

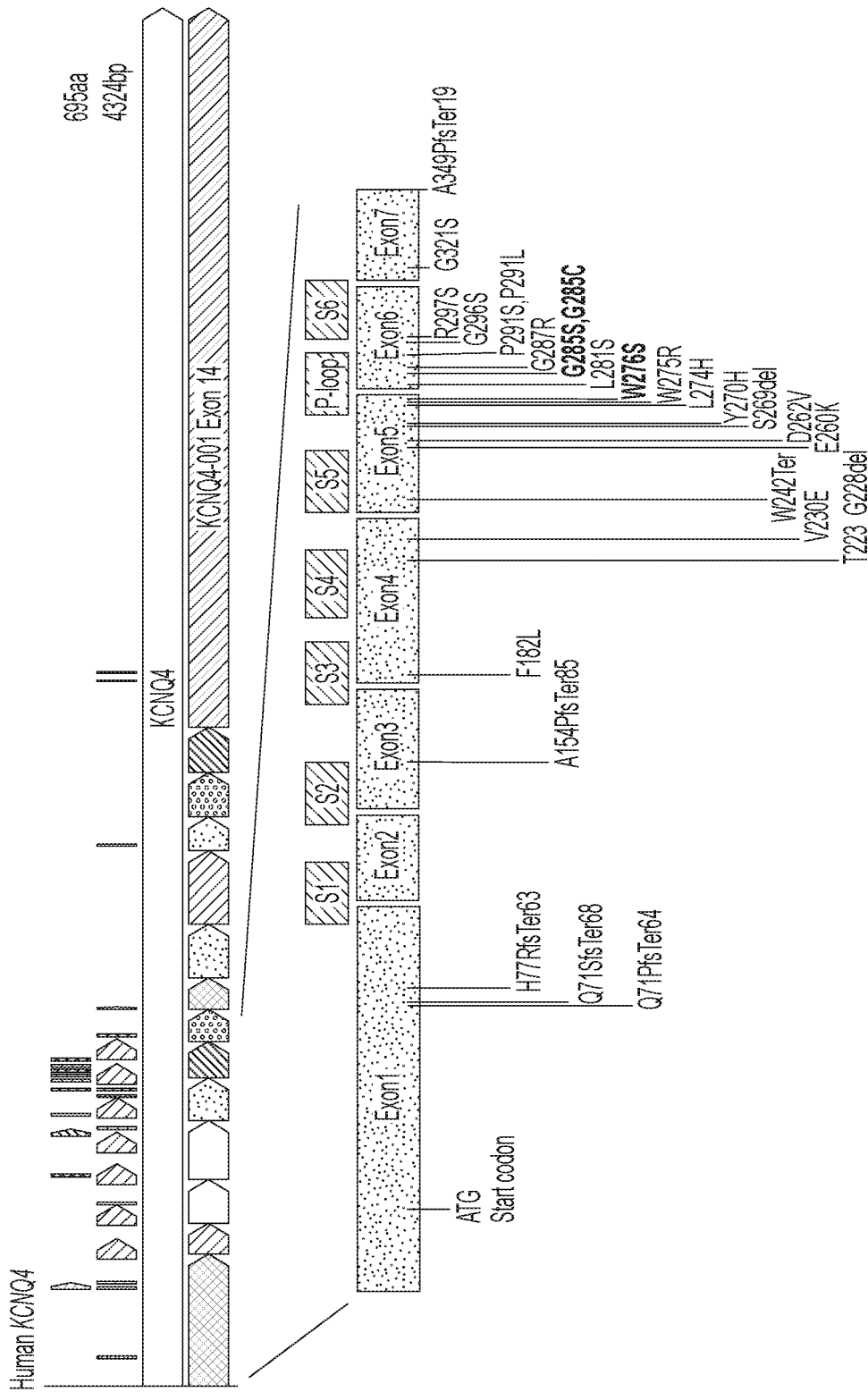


FIG. 1

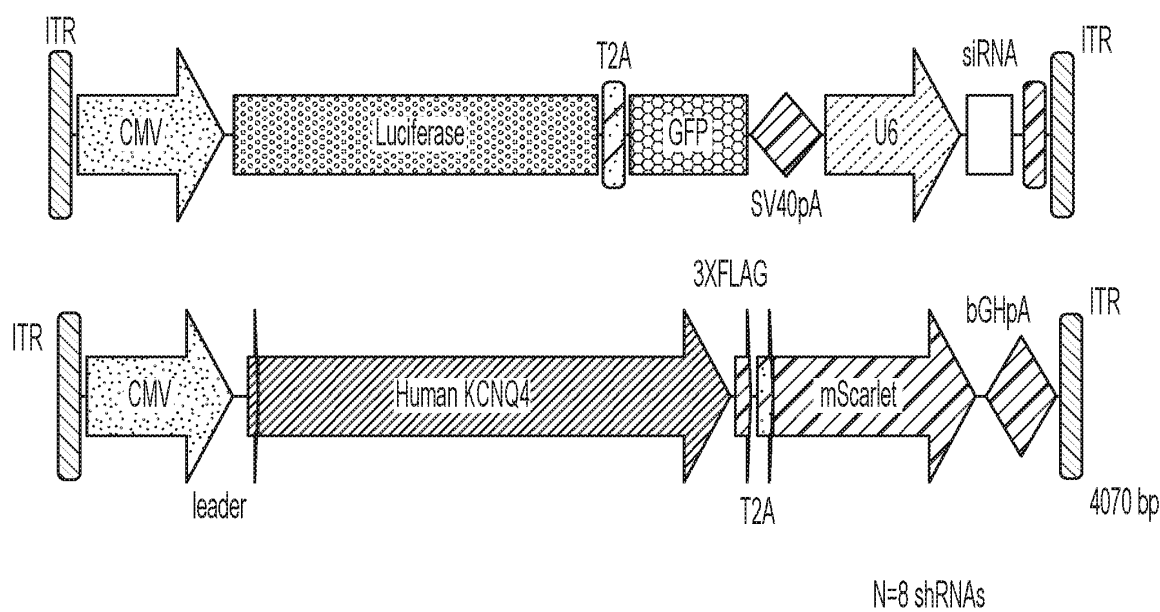


FIG. 2

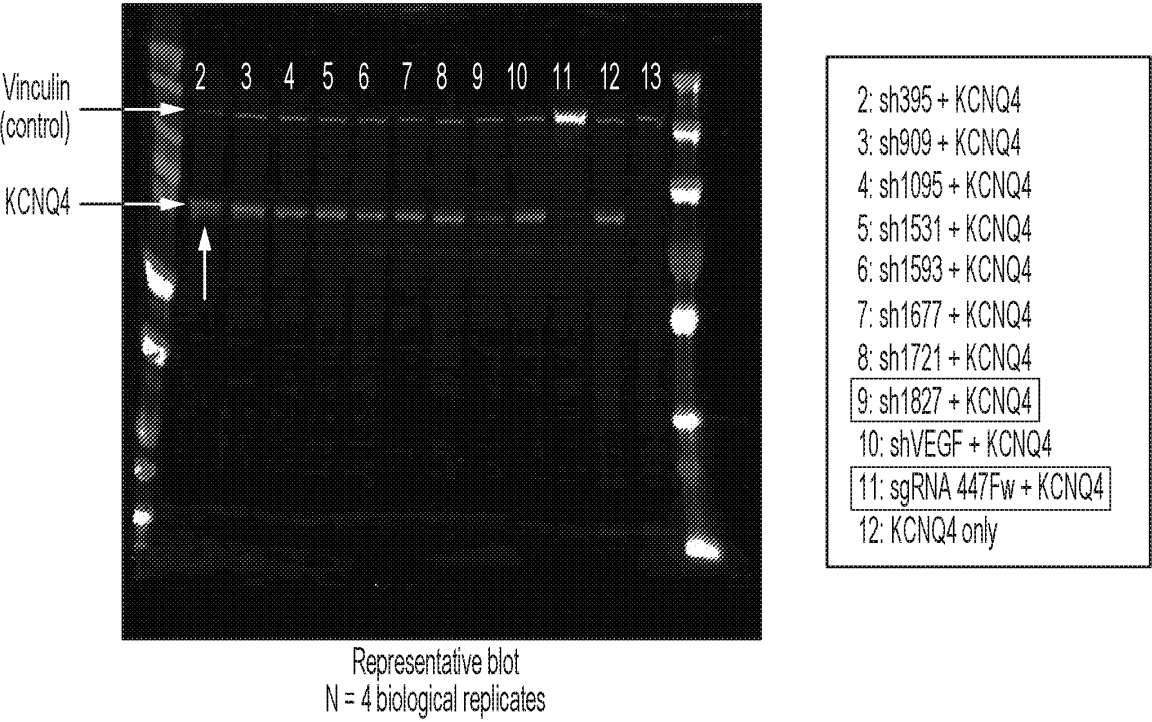


FIG. 3

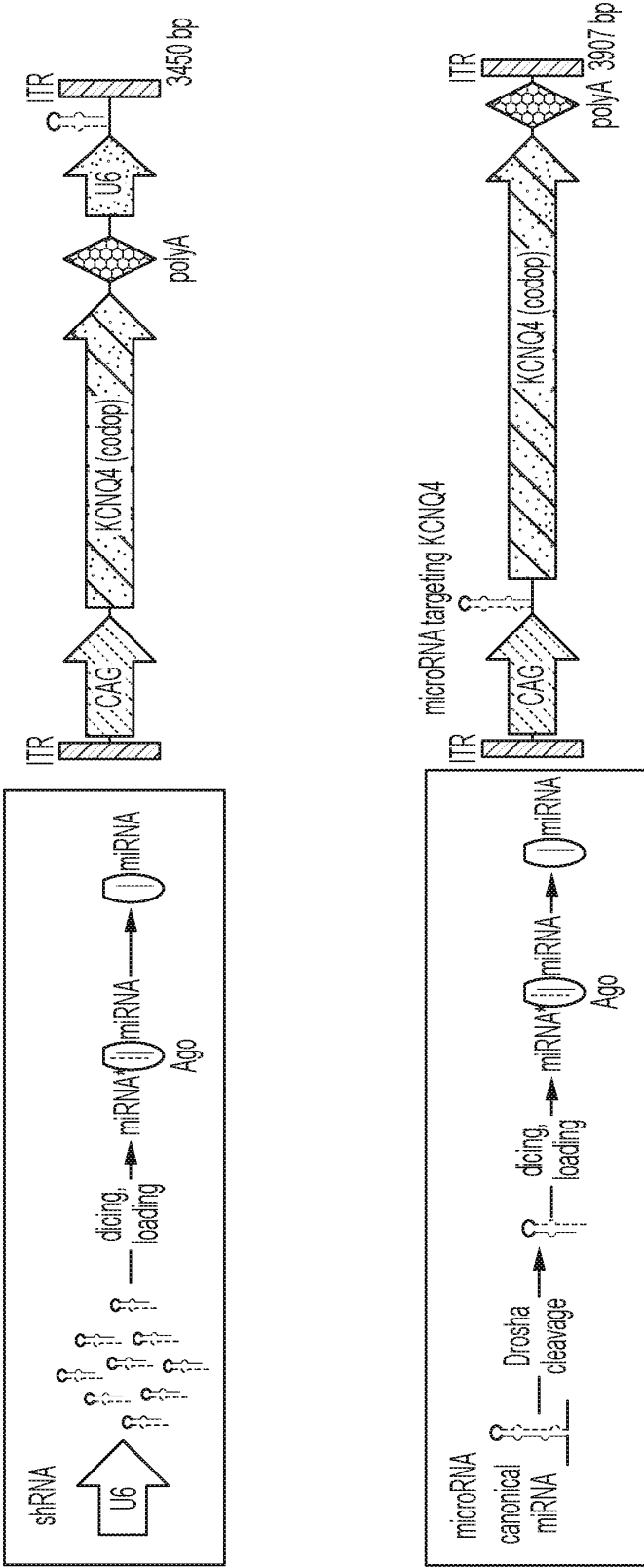


FIG. 4

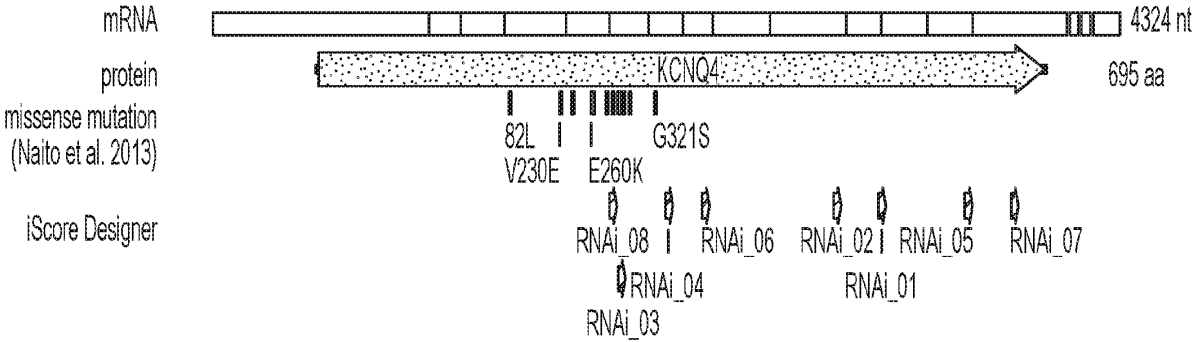


