

FIG. 1

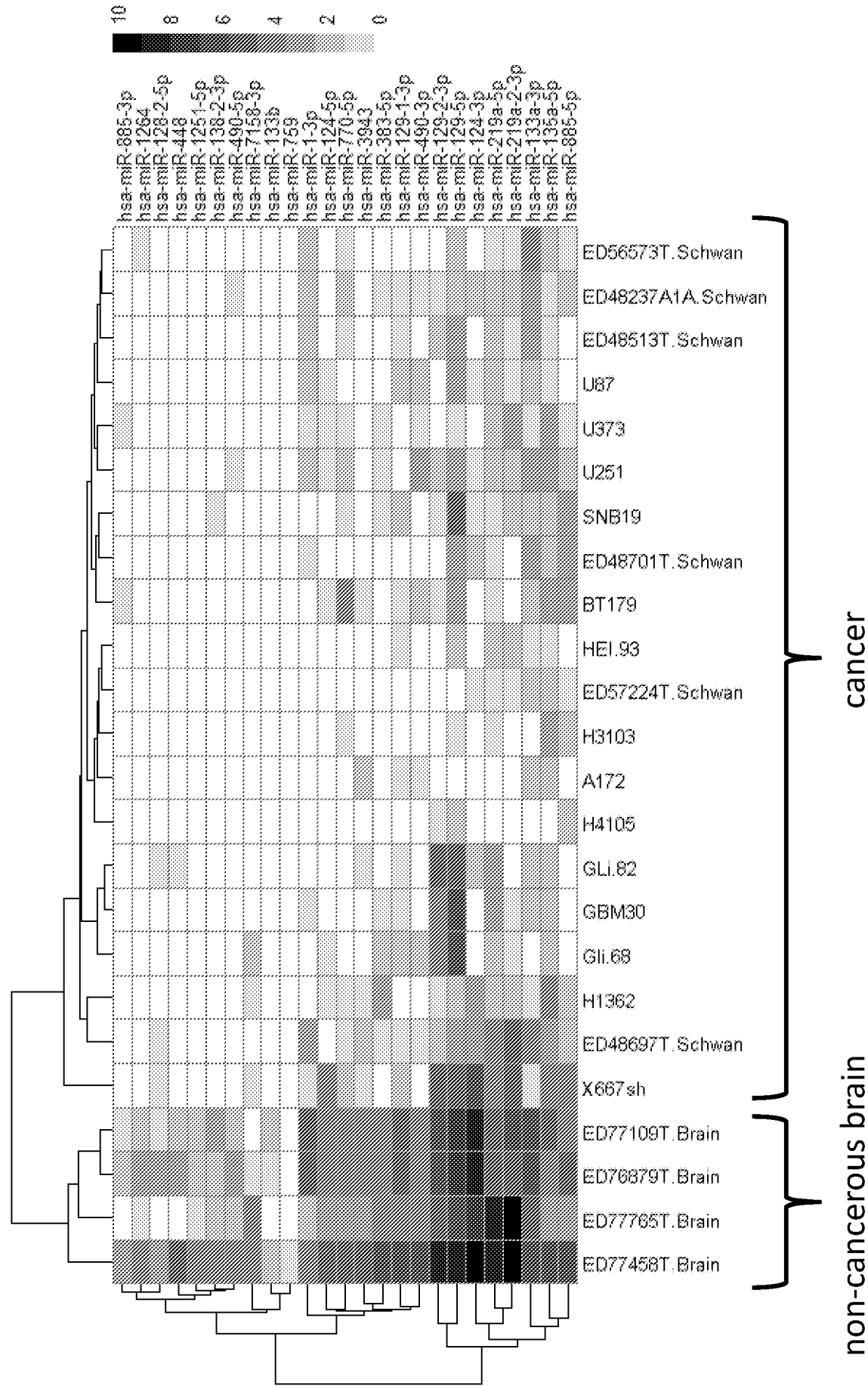


FIG. 2

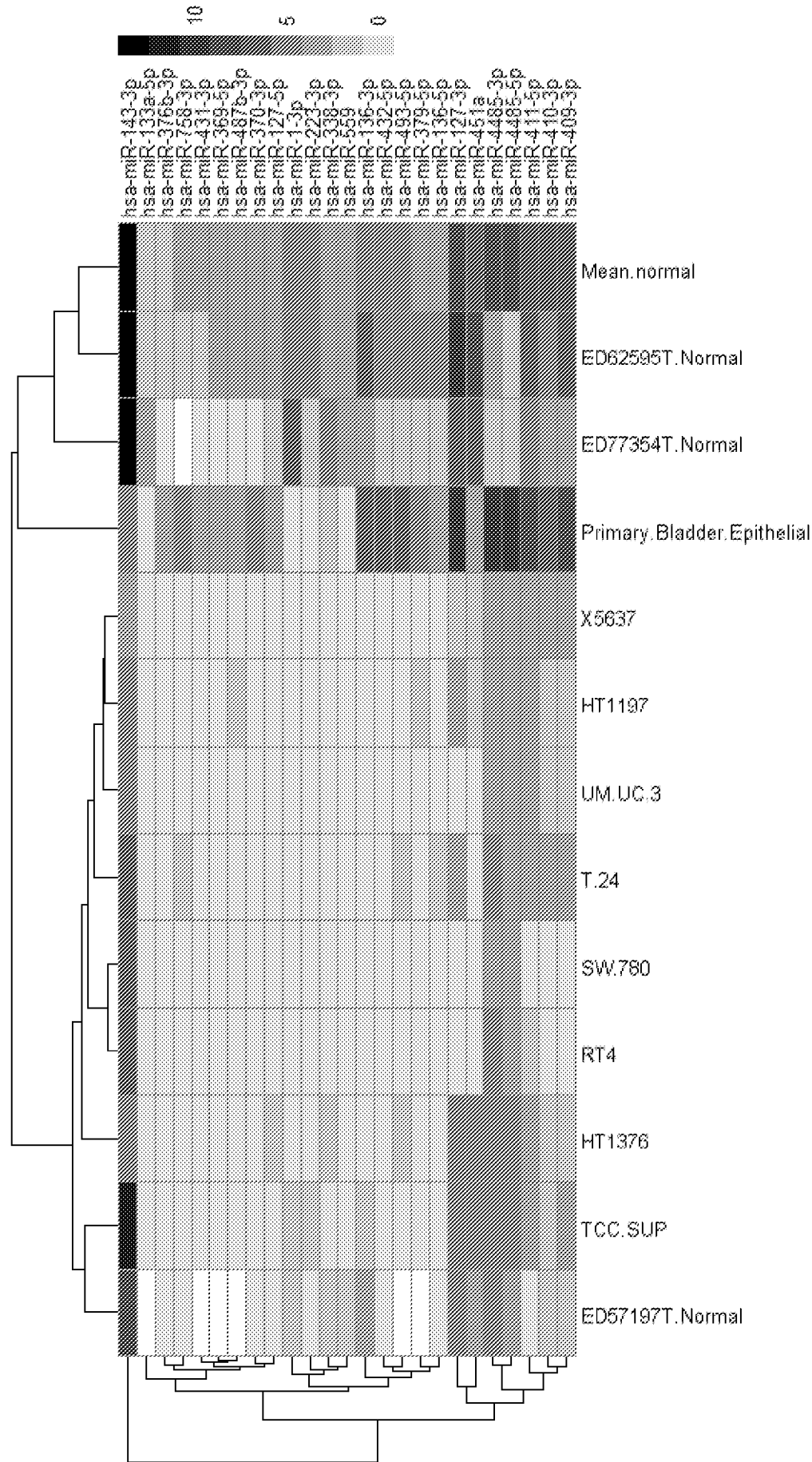


FIG. 3

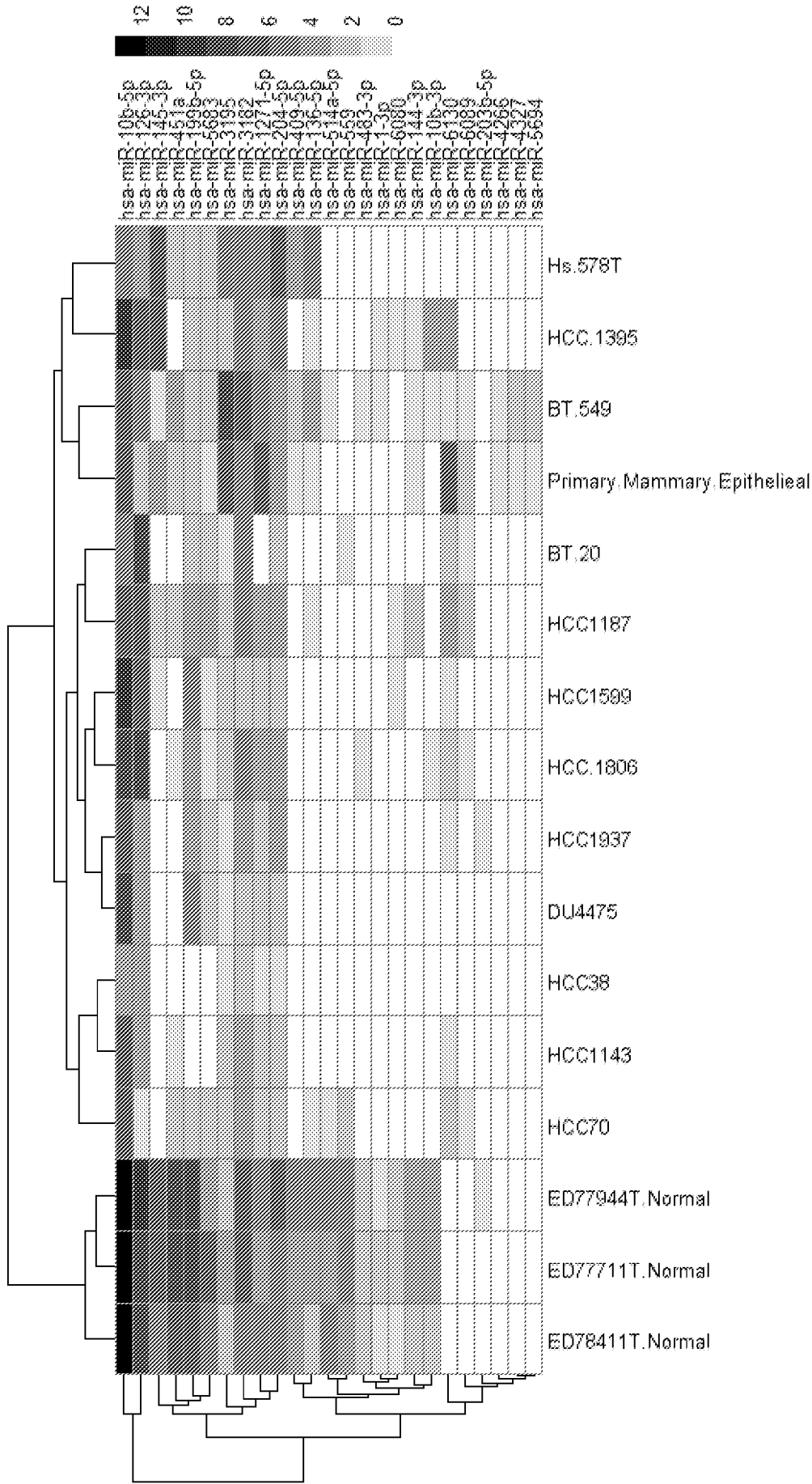


FIG. 4

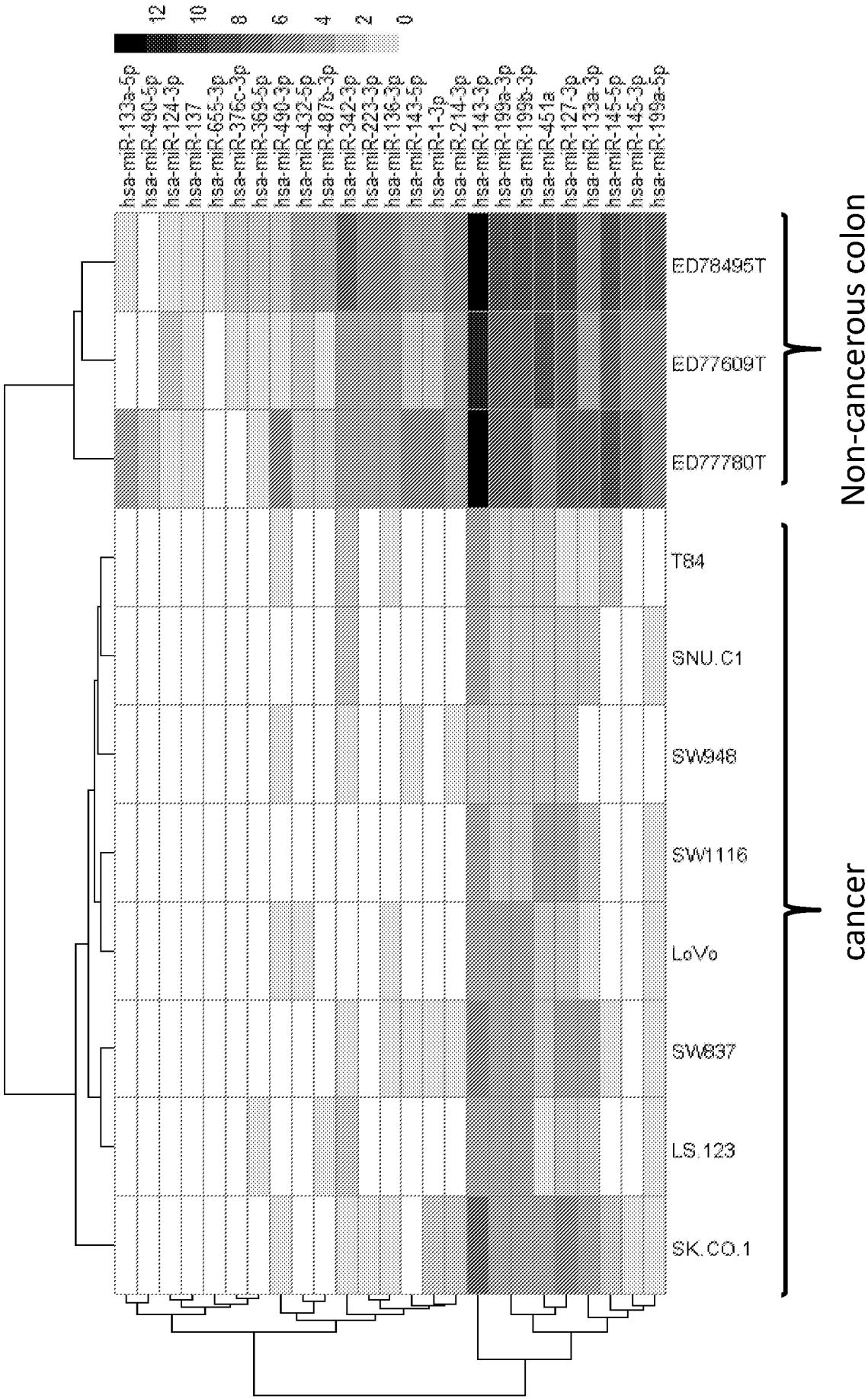


FIG. 5

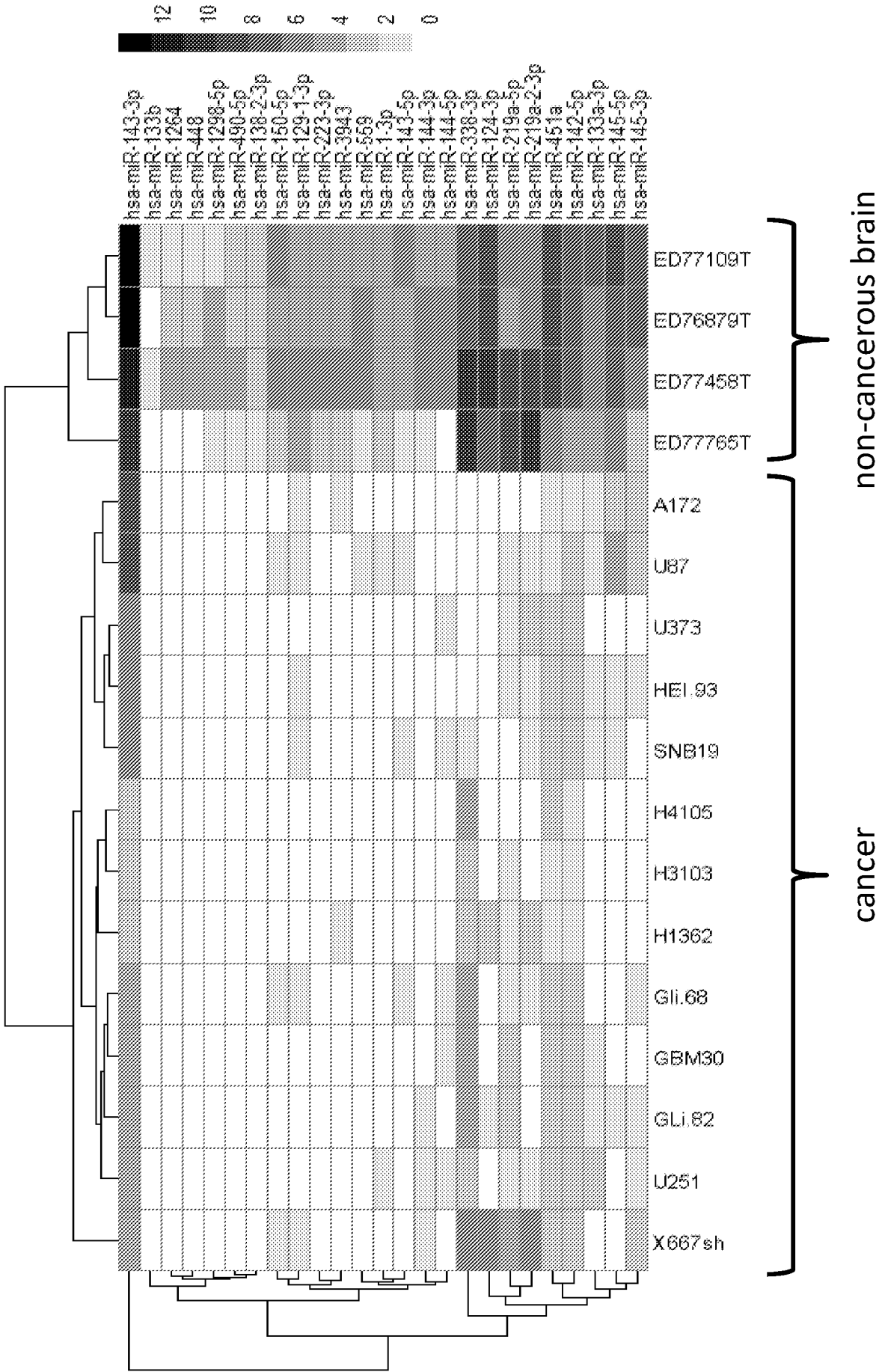


FIG. 6

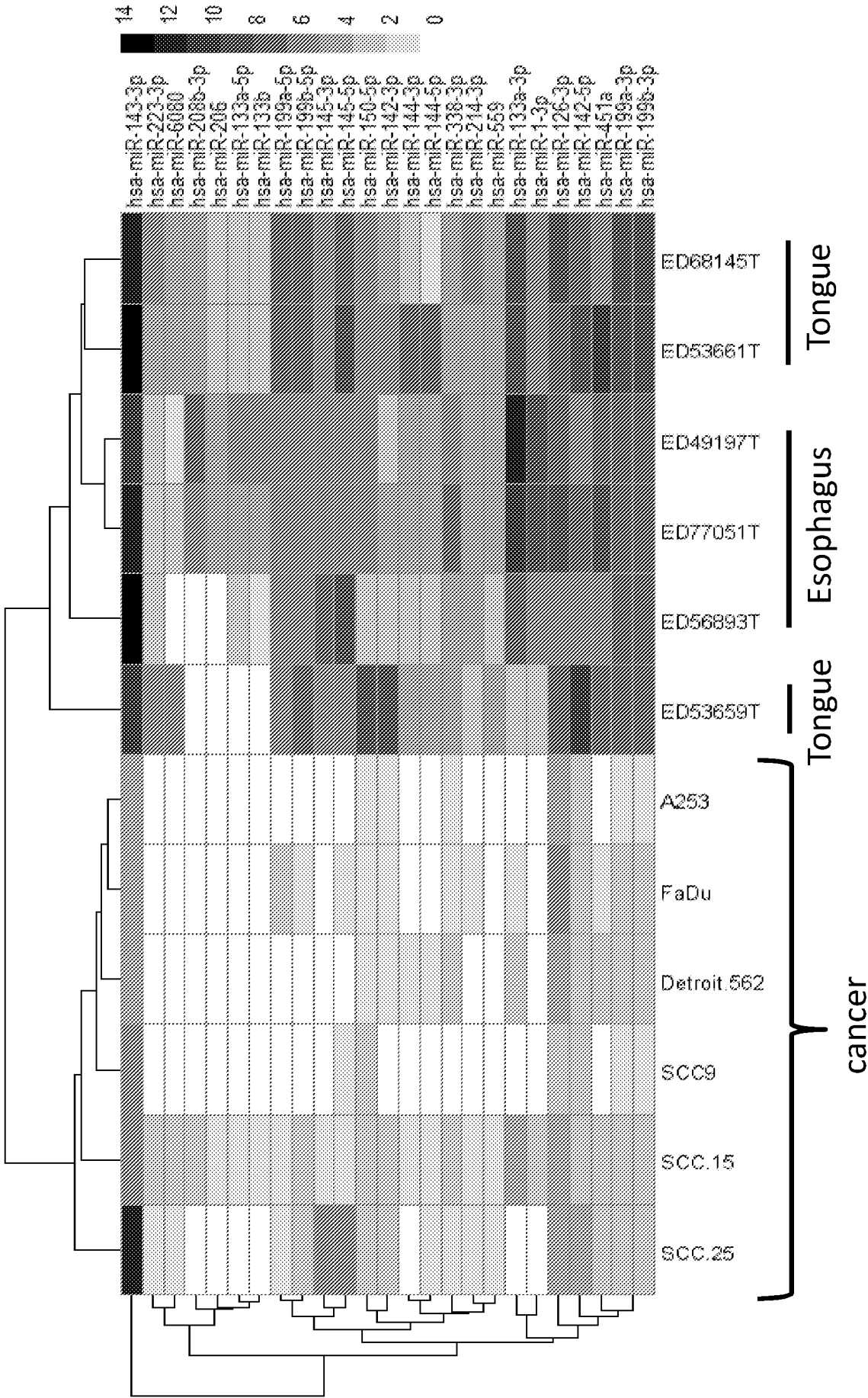


FIG. 7

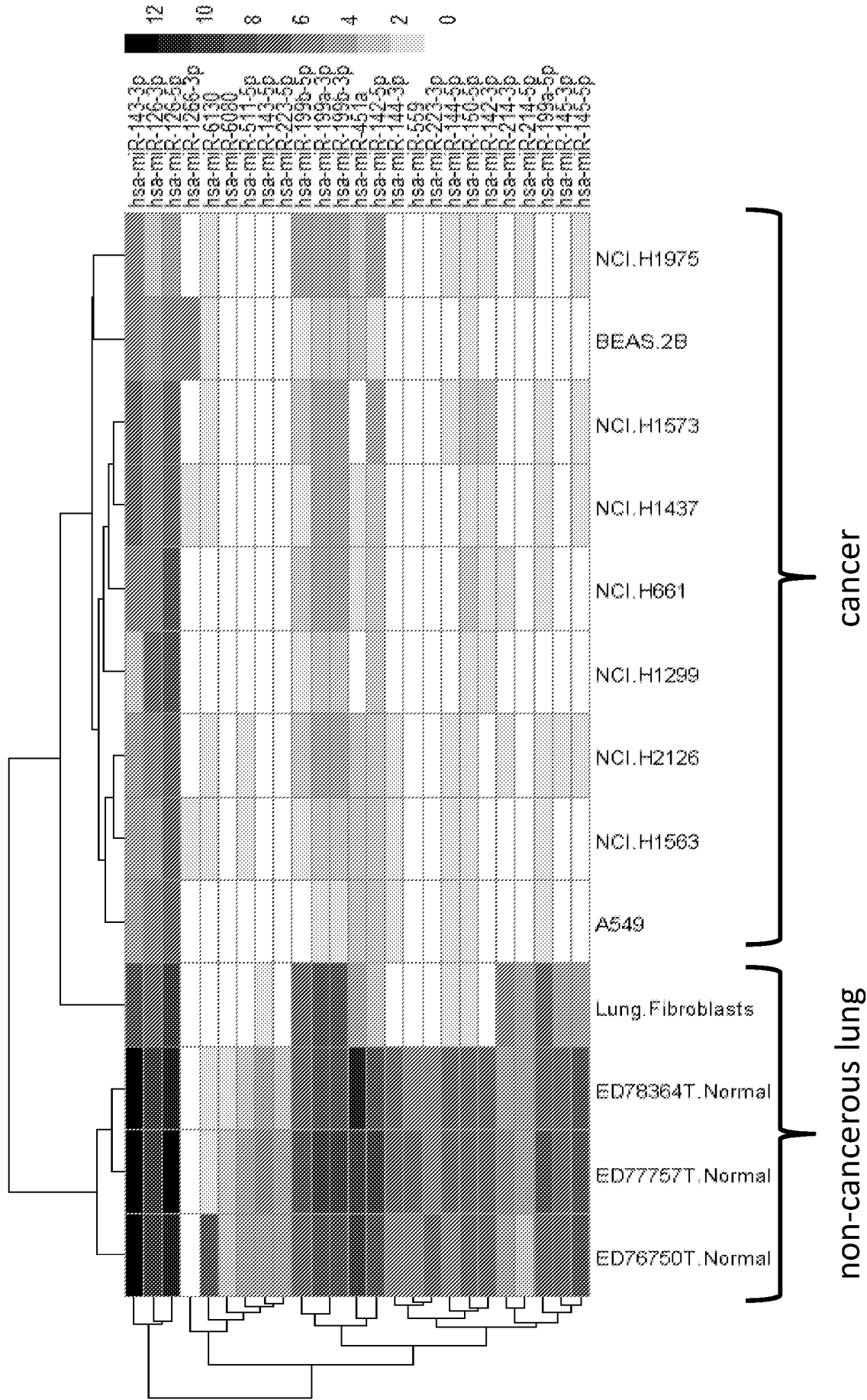


FIG. 8

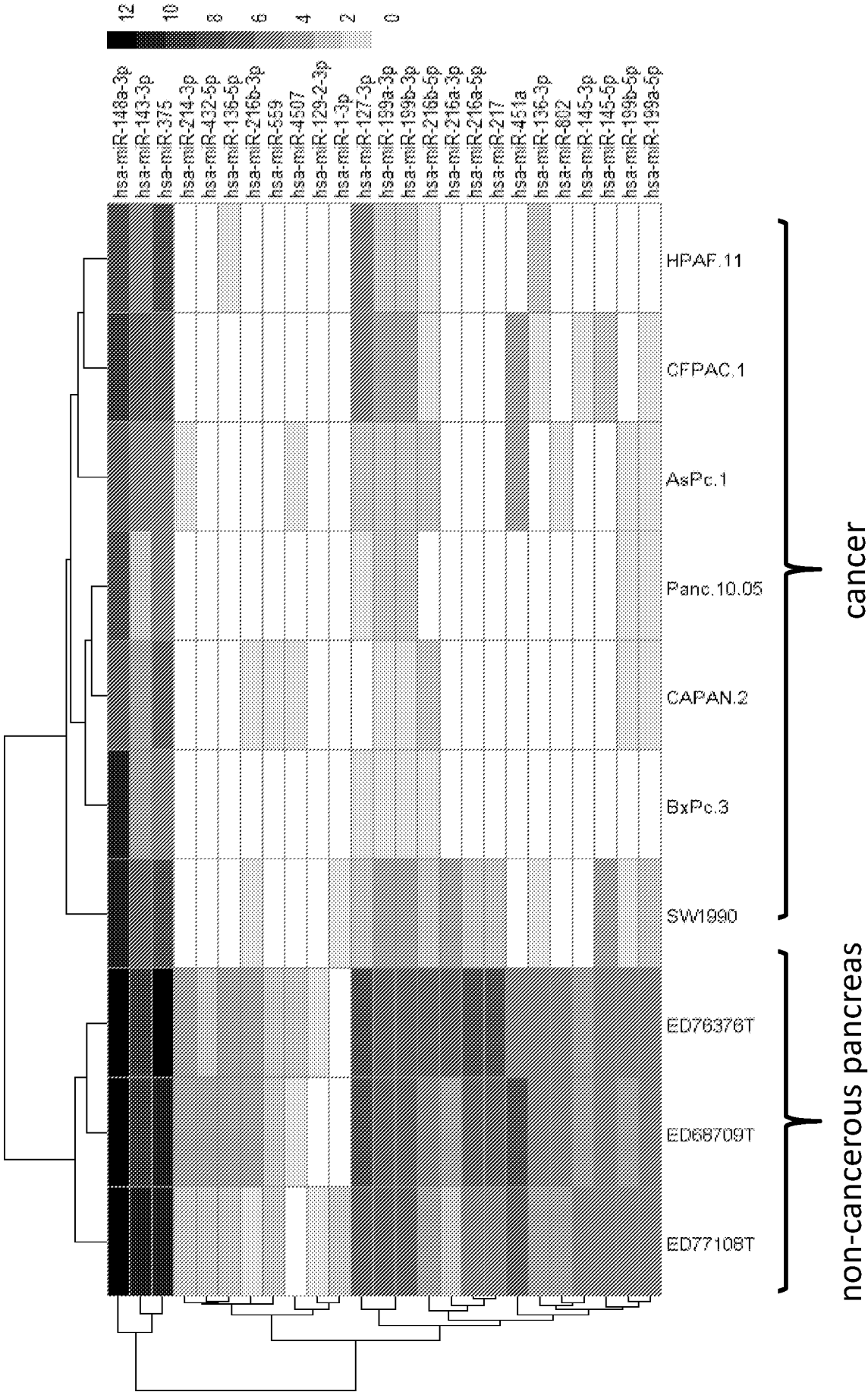
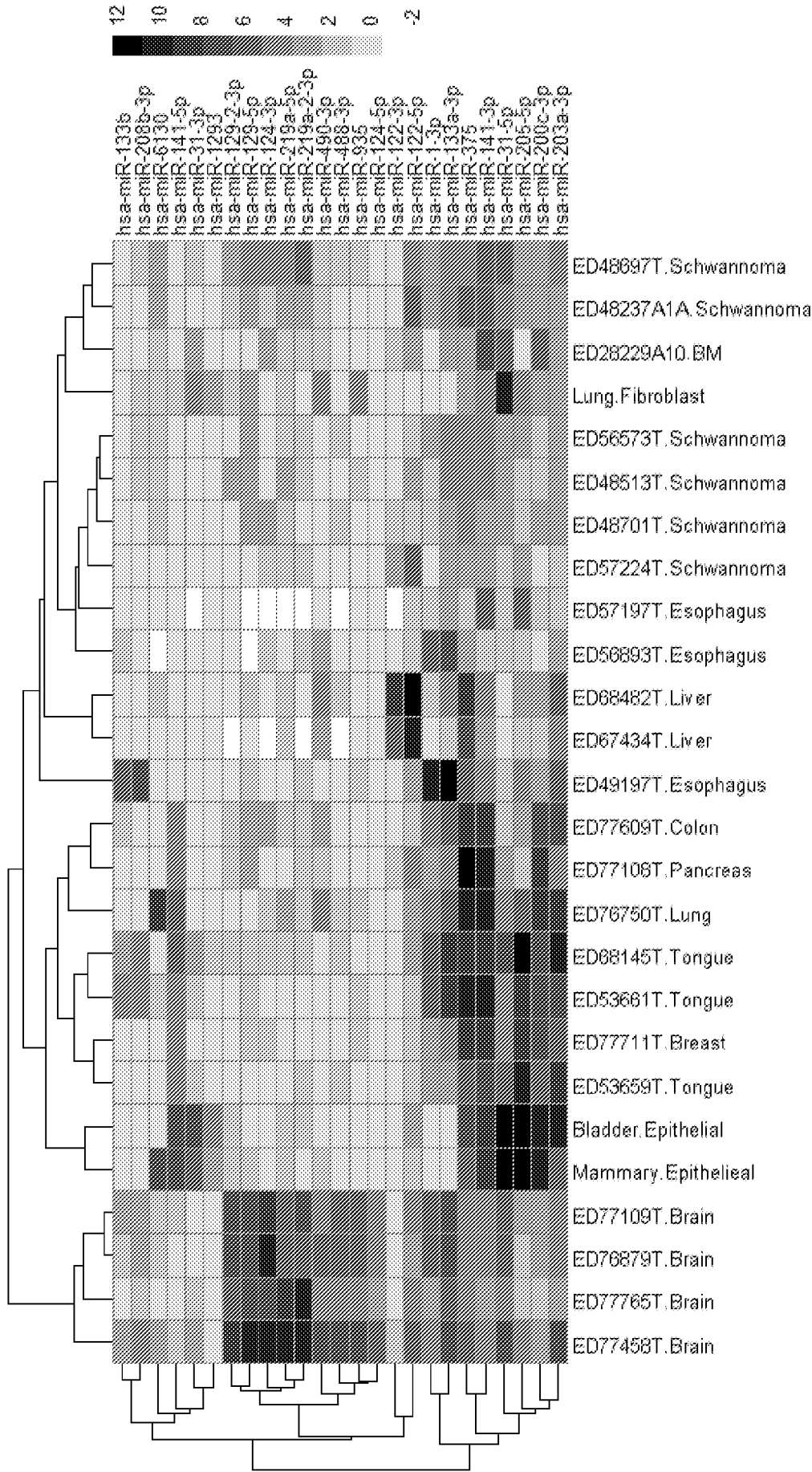


FIG. 9



All non-Schwannoma = non-cancerous tissue
BM = non-cancerous bone marrow

FIG. 10

miR-451a		
Tissue	Norm	CA
Bladder	1402.9	21.1
Breast	2262.1	3.9
Colon	3606.9	22.0
Glioma	4269.7	16.7
H & N	11919.8	10.3
Lung	31442.0	10.5
Pancreatic	1035.8	13.3

FIG. 11

miR-1		
Tissue	Norm	CA
Bladder	175.0	0.8
Breast	3.0	0.3
Colon	149.3	1.6
Glioma	75.2	1.0
H & N	2846.6	2.6
Lung	73.3	1.4
Pancreatic	4.1	0.4

FIG. 12

miR-559		
Tissue	Norm	CA
Bladder	14.0	0.4
Breast	88.4	0.9
Colon	40.8	2.1
Glioma	162.7	0.4
H & N	71.2	2.2
Lung	548.3	0.1
Pancreatic	13.3	0.5

