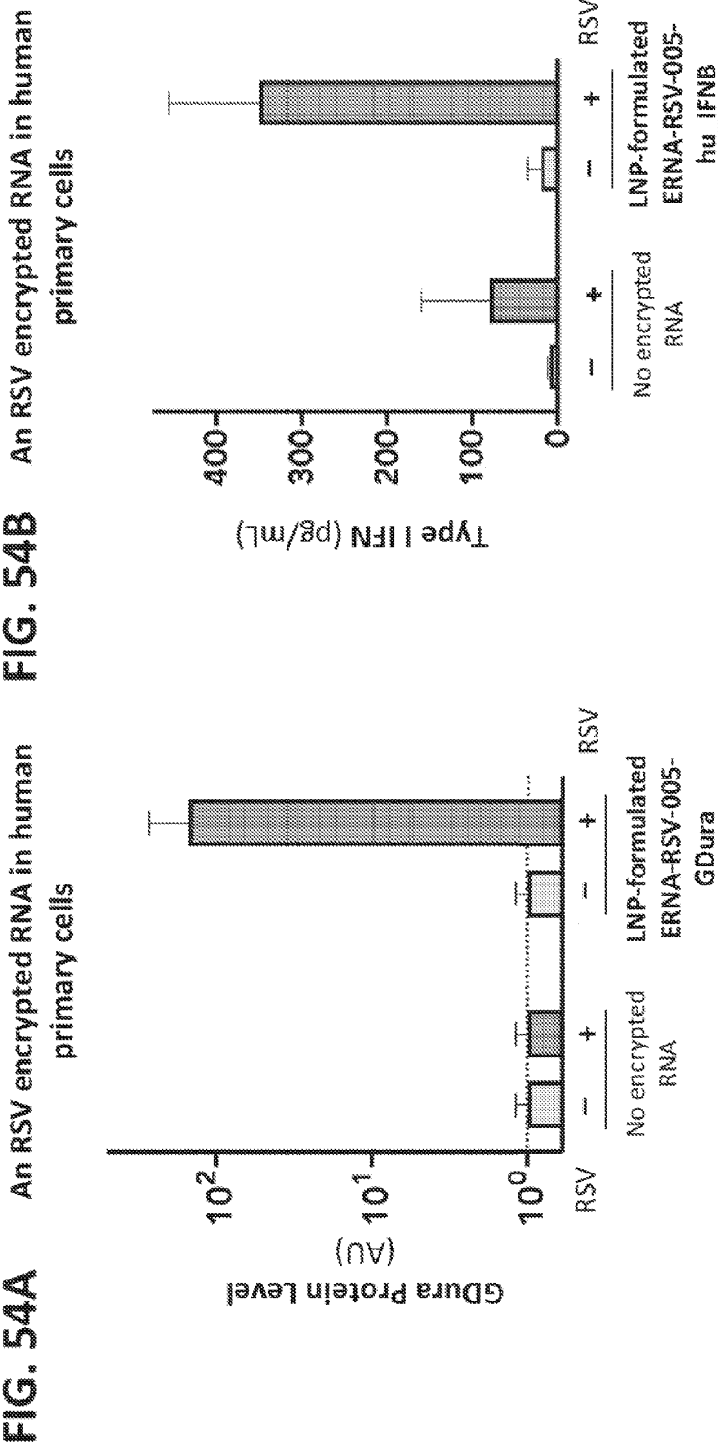


FIG. 55A Encrypted Protein Production

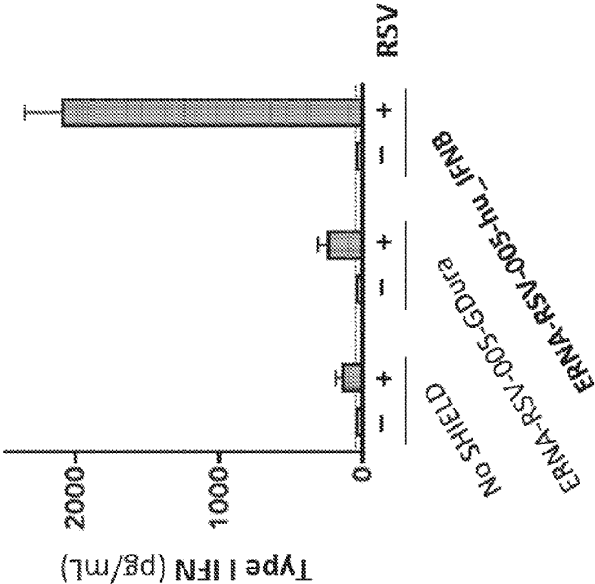


FIG. 55B Antiviral efficacy does not require 5' ppp