FIG. 5

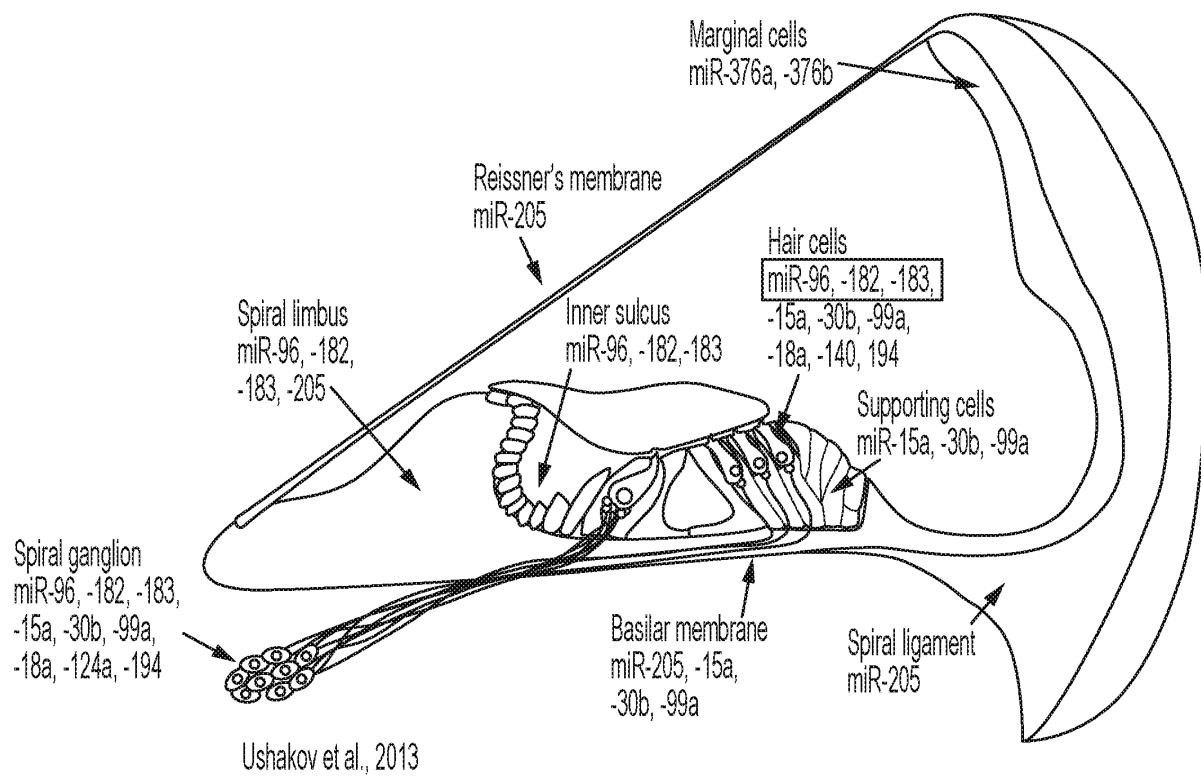


FIG. 6

6 KCNQ4 targeting sequences
9 microRNA scaffolds

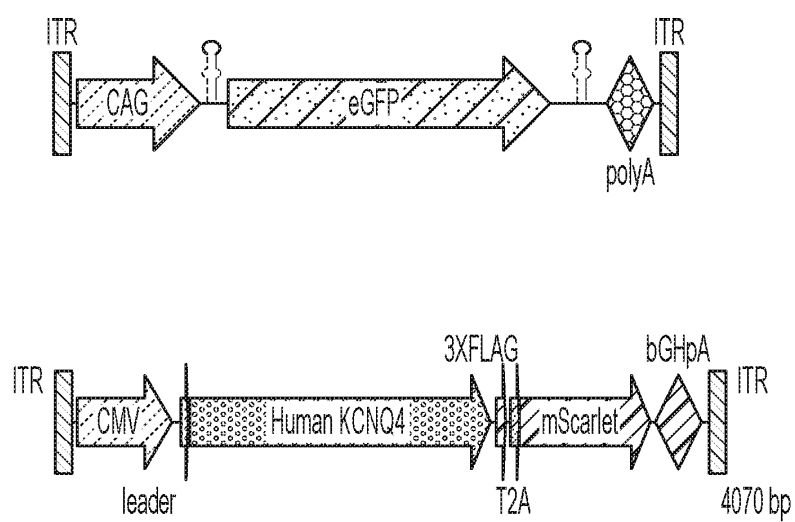


FIG. 7

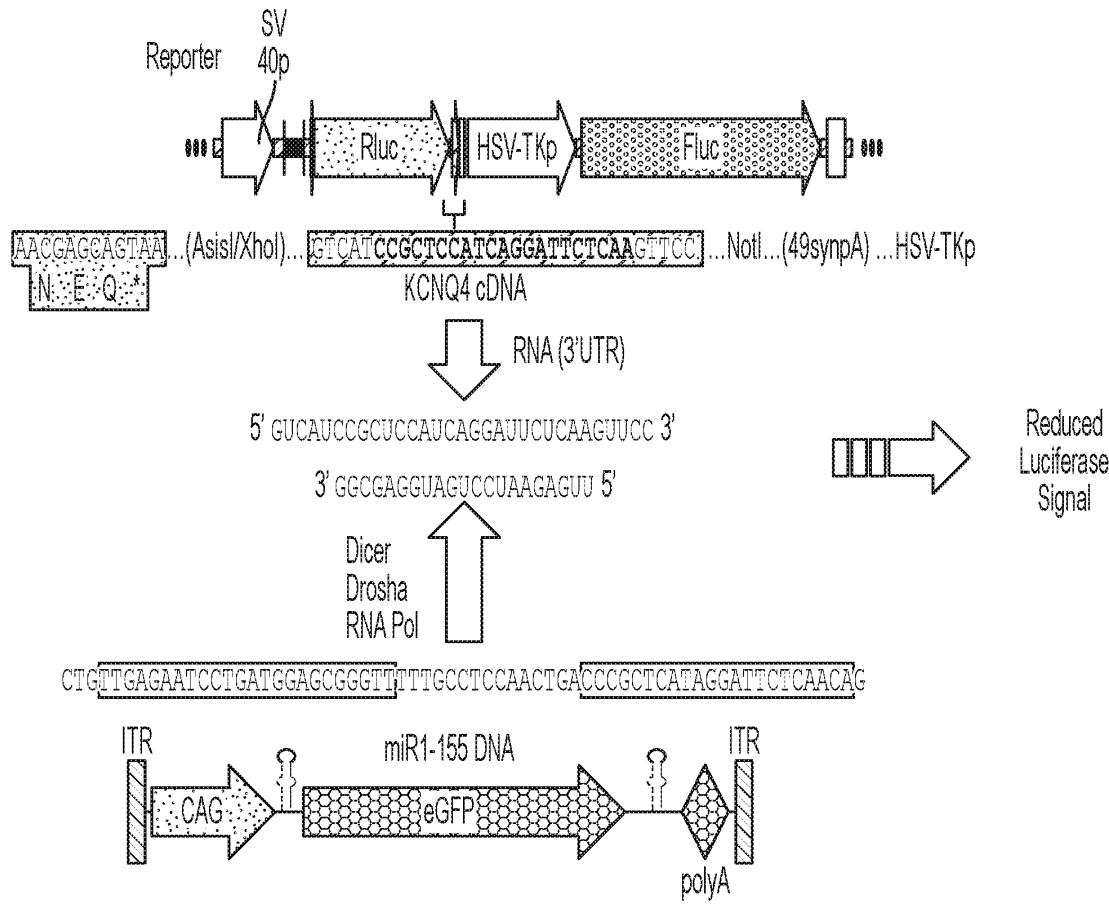


FIG.8

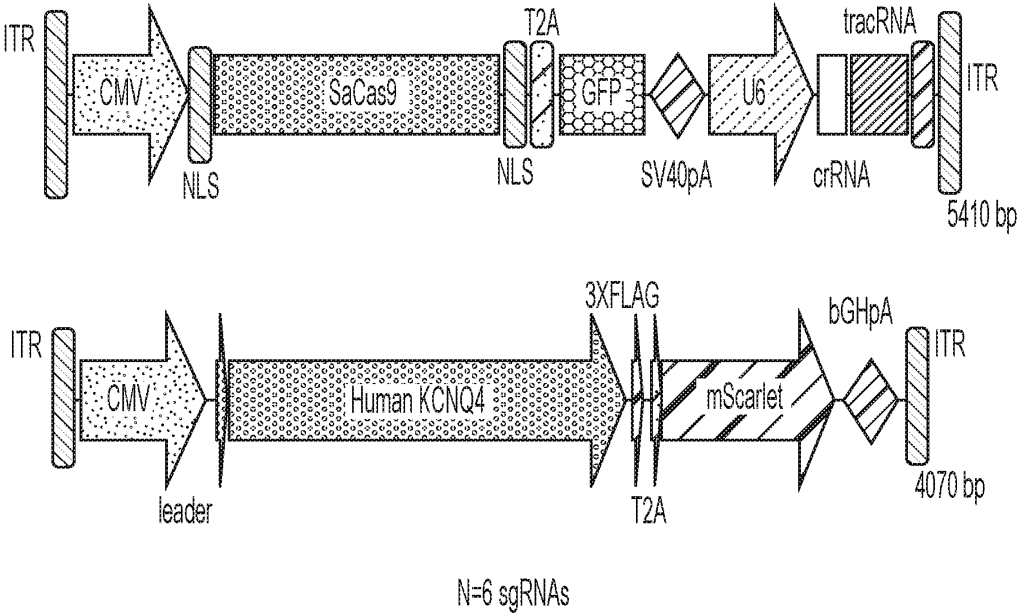