FIG. 13

145-5p		
Tissue	Norm	CA
Bladder	971.5	39.8
Breast	406.1	106.6
Colon	1177.3	0.5
Glioma	2399.2	7.2
H & N	690.9	30.4
Lung	1547.5	1.0
Pancreatic	81.7	0.5

FIG. 14

143-3p			miR-143-3p Breast counts		miR-143-3p H & N counts	
Tissue	Norm	CA				
Bladder	489028.8	14904.6	BT-549	132.1	FaDu	144.5
Breast	125943.9	91543.1*	DU4475	20.1	SCC-15	214.2
Colon	509955.6	193.9	HCC-1395	503387.3	SCC-25	123445.7
Glioma	514114.8	1248.6	HCC-1806	39.7	SCC9	242.2
H & N	331034.2	20706.2	HCC1143	1011.5	A253	54.6
Lung	436136.8	390.9			Detroit-	
Pancreatic	25557.0	269.8	HCC1187	4737.7	562	136.4
			HCC1599	1858.7		
			HCC1937	33.2		
			HCC38	21.9		
			HCC70	174.9		
			Hs-578T	495642.8		
			BT-20	46.9		

FIG. 15A

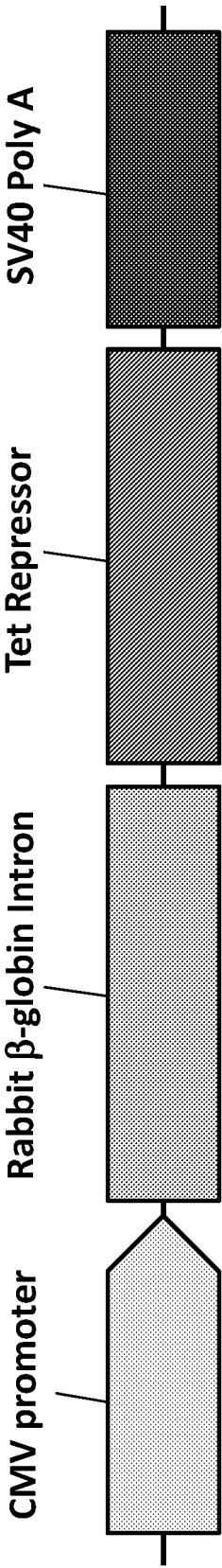


FIG. 15B

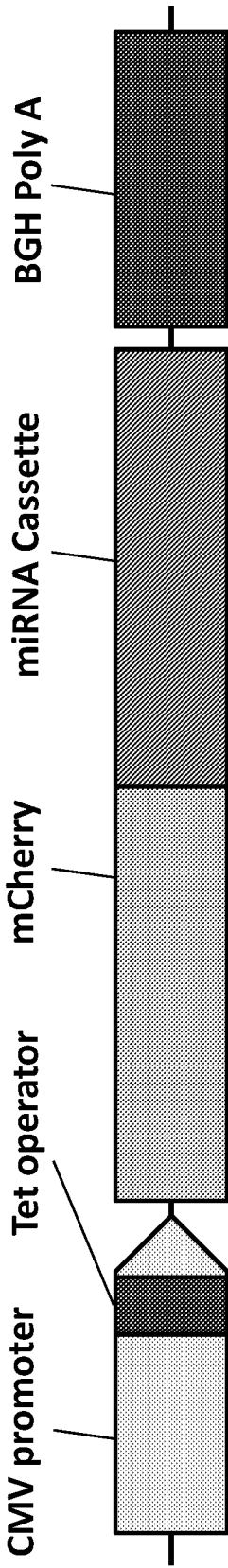


FIG. 15C

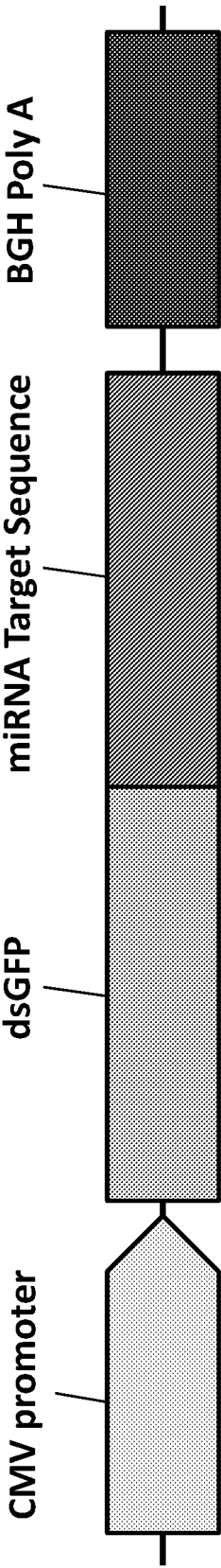


FIG. 16

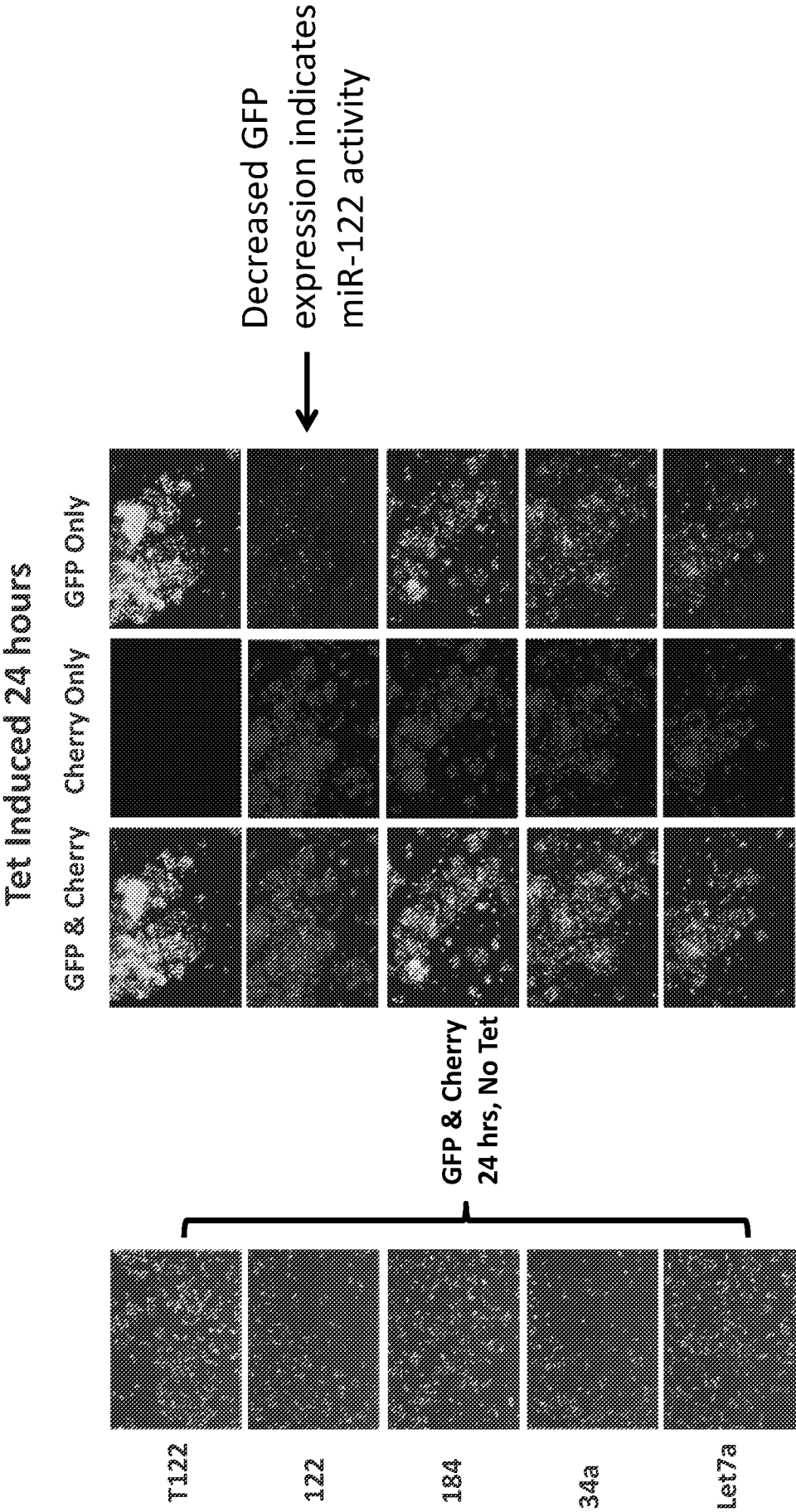
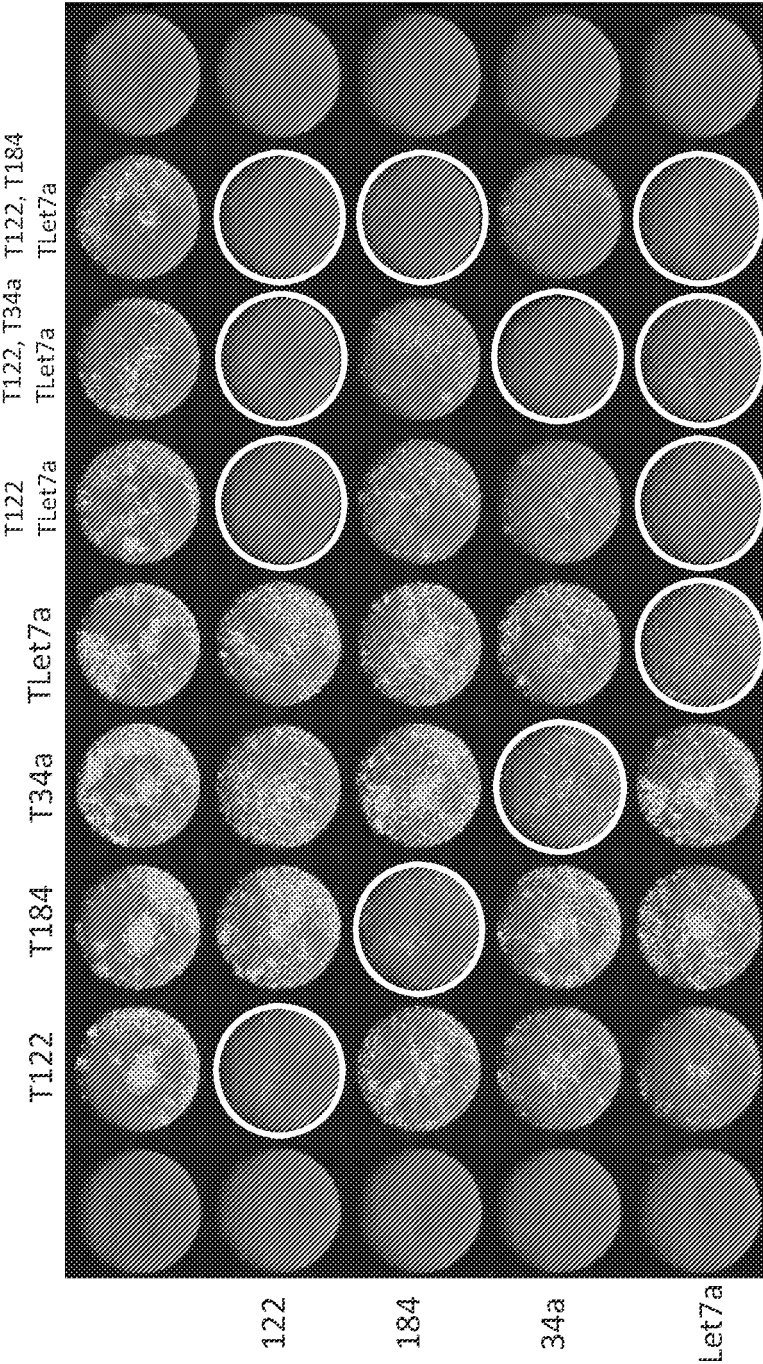


FIG. 17



* Circled wells indicate reduced GFP expression levels

FIG. 18

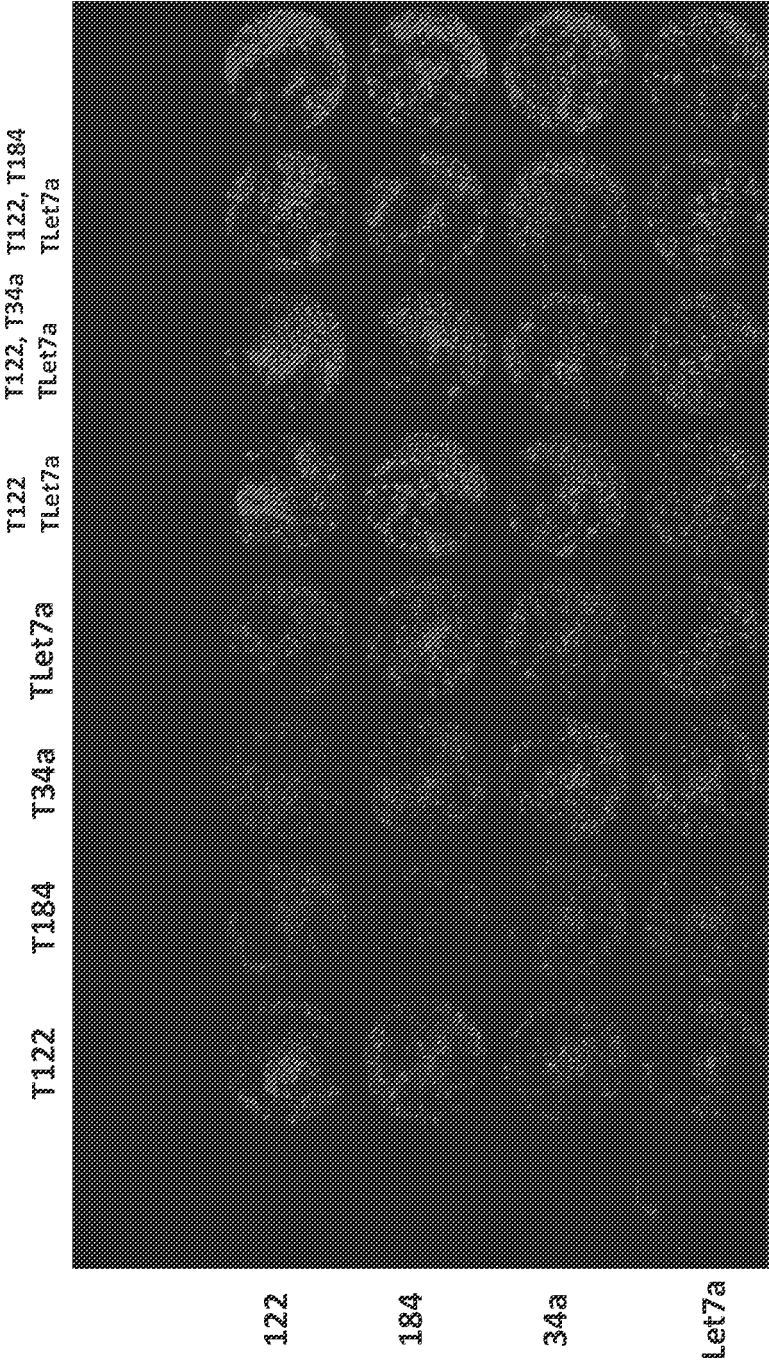
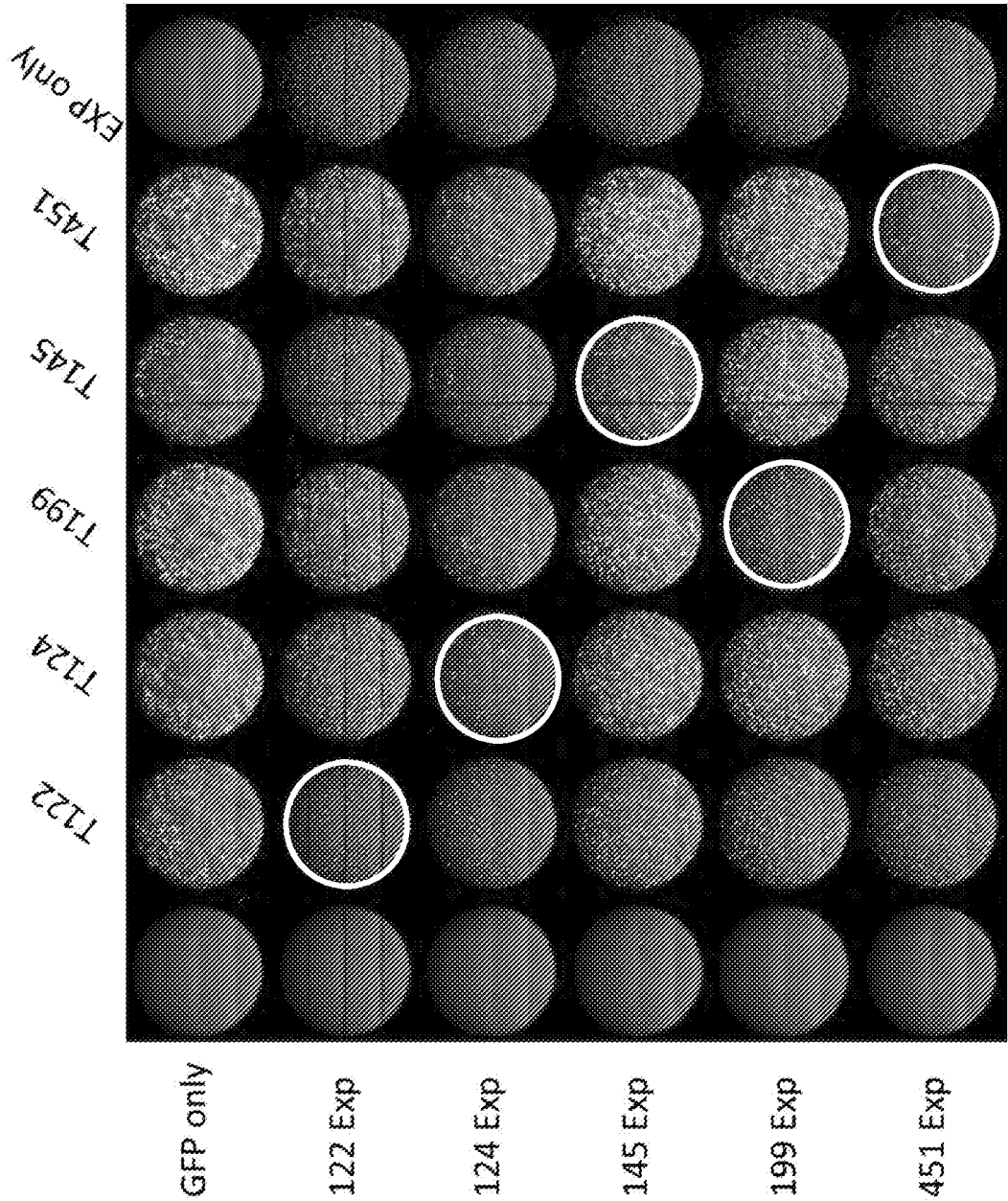