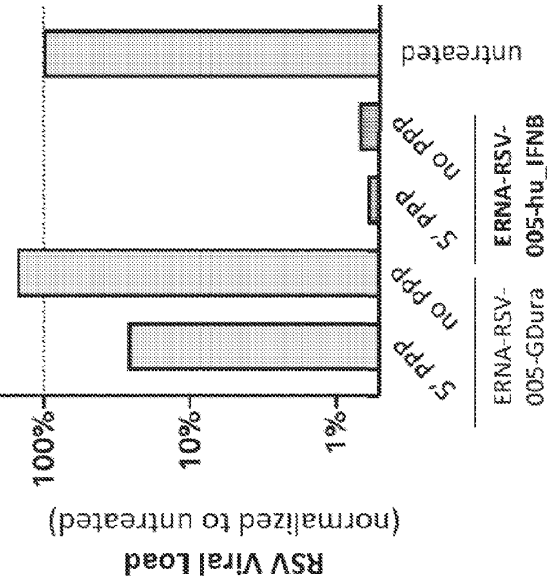


FIG. 56A

A sarbecovirus encrypted RNA
Same scaffold: multiple proteins

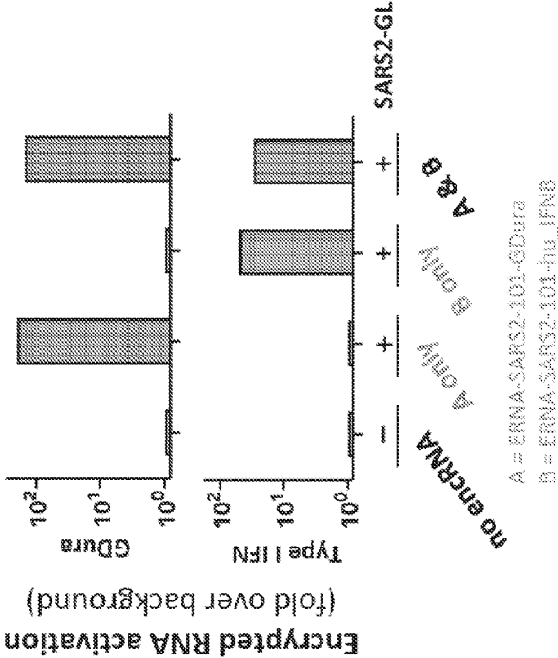
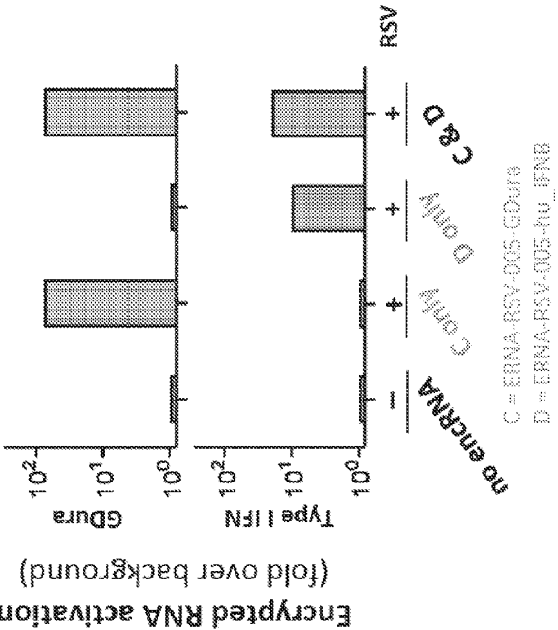