FIG. 9

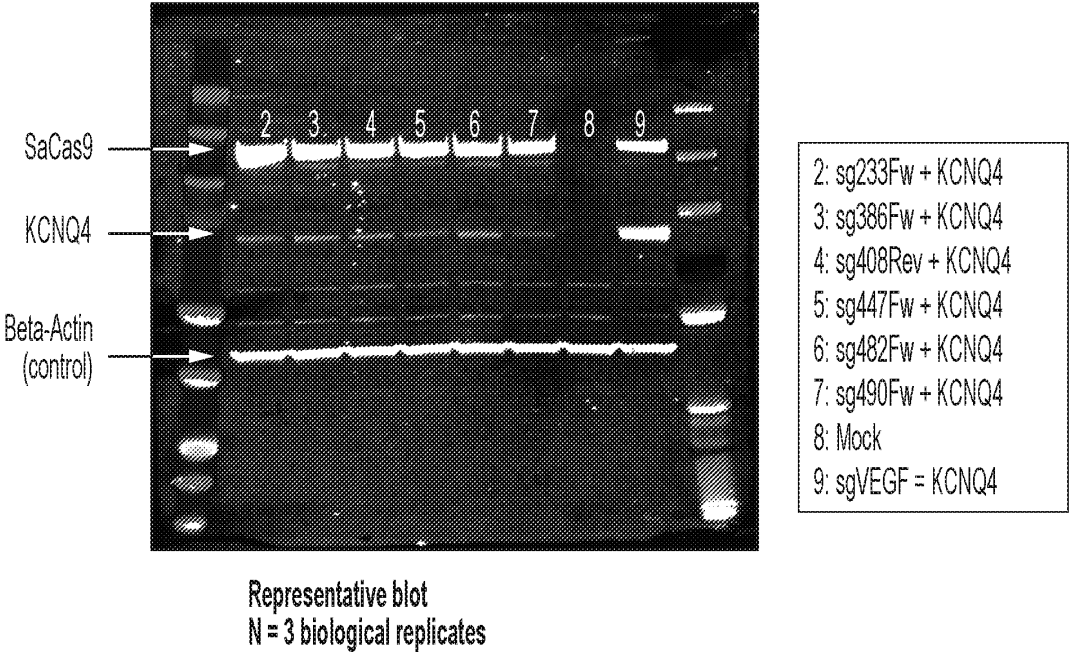


FIG. 10

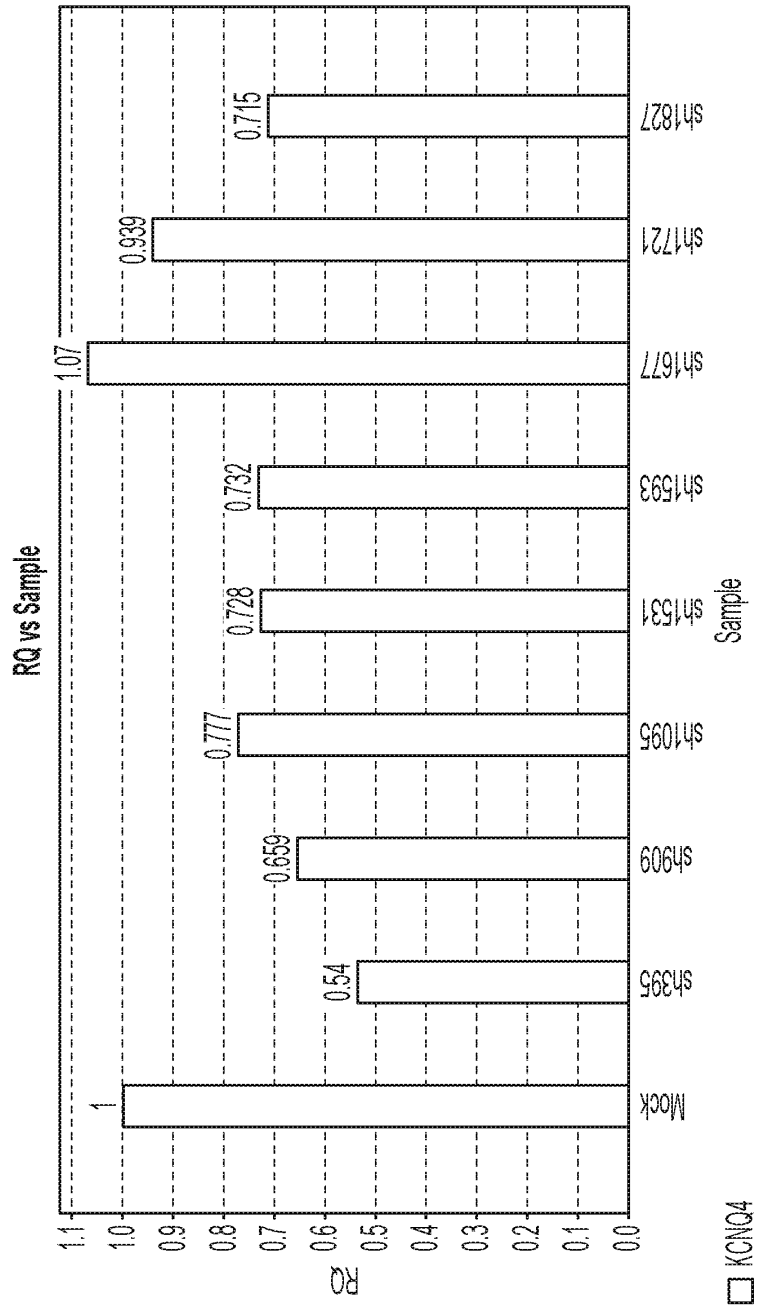


FIG. 11

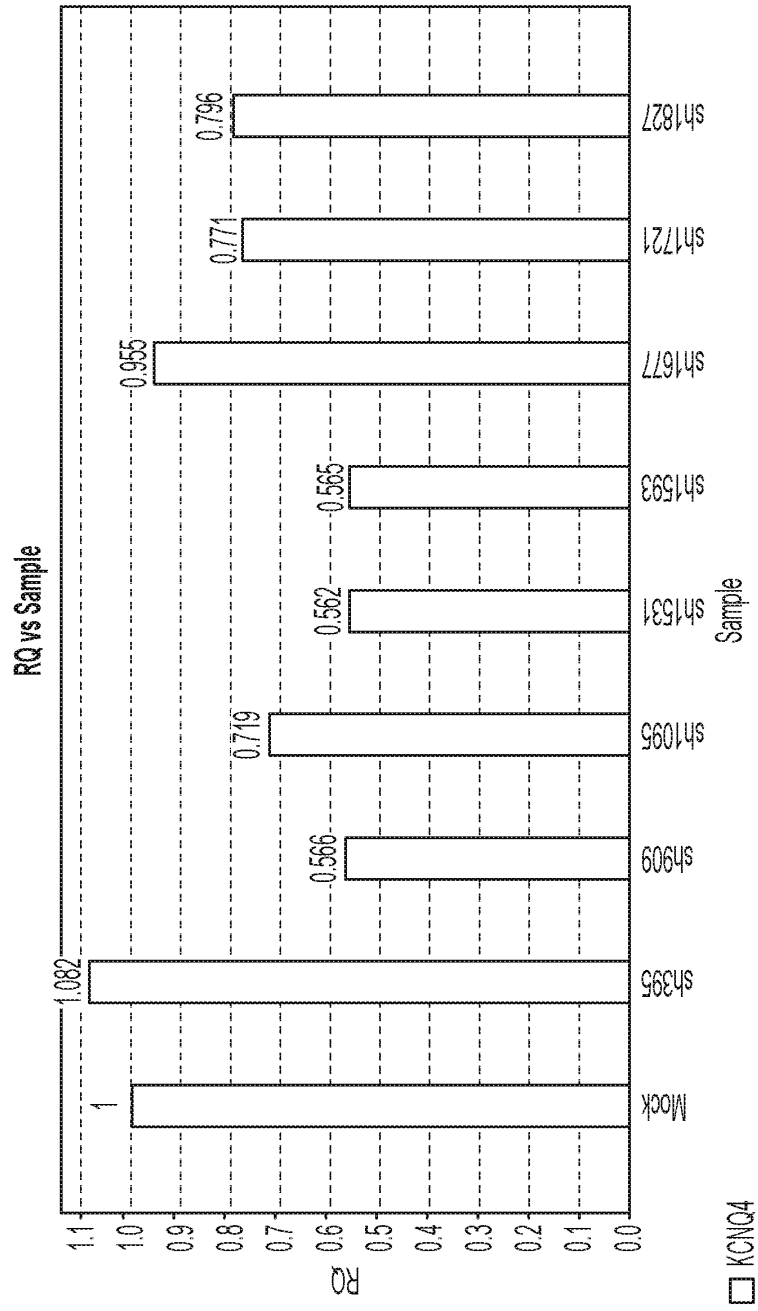


FIG. 12

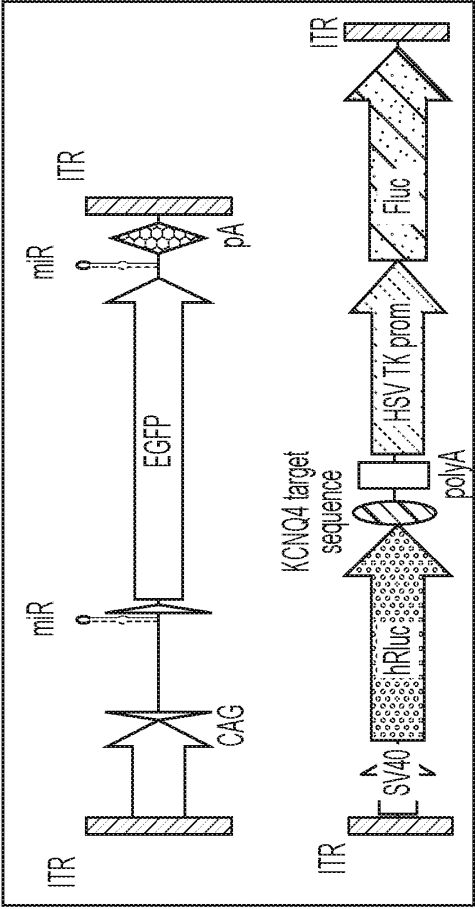
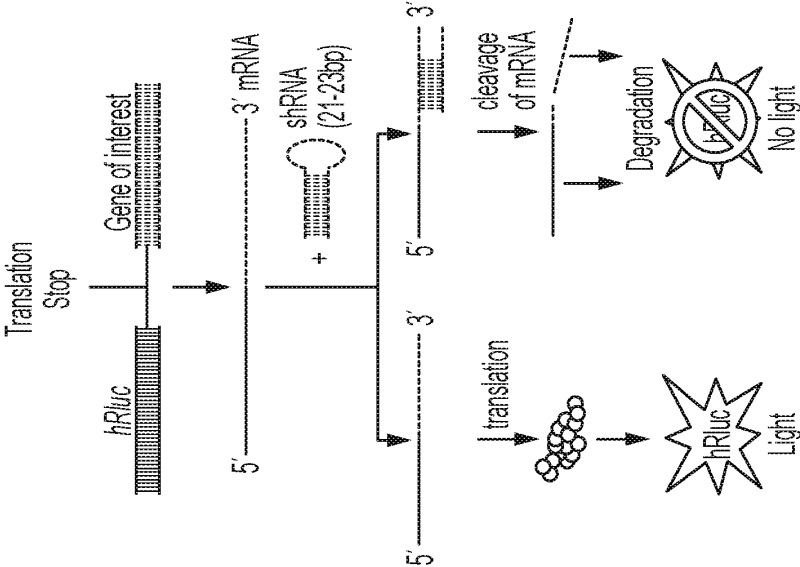