FIG. 19



* Circled wells indicate reduced GFP expression levels

FIG. 20

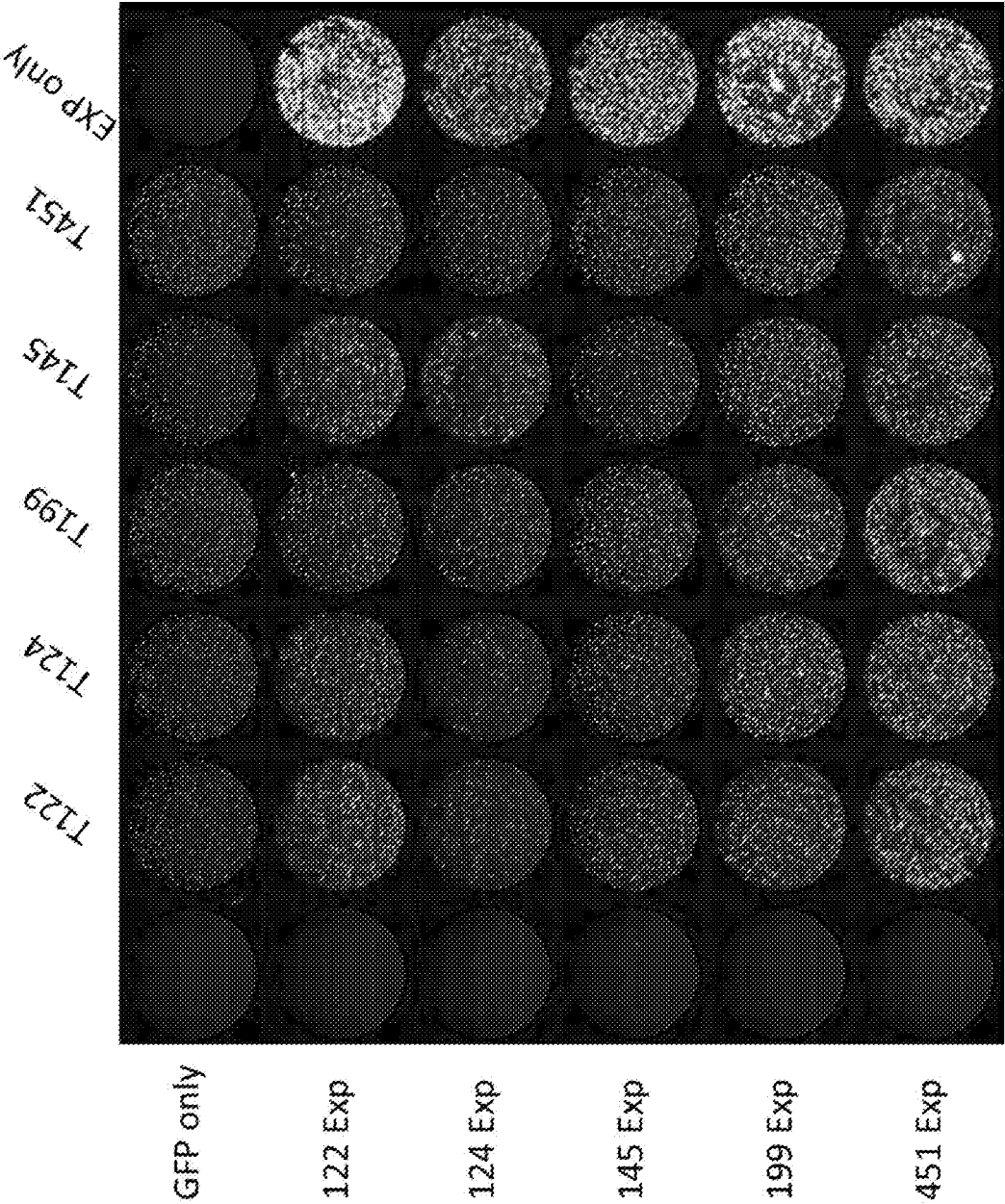


FIG. 21

122-184

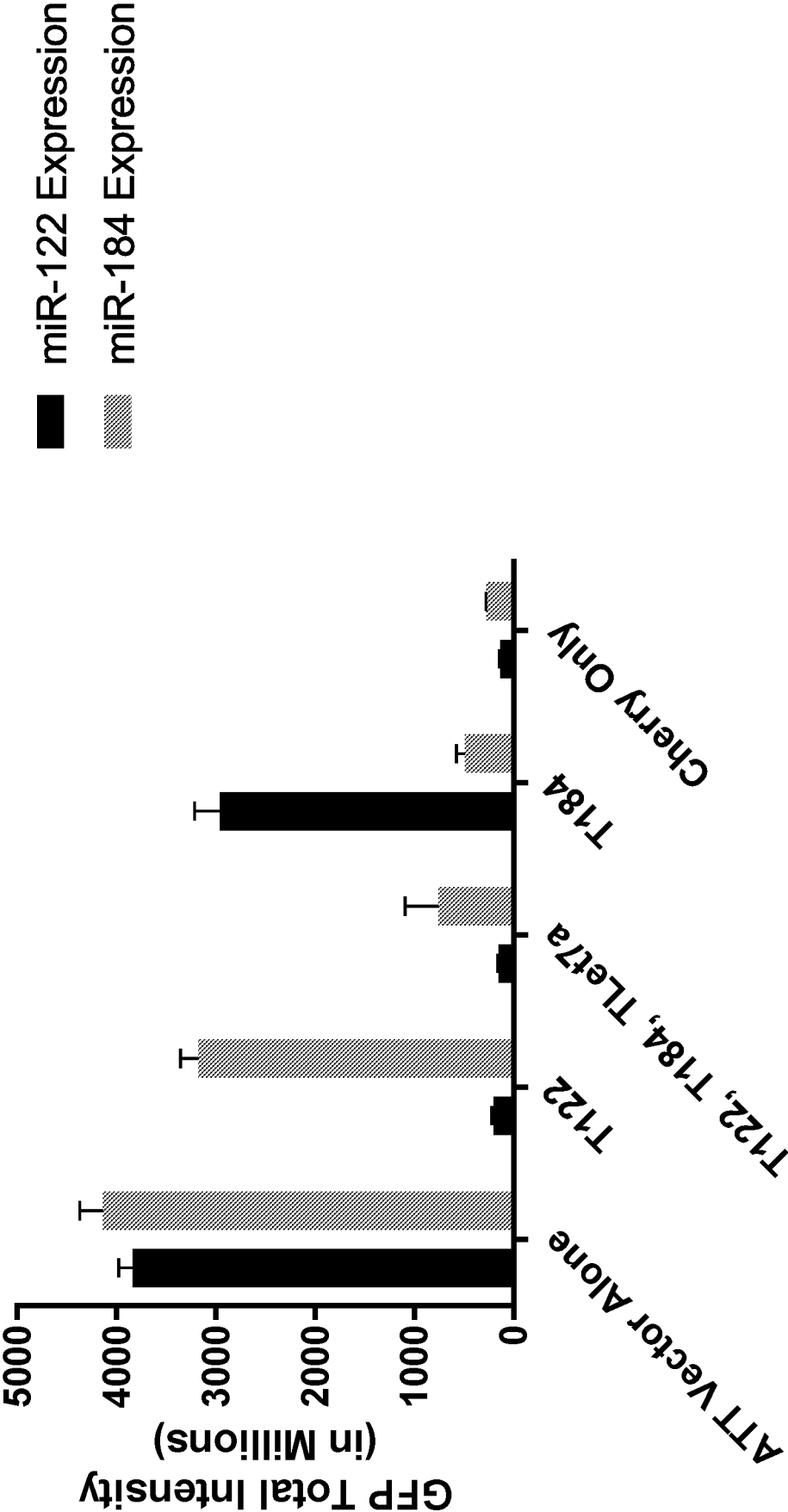


FIG. 22

34a-184

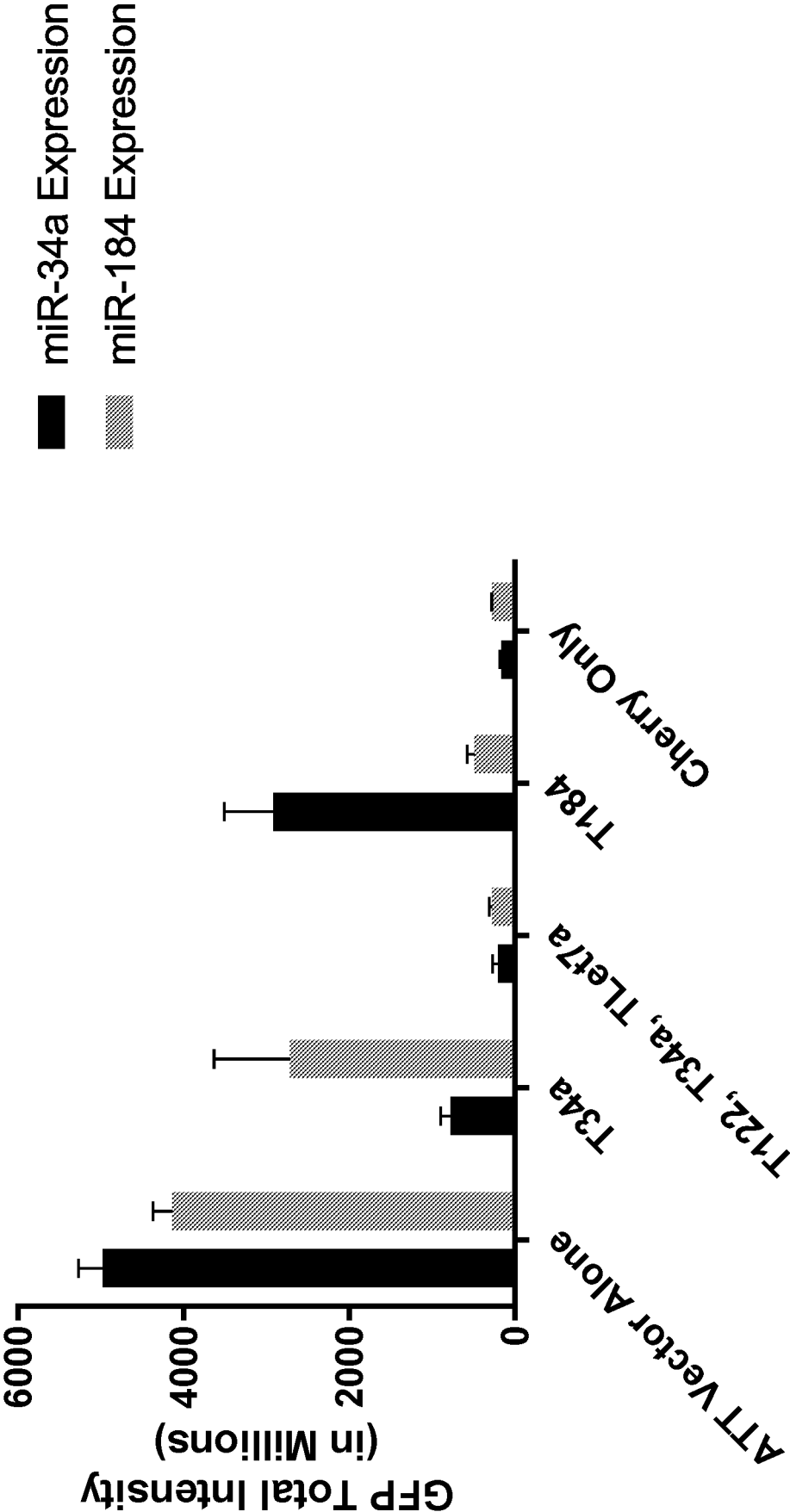


FIG. 23

Let7a-184

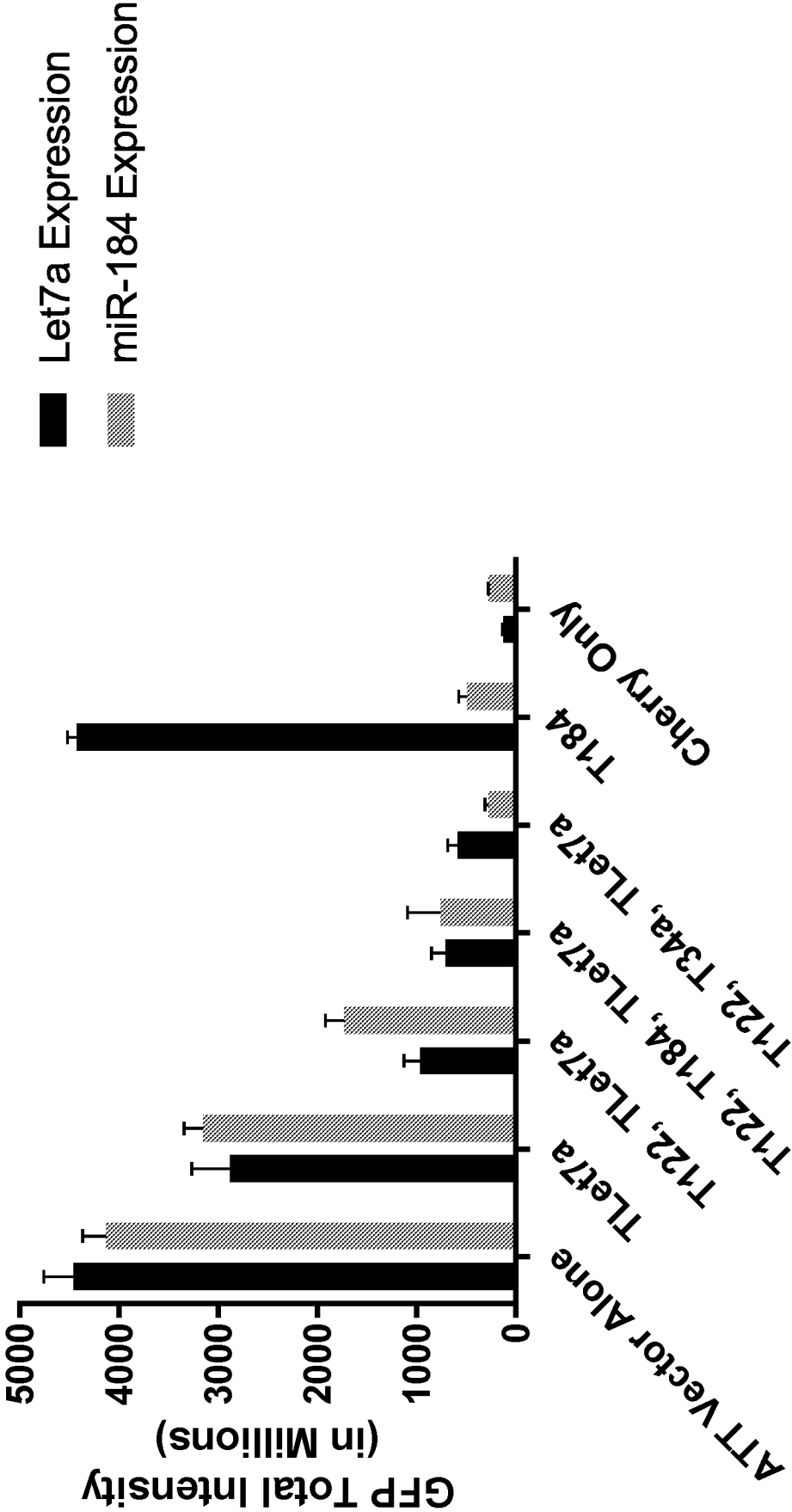


FIG. 24

124-184

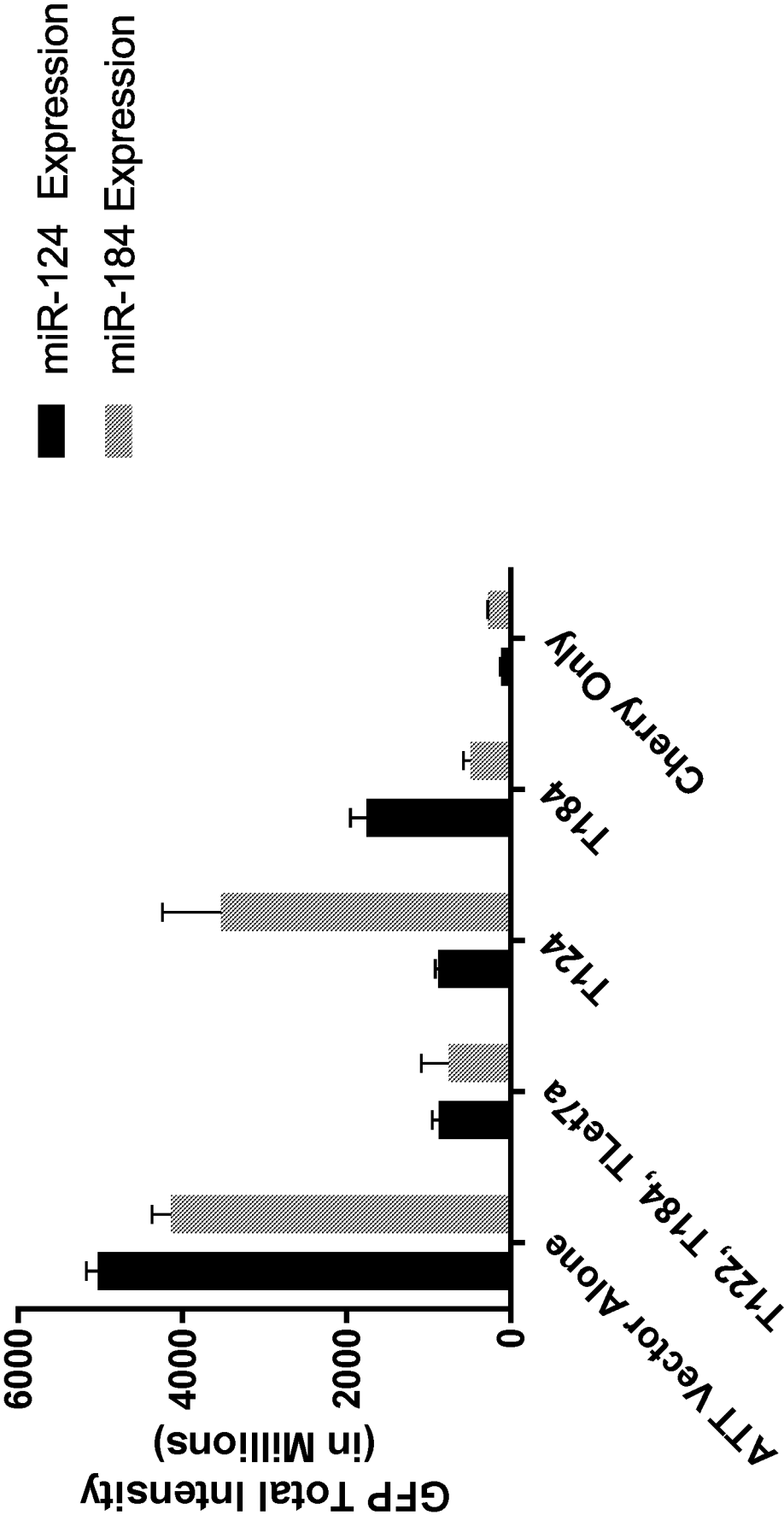


FIG. 25

145-184

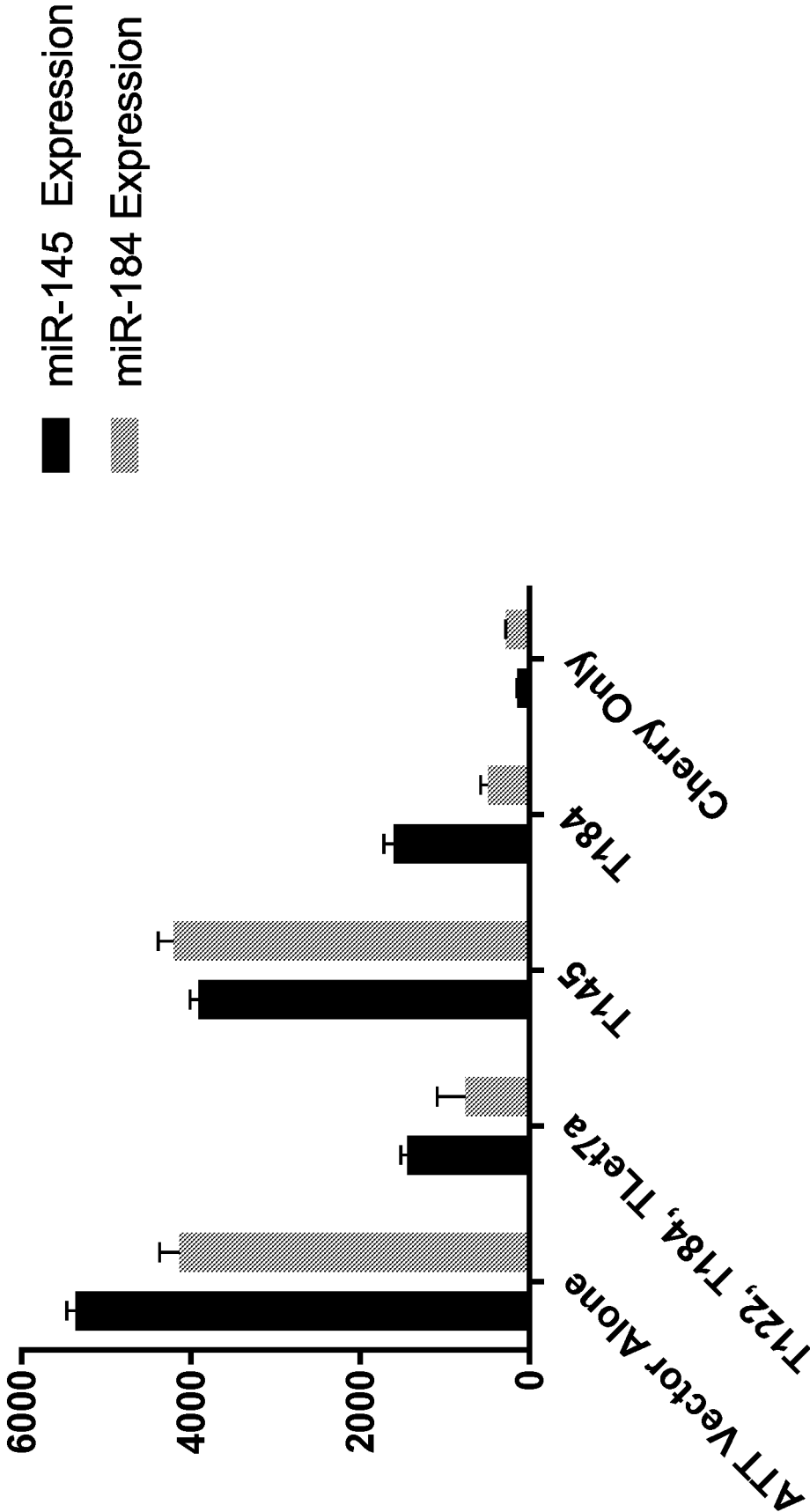


FIG. 26

199-451

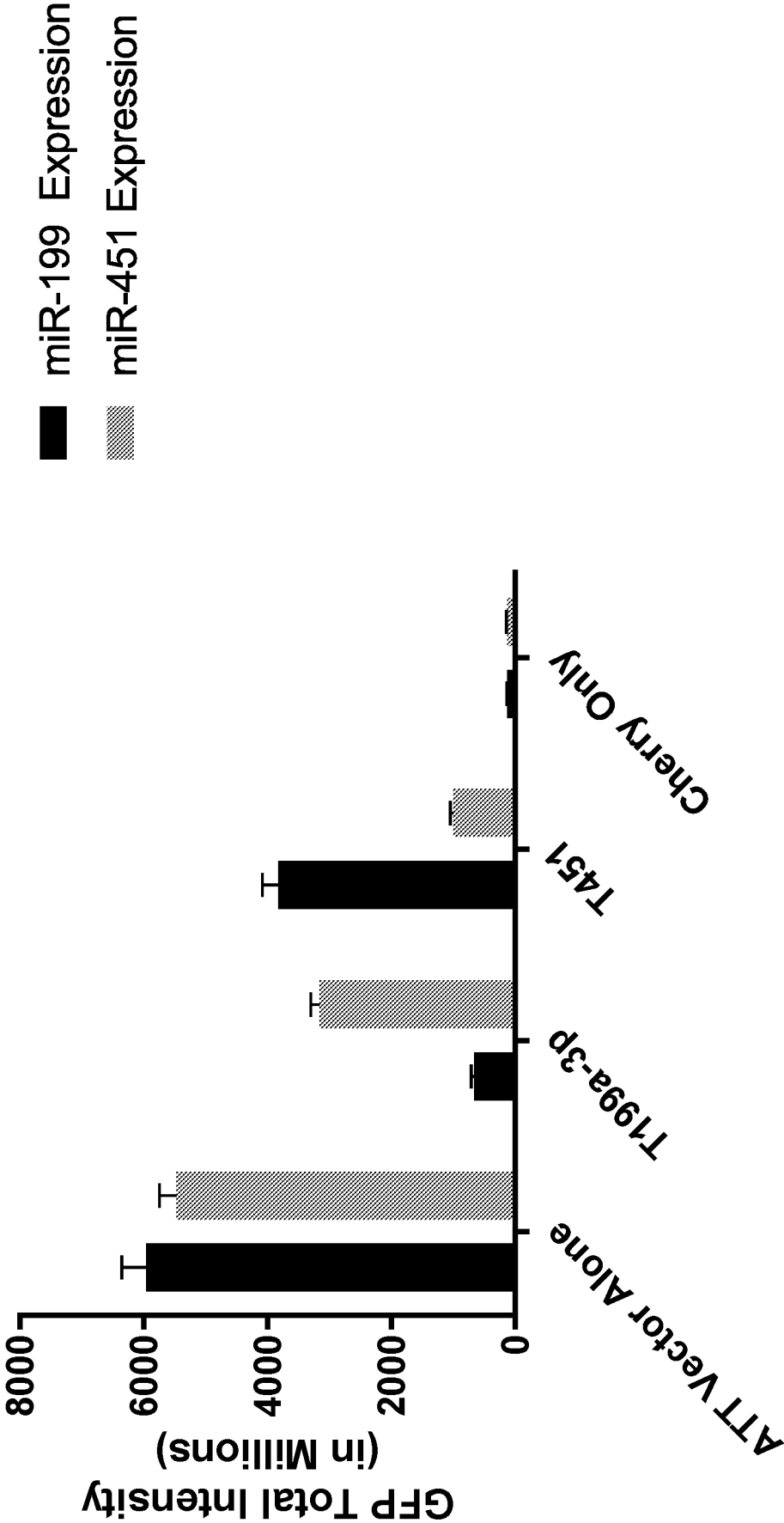


FIG. 27

125-451