FIG. 56B

An RSV encrypted RNA
Same scaffold: multiple proteins



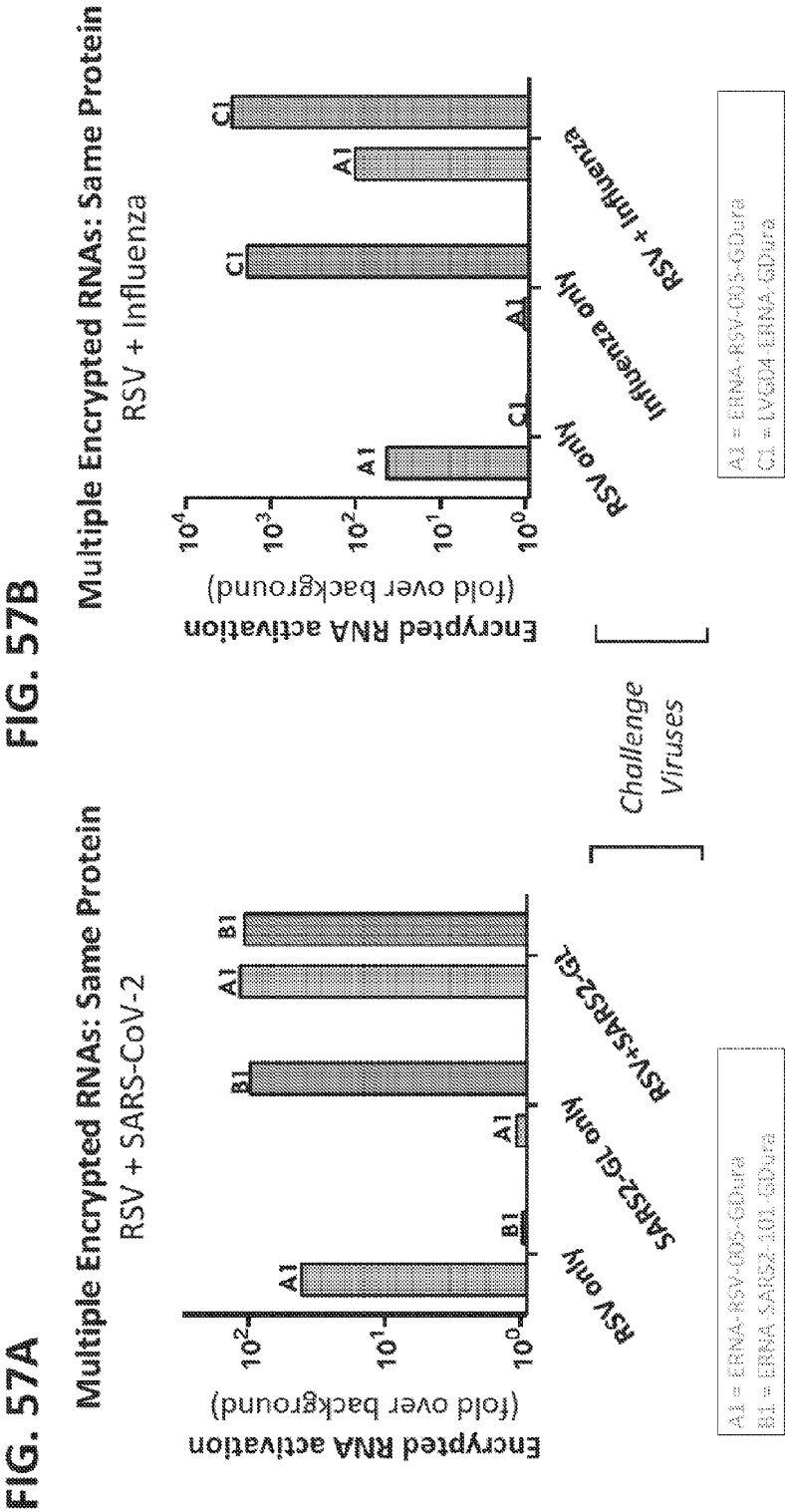


FIG. 58A

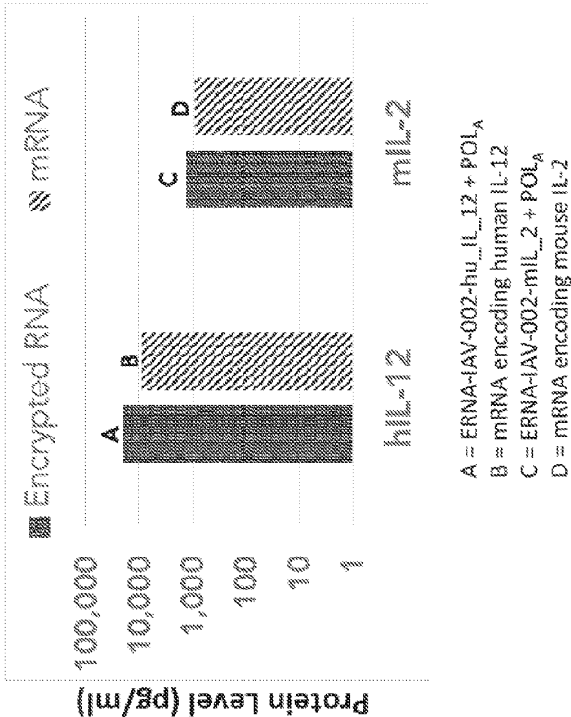