FIG. 13

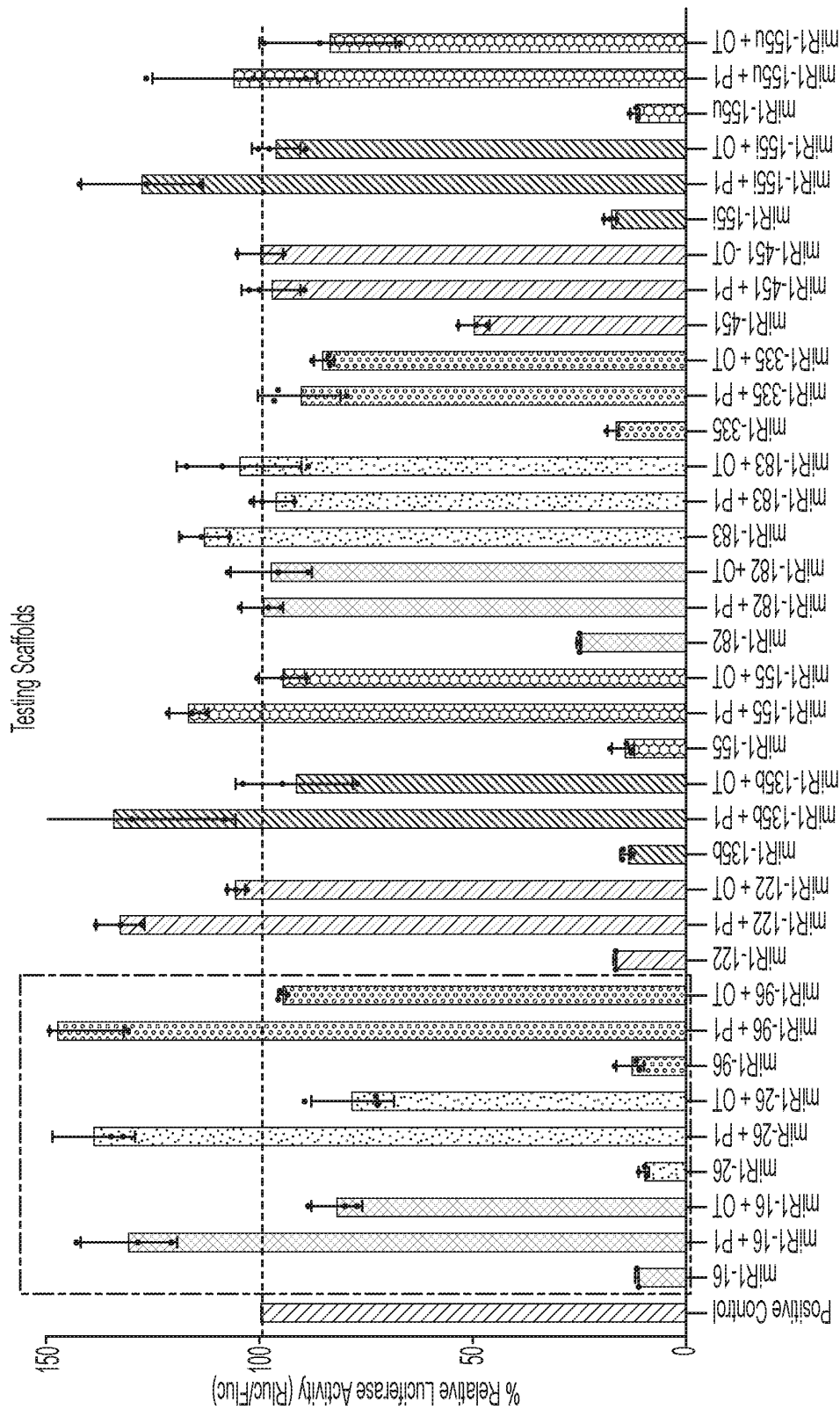
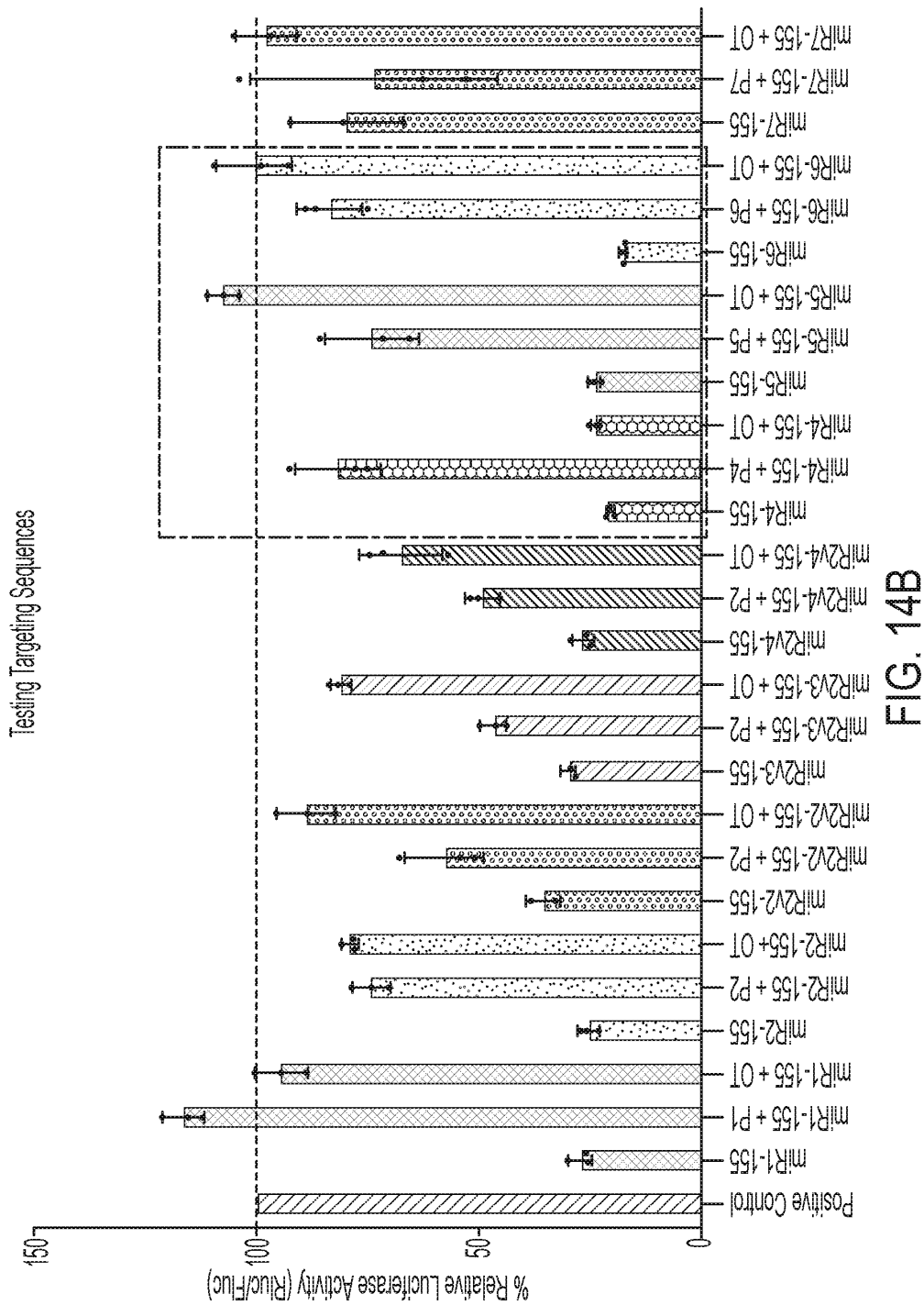


FIG. 14A



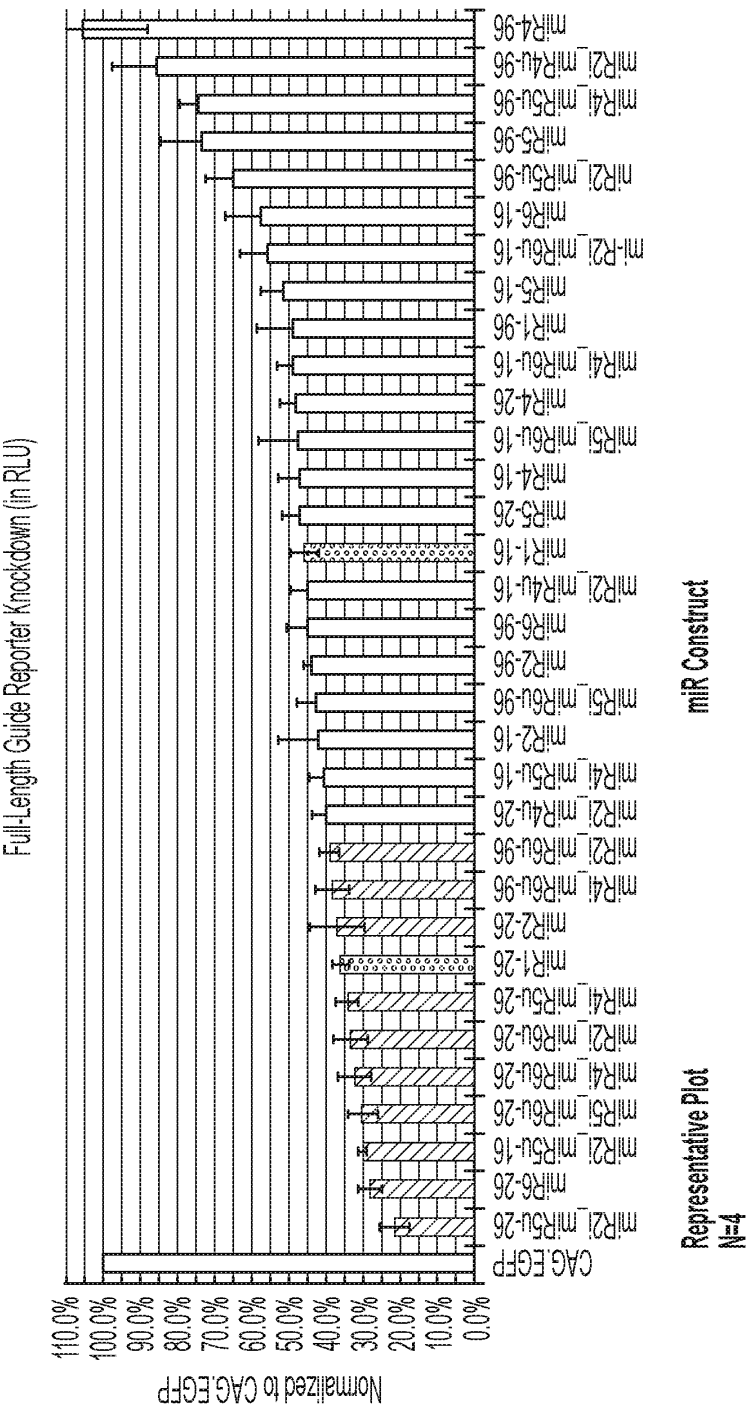
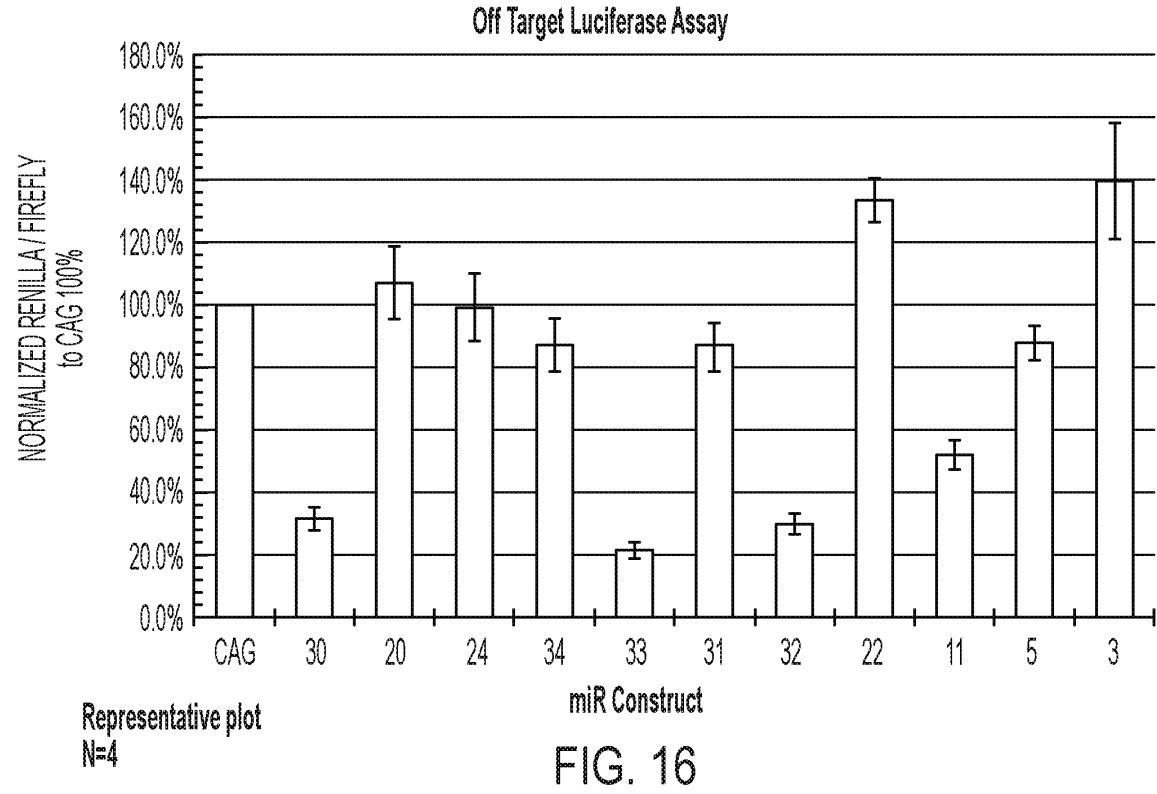
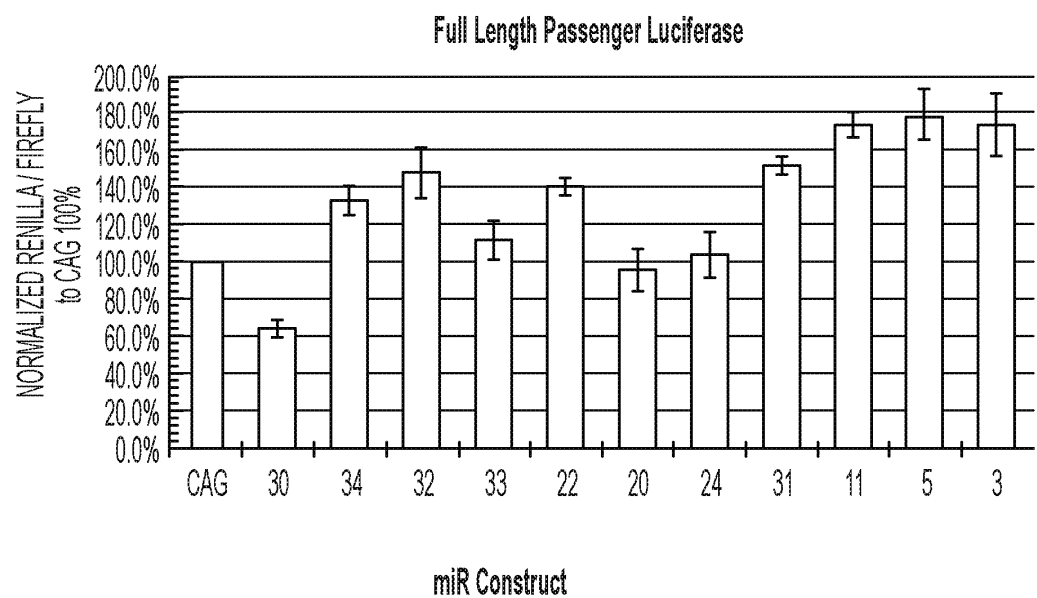