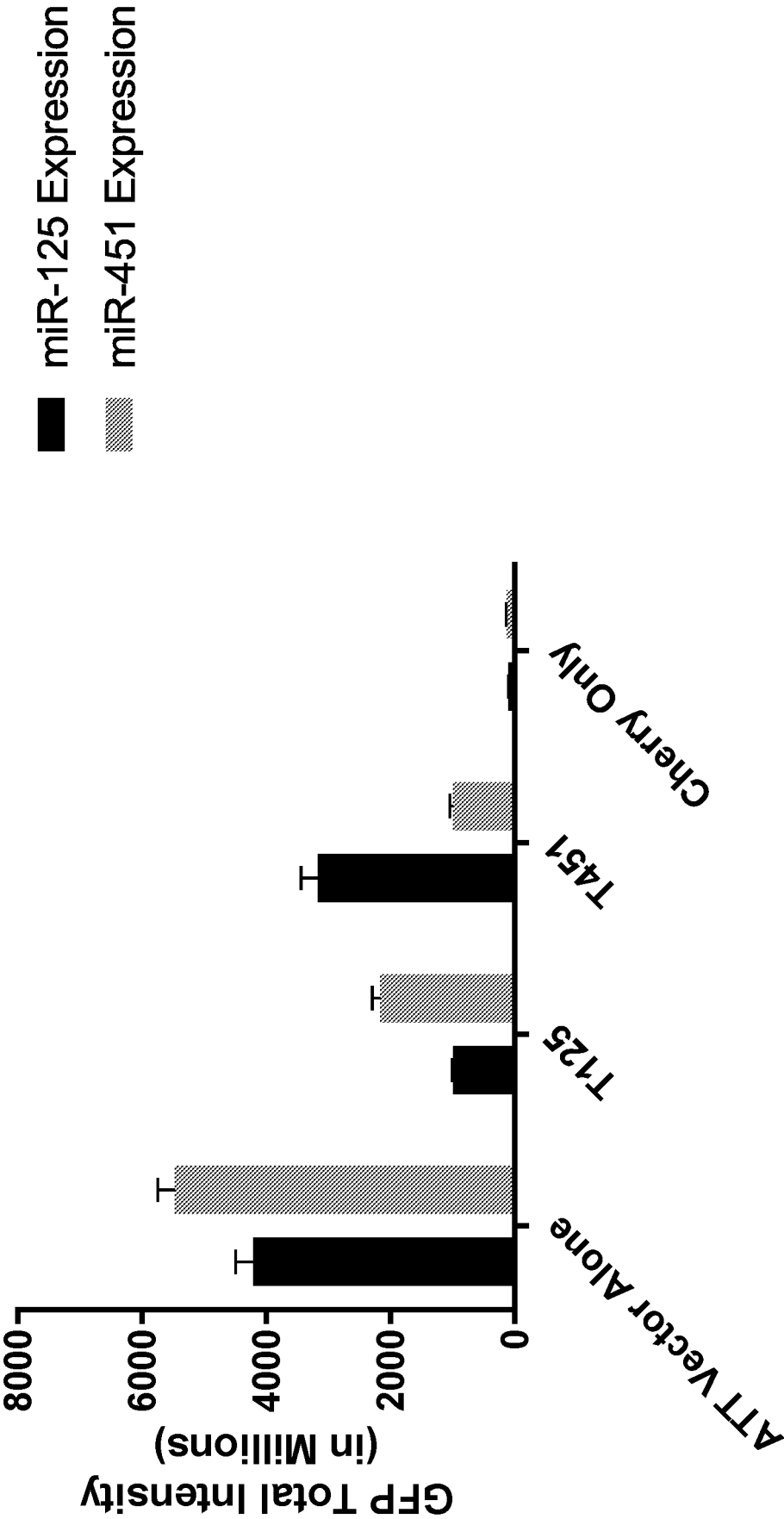


FIG. 28

126-451

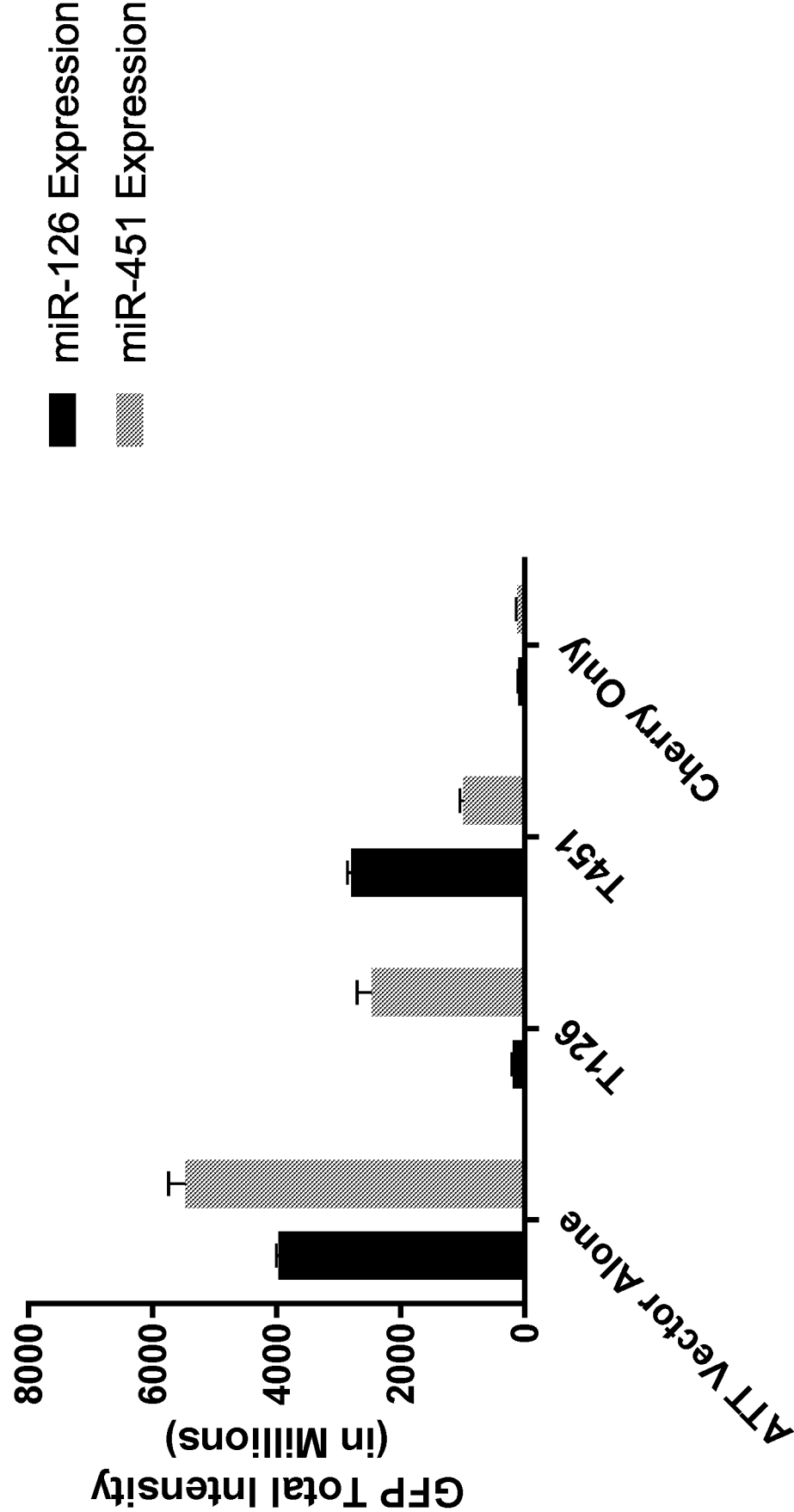


FIG. 29
127-451

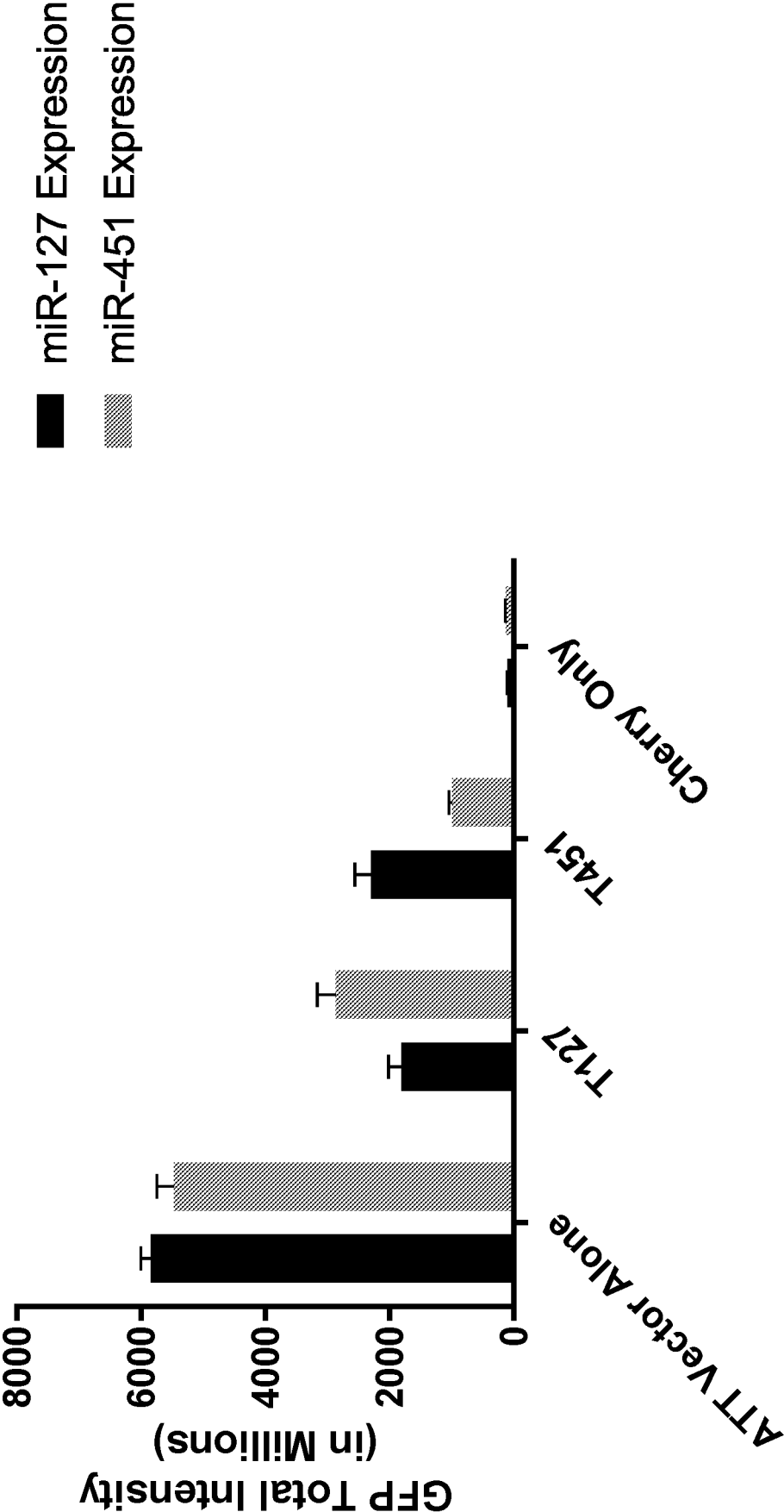


FIG. 30

133-451

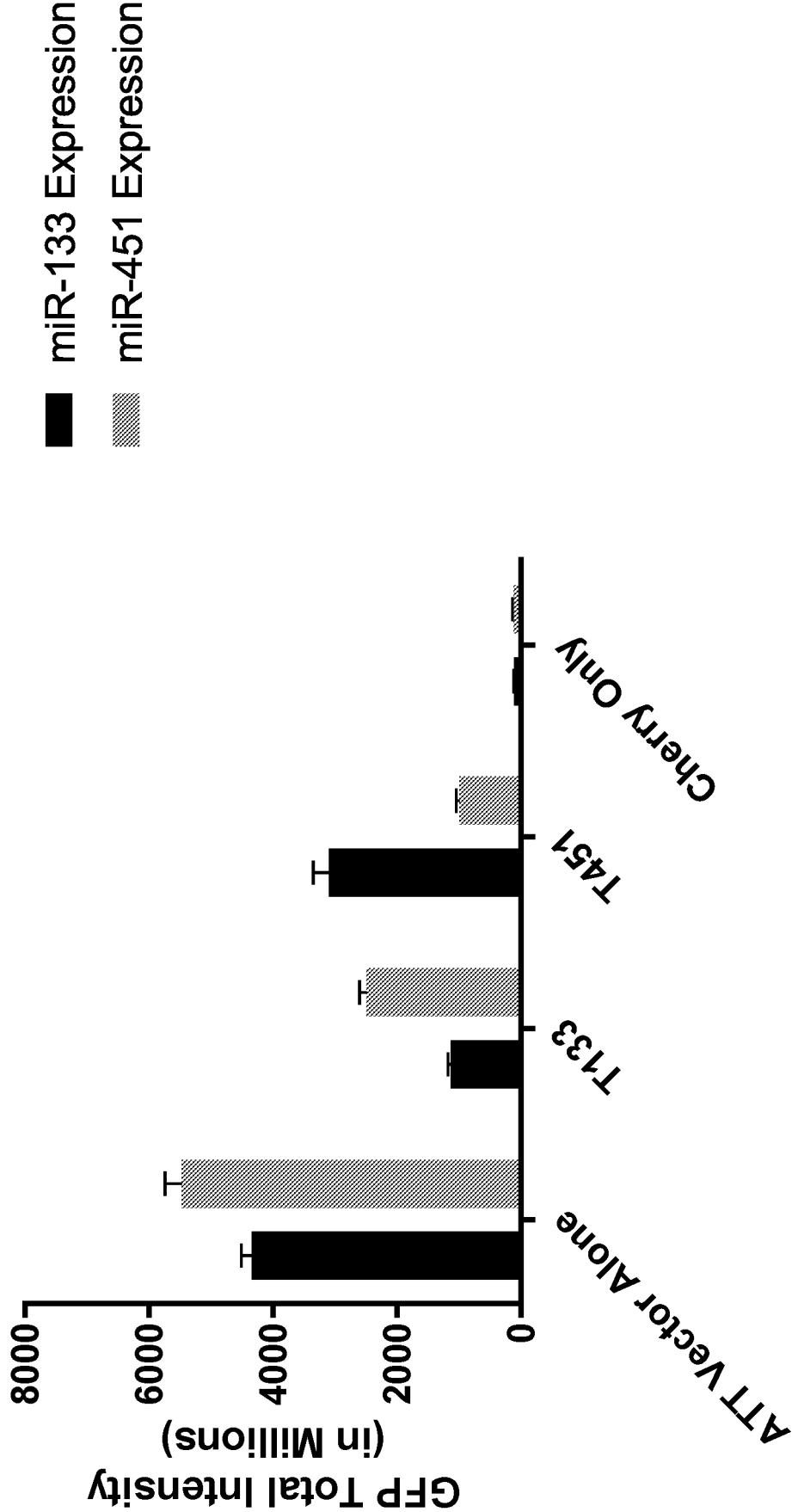


FIG. 31

223-451

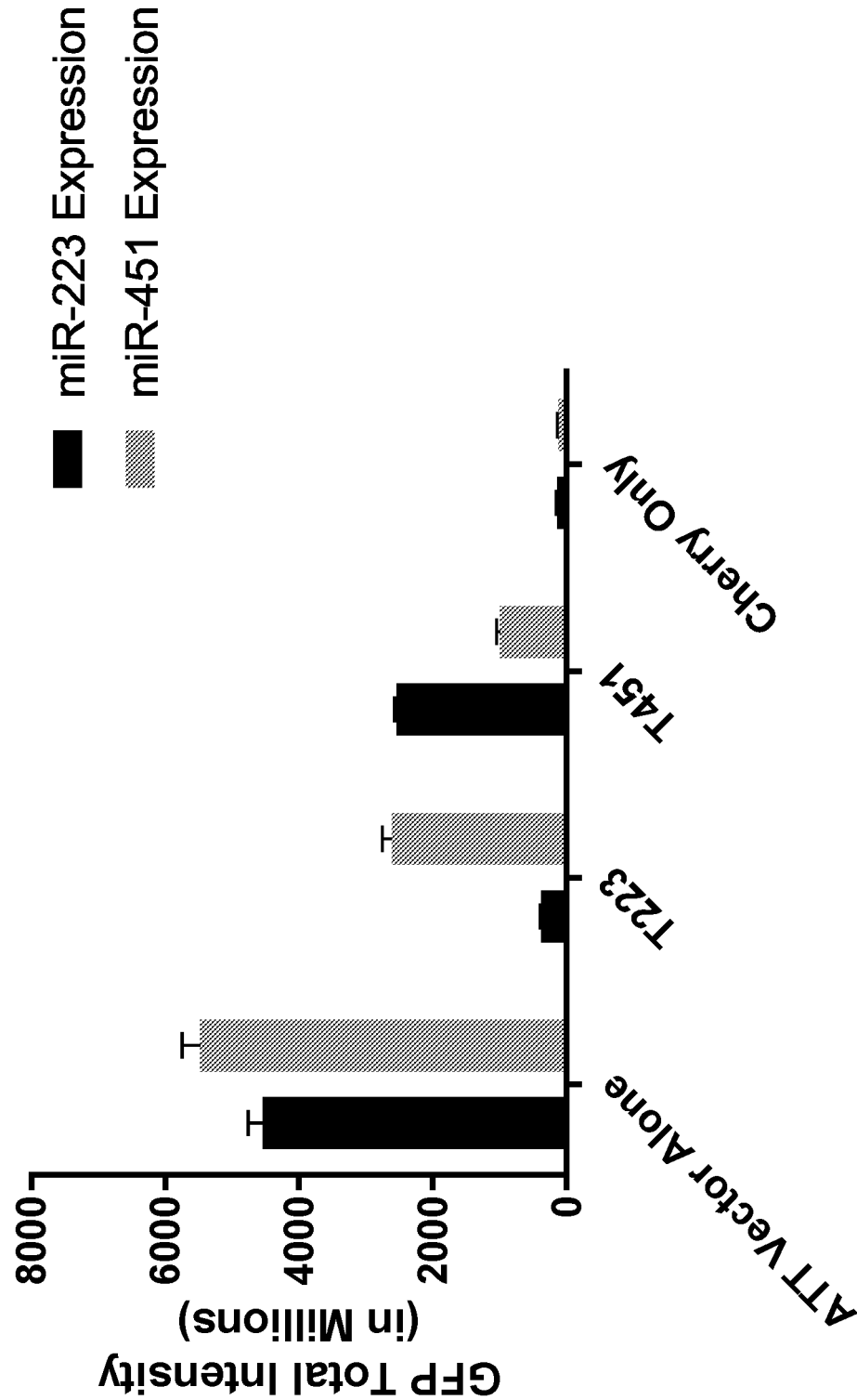


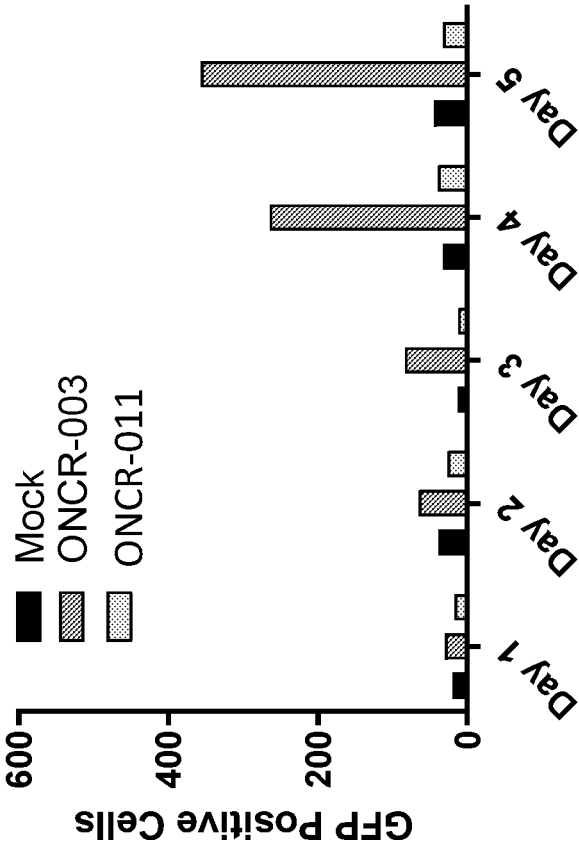
FIG. 32

Construct	ICP27 miRNA site	ICP4 miRNA site
ONCR-003	None	124
ONCR-010	122, 34a, Let7	124
ONCR-011	125a-5p	124
ONCR-012	143-3p	124
ONCR-013	145-5p	124
ONCR-014	199a-5p	124
ONCR-015	1-3p	124
ONCR-016	133a-3p	124