FIG. 58B

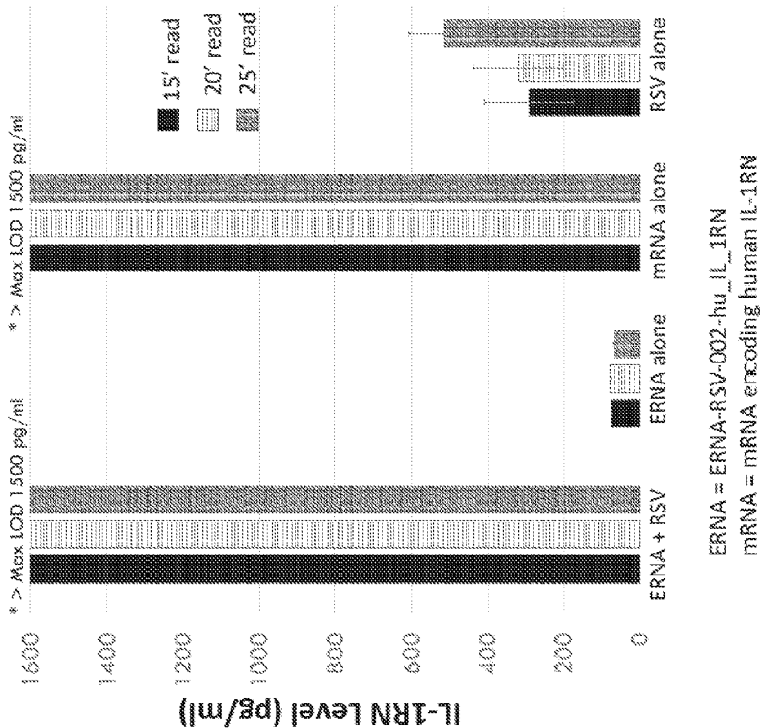


FIG. 59

A sarbecovirus encrypted RNA with modified nucleotides can be substantially activated by SARS-CoV-2