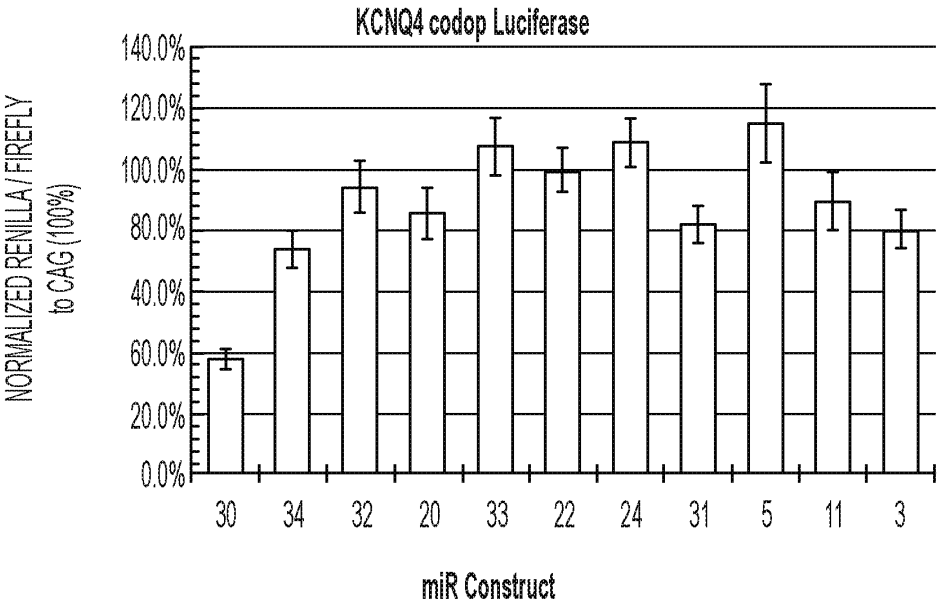
FIG. 15





Representative plot
N=4

FIG. 17



Representative plot
N=4

FIG. 18

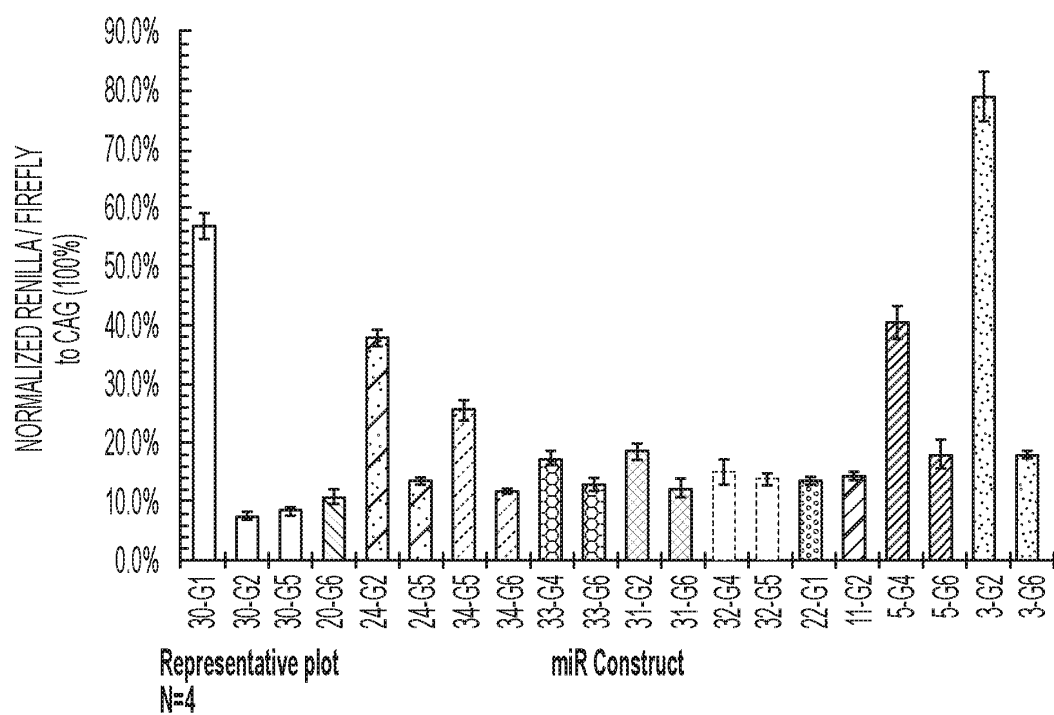


FIG. 19

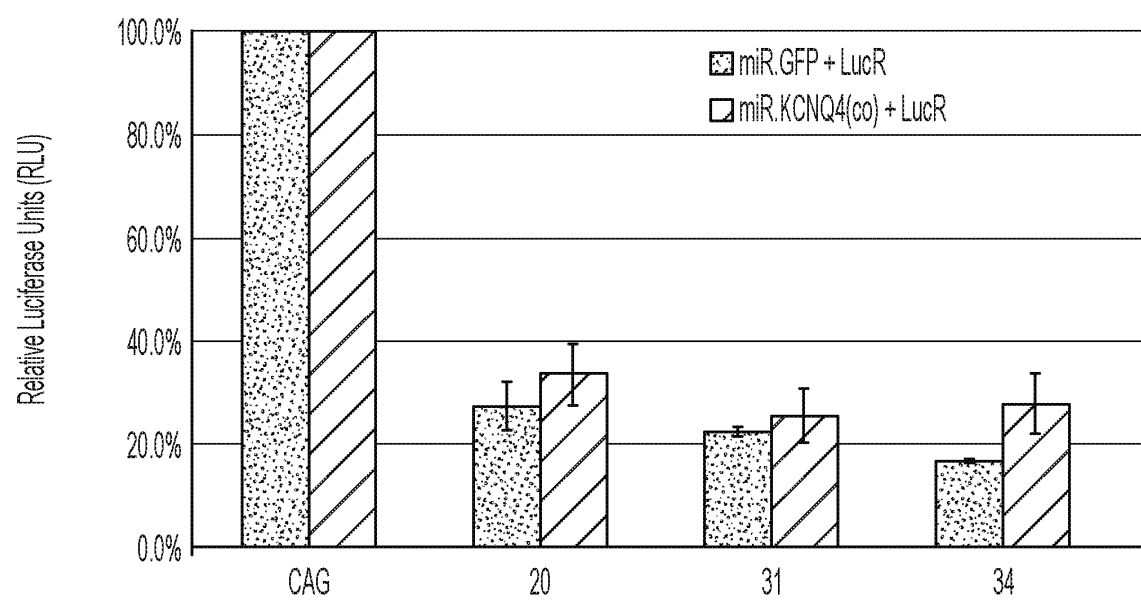
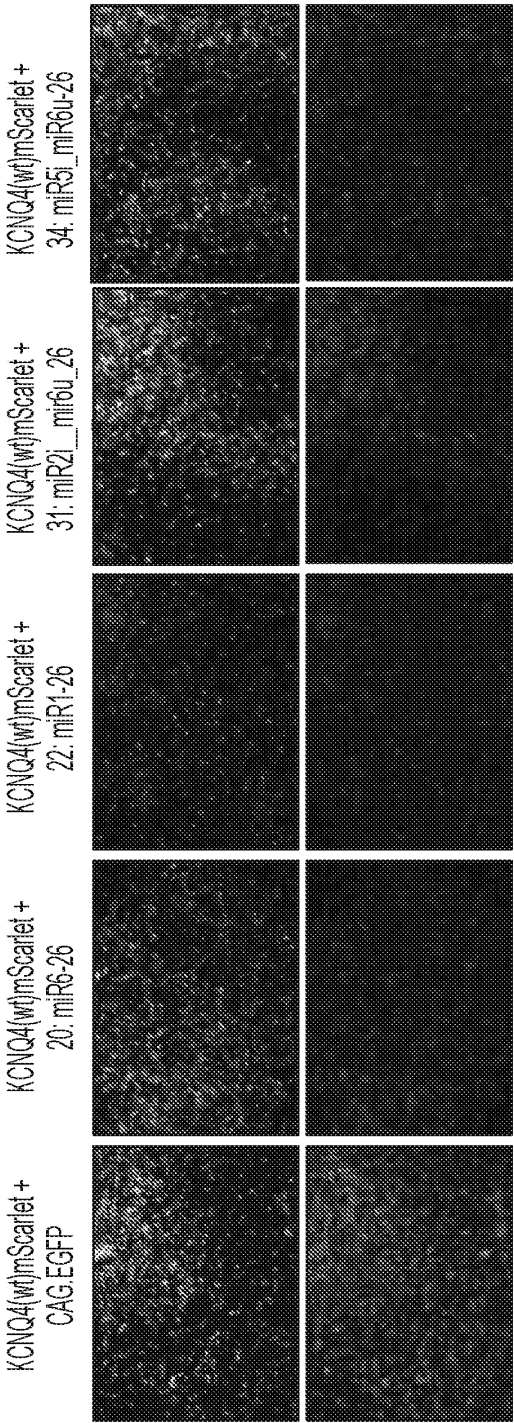


FIG. 20



400ng KCNQ4 reporter : 600ng miR

Representative images
N=3

FIG. 21

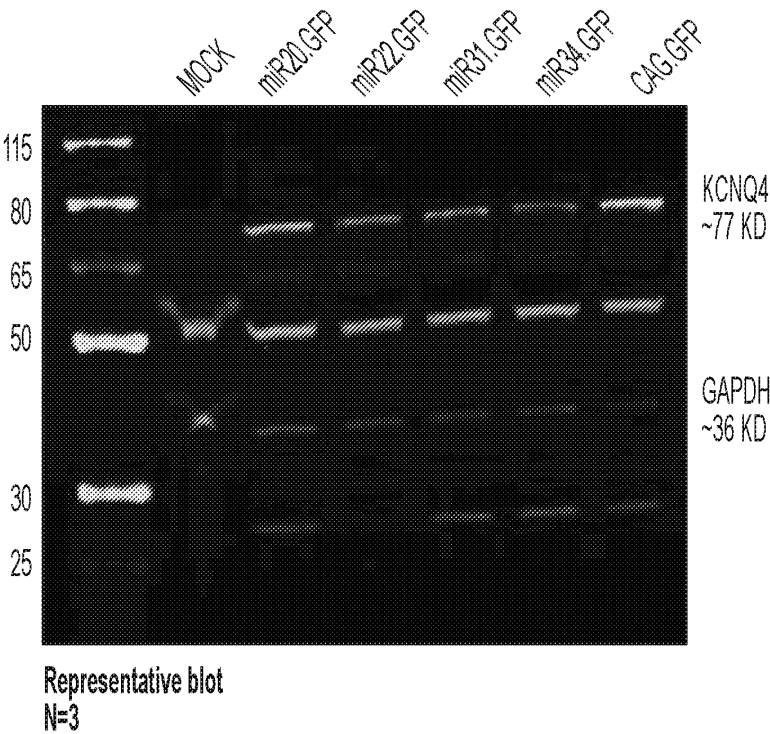
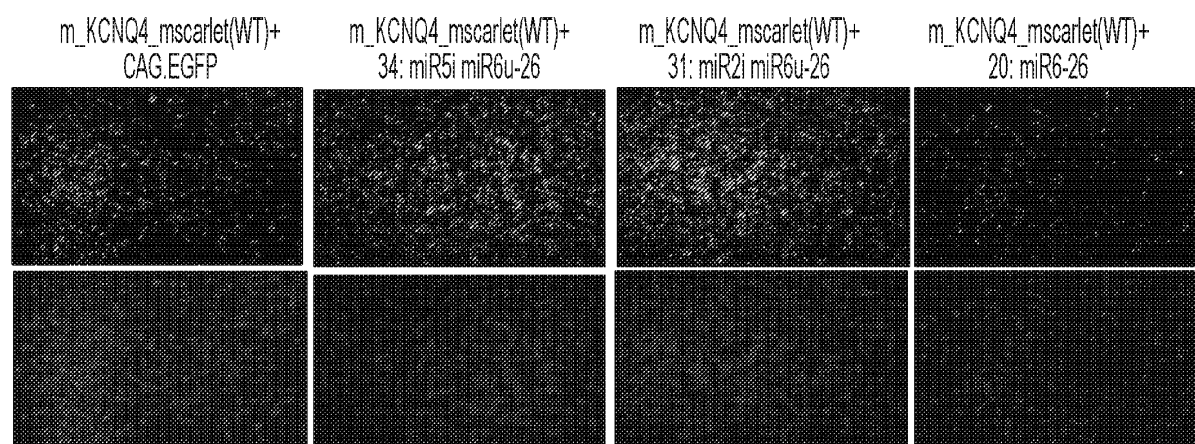