ONCR-017	223-3p	124
ONCR-018	451a	124
ONCR-019	126-3p	124
ONCR-020	127a-3p	124
ONCR-021	133b	124
ONCR-022	134-3p	124

FIG. 33

Vector	ICP4 miRNA site	ICP27 miRNA site	Cells	miR 125a	miR 124
ONCR-003	miR-124	None	PM-Lung	>3000	<100
ONCR-011	miR-124	miR-125	H & N CA	<100	<100

Post-mitotic Lung



A253 H & N Cancer cells

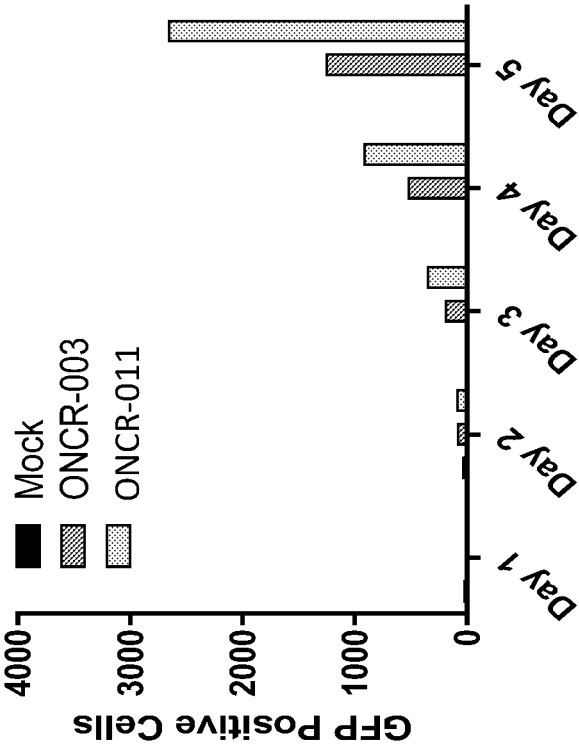


FIG. 34

Vector	ICP4 miRNA site	ICP27 miRNA site	Cells	miR 125a	miR 124
ONCR-003	miR-124	None	PM-Lung	>3000	<100
ONCR-011	miR-T124	miR-T125	H & N CA	<100	<100