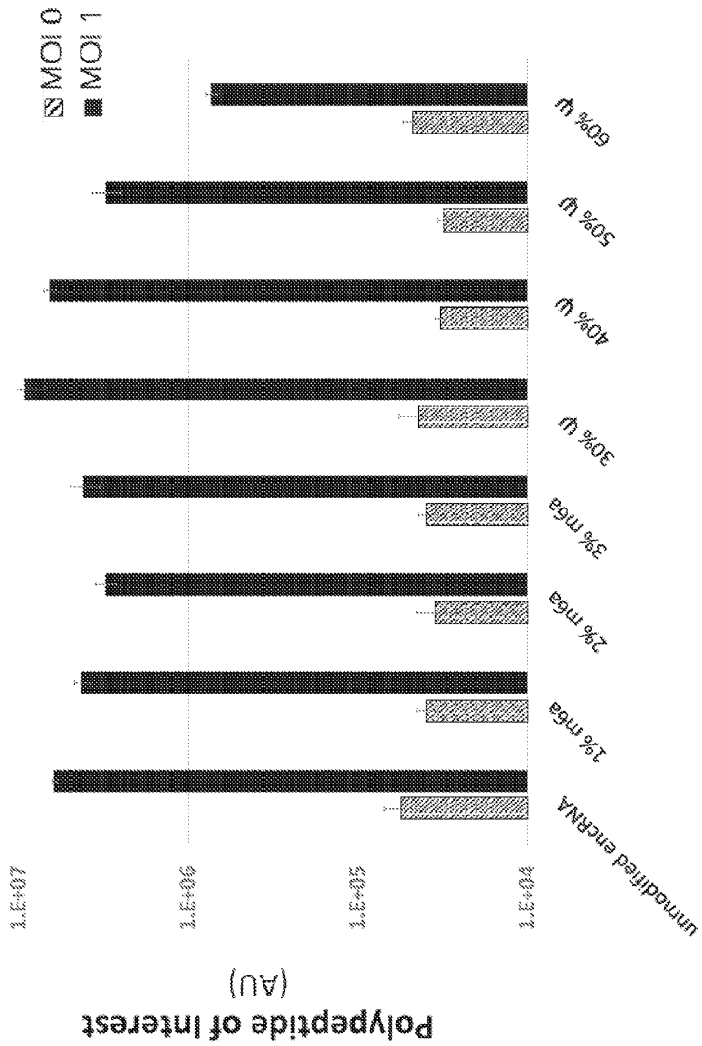


FIG. 60

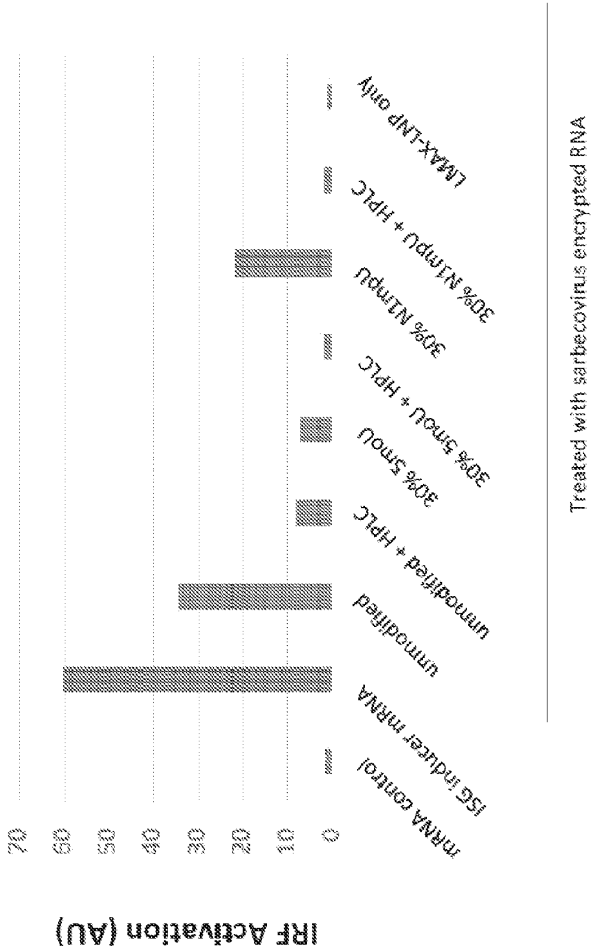


FIG. 61

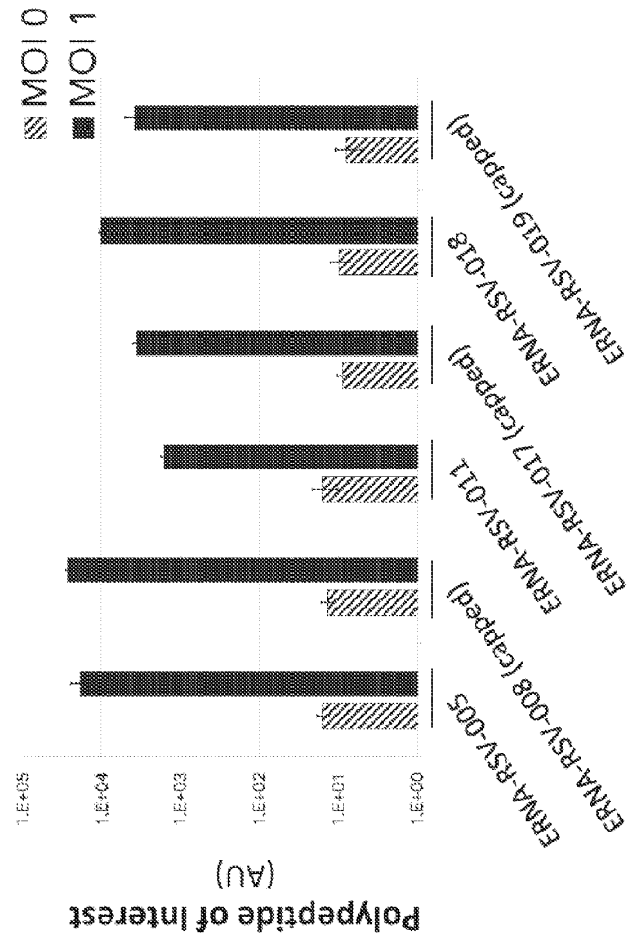


FIG. 62

An RSV encrypted RNA with modified nucleotides