FIG. 22

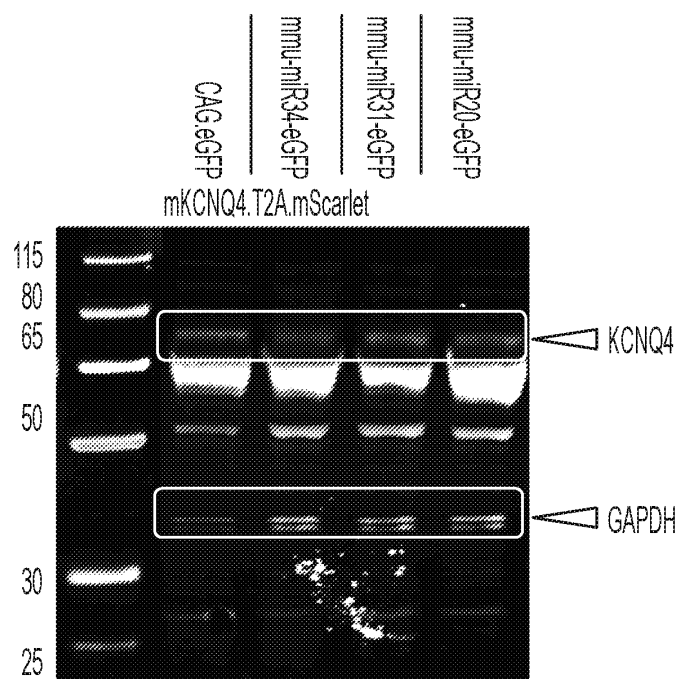


400ng KCNQ4 report: 600ng miRNA

Representative images

N=3

FIG. 23



Representative blot
N = 4

FIG. 24

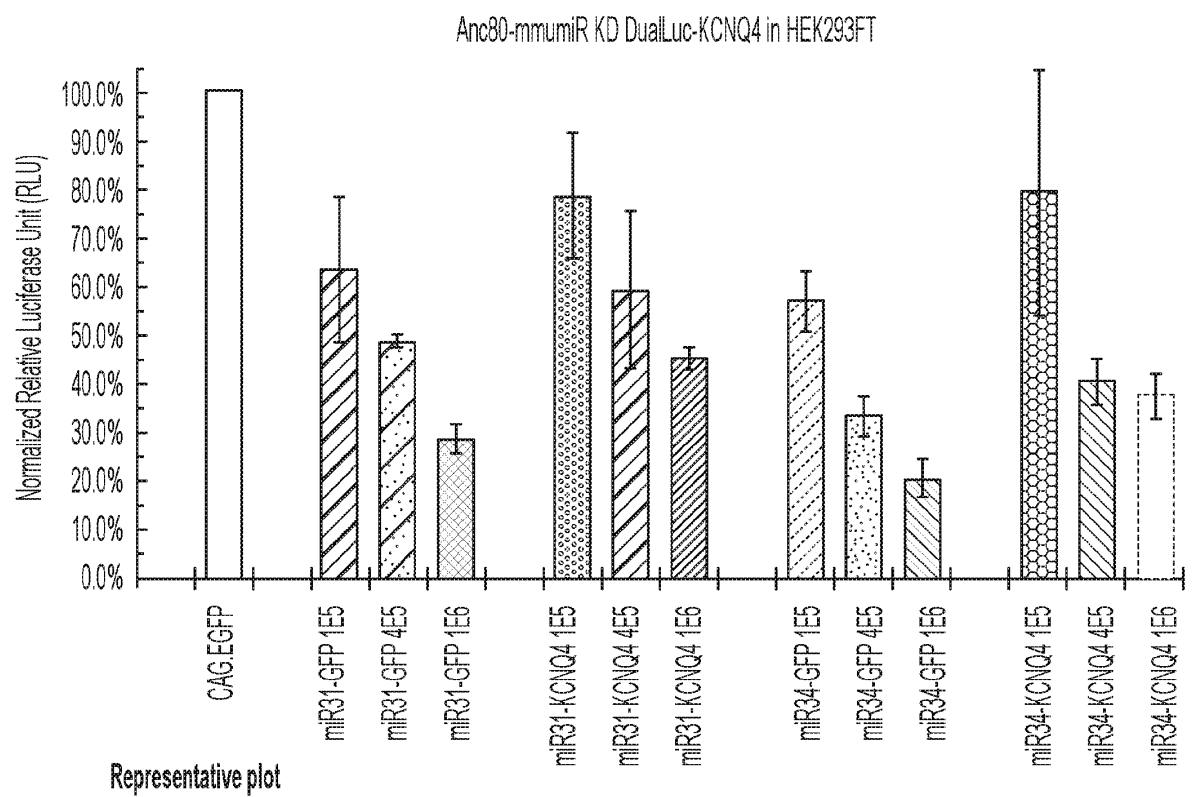


FIG. 25

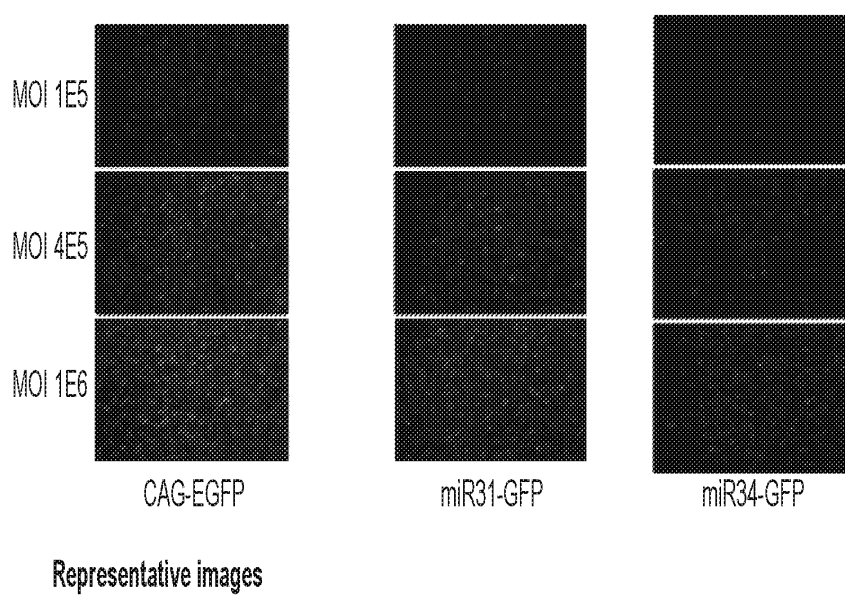
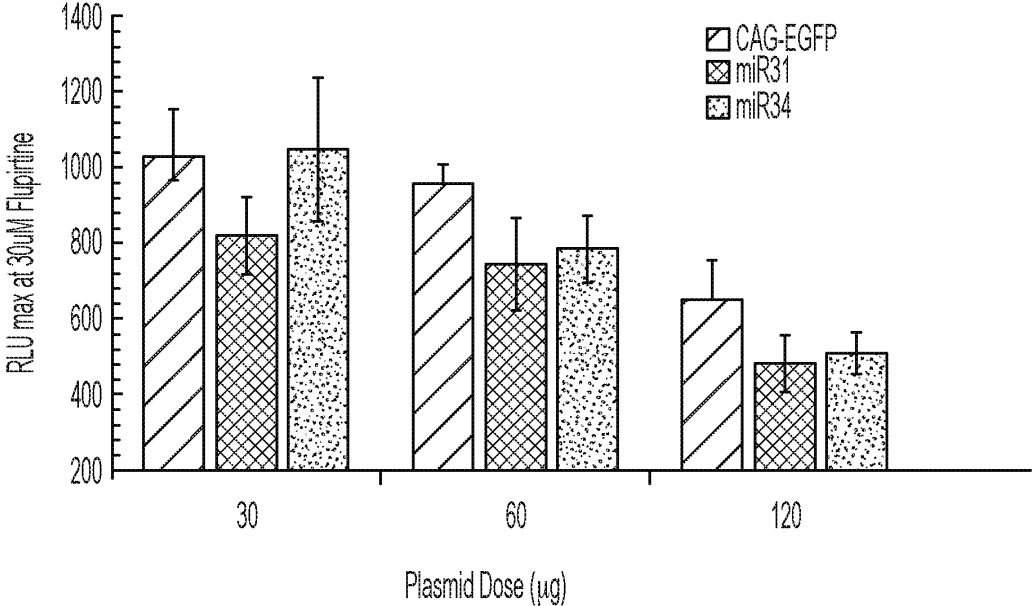