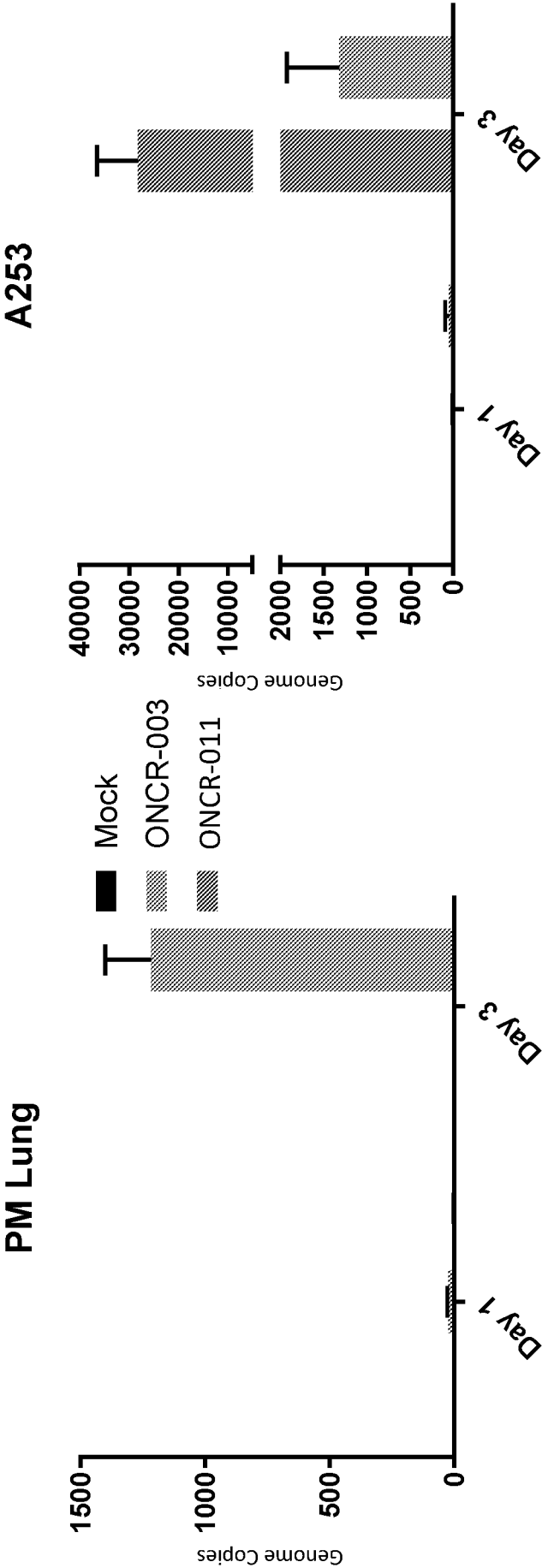


FIG. 35

Vector	ICP4 miRNA site	ICP27 miRNA site	Cells	miRNA counts
ONCR-013	miR-124	miR-145-5p	A253	0
			HCC1395	4487

Oncr 013 (miR-T145-5p)

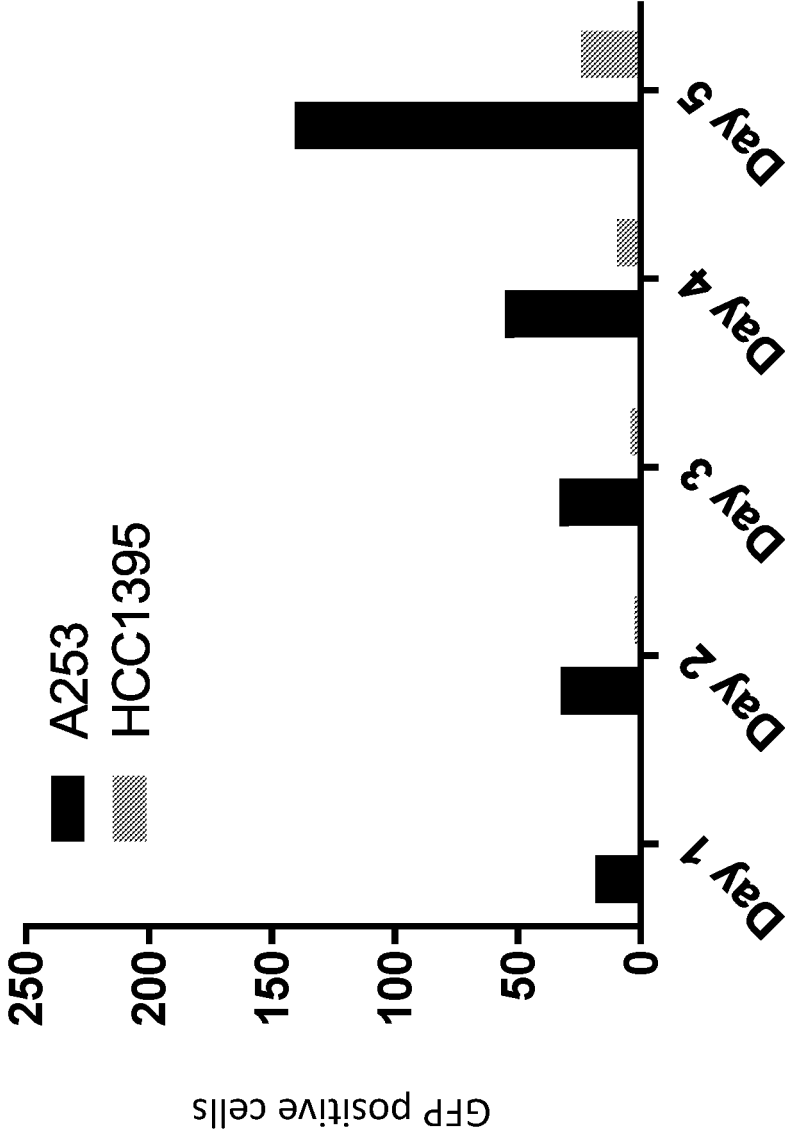


FIG. 36

Vector	ICP4 miRNA site	ICP27 miRNA site	Cells	miRNA counts
ONCR-013	miR-124	miR-145-5p	A253	0
			HCC1395	4487

ONCR 013

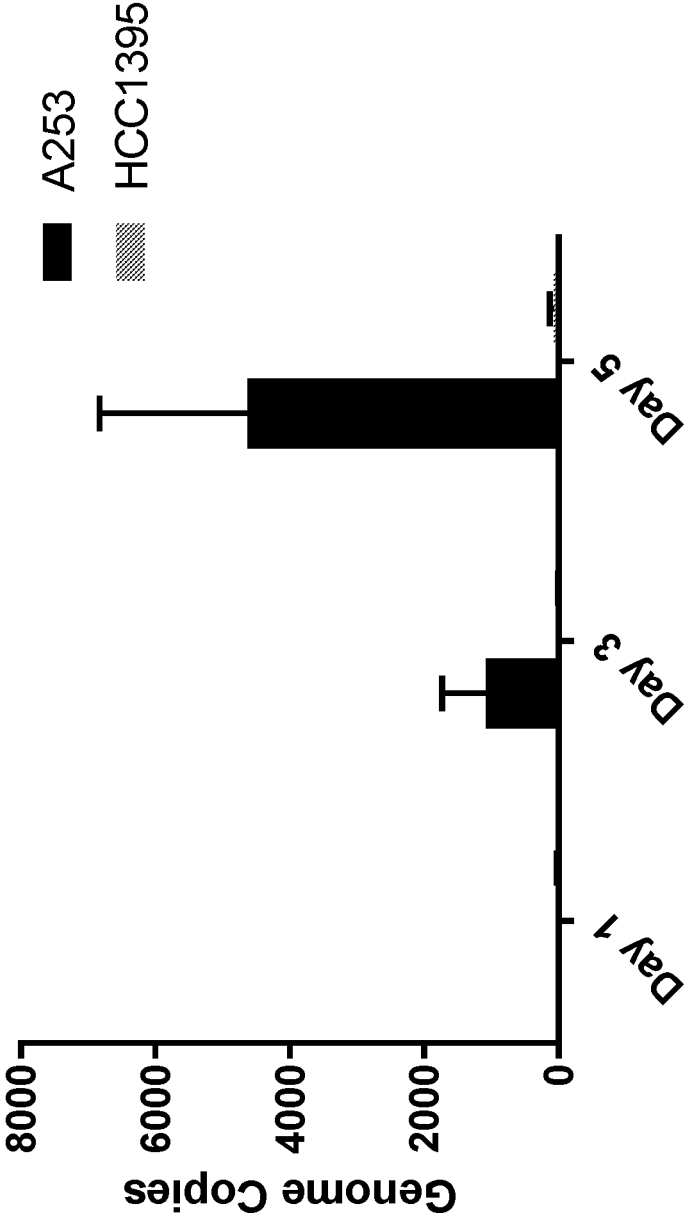


FIG. 37

Vector	ICP4 miRNA site	ICP27 miRNA site
ONCR-003	miR-124	None
ONCR-012	miR-124	miR-143-3p
ONCR-014	miR-124	miR-199a-5p

BEAS-2B, Lung

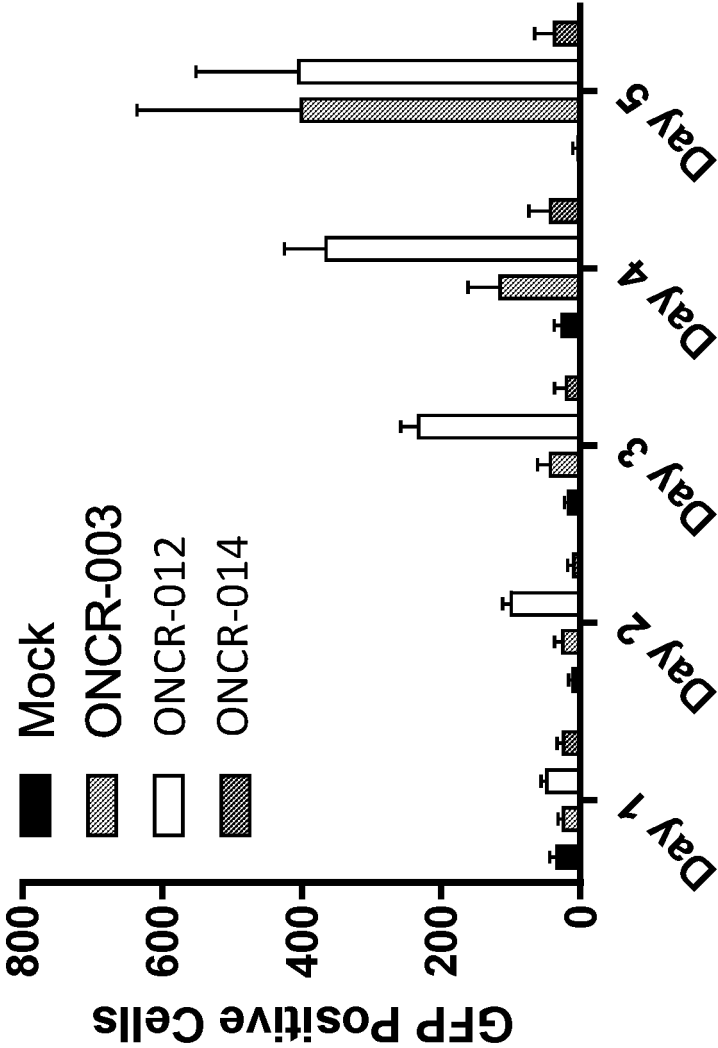


FIG. 38

Vector	ICP4 miRNA site	ICP27 miRNA site
ONCR-003	miR-124	None
ONCR-012	miR-124	miR-143-3p
ONCR-014	miR-124	miR-199a-5p

Beas-2B

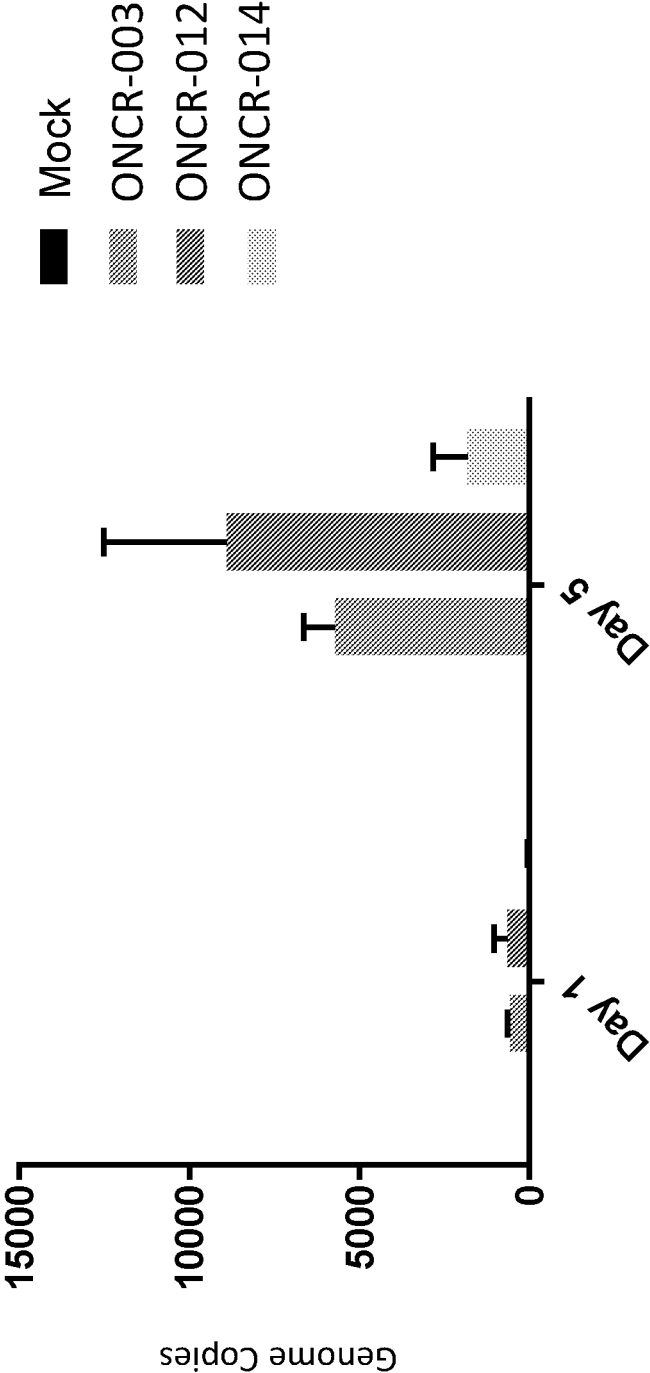


FIG. 39

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP4:TmiRNA: insertion of miRNA target sequences (e.g. let-7, miR-34a, miR-101, miR-125b, miR-145, etc.) into the 3' UTR of the remaining ICP4 gene (also may be placed in 5' UTR)

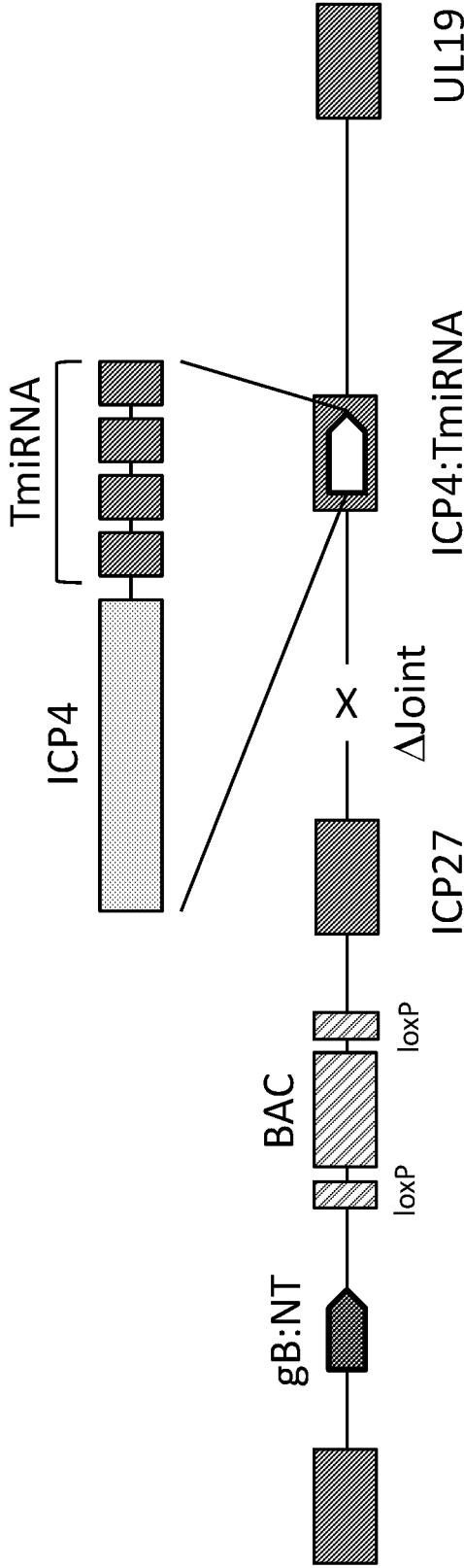


FIG. 40

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP27:TmiRNA: insertion of miRNA target sequences (e.g. let-7, miR-34a, miR-101, miR-125b, miR-145, etc.) into the 3' UTR of the ICP27 gene (also may be placed in 5' UTR)

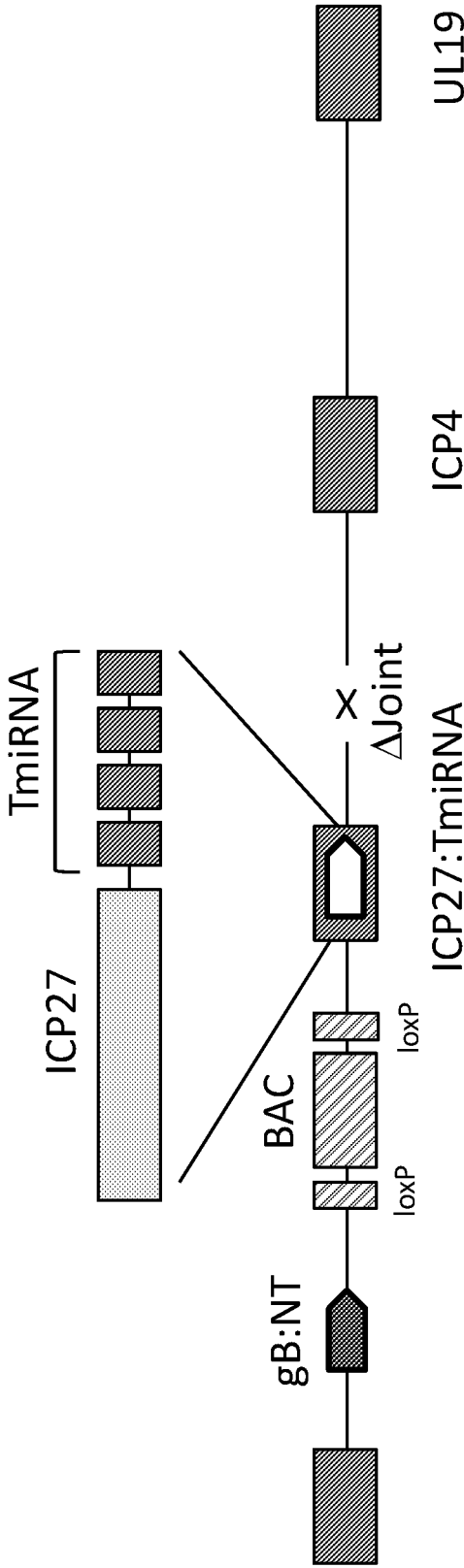


FIG. 41

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δ joint: deletion of the complete internal repeat region including one copy of the ICP4 gene