can be substantially activated by RSV

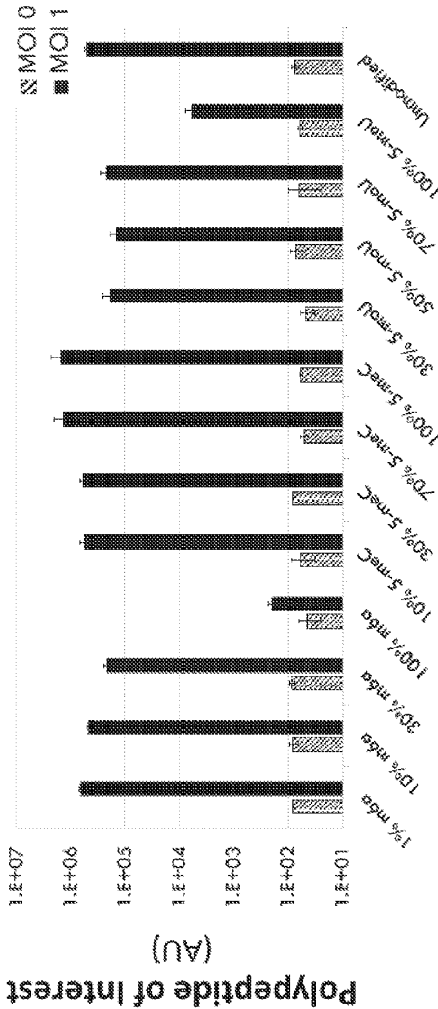


FIG. 63

An RSV encrypted RNA with modified nucleotides
can be substantially activated by RSV