FIG. 26



Representative plot

FIG. 27

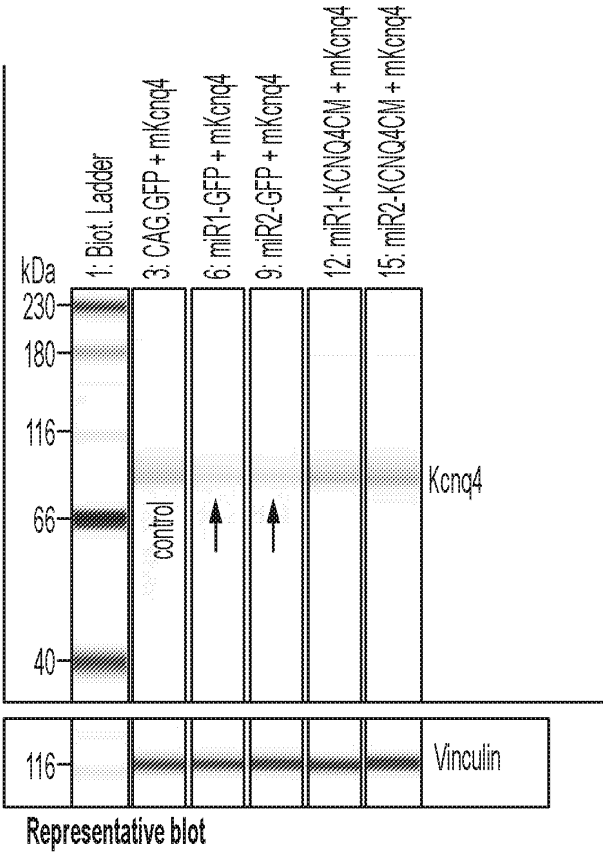


FIG. 28

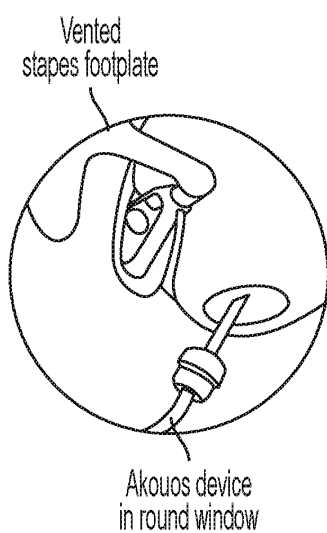


FIG. 29A

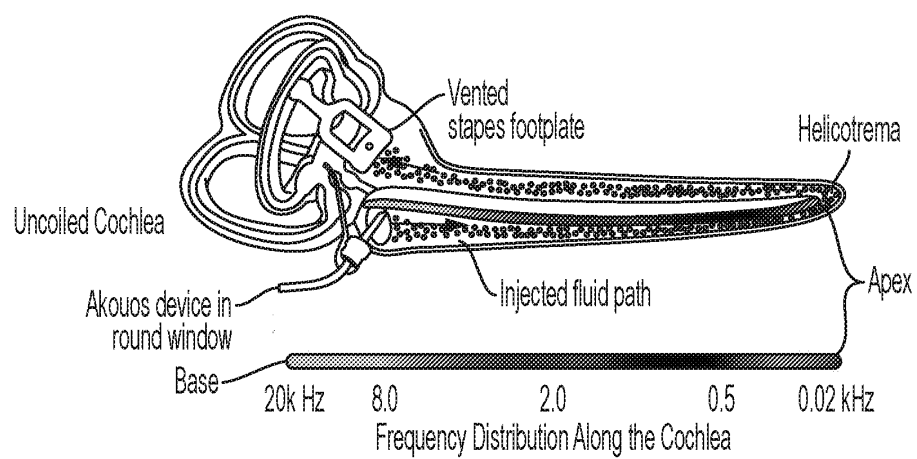


FIG. 29B

RNAi ID	Sense	%GC	s-Biopreds	i-Score	DSIR	Overall	Mouse_Sense	s-Biopreds	i-Score	DSIR	Overall
01	CCGCUCCAUA GGAUUCUCAA (SEQ ID NO: 72)	47.4	0.868	75.1	98.8	260.7	CCGUUCUGUA GGAUUCUGAA (SEQ ID NO: 78)	0.839	67.6	93.6	245.1
02	CCGGGCAUCUC UGAGACUCAA (SEQ ID NO: 73)	52.6	0.871	75.5	96.5	259.1	CCGGGCCUCUC UAAGACUCAA (SEQ ID NO: 79)	0.872	75.4	97.6	260.2
04	CCGGCAGAGC ACUUCGAGAA (SEQ ID NO: 74)	52.6	0.855	71.6	97.4	254.5	CAGGCAGAGC ACUUCGAGAA (SEQ ID NO: 80)	0.855	70.8	93.9	250.2
05	ACGGGUGGUA AGGUGGAGAA (SEQ ID NO: 75)	57.9	0.859	72.3	95.8	254	GCGGCUAGUA AGGUGGAAA (SEQ ID NO: 81)	0.846	75.7	91.2	251.5
06	CUGGUACUACU AUGACAGAU (SEQ ID NO: 76)	36.8	0.843	72.5	95.6	252.4	CUGGUUUAUCU AUGACAGAU (SEQ ID NO: 82)	0.832	69.2	89.8	242.2
07	CCGCACUAC CUCGACUAC (SEQ ID NO: 77)	57.9	0.848	68.5	98	251.3	CCCGCACUA CCUCGACUA (SEQ ID NO: 83)	0.847	67.8	95.8	248.3

FIG. 30

RNAi ID	Sense	%GC	s-Biopreds	i-Score	DSIR	Overall	ACC ID	Gene	Sequence
01	CCGCCCAUCAGG AUUCUAA (SEQ ID NO: 72)	47.4	0.868	75.1	98.8	260.7	NM_183238.4	ZFN605	...AUGAUUCCACCAUC AGGAUUCUCCCAUGCC ... (SEQ ID NO: 84)
02	CCGGCAUCUCUG AGACUCAA (SEQ ID NO: 73)	52.6	0.871	75.5	96.5	259.1	NM_001007231.3	Rho GTPase	...ACCCUCAGGGCAUCU CUGAGACACAGGGCCA ... (SEQ ID NO: 85)
04	CCGGCAGAGCAC UUCGAGAA (SEQ ID NO: 74)	52.6	0.855	71.6	97.4	254.5	NM_172107.4	KCNQ2	...CAGCACAGGAGAG CACUUGAGAGAGGC ... (SEQ ID NO: 86)
05	ACGGCUGGUCAG GUGGAGAA (SEQ ID NO: 75)	57.9	0.859	72.3	95.8	254	NM_001080450.2	BEND3	GACAUCUCACUGGUC AAGGUGGAGGACACU ... (SEQ ID NO: 87)
06	CUGGUACUACU GACAGU (SEQ ID NO: 76)	36.8	0.843	72.5	95.6	252.4	NM_001114123.2	ELK1	...GCCUUGCGGUACUAC UAUGACAAGACA (SEQ ID NO: 88)
07	CCCGACUACCU CCGACUAC (SEQ ID NO: 77)	57.9	0.848	68.5	98	251.3	NM_199289.3	NEK5	...CAGUGCGGACAUCA CCUCCACUGCCCCAC ... (SEQ ID NO: 89)

FIG. 31

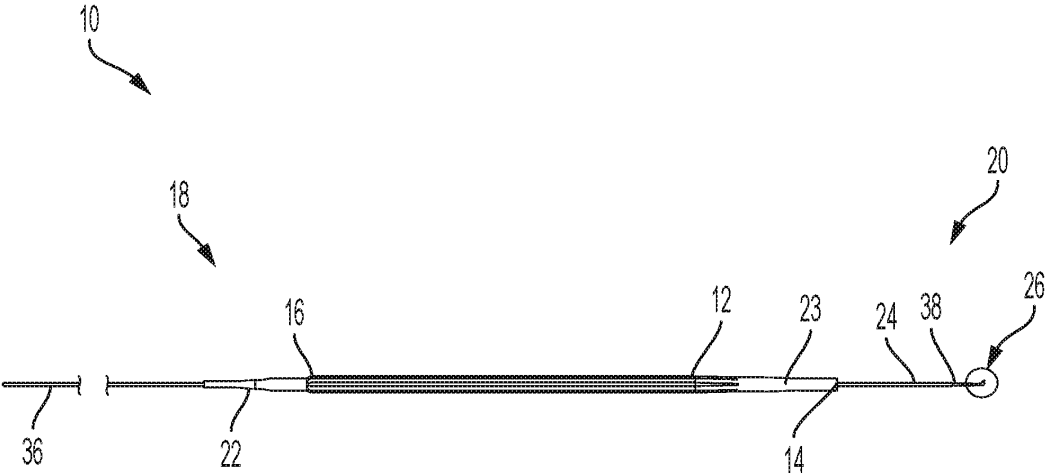


FIG. 32

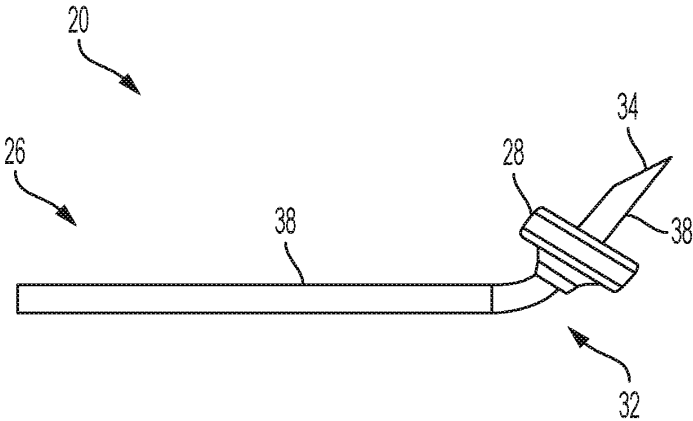


FIG. 33

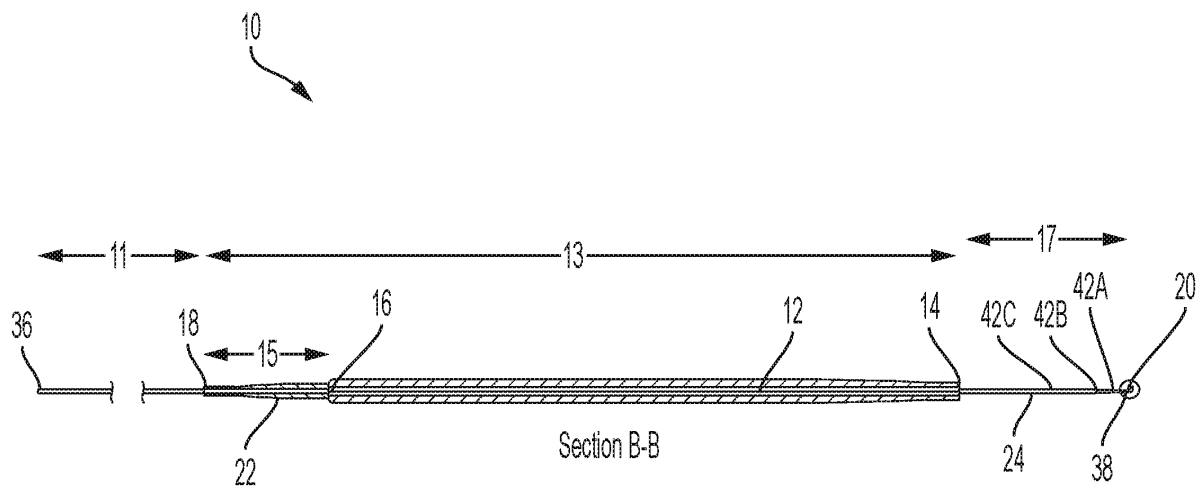


FIG. 34

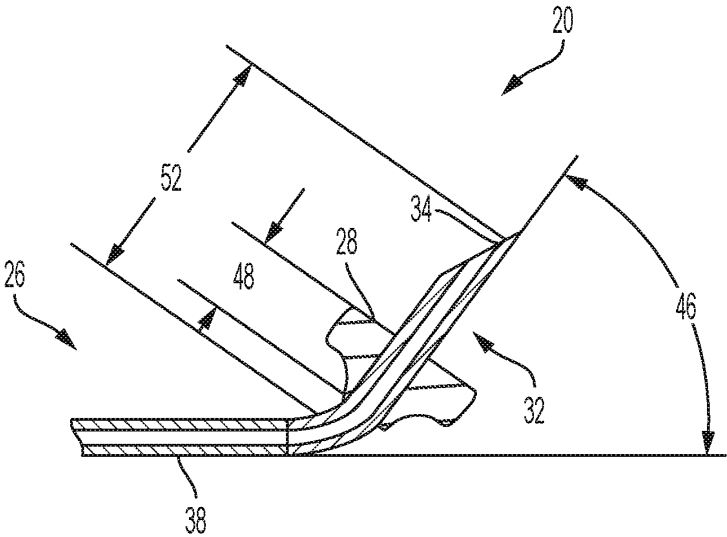
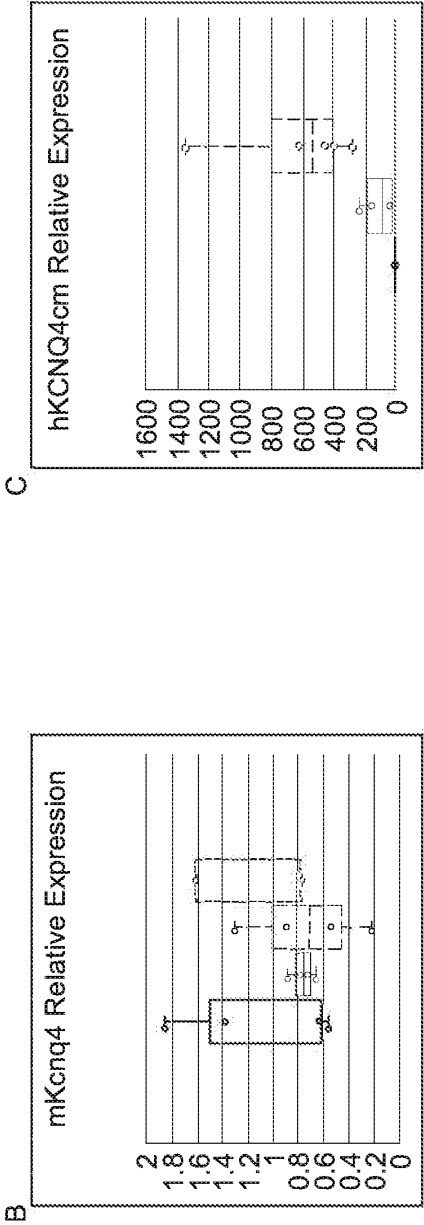