UL19:TmiRNA: insertion of miRNA target sequences (e.g. let-7, miR-34a, miR-101, miR-125b, miR-145, etc.) into the 3' UTR of the UL19 gene (also may be placed in 5' UTR)

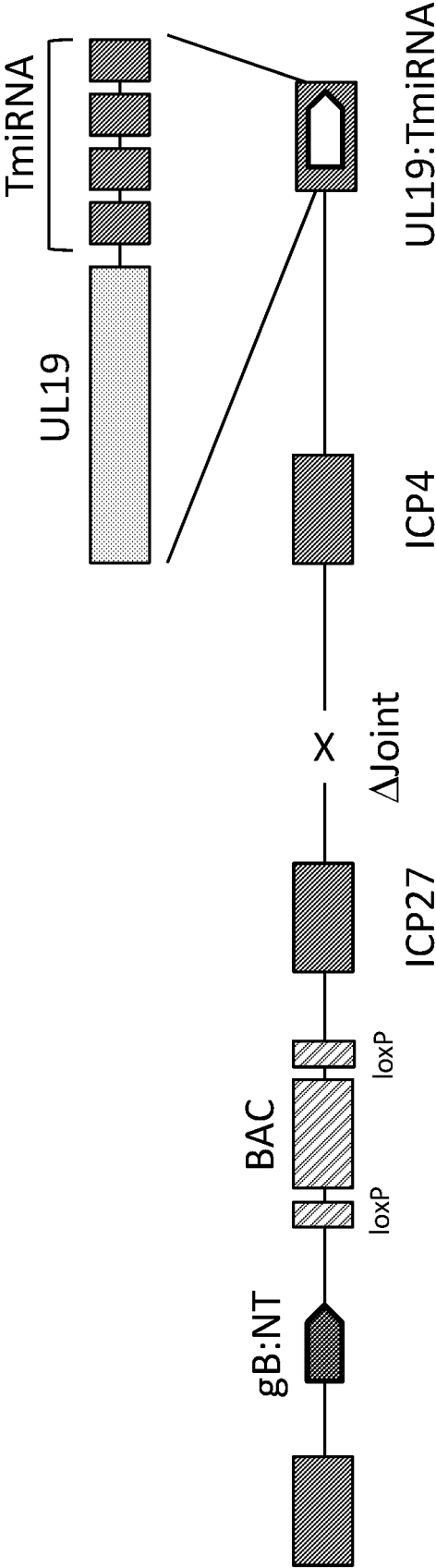


FIG. 43

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

UL19:TmiRNA & ICP4:TmiRNA: insertion of miRNA target sequences (e.g. let-7, miR-34a, miR-101, miR-125b, miR-145, etc.) into the 3' UTR of the UL19 and ICP4 genes (also may be placed in 5' UTR)

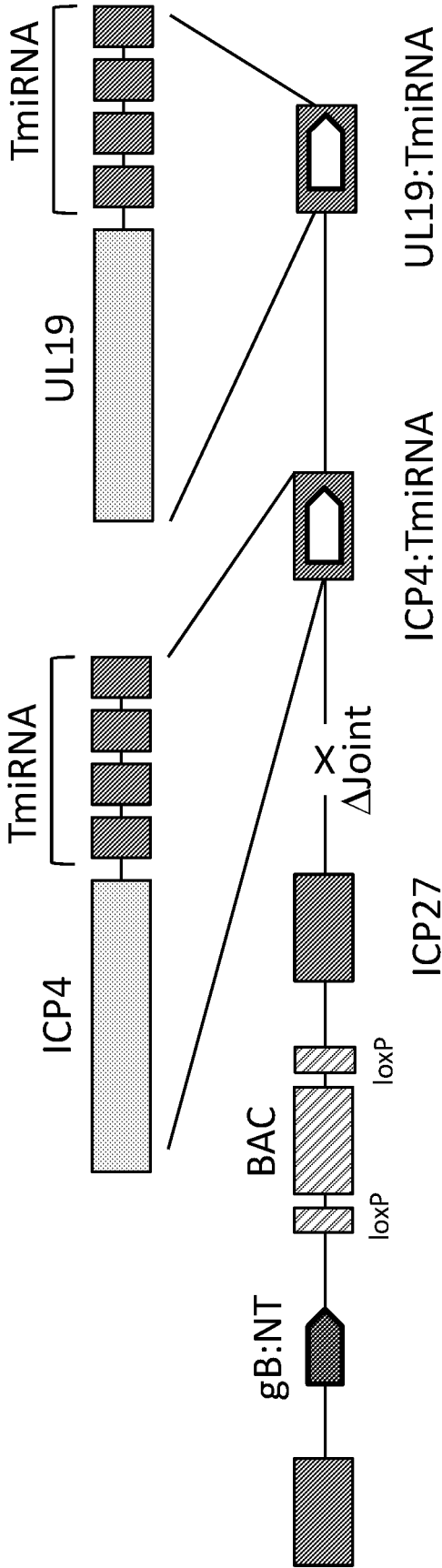


FIG. 45

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP4:TmiRNA: insertion of tumor suppressor miRNA target sequences (e.g. let-7, miR-34a, miR-101, miR-125b, miR-145) into the 3' UTR of the remaining ICP4 gene (also may be placed in 5' UTR)

Pol II promoter: Constitutive (CAG, UbC, EF1α, PGK) or cell-specific (e.g. TRPV1, Nav1.7, hSYN)

Endonuclease: CRISPR associated endonuclease (e.g. SpCas9, SaCas9, FnCpf1, FnCas9, etc.)

Poly(A): polyadenylation signal (e.g. bGH)

gRNA: Single crRNA-trRNA fusion (DR-crRNA-DR-trRNA); crRNA targeted to oncogenic microRNA (e.g. miR-17, miR-21, miR-155)

Pol III promoter: E.g. U6, H1, 7SK

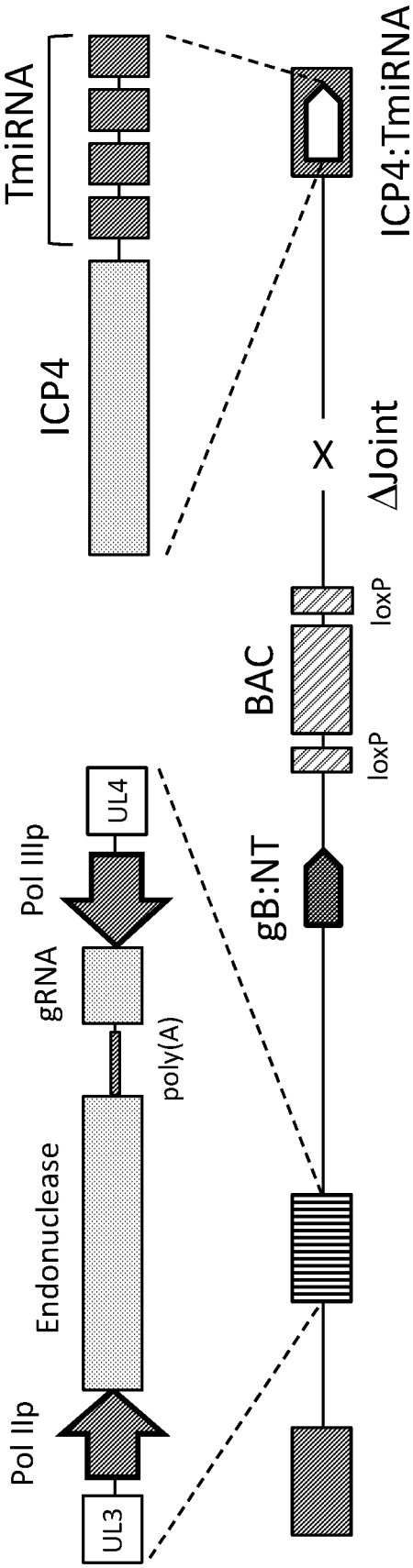


FIG. 46

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP4:TmiRNA: insertion of tumor suppressor miRNA target sequences (e.g. let-7, miR-34a, miR-101, miR-125b, miR-145) into the 3' UTR of the remaining ICP4 gene (also may be placed in 5' UTR)

Pol II promoter: Constitutive (CAG, UbC, EF1α, PGK) or cell-specific (e.g. TRPV1, Nav1.7, hSYN)

Endonuclease: CRISPR associated endonuclease (e.g. SpCas9, SaCas9, FnCpf1, FnCas9, etc.)

Poly(A): polyadenylation signal (e.g. bGH)

gRNA1: Single crRNA-trRNA fusion (DR-crRNA-DR-trRNA); crRNA targeted to oncogenic microRNA (e.g. miR-17, miR-21, miR-155).

gRNA2: crRNA targeted to microenvironment remodeling miRNA (e.g. miR-143, miR-218) or TIMP (e.g. TIMP1, TIMP2).

Pol III promoter: E.g. U6, H1, 7SK

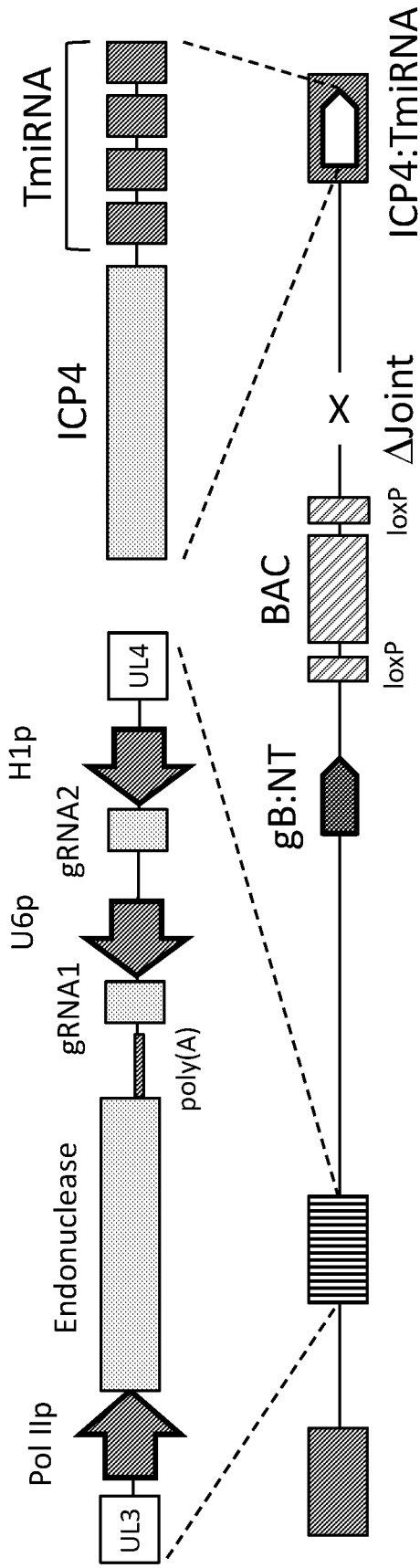


FIG. 47

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP4:TmiRNA: insertion of miR-124 target sequence cassette into the 3' UTR of the remaining ICP4 gene (also may be placed in 5' UTR)

ICP27:TmiRNA: insertion of miR-451a, miR-143-3p, and miR-559 target sequence cassettes into the 3' UTR of the ICP-27 gene (also may be placed in 5' UTR)

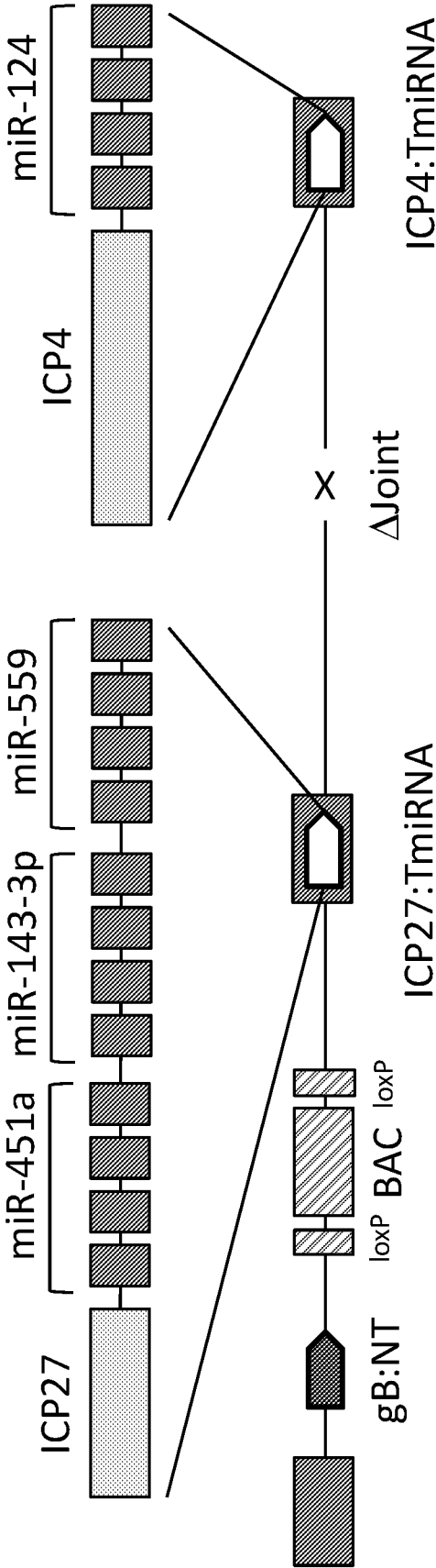


FIG. 48

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP4:TmiRNA: insertion of miR-124 target sequence cassette into the 3' UTR of the remaining ICP4 gene (also may be placed in 5' UTR)

ICP27:TmiRNA: insertion of miR-451a, miR-145-5p, and miR-559 target sequence cassettes into the 3' UTR of the ICP-27 gene (also may be placed in 5' UTR)

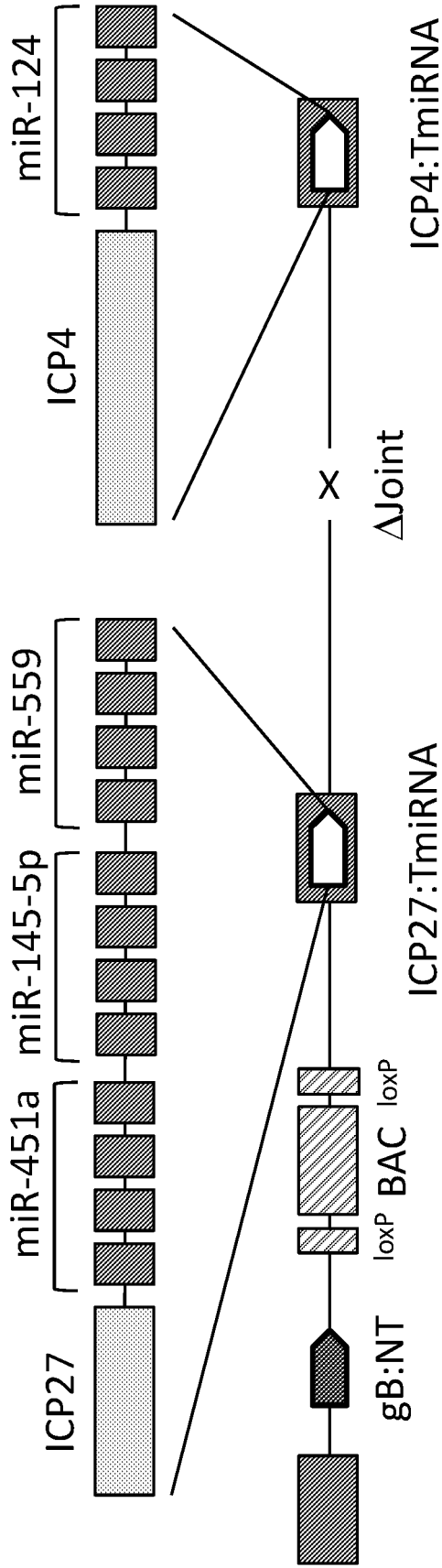


FIG. 49

gB:NT: virus entry-enhancing double mutation in gB gene

BAC: loxP-flanked choramphenicol-resistance and lacZ sequences

Δjoint: deletion of the complete internal repeat region including one copy of the ICP4 gene

ICP4:TmiRNA: insertion of miR-124 target sequence cassette into the 3' UTR of the remaining ICP4 gene (also may be placed in 5' UTR)

ICP27:TmiRNA: insertion of miR-205p, miR-141-5p, and miR-31-5p target sequence cassettes into the 3' UTR of the ICP-27 gene (also may be placed in 5' UTR)