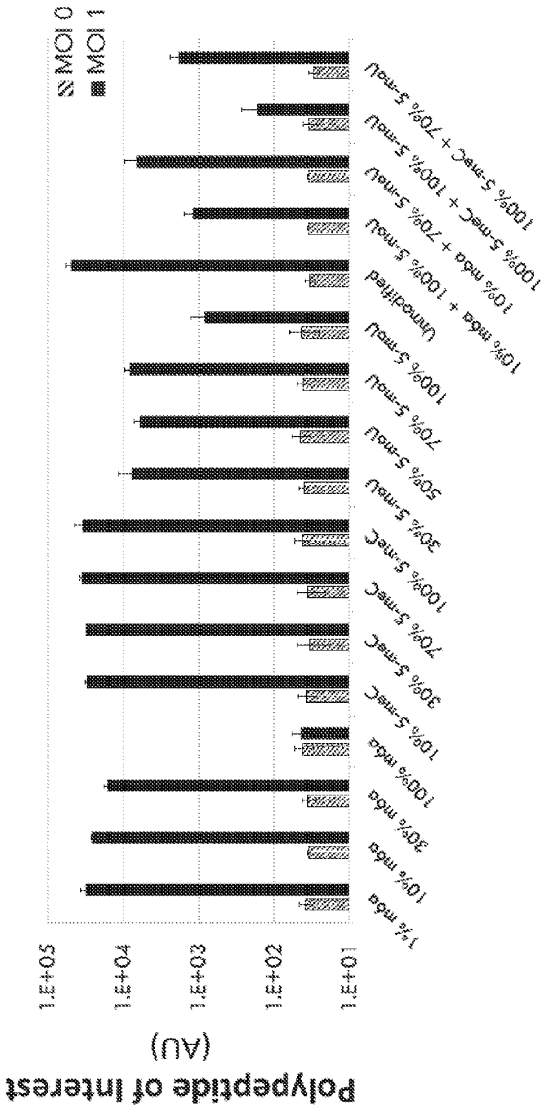


FIG. 64

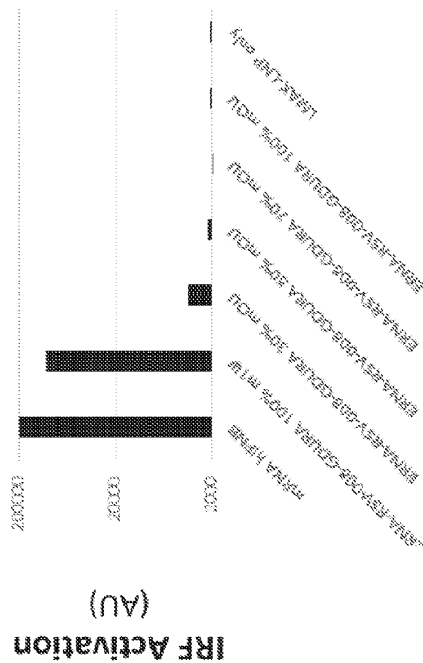


FIG. 65

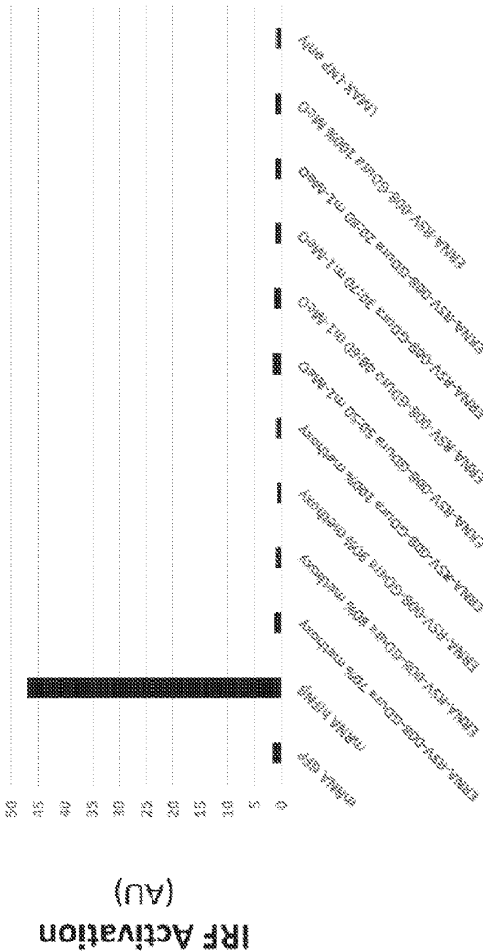


FIG. 66

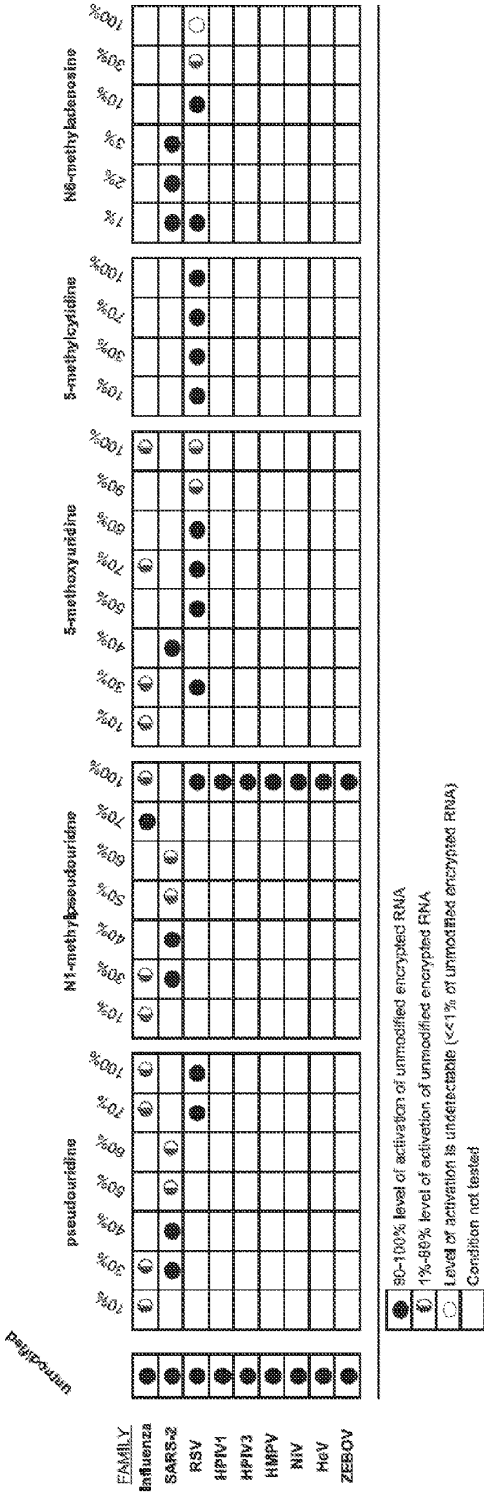


FIG. 67

Relative
Activation Level
(Normalized to
Prep 1 (nonmodified))

Preparation	A-modification	C-modification	G-modification	U-modification	
1					100%
2	N6mA (10%)			mo5U (100%)	65%
3	N6mA (10%)			mo5U (70%)	90%
4		m5c (100%)		mo5U (100%)	20%
5		m5c (100%)		mo5U (70%)	70%
6				N1mpU (50%) & mo5U (50%)	100%
7				N1mpU (60%) & mo5U (40%)	60%
8				N1mpU (70%) & mo5U (30%)	50%
9				N1mpU (80%) & mo5U (20%)	50%

Test Scaffold: ERNA-RSV-008

N6mA: N6-methyladenosine; N1mpU: N1-methylpseudouridine; m5c: 5-methylcytidine; mo5U: 5-methoxyuridine