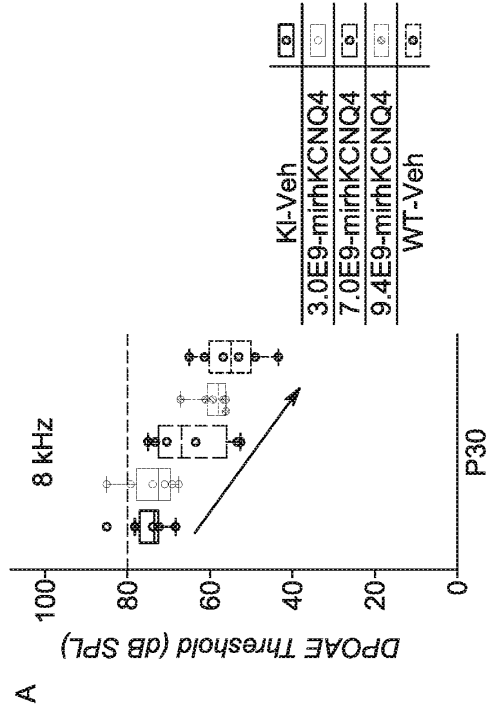
FIG. 35

A

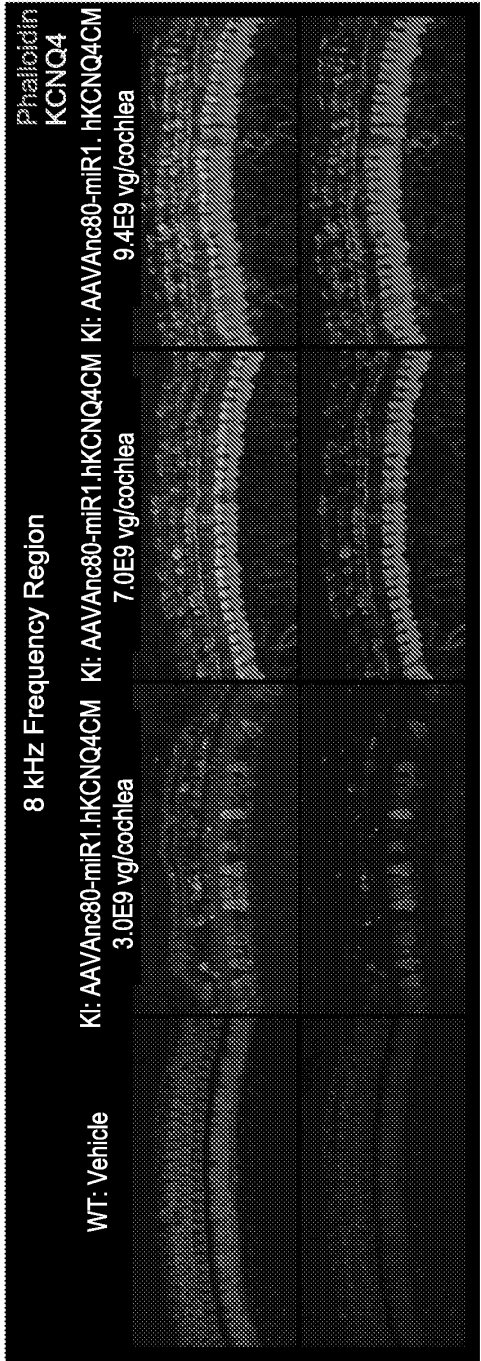
Grp	Geno	N	Vector	Relative Dose	Survival (days Post-Sx)	Physiology Readout	Histology Readout	PCR Readout
1	KI	6	AAVAnc80-miR1.hKCNQ4CM	Low	30±2	6 ✓	N/A	4/6
2	KI	6	AAVAnc80-miR1.hKCNQ4CM	Medium	30±2	6 ✓	N/A	4/6
3	KI	6	Vehicle	–	30±2	6 ✓	N/A	4/6
4	WT	6	Vehicle	–	30±2	6 ✓	N/A	2/6



FIGS. 36A-36C



B



FIGS. 37A–37B

A

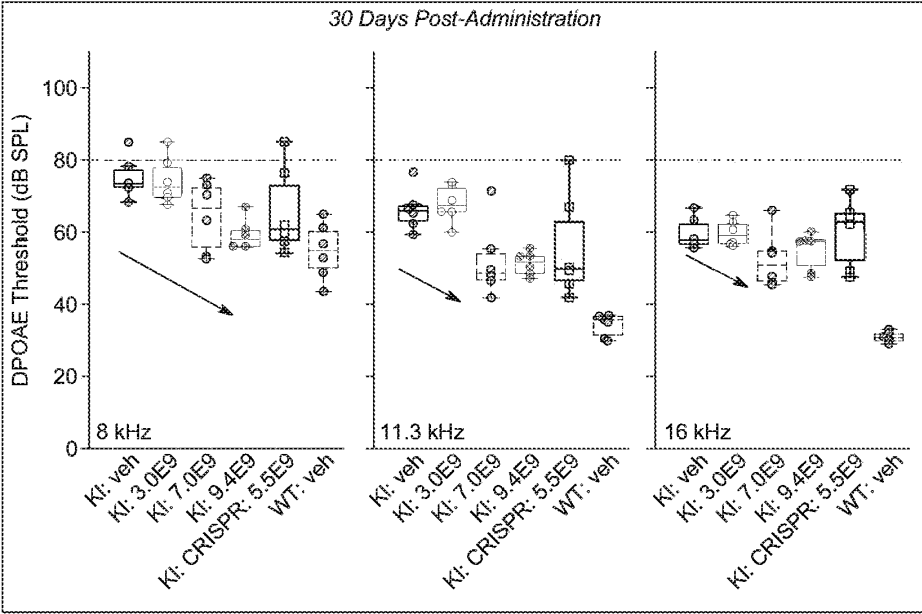


FIG. 38A

B

	30-day survival
KI-Veh	6
3.0E9-mirhKCNQ4	6
7.0E9-mirhKCNQ4	6
9.4E9-mirhKCNQ4	6
5.5E9-CRISPR	6
WT-Veh	6

FIG. 38B

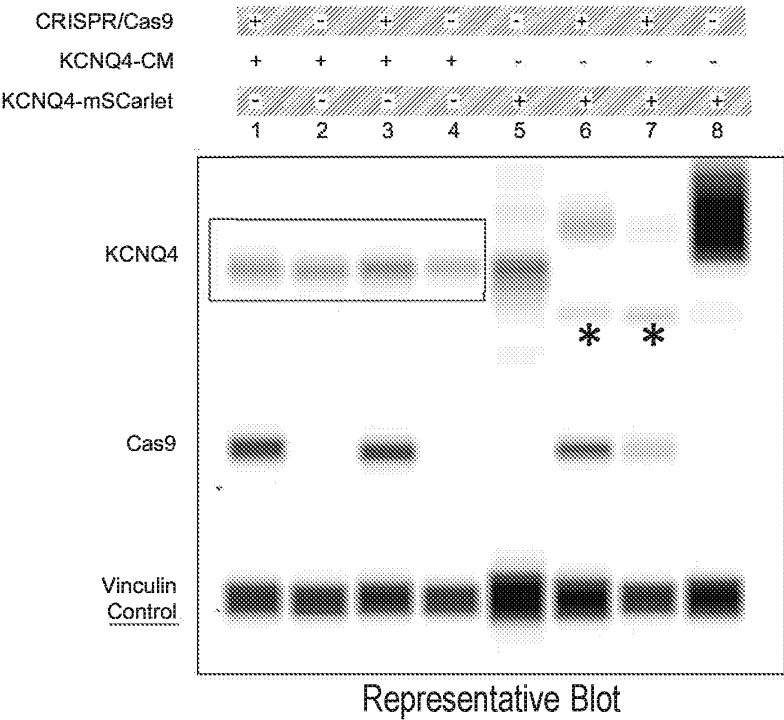


FIG. 39

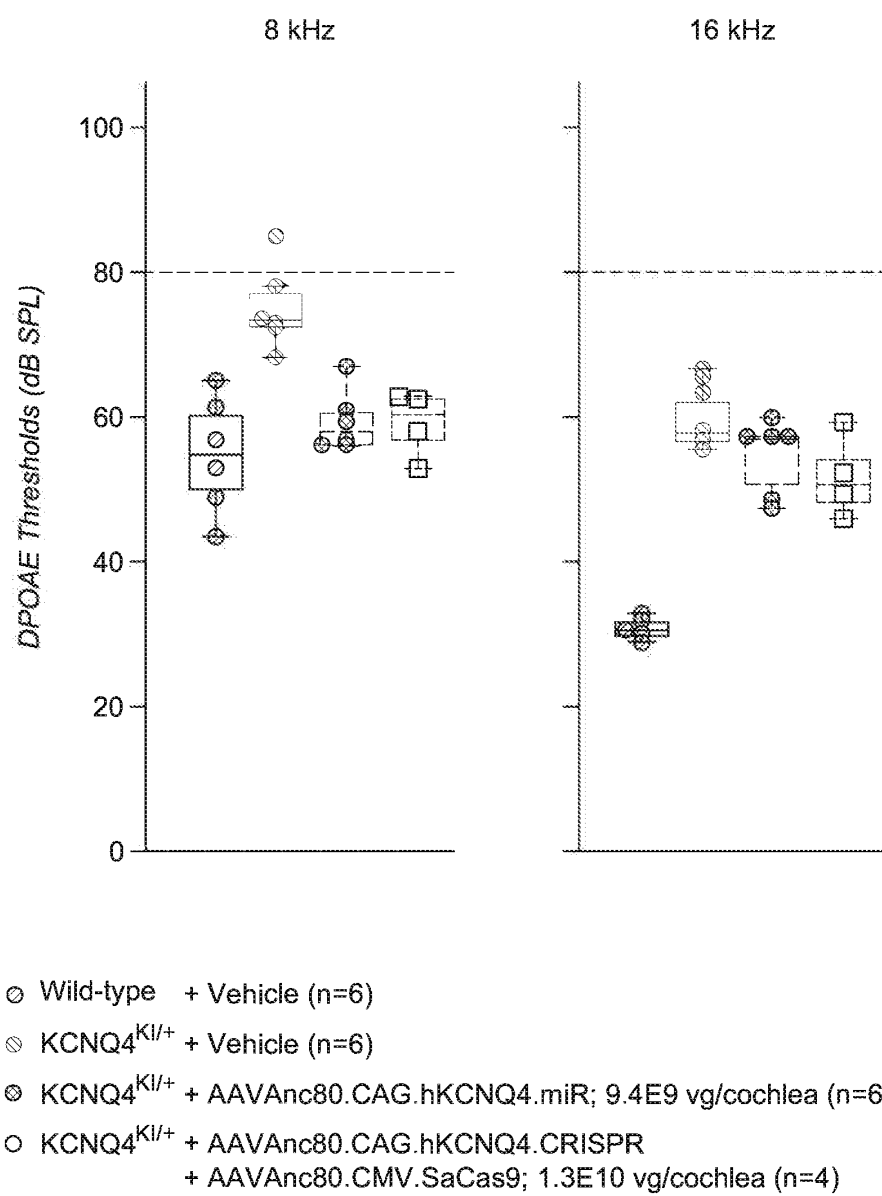
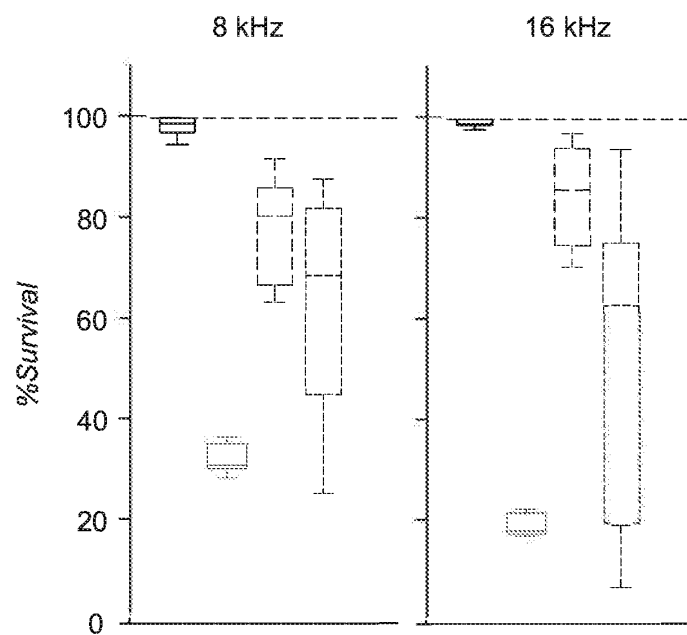


FIG. 40



- Wild-type + Vehicle (n=7)
- KCNQ4^{KI/+} + Vehicle (n=6)
- KCNQ4^{KI/+} + AAVAnc80.CAG.hKCNQ4.miR; 9.4E9 vg/cochlea (n=6)
- KCNQ4^{KI/+} + AAVAnc80.CAG.hKCNQ4.CRISPR + AAVAnc80.CMV.SaCas9; 5.5E9 vg/cochlea (n=6)

FIG. 41